# Best Practices in Long-Term Safety Follow-Up Studies in Oncology

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As the quest to develop more effective treatments for cancer continues, a growing number of therapies are receiving accelerated approval from the U.S. Food and Drug Administration (FDA).[1] The percentage of new oncology drugs that have gone through the Accelerated Approval Program increased approximately 30% between 2012 and 2020.[2] Accelerated approval often comes with a commitment for post-approval follow-up safety studies that can extend for many years, and for some treatments, decades. A CAR-T therapy receiving accelerated approval might, for example, require a 15-year follow-up safety study.

Such long study periods pose challenges for sponsors and contract research organizations (CROs) in minimizing patient attrition and data loss. At the same time, sponsors and CROs must develop cost-effective approaches to these studies so that they are sustainable and produce regulator-grade data. Here, we explore how the demands of long-term follow-up studies of oncology therapies are changing and present recommendations for keeping sites and patients engaged in the ongoing research effort.

## How Long Is Long Enough?

Current guidelines from the FDA and the European Medicines Agency (EMA) provide for a range of follow-up periods that reflect the risk factors associated with, and the existing body of knowledge about, a treatment. For example, the follow-up period for a bone marrow graft in a 2-year-old patient may extend for decades both because of the high risk of leukemia from genetically modified blood cells and because it is too early to understand the effects over a lifetime. In other therapy areas — even in other gene therapies in which there is a low risk of integrating a gene in the wrong place — the risk to the patient can be perceived to be much lower, and the follow-up period may be as little as five years. It is likely that as new technologies become more established, regulators will show a willingness to reduce follow-up periods as more information becomes available and the long-term risk profile of the treatments are better understood. Yet, in some therapies, such as the bone marrow graft example, it is likely that authorities will continue to be very conservative in their approach and require long follow-up periods.

## Challenges in Meeting the Demands of Data Collection

It used to be that data collection in oncology follow-up studies was relatively simple as it was largely limited to monitoring duration of response and overall survival, especially when patients' life expectancies were, unfortunately, measured in months.

Today, follow-up with many oncology treatments can be more complex since patients are receiving investigational therapies in earlier lines of treatment and are living longer, post-therapy. Especially in relation to more immunotherapies and the risks they pose, follow-up must be much more rigorous and safety-focused — akin to the monitoring conducted during the treatment phase of the clinical trial. Since there are so many more treatment options and different approaches to sequencing their combination, long-term follow-up studies present an opportunity to understand how patient outcomes are holistically affected by their individual treatment journey. Additionally, the follow-up period often provides an opportunity to differentiate competitor products in immuno-oncology — particularly around long-term health resource utilization and overall cost effectiveness, which is being demanded by both regulators and payers.

## Implications for Protocol Design

Sponsors can minimize the expense of long-term safety studies and improve the ease with which they are implemented through robust planning, starting with their original protocol design.

In randomized controlled trials (RCTs), data collection is fit for purpose. However, in long-term follow-up studies, data collection can quickly become unmanageable, especially for a submission that is intended to cover more than one indication or when a company plans to submit multiple marketing approval applications. There is a tendency to want to collect as much information as possible in the hope of discovering a valuable nugget in the data that will shed new light on product performance. This increases the burden on sites and patients and makes data aggregation and analysis unwieldy. By adopting a quality-by-design approach, Sponsors can determine at the outset what data will ultimately be necessary and then limit data collection to what is relevant.

Additionally, the data collection requirements are broader in oncology follow-up studies than the hard response endpoints that Sponsors are accustomed to assessing. For so long, the industry's focus has been on what evidence is required to get to market and to penetrate the market, that Sponsors have not necessarily concentrated on the evidence points that often matter very much, if not more, to patients. This must change if sponsors are to motivate patients to remain in long-term safety studies.

Some sponsors have streamlined study implementation by taking a modular approach through an overarching "parent" protocol, followed by sub-protocols that are deployed as the product moves through development and/or through different tumor targets. Each sub-protocol is designed with different data collection goals. The first, for example, might focus on primary endpoints. The second might

provide intensive follow-up for patients remaining on treatment, and the third might involve more traditional long-term follow-up data collection for patients who have completed treatment.

With this type of flexibility built into the protocol at the outset, modules can be added that reflect the sponsor's current needs and understanding of the molecule and the disease. Once sponsors have a core protocol approved, they can implement the subsequent modules more easily and cost-effectively.

Another cost-saving solution when multiple, related RCTs are coming to a close is to roll all of them into a single, long-term safety protocol, such as a registry, regardless of whether or not patients are still receiving therapy. This is dramatically more cost-effective than running multiple, parallel individual long-term follow-up studies.

## Recommendations for Sponsors

**Begin with the End in Mind:** Plan ahead, with an understanding of what will be required in terms of evidence for the product to succeed. This does not always come naturally to clinical teams as their focus is on meeting primary endpoints for marketing approval. Consider the follow-up that will be required to produce that evidence, and encapsulate that into the protocol from the outset. The reference may be as broad as indicating that the intention is to put patients into a long-term safety study to collect a certain, specified type of data. While amendments may eventually be necessary, their development will be less onerous and costly than the requirement to develop a fundamentally new design. Time will be saved by not having to go through the site contracting and patient consenting processes again.

**Perform Holistic Evidence Planning that Considers All Stakeholders:** From early in the development process, Sponsors should explore, and be prepared to address, the information needs of all stakeholders — regulators, prescribers, patients, caregivers, and payers. A best practice is to conduct interviews with physicians and payers during the Phase II/III design period to gather insights as to what evidence they will require. Regulators will be able to give insight on which safety endpoints will be considered to be critical and whether they will accept the data collection methodologies proposed. Similarly, payers will be able to shed light on which efficacy endpoints will be key to gaining access. Long-term follow-up studies present Sponsors with an opportunity to gather evidence on how a treatment performs in a less restricted, less controlled environment. While a follow-up study may not provide real-world data in its truest form, it is certainly moving in that direction and can offer insight into how the treatment might perform in a real-world setting. That will become important in helping differentiate the treatment from the standard of care or competitor products.

**Best Practices in Long-Term Safety Follow-Up Studies in Oncology:** Think creatively about ways to either reduce the burden for them, or "make it worth their while." Make long-term participation relevant to patients — even to those who are in remission or have been cured of their disease — by providing feedback at intervals in a variety of patient-facing media, not only on the study results, but on product milestones. Use new platforms — and consider a variety of platforms — to give feedback to patients on their own results as well as on product milestones.

**Adopt Patient-Centric Designs:** This includes understanding what endpoints are of interest to patients and minimizing the patient burden. The patient burden of a given protocol can be evaluated so that sponsors can make judgment calls about what information is essential to the value of the study vs. what is nice to have. Recognize that patients are on an emotional journey through their treatment and beyond that will impact their interest in participating.

**Consider Innovative Study Designs:** The way that studies are structured can streamline operations, reduce costs and ease the burden on patients. Elements of virtualization can be key to all three goals.

**Employ the Latest Technologies:** Technological solutions are available to reduce the burden on sites and patients in providing data, and even to increase the value that patients receive in participating in studies.

**Rely on Experts:** Engaging sites and patients requires forethought, resources and specialized expertise. While sponsors may be tempted to gather patient insights for protocol design and handle ongoing patient communications on their own to manage costs, a less-than-ideal effort could pose a serious risk to patient participation and ongoing engagement.

## The Overall Key to Success

Planning is the overall key to success in long-term follow-up studies in oncology, just as in all clinical trials. Yet, even more than in other studies, long-term safety studies of oncology treatments demand that strategies be developed to keep sites and patients engaged, as their participation is required over the course of many years. Fortunately, by taking a quality-by-design approach, employing new tools and technologies, and focusing on patient centricity, patient attrition, and data loss can be minimized.

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*Notes: [1] Beaver JA, Howie LJ, et al, "A 25-Year Experience of US Food and Drug Administration Accelerated Approval of Malignant Hematology and Oncology Drugs and Biologics: A Review," JAMA Oncol. 2018 Jun 1;4(6):849-856. doi: 10.1001/jamaoncol.2017.5618. [2] https://www.fda.gov/drugs/nda-and-bla-approvals/fast-track-approvals*