Modernizing Oncology Approvals

▶ Using real world evidence to bolster oncology accelerated approvals and label extensions

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Regulators are increasingly leveraging real world evidence (RWE) to inform their understanding of the benefits and risks of using targeted therapies in patients who are treated as part of routine clinical care, including patients who are very ill, who suffer from co-morbidities, or who have failed on other lines of therapy.

That kind of data doesn't show up in clinical trial results, because these patients are often excluded from trials due to strict inclusion/exclusion criteria. One 2019 study[i] found that of the 90% of cancer patients who say they would like to participate in trials, more than half are rejected because they do not meet strict study criteria. Strict study criteria are intended to isolate the effects of the investigational intervention from the variability of the enrolled population. However, by necessity, this constrains the diversity of the patients enrolled into the study and generates evidence on a subset of the wider patient population that may receive, or who may derive benefit from the intervention in the real world.

Oncology trials also tend to focus on highly specific outcome measures, like exact changes in lesion diameter over a specific time period (referred to as Response Evaluation Criteria In Solid Tumors, or RECIST). These outcomes may be objective and useful for controlled, randomized trials to inform decisions about whether a therapy has a sufficient benefit-risk profile, but fail to consider the clinician and patient assessments that are equally relevant in real-world care for assessing effectiveness of treatments at an individual, personal level.

In routine care, physicians will monitor tumor size with clinical scans, however these observations don't necessarily align with the specific timelines and quantitative measures of RECIST criteria. Physicians will also track patient centered outcomes, like how the patient is feeling or whether their appetite or quality of life has improved. These measures are an important part of the treatment decision-making process and are best gathered in real world settings that accurately reflect the true patient experience.

Simply put, how clinicians measure "success" in real-world settings differ from what is measured in a controlled trial setting. That is why RWE, and the platforms used to capture and analyze this data, is so important as complementary evidence to trial data.

RWE in Action

Regulators recognize that there are numerous questions RWE can address beyond examining if a product is safe for its intended use:

- RWE is fundamental to understanding use of standard of care and describing unmet needs.
- RWE can serve as an external comparator to provide complementary, supportive evidence to single-arm trials
- RWE can help regulators understand long-term outcomes in patient groups after they leave the clinical trial setting.
- RWE can be used to measure the effectiveness and safety of treatments as used in routine care.

The US Food and Drug Administration (FDA) has been signaling its interest in RWE for several years. In December 2018, FDA released its Framework for RWE Program[ii] that lays out the potential uses of RWE to help improve regulatory decision making, and later this year FDA plans to release a formal guidance for submitting RWE as part of new drug applications and label expansions.

We've already seen several examples of regulators using RWE to support accelerated approvals and label expansion decisions in oncology.

For example, in 2017, two RWE studies were used to support the accelerated approval of Bavencio[iii], a treatment for a rare and lethal skin cancer. Data from US electronic medical records (EMRs) were analyzed to examine the effectiveness of standard of care regimens among similar patients as context to interpret results from their single-arm trial; and in Europe, a German registry was used to estimate overall survival and response rates to standard of care regimens, providing context on how lethal the skin cancer is.

In 2019, RWE was used to support a label expansion for Ibrance[iv] to include men with advanced or metastatic breast cancer. The drug was previously only approved for women with HR+/HER2- locally advanced or metastatic breast cancer. However, an analysis using claims data and an oncology EMR was submitted to the regulators as part of the totality of evidence to win approval for the label expansion in men treated with Ibrance.

Welcome to the Real World

The value of RWE to create a more robust view of the impact of an oncology drug is clear – it can complement, augment, and extend our understanding of when and how to use new medical products. Yet, companies are still hesitant to make real-world studies an official part of their development process for several reasons.

These studies are observational, requiring different methods to monitor the results of treatments using a lighter touch. Real world research doesn't require study visits for data collection; instead, the data gathered are based on observing routine care and are less structured than in a trial setting. The lack of formal guidance from regulators about when and how to capture RWE, as well as the underlying risk of non-acceptance, is hindering the adoption of RWE as an inherent part the drug development process.

But this change will happen — it is already happening. As cancer is increasingly stratified by molecular subtypes, conducting a clinical trial may not be feasible for these rare and/or aggressive cancers and RWE will need to be included in their submissions.

There is an opportunity for companies to create more robust submission packages with complementary RWE that demonstrate the value of treatments in the real world. The companies who embrace this new model for data collection and make these studies part of their overall oncology development strategy will have a competitive edge over those who are slower to catch on.

Plan Ahead

Advances in technology and analytics are enabling RWD to be gathered in real-time and analyzed for clinical, payer, policy, and regulatory decisions. These data may be derived from an array of sources, including EMRs, laboratories, pharmacies, healthcare insurance claims, registries, and even consumer devices.

The key is in the planning. To get the best data in the most efficient way possible and to ensure that the regulators are aligned with the approach, RWE should be part of the clinical development plan from the beginning. Below are some keys for successful implementation.

Timing. There are many types of designs to consider based on the research purpose. Natural history studies may be done as early as phase 1/2 to better understand the disease or condition and determine which endpoints to study. External comparator studies may be done in phase 2 or later to provide clinical context for interpreting single-arm trial results. Extension studies aim to examine longer-term safety and effectiveness outcomes among patients who have been participating in one or more clinical trials. Regardless of the approach, planning ahead to incorporate RWE in the clinical development plan takes time.

Consistent endpoints. Endpoint selection for the clinical study can be aligned to common real-world measures. For example, physicians may track progression of disease, however they may not measure exact lesion size, especially if repeated biopsies were required solely for measurement purposes. Including clinical endpoints in trials that are important and captured in the real world can make it easier to validate improved outcomes using real world external comparator studies.

Speed to submission. When companies conduct real world studies during clinical development, they will be generating RWE to support the approval and launch — useful for regulatory decisions but also for clinicians and payers. Trials can link to real-world data to capture additional endpoints on their patients sooner. And, if they wait, it can add months or even years to generate longer term outcomes and/or complementary evidence to inform treatment decisions.

Regulator Engagement

Before launching any real-world study for regulatory purposes, it is important to review the study plan with regulators in advance. For example, engagement with the FDA may occur as part of the typical Type A/B/end of phase meetings or be requested outside of the planned meetings through a Type C meeting. If companies decide to make a formal request for a Type C meeting, they should be aware that it could take up to 75 days to schedule following the request.

In these meetings, regulators won't tell you what to do, and they won't endorse one type of RWD over another. But, they will review the study design, data sources, analysis strategies, and offer input on whether it will provide adequate scientific evidence to answer regulatory questions — and where it may fall short.

When reviewing these plans, regulators will want to be sure the real-world data used for the analysis are "fit-for-purpose," which means the data should:

- Be relevant and accessible.
- Have clear provenance, meaning that there is transparency in where the data came from, how they were reviewed, curated, and assembled.
- Produce actionable evidence with credible methods and study design,
- Include enough patients of interest and over a sufficient period of follow-up time to detect an effect should one exist.

Companies also need to be confident that the technology used to capture and analyze these data are up-to the task. Many real-world data sources, including EMRs, are unstructured, which means that at least some of the data are written as a narrative with no forms or fields. For effective use of these data, study leaders will need tools that can translate natural language narratives into anonymized and structured formats that can be consistently analyzed as part of the larger data set.

The FDA's Real World framework offers some information about when and what RWD will be considered reliable. Companies can also review the Duke-Margolis Center for Health Policy paper: Determining Real-World Data's Fitness for Use and the Role of Reliability[v], which provides a systematic framework to characterize the reliability of RWD in drug development and regulation.

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Notes:

[i] Systematic Review and Meta-Analysis of the Magnitude of Structural, Clinical, and Physician and Patient Barriers to Cancer Clinical Trial Participation. https://academic.oup.com/jnci/article/111/3/245/5307078

[ii] FRAMEWORK FOR FDA'S REAL-WORLD EVIDENCE PROGRAM. https://www.fda.gov/media/120060/download

[iii] Avelumab (BAVENCIO). https://www.fda.gov/drugs/resources-information-approved-drugs/avelumab-bavencio

[iv] CDER-Approved sNDA for IBRANCE® (palbociclib). https://aetion.com/evidence-hub/fda-decision-alerts/cder-approved-snda-for-ibrance-r-palbociclib/

[v] Determining Real-World Data's Fitness for Use and the Role of Reliability. https://healthpolicy.duke.edu/publications/determining-real-world-datas-fitness-use-and-role-reliability