How to Run a Successful, Decentralised Oncology Trial

As interest in decentralised study designs grows, oncology researchers should be aware of the components necessary for a successful trial

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Oncology studies are going through a profound transformation. The traditional endpoints of tumour response and survival only capture a portion of a patient's experience with cancer. However, measuring tumour response and survival alone does not necessarily inform researchers on the primary concerns of patients undergoing cancer treatment. Nor does it provide insight into whether patients believe the burden of treatment was worth the result. Understanding how patients cope with their disease and manage their treatment-related symptoms is also important. As a result, there is increasing interest in patient-reported outcome measures (PROMs). This goes beyond simply adding a few health-related, quality-of-life questionnaires to a protocol. There is also increased interest in both the types of patient-reported data collected and when it is collected.

At the same time, the COVID-19 pandemic has forced physicians to quickly implement remote patient management and care delivery methodologies. Rapid patient and physician acceptance of these new clinical paradigms is now affecting clinical trial design.

New digital solutions combined with a reimagining of oncology trial protocols offer cancer patients new opportunities to participate in cancer research while providing researchers with new insights into the entirety of the cancer treatment experience.

The Catalysts for Change

Regulatory guidance

Systematic monitoring of symptoms as part of routine clinical care can result in significantly better outcomes, and patient reporting can improve communication, drive satisfaction, and ease symptom management (1, 2). Despite this, oncology trials have been slower to include PROMs. A review of oncology drug approvals from 2012-2016 revealed that while the EMA granted labelling based on PROM endpoints for a third of submissions, the FDA did not approve any labelling claims based on PROM data during the same timeframe (3). An earlier review of FDA approvals from 2010-2014 revealed that only three of the 40 cancer treatments approved for use in the US received any PRO-related labelling with all three approvals granted in 2011 (4).

In recent years, we have seen enhanced emphasis on the importance of PROMs collected in oncology clinical trials reflected by the FDA. Project Patient Voice, for example, has been established to provide a mechanism to share patient-reported symptom data from cancer clinical trials for marketed treatments to provide more information to patients and healthcare providers in treatment decision-making (5). This information provides insights into side effects not currently available in standard FDA safety tables, including existing symptoms before the start of treatment, symptoms over time, and the subset of patients who did not have a particular symptom prior to starting treatment.

Despite this increased emphasis on the importance of patient-reported outcomes in oncology trials, there is still uncertainty around what to measure, the collection methodologies, the frequency of collection, and when assessments should be performed. The FDA's recent draft guidance proposes several approaches to addressing many of these concerns (6). Specifically, the guidance identified a core set of PROMs to separately measure:

1. Disease-related symptoms
2. Symptomatic adverse events (AEs)

3. Overall side effect impact (single item)
4. Physical function
5. Role function

For some of these concepts, standard instruments already exist and are commonly in use. For other concepts, additional instruments will need to be developed or existing instruments modified.

Also addressed is the frequency of data collection. Historically, cancer patients in clinical trials have completed PROMs during on-site visits at the end of a treatment cycle or at the beginning of a new cycle. This cadence often results in the assessments being completed at a time when patients have adequately recovered from the previous treatment cycle and are well enough to begin the next cycle. If patients are not well enough to continue treatment, the next cycle and associated PROM assessments are delayed. This assessment schedule is not optimal to provide a comprehensive or accurate portrayal of mid-cycle treatment experience. The guidance therefore recommends that assessments be performed more frequently during the early cycles of treatment, with fewer assessments later in the treatment process. This paradigm shift will require at-home measurements in addition to, or instead of, the traditional on-site assessments.

Telehealth

The COVID-19 pandemic has resulted in a dramatic shift in the delivery of medical care to patients. In January 2020, prior to the initiation of nationwide lockdown measures, only 0.24% of total medical claims in the US were telemedicine related (7). One year later, this had increased to 7% (8). To put this in perspective, it took e-commerce adoption 15 years to rise from less than 1% to more than 7%. Telemedicine during the pandemic accomplished this in only one year (9).

Telehealth solutions have demonstrated that they can improve access to care and provide disease management and safety monitoring opportunities not previously available with traditional site-based care. Telehealth is a natural evolution of medicine in the digital age, and patients' preferences for receiving care in-person or via telehealth should be respected in the future (10). This focus on patient preferences and expectations will also apply to care delivered in the context of clinical trials.

Despite the need for certain visits to be conducted on-site for tasks such as administering a further cycle of treatment or performing a medical imaging assessment, telemedicine visits use live video to connect patients and investigators between clinic visits and during longer term follow-up periods.

Remote patient monitoring using sensors and wearables

The continued miniaturisation of sensors and circuitry, in addition to the innovation this has brought to the health and wellness industries, provides the opportunity to measure aspects of health not previously possible, via new and novel data sources. Understanding the impact of treatments can be achieved using PROMs, but wearable devices measuring activity and sleep can provide an additional perspective on the impact of treatment during cycles. Sensors and wearables also enable regular measurement of other safety signals during oncology treatment, such as blood pressure and blood oxygen saturation. Remote patient monitoring using wearables and sensors can provide rich insights to better understand the treatment's impact and oversee patient safety.

Oncology Trials of the Future

The challenge now is to reimagine what oncology trials can be in the context of these new paradigms. Digital solutions provide researchers with the opportunity to move away from traditional clinical trials that occur completely on-site and design studies that utilise any number of new methodologies for delivering care to, and gathering data from, patients. These designs have recently taken on the monikers of 'decentralised' or 'hybrid' trials. While there may be some truth in these new industry buzzwords, ideally future trials should be 'optimised' for the digital age.

Currently, most attempts at developing decentralised trials begin with a traditional protocol designed entirely around site visits and site-based assessments, and then 'decentralising' it. Such an approach is inefficient, and great effort is spent trying to find a suitable remote solution for a site-based activity, when what is really needed is to begin with the end in mind and carefully consider what activities truly need to be completed and what data need to be collected. Once decided, simply choose the most convenient, efficient, and effective methodologies for achieving those objectives.

When setting out to design a decentralised trial, it is important to challenge conventional wisdom by asking:

1. What data must be collected?
2. What data that are traditionally collected do not need to be collected?
3. Where can these data be collected?
4. What is the ideal cadence for data collection? Should this cadence be static, or should it be dynamic based on phases of treatment or the needs of the patient?
5. What additional data can be gathered to provide a more comprehensive assessment of patient experience and response?
6. What can make this study safer for patients?
7. What can make this study more convenient for patients and/or research sites?

Honest answers to some of these questions may be surprising. Are laboratory assessments collected at intervals that truly affect safety monitoring and final analysis? Or, are they simply collected because the patient is on-site? When decentralising a traditional site-based schedule of events, some will maintain the traditional safety assessment schedule, and then spend too much time trying to find a way to collect lab specimens

at home, when what is really needed is to simply adjust the schedule of assessments and/or perform fewer lab assessments.

Are PROMs assessed at times when the data provide the most comprehensive insights? Or, are they simply collected on-site when the patient is available? Employing electronic clinical outcome assessments (eCOA) allows patients to provide important inter-visit data regarding treatment-related side effects as well as the impact of treatment on their quality of life, physical function, and role function within their family, work, and social settings.

Are there alternative data streams that could add value to traditional datasets? Home-based monitoring of vital signs can be an important part of inter-visit safety monitoring when decentralised designs result in fewer on-site visits. Such assessments can be performed easily with integrated devices that transmit data directly to investigators. Passive monitoring of activity and sleep quality through sensors and wearables can provide additional insights into patients' inter-cycle response to treatment.

Can adequate patient oversight still be accomplished when patients visit the site less frequently? Telemedicine visits provide the opportunity to monitor patients more frequently without requiring travel to and from the clinic. Also, site staff can often complete multiple, short, telemedicine visits in the same time it takes to complete a single on-site visit. For more complex assessments, home-health nurses can complete examinations or assessments, while the investigator provides oversight via a telemedicine visit. More frequent, efficient monitoring of patients may eventually lead to earlier detection of clinical deterioration and timely deployment of interventions to quickly address adverse events or prevent hospitalisation.

Advances in digital technologies combined with the activation energy provided by the pandemic have led to a rapid shift in the delivery of medical care. Patients and physicians alike have quickly become comfortable with remote medicine and disease management, to the point that this alternative delivery model is now an accepted and expected method for the practice of medicine. As patients and physicians become reliant on these care delivery models, clinical trials will have to adjust accordingly. Researchers should accept this challenge, not by tacking on new technologies to old study designs, but by thoughtfully starting with the end in mind and designing a truly modern, optimised trial using all of these wonderful new digital tools.

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