The Role of Real-World Data in Clinical Development

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KEY POINTS

An increasing amount of electronic data is being generated in healthcare.

Real-world data (RWD) are collected from a wide variety of sources to capture patient experiences during care.

RWD and advanced analytics hold the promise to transform every aspect of clinical drug development.

Healthcare is experiencing an avalanche of electronic data with sources that include social media, smart phones, activity trackers, electronic health records (EHRs), insurance claim databases, patient registries, health surveys, and more. Managing the wealth of available healthcare data allows health systems to create holistic views of patients, personalize treatments, improve communication, and enhance health outcomes. Collected outside of controlled clinical trials, RWD, has the potential to deliver vast amounts of insights into patient health and medical care. These insights can help create a full 360-degree view of patients to deploy personalized medications and also improve population health outcomes by tracking health trends and assisting in predicting upcoming developments. This article will give an overview of how RWD can influence the way clinical trials are designed and conducted today.

UNDERSTANDING THE IMPORTANCE OF RWD IN CLINICAL DEVELOPMENT

Randomized clinical trials (RCTs) are considered the "gold standard" in clinical development for establishing the safety and efficacy of an investigational product, because they are conducted in a way that helps remove as many sources of bias as possible from the process. RCTs operate in a controlled setting and are carefully planned to compare the safety and/or efficacy of the treatment (intervention) as compared to the control in a limited

from a wide variety of sources such as observational studies, retrospective database searches, case report form reviews, patient or disease registries, EHRs, and payers' databases. These data are being increasingly obtained via electronic tracking systems used in healthcare to capture patient experiences during care.

Despite the extensive clinical research needed to get new medicines approved, it can still be hard to answer a patient's basic questions about a drug. Is this the right medicine for me? Will I likely get the side effects they warn about? Patients often have different characteristics, experiences, and treatment protocols compared to the controlled environment of RCTs. Thus, it may not be possible to "generalize" the information gained from RCTs to broader groups of patients. Research conducted using RWD can help fill the gap between clinical trials and clinical practice, while properly analyzed RWD can provide key insights to help reduce medical costs, as well as improve safety and effectiveness profiles of drugs.

As pharmaceutical companies face the increasing challenges of ever more costly and complex clinical development, the combination of more accessible RWD and advanced analytics holds the promise to transform every aspect of clinical drug development. Furthermore, with advances in technology, it is now possible to analyze big datasets more efficiently. Statistical

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and homogenous population consisting of subjects with similar characteristics who are selected using precise inclusion and exclusion criteria. RCTs prioritize internal validity over the external validity.

Conversely, RWD collection occurs under normal day-to-day circumstances found outside of a typical RCT, and therefore, includes a much larger number of patients and patient types. RWD is collected

methods have also evolved, leading to greater confidence in deriving accurate inferences from these data. Retrospective data can serve as a source for determining the various patterns of the data, which are not usually seen during controlled RCTs. RWD can help determine the right patient population for a particular drug in order to arrive at the best outcomes. Even though the real-world studies aim for greater generalizability, there are some limitations.

For example, selection bias is a critical issue in real-world studies because patients are not randomized to treatment. This lack of randomization can produce situations in which treatment effectiveness is either under or overestimated, and also makes it difficult to avoid unmeasured confounding factors.

HOW CAN RWD HELP REDEFINE EXISTING CLINICAL DEVELOPMENT PRACTICES?

Real-world evidence (RWE), which is derived from the aggregation and analysis of RWD, can enable real-time protocol simulation, providing an opportunity to further examine study hypotheses before moving the investigational product into the clinical trial phase. This allows fine-tuning of clinical study protocols and more accurate selection of patient population for given clinical trials. The sponsors can validate opinions, assumptions, and historical experience by using RWD to back-test assumptions made in the clinical development plan. RWD can help in the selection of appropriate study endpoints including novel endpoints for testing both efficacy and safety of the investigational product, benefitting both the patients and providers. It may also help in identification of optimal trial duration, by calculating sample size using the actual background risk that takes into consideration trial-specific inclusion/exclusion criteria.

RWD can help in the clinical protocol feasibility assessment by providing insights into how stringent the inclusion and exclusion criteria are to determine patient eligibility. Using RWD to optimize the eligibility criteria can help accelerate patient recruitment and would ensure that obtained results are more broadly relevant. It will also provide guidance on how large (right size) and/or long (right duration) a study needs to be to allow a test drug to demonstrate a significant impact on disease outcomes.

By utilizing RWD, it is possible to identify the appropriate group of patients to enroll in a RCT and define who would or would not respond well to a particular drug or therapy. For example, one of Amgen's cancer therapies gained its first regulatory approval based on a single-arm phase II study supported by RWE obtained from medical records [1]. The company did not include a traditional standard-of-care comparator arm in the study because the patients enrolled in the study had already failed to respond to standard therapies based on RWE.

In another study, published in the *American Journal of Cardiology*, findings suggested that patients with atrial fibrillation (AF) may benefit from a structured weight reduction program [2]. Such findings from real-world studies (RWS) can be used to identify covariates to be included while modeling clinical trial data or to fine-tune the subgroups that are used and analyzed in RCTs.

As part of a US multisite prospective registry of patients with AF, researchers analyzed 3 years of data (2013-2016) and found that 13% were not treated with the recommended doses. In addition, 6% of registry patients were not included in this study because renal function was not checked during the 1-year follow-up, which was another deviation from the package insert recommendations. Such insights can be useful to determine specific aspects to be considered during clinical trial conduct to ensure required dosing and minimize deviations.

RWD, along with new models and analytics, helps to identify high performing sites and investigators based on quality, prior performance, participation and data delivered in previous studies. This is critical information to identify the right sites to reach the target number of patients. RWD and site-specific data on existing and available patients helps plan the recruitment at sites. This eliminates the risk of over committing and under delivering on recruitment. Utilizing EMRs (electronic medical records) can double enrolment rates, which can lead to 30% reduction in trial enrolment costs.

Clinical development programs can be substantially strengthened by use of RWD. The Salford Lung Study (SLS) is an example of this and is the world's first digitally enhanced RCT. The data provided by SLS complement the existing data provided by the conventional RCTs [3]. A pragmatic trial such as SLS, which enrolled patients in an everyday clinical practice setting who would often be excluded from a traditional RCT, would especially benefit from use of RWD in designing the trial. For example, SLS included patients who are concomitantly being treated for other chronic diseases. RWD about concomitant conditions and treatments would aid in granular definitions of inclusion and exclusion criteria, requirement for stratified sampling, subgroup analyses, and more.

SUMMARY

RWD has already started changing the way clinical trials are being conducted. RWD has the potential to provide evidence for expanding the approved uses of a drug to new types of patients and new diseases as well as identifying populations of patients whose needs aren't being met by current therapies. The evidence can be used to support investments in clinical studies to gain approval for new indications. The combined use of RWD, statistical analysis, machine learning, and predictive modelling will likely change the face of clinical development in the coming years with the promise of streamlining drug development processes, improving speed to market and reducing costs. ●

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