WORLDWIDE CLINICAL TRIALS

WHITE PAPER

UTILIZING A REGISTRY TO INFORM AN EXTERNAL CONTROL ARM: A CASE STUDY IN DRUG-INDUCED LIVER INJURY

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In Part 1 of this series (External Controls In Clinical Research (Part I): The Clinical Imperative), it was noted that regulatory concepts referable to the creation of an external control group have long been noted and occasionally implemented, particularly for diseases with severe morbidity, mortality, and unmet medical need. In Part 2 (External Controls (Part II): Informed Choices Amidst a Portfolio of Options), the potential benefits and risks of using an external control within a program were explored, and key criteria from representative programs that have successfully navigated the challenges of using an external control in a registrational program were identified. This case study looks at the important role a registry can play as an external control arm in situations where use of a placebo could compromise patient participation or patient safety.

BACKGROUND

Randomized clinical trials are the gold standard for the evaluation of experimental interventions. In randomized clinical trials, patients are randomized to either an experimental intervention arm or a control arm that consists of placebo or standard of care alone. Patient recruitment and retention are two key factors for the success of any trial, particularly so when there is a significant unmet clinical need and the study is potentially transformative. In this circumstance, the use of a control arm in which participants do not receive the experimental intervention can impose recruitment and retention challenges as well as potential ethical challenges. Patients have been shown to be less willing to participate in placebo-controlled randomized clinical trials in part due to the chance of receiving placebo.[1] The ability to establish a simulated control arm based upon data present within an external, accessible historical database of patients, as an example, is an important step in clinical trial design, particularly for rare diseases.

SOURCES OF DATA

Regulatory authorities, particularly in the United States, have begun to endorse the concept of utilizing data sources external to a clinical trial for simulation of a study arm representing a cohort of patients not exposed to an experimental agent.[2] These patients would have been candidates for randomization to a control group representative of the standard of care at the time the data is first acquired. The external source of data representing this potential control arm must contain data fields essentially identical, within a prespecified window of acceptance, to those planned for the prospective clinical trial. Additionally, and of critical importance, the data fields must contain sufficient detail to ensure the evaluability of patient groups with comparable demographics, history, disease characteristics, and outcome measures. Regulatory authorities have shown themselves to be open to the establishment of simulated control arms in rare disease scenarios where the numbers of patients are quite limited as well as in situations where randomization to anything other than the active/experimental agent might be considered ethically argumentative or unattractive to study subjects.[3]

ELECTRONIC MEDICAL RECORDS

While an increasingly wide array of databases are accessible today, these databases present an equally wide range of variability in terms of data detail and sources. Accordingly, important constraints and biases may exist in the establishment and utilization of an external simulated control arm, and analyses may be unable to account adequately for such constraints and biases. Today, the most common sources of data reflect medical information compiled routinely from medical records, which are increasingly electronic, and show actual treatment and patient outcomes and/or datasets derived from billing or claims submitted to insurance entities for provider reimbursement.

Both the medical record and billing datasets can be considered "real-world data," but the data is often substantially richer in the datasets derived from electronic medical records. For example, while a medical claims dataset may contain billing records for a particular laboratory test, rarely will the claims dataset contain the specific laboratory finding (although in some cases claims data can be linked to data from laboratories or one or more other ancillary service providers). At the same time, one potential disadvantage of an electronic medical record dataset lies in the use of medical records systems with proprietary database models; however, increasingly, providers of electronic medical record datasets are agnostic to the electronic medical record system and can combine data from multiple systems into a dataset containing data variables common to each. Increasingly, both electronic medical records and claims data vendors are recognizing the value of their data. As such, access is generally increasing, but so too, often, is the price of access (though the cost typically remains a fraction of what it would cost to acquire the same data through a similarly sized clinical trial).

BESPOKE REGISTRIES

De novo disease registries, rather than clinically available electronic medical records data, represent another increasingly common source of data. Such registries have been established to track patients, treatments, and outcomes associated with a specific condition, disease, or disorder and may be established and managed by academic groups, patient advocacy groups, medical specialty associations, countries (i.e., governmental agencies) or geographic regions, or, in some cases, by medical product developers. Typically, *de novo* disease registries compile data through prospective data capture, using case report forms developed specifically for the registry. An important advantage of prospective patient registries is the frequent availability of patient-reported outcomes, such as quality of life or satisfaction with treatment, as well as potentially more systematic reporting of causality associated with important clinical events.

Access to aggregate registry data ranges from open to very limited. When access is available, the access fee is typically nominal, provided the research intent is articulated and scientifically sound.

DISEASE CHARACTERISTICS AS A MODIFYING VARIABLE

Another important consideration in data access is the nature of the condition/disease/disorder itself. Continuous and historical datasets are, predictably, more likely to be available for chronic diseases. Typically, patient and disease history, treatment history, as well as various events and outcomes are available over a fairly long period of time. Even the transfer of a patient from one provider to another tends not to be a major constraint, as electronic records essentially remain attached to the patient even as they move among locations and providers. In contrast, piecing together a full picture of patients with either acute exacerbations of a chronic disease or a first-time presentation of an unexpected acute medical condition often creates a more challenging data capture situation.

THE ACUTE LIVER FAILURE REGISTRY: A CASE STUDY

As noted above, rare and especially critical diseases are generally more amendable to external control use, including those informed by a registry. Take for example, acute liver failure caused by drug-induced liver injury (DILI). DILI is an adverse reaction to drugs or other xenobiotics that can occur predictably, such as when a patient is exposed to toxic doses of some

compounds (e.g., acetaminophen overdose, aspirin, methotrexate), but that also can occur unpredictably as a consequence of an adverse interaction with many drugs or supplements in common use. In a randomized clinical trial utilizing external controls in DILI, the external control would be used as a contrast for the investigational compound. Thus, it serves as an alternative to the enrollment and potential randomization of patients employing standard of care for acute drug-induced liver toxicity leading to acute liver failure and, in some cases, transplantation. Establishment of such a simulated control arm (i.e., an external control) would require access to data of sufficient detail to inform eligibility criteria and outcome measures comparable to those proposed within a planned study (such as significant medical morbidity, mortality, or liver transplantation). This would potentially improve the speed and cost-efficiency of the clinical trial without compromising data quality, analytical integrity, regulatory expectations, or research ethics.

Consider the example of the Acute Liver Failure (ALF) registry, created in 1998 by the Acute Liver Failure Study Group (ALFSG). Affiliated with the University of Texas Southwestern (Dallas), the ALFSG had been established in 1997 to develop a consortium of investigators and clinical centers that could collect and consolidate clinical and epidemiological data as well as biospecimens (serum, plasma, urine, tissue, DNA samples) from individuals who have acute liver failure, regardless of etiology, and on individuals who have acute liver injury. This group represents a less severe cohort of patients who have coagulopathy but do not reach the threshold of encephalopathy. The ALF registry makes available a complete study description, protocol, case report forms, and a data dictionary for use in observational and clinical trials concerning acute liver failure.[4]

While the ALF registry offers a rich dataset, the primary concern regarding use of this dataset, or any external control, is the potential challenge in comparing similar outcomes from a clinical trial to historical controls from the registry database. The registry contains many shorter-term outcomes, such as those that would be expected to be associated with immediate resolution or planned resolution (e.g., referral for transplant) of the emergent overdose, either acetaminophen or alternate drug-induced liver injury, and these may not be applicable as an external control for a longer-term study. Similarly, the registry contains an extensive array of laboratory values from extemporaneously collected serum and tissue samples that may not have been collected in a manner coordinate with a proposed study.

The Acute Liver Failure Study Group (ALFSG) has maintained, since 1998, a clinical registry now numbering more than 3,400 patients who have been enrolled over this period of time at 32 sites over the 22-year period. The study is now closed, and the database locked. This study has provided critical information on all forms of ALF with detailed clinical histories and laboratory and outcome data available. A searchable public-use website is accessible via NIDDK for data prior to 2010. In the next year, the searchable database will be updated with data through the end of the study. All the patient information is thoroughly de-identified in strict accordance with HIPAA regulations. https://www.utsouthwestern.edu/labs/acute-liver/clinical-trials/

DATA ACCESS AND STATISTICAL ANALYSIS

In a clinical study on drug-induced liver injury, for example, Worldwide would rely on a flexible five-step plan for acquiring the external control data from the ALF registry and performing the statistical analysis. In principle, this approach can be applied to many different indications.

STEP 1:
After obtaining access to the ALF registry dataset, identify the cohort of subjects who were enrolled with acute liver failure and who proceeded either to death or liver transplant as a consequence of overdose.

The baseline demographic and disease characteristics of the identified cohort could be used to identify key characteristics of importance that will inform the inclusion/exclusion criteria for the interventional study. Those characteristics might include age, liver transplant status, cause of acute liver failure (acetaminophen or non-acetaminophen drug-induced toxicity), baseline laboratory values, concomitant medications, and/or historical medical conditions.

The intent of this step is to identify the inclusion/exclusion criteria for the interventional study so that baseline demographic and disease characteristics among patients in the interventional study are as similar as possible to those in the selected cohort of registry subjects.

STEP 2:
Define the primary efficacy endpoint of the interventional study and confirm it can be derived from the registry database.

An example of a primary endpoint for a study focusing on DILI could be the proportion of patients diagnosed with drug-induced acute liver failure presenting for medical attention with an increase in survival 30 days after receiving treatment. In this scenario, the registry would allow for matched historical controls utilizing this primary outcome, defining a window of acceptability within which a match for survival could be confirmed.

STEP 3:
Utilize 30-day survival as a primary dependent variable to determine the rate of drug-induced liver failure. Alternately, one could use clinical assessments such as the MELD score (Model for End-stage Liver Disease) or the KCC score (King's College Criteria) as primary dependent variables.

Based on the results of step 3, it may be decided that the selection process in step 1 was either too restrictive or not restrictive enough. Step 1 may need to be repeated after either loosening or tightening the criteria for selection.

STEP 4:
Determine important covariates to include in adjusted statistical models and determine the availability of these data in the registry cases. Consistent with the proposed adjusted analysis, candidate variables should be clinically relevant to the primary endpoint — including the strength of correlation that is generally established. Consideration should be given to avoid collinearity (i.e., two or more variables are highly correlated with each other). Variables that are missing from many of the selected records should also be avoided. It is important to select data variables that have been consistently captured for a majority of subjects, such as specific comorbidities or alcohol consumption.

STEP 5:
After successful completion of steps 1, 2, 3, and 4, a propensity score matching comparison should be conducted. Propensity score matching compares the treatment group to the registry group in the study analysis and matches one population to another on those observed variables that are thought to be prognostically important to outcome. Traditionally, the literature on propensity score matching suggests

that different techniques may be applicable to ensure a proper balance between registry and treatment groups, and the proper model for selection will be determined based upon a review of the registry data.[5, 6]

It is important to note that the propensity score matching algorithm for assuring balance only applies to those measures that were actually observed; it does not apply to unobserved variables that might be prognostically important and addressed through the randomization process. The comparison of treatment to registry could serve as a sensitivity analysis of treatment effect. The primary analysis would be a comparison of treatment vs. an assumed historical control rate in a manner somewhat similar to that used in a Simon two-stage design.

An alternative method of comparison, such as Bayesian Dynamic Borrowing, could conceivably be used. In this approach, the sponsor would combine registry and placebo subjects into a single control arm for the purposes of comparing to treatment.[7] This approach would need to be given careful consideration because while the literature suggests that the technique may be biostatistically plausible and supportive of more definitive analyses, the lack of precedent in specific indications may limit its utility in a drug development program. However, post analysis statistical reviews have indicated this model enables fewer patients to be enrolled into the control group and optimizes the use of data already collected.

SUMMARY

Worldwide endorses the concept of external controls in diseases with significant unmet clinical needs. The ALF database registry example shown above illustrates how a registry database may be a source of matched historical controls while concurrently acting as a broadly informative database. Best prospects for success when using an external controls strategy have been summarized in the second installment of this series[8] and are generally associated with key attributes such as a clear unmet medical need with serious or life-threatening disease and a historical database that contributes to a well-defined/robust natural history data with objective/quantifiable endpoints. Ideally, this would be acquired through a purpose-made natural history study or registry that follows a defined population of interest over a time period during which no significant changes in the standard of care or management have occurred. Finally, how this data will be used and contrasted against prospective data must be defined a priori in the analytical plan.

Ultimately, for the patients involved in the new study, distinct benefits arise from use of an external control. All active trial participants receive the test product, which increases the likelihood of patient and physician buy-in. From a sponsor's perspective, a trial may require fewer patients than a traditionally randomized trial because the external control is effectively acting as the arm randomized to placebo. When correctly planned, informed, and executed the utilization of external controls and the resulting analyses have the ability to provide compelling, potentially pivotal investigations with benefit to both sponsors and the patients alike.

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