Rare Cancers – What to Consider for Complex Clinical Studies

Highlights:

- Trial design hinges on defining target population, sample size, and endpoints
- Understanding the scale of the study and using data and technology help determine feasibility
- Engaging patients can involve patient advocacy groups and focused social media networks
- Partnerships are vital

Introduction

According to the World Health Organization (WHO), there are more than 18 million new cancer diagnoses globally every year. Cancer has always been complicated, but of all cancer types, 22% are considered rare, according to Rare Cancers Europe (RCE) and correspond to over 200 different tumor types, a higher diversity than the most frequent breast, colon, prostate, and lung cancers taken together.

Therapies have mainly been developed based on the differing histologies of various cancers; breast cancer responds to treatment differently than lung cancer, for example, so a greater understanding of the molecular basis of the disease has transformed research tremendously, especially over recent years. Given this, there are different medical and protocol considerations, especially when factoring in rare cancers.

Rare Cancers: Not a Rare Problem, But a Broader One

In a report published by the FDA in 2011, 99 trials supporting rare cancer drug approvals on 45 different products were reviewed. Of those, there were four different types of results. Two-thirds of the trials that led to approvals were not randomized; they were performed with single arm studies. Most (64%) had priority reviews, which is very important in achieving faster approval. Still, only 37% of the accelerated approvals were for rare cancers.

As research progresses, the shift has gone from only a histological definition to a biological and genetic definition of rare cancers. Collectively, rare malignancies represent about a quarter of all cancers. Today, pediatric studies are increasing. And advancements in research, receptors, and biomarkers have generated new rare groups,

such as triple-negative breast cancer. Male breast cancer has also been a more recent subgroup and topic for research. The molecular landscape being created by genetic testing of tumors provides new insights, which creates new subgroups that correspond to genetic variants.

Medical Considerations

Rare cancers have a poorer prognosis than other malignancies, but they tend to have a better response to targeted therapies, because there is less variability in their molecular profile. However, the disparity and rarity of cases indicates a need for multicenter studies, from network-based to international, as well as the need for population-based cancer registries, biobanking, and real-world clinical data.

Beyond having a strong network, there's also a need for data and data organization, data access, and the creation of databanks. The feasibility of these rare cancer trials will be obtained by centralized referrals to clinical trials, communicating on study information, and organization of sites to let people know about trials and create a strong awareness that will enable all patients to be referred to the appropriate trial and treatment.

New Tools: Designing Your Protocol

Statistical design is key in any clinical study, but even more in rare cancer trials, where low accrual is anticipated because of the small population available. The detection of the benefit is increased by adding some shorter-term endpoints, such as three- or six-month progression-free survival. Retrospective review of databases offers insight on disease patterns and management, and using designs like Bayesian, adaptive, and continuous reassessment methods may also provide reliable data and faster trial completion in small populations.

With genetic information now creating a whole new series of groups of tumor variants, next generation sequencing can detect these genetic abnormalities and should be included in rare cancer protocols. Next generation sequencing detects most mutations, deletions, translocations, and more. This leads to not only detection and diagnosis but opens the possibilities of appropriate treatments as well.

Assessing Feasibility

With rare diseases, it's critical to assess the feasibility at the earliest stages of study planning, ideally before protocols have been developed. It's also critical to assess feasibility throughout development and during the conduct of the study, where things can change very quickly.

Key to assessing feasibility is identifying where the patients are, how to access them within the context of a trial, and understanding the patient perspective for participation. Especially with rare diseases, every effort should be made to conduct a global feasibility assessment to include:

- Patient access, including the patient pathway, incidence / prevalence data, biomarker frequency, and line of therapy

- Treatment landscape, including available treatments, standard of care and reimbursement, and upcoming drug approvals
- Risk analysis, including ongoing and planned studies, depleted patient pools, and countries/regions without competition
- Site identification, including investigator experience, eligible sites per country, and genetic testing
- Stakeholder collaboration, including national and international advocacy collaboration, consortiums, and site networks

Establishing Partnerships

Given the operational complexities of rare cancer clinical trials, it's important to evaluate and use resources that might be beyond just the development of oncology treatments. This involves identifying partners that can provide access to data, patient identification, and engagement, all of which can be critical to success.

Real-world data can be used to generate new hypotheses, to create external controls for future studies, or when internal controls are impractical. And it can also help study the effectiveness of new treatments in real conditions. But to effectively put real-world data to work, it needs to be high-quality data that is:

- From relevant patient populations (not only from academic centers, for example)
- Properly de-identified and directly sourced from providers
- Documented and automated mapping of variables
- Comprised of various types of data, such as surgery, radiation, medical oncology, and treatment

Finding and engaging patients involves tapping into health-focused social media networks, to connect with patients who have specific types of cancer. Patient communities and advocacy groups are another important resource, letting patients know there is value in entering clinical trials. Casting a wide net will help not only engage patients but will ultimately result in successful trials to the entire rare disease community as well.

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