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Review Article

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Incorporation of real-world data to a clinical trial: use of external controls

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ABSTRACT

As real-world data (RWD) becomes more available and the methodology for handling RWD evolves, the use of RWD in drug development and drug approval is drawing interest. One of the ways RWD can be applied to a clinical trial is using an external control, a cohort of patients established separately serving as a control group for the clinical trial's treatment group. Although external controls have the possibility of bias as a result of differences in baseline characteristics between the external control and experimental groups, selecting an appropriate data source and ensuring comparability through proper handling of the data can increase the utility of external controls, raising the efficiency of drug development. This article discusses several topics relevant to using external controls in clinical trials, including the definition of external control, the selection of data sources, the strategy ensuring comparability, current regulatory circumstances, and future directions.

Keywords: External Control; Real-World Data; Clinical Trial

INTRODUCTION

Real-world data (RWD) is health data routinely collected from a range of sources regarding the health status of the patient or the delivery of healthcare. RWD encompasses data originating from a patient's electronic health record (EHR) in a hospital, insurance claims data, information gathered by monitoring devices (e.g., wearable technologies or fitness trackers), and registries that support various elements of care and research. Real-world evidence (RWE) is clinical evidence produced by RWD analysis [1].

Recently, there have been efforts to accelerate new drug development using RWE. RWE is not a new strategy for regulatory decision-making in post-marketing safety surveillance and risk management, but it's gaining traction in the area of efficacy. In the United States, the 21st Century Cures Act was signed into law in December 2016, aiming to accelerate medical product development and bring innovations to patients who need them more efficiently. Accordingly, Food and Drug Administration (FDA) has released a framework for FDA's Real-World Evidence Program [1], and is working on guidance for utilizing RWE in drug regulation at all stages of the product life cycle including preauthorization [2-5]. Similarly, European Medicines Agency (EMA) has acknowledged RWE as a critical component in supporting regulatory decisions

for the safety and effectiveness of medicines in the European Medicines Agencies Network Strategy to 2020 published in 2015 [6]. EMA and Heads of Medicines Agencies (HMA) formed a joint task force to develop practical steps for the regulatory use of RWD [7]. In China, the National Medical Products Administration has also published guidance on key considerations in generating and using RWE to support drug development [8,9].

There is no doubt that a randomized controlled trial (RCT) is the gold standard to prove the safety and effectiveness of a drug. However, there may be several difficulties in performing RCTs. For example, in RCTs, patients are randomized to either an experimental treatment group or a control group that usually consists of placebo or standard-of-care (SOC). The use of placebo, however, can cause recruitment and retention challenges as patients are less willing to participate in placebo-controlled RCTs. In disease settings with no available SOC treatment, a patient's allocation to a control group may be a suboptimal decision. In the case of rare diseases, RCT may be impossible to execute because patients are scarce regardless of ethical issues. At present, there are a variety of RWD sources available, and the strategies for dealing with these sources have evolved dramatically. Aside from circumstances where an RCT is not feasible or not ethical, RWD/RWE has a lot of potential when it comes to providing meaningful data during a drug development process.

One of the ways in which RWD/RWE can be used to demonstrate drug effectiveness is the pragmatic clinical trial. This type of clinical trial is close to clinical practice in trial designs including less stringent eligibility criteria and endpoints and visit-schedules which can be embraced in routine clinical practice for a targeted disease, allowing for the generalization of research findings to patients in the real-world. Another option is a clinical trial using an external control. It incorporates RWD in the RCT by using RWD as a control group to a treatment group of a clinical trial. The third option is to examine collected RWD without conducting a clinical trial.

Among those strategies to use RWD for proving drug effectiveness, external RWD controls were described in this article. Considerations for implementing RWD in a clinical trial as well as the cases of external RWD control utilized for regulatory decisions were discussed.

DEFINITION AND TYPES OF EXTERNAL CONTROL

External control means a cohort of patients established separately to serve as a control group to a treatment group of a clinical trial. In ICH E10 guidance [10], an externally controlled trial is defined as one in which the control group consists of patients who are not of part of the randomized study as the group receiving the investigational agent.

Externally controlled trials can provide solid evidence of efficacy, especially when the disease progression is fully understood, the outcome measure is objective, disease-affecting components are clearly defined and the treatment effect is dramatic [10,11].

External control can be divided into 3 types according to the times that data were accumulated.

✓ Concurrent control: If an external control arm starts to be collected after the first participant in a clinical trial has been enrolled, the external control arm is concurrent control. The therapeutic method for a disease evolves as causes and predispositions are discovered,

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and diagnostic criteria can be altered. In light of this, concurrent control, which consists of patients who are being treated at the same time as the clinical trial is being conducted, has the advantage of ensuring that the clinical trial's treatment arm and the external control arm are comparable and that reliable analysis results can be obtained. Furthermore, because the registry for external control would be developed before the commencement of the clinical trial, the data may be collected for research purposes. Concurrent control, on the other hand, is more expensive than historical control, thus the methodology and resources for collecting data should be considered using concurrent control.

✓ Historical control: A historical control is an external control that consists of the data that had been gathered before the first participant of a clinical trial was enrolled. These data have value as an external control only if there are no significant differences in medical practice or in diagnostic criteria from current ones although it is a past record. If a historical control includes records with wide time spectrum, a sensitivity analysis may be needed to determine whether there is a difference between past data and recent data in the historical control.

✓ Hybrid control: A hybrid control contains obtained before the clinical trial's first subject was enrolled as well as data collected after the trial's first subject was enrolled. For example, in addition to historical records, outcomes that cannot be detected in the previous record, such as patient reports, can be collected concurrently. Due to the possible bias, caution must be exercised in the analysis, just as it was in the historical control.

CONSIDERATIONS IN INCORPORATING EXTERNAL CONTROL

Choosing a data source

Data sources for external control might come in a variety of forms. RCTs can serve as external controls if the patient population is comparable and the endpoints are available and measured in a similar manner. The data from RCTs has an advantage in that the data were collected with high rigor. Exposure, prognostic factors, and endpoints are generally well defined, precisely measured, and captured with few missing data or errors. In this regard, recently completed RCT in the same disease area is an ideal choice. It's also possible to use a prospective cohort or registry. The data in these sources is typically collected for research purposes and is of reasonably high quality and completeness. However, endpoint definitions and other parameters may differ from those used in clinical trials, raising the risk of misspecification and comparability issues. EHRs or claims data are alternative sources of external control. EHRs or claim data are true RWD reflecting clinical practice. Thus, in these cases, the availability and ascertainment of key data elements are essential. Once exposure, outcome, and factors are appropriate for the clinical trial, definitions for these elements should be evaluated. Misspecification and misclassification are major concerns in using these data.

Regardless of the form of data source, it should be selected based on relevance, also referred to as fit for purpose: whether the patient groups or subgroups are sufficiently similar to the clinical trial population, whether the endpoints that match those of the targeted clinical trial are available, and whether the duration of follow-up in a given data source can cover the follow-up period of the clinical trial. Exposures, outcomes, and prognostic variables that are clearly defined and correspond to those of targeted trials are ideal.

https://doi.org/10.12793/tcp.2022.30.e14

Quality is also the major point that should be considered. Although key data required for the investigation are available in the data source, it may not be appropriate if the extent of missing is considerable [12,13]. Selection of a data source that is fit for purpose and of high quality is a prerequisite condition to generating reliable evidence.

Ensuring comparability

The major challenge in introducing an external control into a clinical trial is the issue of comparability. Because the characteristics of the individuals in a data source of external control differ from those in a clinical trial, efforts should be made to ensure comparability between an external control group and an experimental group. In 1976, Pocock [14] described 6 elements for the external control to be exchangeable with the internal controls of the targeted clinical trial: eligibility criteria, patient characteristics, mode of treatment, outcome measure, data collected time, and setting. Although all these criteria are unlikely to be met when using RWD, they serve as a guide for recognizing and adjusting a bias.

To reduce the differences between the external control group and the experimental group of the targeted clinical trial, Schmidli et al. [15] suggested constructing a subset of the individuals who have similar characteristics to those of clinical trial subjects. Individuals are first selected based on the inclusion/exclusion criteria of the clinical trial. The matched people are then secondarily selected using the propensity score estimated based on baseline data.

Instead of matching, propensity scores can be utilized in other ways to balance external control and internal experimental groups. Propensity score inverse probability of treatment weighting (IPTW) weights individuals based on the propensity score to create a synthetic sample in which the distribution of measured baseline covariates is balanced between groups. Propensity scores can also be used as a covariate in statistical analysis or as a stratification factor [16,17].

Although employing propensity scores is an excellent methodology to assure comparability between the external control and the internal experimental group, it does have certain limitations. The main assumption for propensity score methods is that baseline covariates explain all the differences between the external control and internal experimental groups. However, unknown influences that were not captured as covariates may exist. Beaulieu-Jones et al. [18] indicated that these factors include physician opinion, patient request, knowledge of a trial, and differential access to treatment.

Sensitivity analysis should be considered to assess the robustness of the method for incorporating an external control. To this end, multiple comparisons with different approaches might be performed to investigate the concordance of results [15].

REGULATORY CIRCUMSTANCES

External control is an important example of RWD being used for demonstrating drug efficacy. Although the use of an external control for drug approval is not new, the use of RWD as data sources for external controls is more widely adopted. Jahanshahi et al. [12] reported that external controls were employed for 45 FDA approval decisions of non-oncology products between 2000 and 2019. Of those 45 approval cases, RWD was utilized in 24 cases (20 retrospective natural history data and 4 previous RCT data), with 10 cases approved between 2015 and 2019, indicating a recent increase in usage of RWD as an external control.

https://doi.org/10.12793/tcp.2022.30.e14

RWD/RWE is mostly used for drug approval in rare diseases and oncology [19,20]. This phenomenon seems to result from high medical unmet needs and the infeasibility of conducting RCT in these therapeutic areas. The RWD sources for external control were retrospective in nature, and the most common form was existing medical records or a previously collected registry [12,20,21].

The review comments from the regulatory body for the submitted data including RWE indicate some important aspects for regulatory approval. They pointed out a prespecified study protocol, inclusion/exclusion criteria matching to the clinical trial, comparability of endpoint definitions, minimizing confounding, and appropriate handling of missing data [21,22]. These comments show that a transparent process, as well as comparability between the experimental group of a targeted clinical trial and external control group, and statistical robustness, are critical for the RWE to be accepted for a regulatory decision.

The followings are 2 cases in which the external controls derived from RWD were used for regulatory approvals.

Case 1: Blinatumomab (Blincyto®)

Blinatumomab (Blincyto®; Amgen Inc., Thousand Oaks, CA, USA) has been developed for the treatment of patients with Philadelphia chromosome-negative relapsed or refractory B-cell precursor (BCP) acute lymphoblastic leukemia (ALL). An external control was used as a supportive analysis for a single-arm, multicenter trial (NCT01207388) that included 189 adult patients with BCP ALL. The external control data were derived from hospitals in Europe and the United States, along with European national study groups. The individuals were selected based on key inclusion/exclusion criteria from the single-arm trial. The individuals in the database sources were 2,373, and 1,139 were selected for the analysis. The primary and secondary endpoints were complete remission (CR) and overall survival (OS). CR and OS were estimated in six strata based on known prognostic factors. Combined estimates were obtained with each stratum weighted to the percentage of patients observed in that stratum from the single-arm trial. To balance characteristics between patients in the clinical trial and patients in the external control, CR and OS were also estimated using IPTW methods. Sensitivity analyses were carried out in different time periods to verify the robustness of the findings. In this single arm trial incorporating external control, patients treated with blinatumomab showed significantly higher CR rates and longer OS [19,22-25].

Case 2: Cerliponase alfa (Brineura™)

Cerliponase alfa (Brineura™; BioMarin, San Rafael, CA, USA) has been developed for the treatment of neuronal ceroid lipofuscinosis type 2 (CLN2) disease, a rare pediatric neurodegenerative disease and a form of Batten's disease. An external control was used for a single-arm, multicenter trial that included 24 patients with CLN2 disease. The external control data were derived from Dementia in Childhood database. The individuals were selected based on key inclusion/exclusion criteria from the single-arm trial. Forty-two patients were selected from 69 patients with CLN2 disease in the database for the analysis. The primary endpoint was the time until a 2-point decline in the score on the motor and language domains of the CLN2 clinical rating scale.

The primary endpoint was compared between patients in the trial and patients in the external control who were matched regarding age, baseline motor and language score, and

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genotype. Sensitivity analyses were conducted, in which one treated patient was matched with numerous historical controls.

This single-arm trial incorporating external control showed that cerliponase alfa treatment in patients with CLN2 disease was able to slow down the decline in motor and language function compared to that in historical controls [19,26].

LIMITATION AND FUTURE DIRECTION

With increased accessibility to RWD through various sources and advances in technology in generating RWE, there is an explosion of information sources and methods for generating and utilizing RWE.

While frameworks are being developed for utilizing RWD/RWE in the process of drug authorization, a concrete methodology for this process has yet to be established. One of the biggest concerns with using external control is that there can be a bias originating from the difference in characteristics between the external control group and the treatment group of the targeted clinical trial. While best practices for study design and statistical analysis plans can be helpful, practical insights are still lacking with regard to what methodology should be applied for the RWD/RWE to be accepted at the regulatory level.

Another challenge is the data source. Since most data sources such as medical records or claim data have not been collected for research purposes, there are several problems with using these data sources. For example, there may be no sufficient data for prognostic factors required to achieve a balance between groups; unclear diagnostic criteria or varying definitions regarding the diagnosis of other conditions can be a source of confounding. These data sources can be deemed ineligible if a high proportion of major endpoints are missing.

For RWE to be used more widely and provide reliable evidence, appropriate study designs and data-handling methods need to be established. There is an ongoing effort to develop optimized analysis methods.[27] For regulatory purposes, transparency in study design and analysis should be guaranteed. To this end, U.S. FDA requires a protocol review and registration with the ClinicalTrials.gov website before starting research.[1] Standardized data collection and collaboration for data sharing are also needed to strengthen generated evidence.

While the use of RWD as external control has been largely limited to rare diseases and oncology so far, it can be expanded into other areas of drug development. For example, the efficacy of a combination therapy of approved drugs can be obtained by comparing it to an external control group established from the RWD which is created by the use of individual drugs in the clinic. In populations where a clinical trial is not always feasible such as patients with rare diseases, children, or pregnant women, external control can help reduce exposure to the investigational drug and the burden of clinical trials.

CONCLUSION

This article reviewed several aspects to consider when using RWD as external control as well as its use in the drug approval process and its limitations and future directions.

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Despite several limitations, Incorporating RWD to a clinical trial as an external control has great potentials for future clinical research and drug development. With the support of an optimized methodology, standardized data sources and assurance of transparency, RWD is anticipated to be a valuable tool to improve the efficiency of drug development.

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