Bringing Real World Evidence into Clinical Research

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I. INTRODUCTION

Life sciences companies are embracing the essential roles that real world data (RWD) and the generation of real world evidence (RWE) play in the development of new treatments for patients. Regulators, payers and pharmaceutical manufacturers alike have recognized the immense potential of RWE in accelerating the ability to answer important questions on safety and effectiveness.

RWD is distinct from RWE. As the FDA has noted, RWD relate to patient health status or healthcare information that is routinely collected from a variety of sources, such as:

- Electronic health records (EMRs)
- Claims and billing activities
- Product and disease registries
- Patient-related activities in out-patient or in-home use settings
- Health-monitoring devices[1]

1 https://www.fda.gov/scienceresearch/specialtopics/realworldevidence/default.htm

RWD must be curated through the application of quality research methods to produce evidence that addresses research questions in an interpretable manner in order to be considered RWE. RWE is the clinical evidence on the epidemiology or natural history of disease, key characteristics of the relevant patient population (especially how patients treated with commercial product may differ from those studied in clinical trials), medical product utilization and the product's potential benefits and risks derived from analysis of RWD.

Whereas there is the potential for both RWD and RWE to span a wide range of domains, until recently clinical study design and execution have not realized the potential of RWD / RWE. The opportunity to improve clinical study design and execution is perhaps one of the most imminent and easily applied. It is no surprise that life science companies consider this realm a priority within their overall RWE strategy.

This paper will explore three areas where RWD and RWE are being applied to improve the design and execution of clinical studies:

Figure 1

STUDY DESIGN

Sponsors of pharmaceutical research are turning to RWD and RWE to obtain a better understanding of disease natural history (e.g., patient characteristics, background rates of comorbidities and adverse outcomes, and treatment patterns). Such studies can provide critical information on what happens to patients absent exposure to an investigational product. These insights are informing the development of new hypotheses and have fostered a movement toward modernized study designs involving synthetic control arms.

Adverse outcome rates in the disease "background" can be estimated and used for reference during clinical trials. This is particularly important when a control arm may not be sufficiently powered to make adverse event or safety comparisons in the trial. Such RWD

can shed light on whether a specific adverse event observed in the clinical trial is also observed in patients not exposed to the investigational product, as well as to what degree, potentially highlighting a safety issue in the trial.

In some situations, RWE study designs can provide a comparator group for an uncontrolled clinical trial. RWD and RWE can guide the use of synthetic control arms, using historical data in current studies. Doing so can help in studies in rare disease states or those in which a control arm may be considered unethical.

Understanding the background rates of clinical outcomes to be used as trial endpoints may help in sizing the trial appropriately. Understanding of real-world practice patterns, utilization of current treatments, and adherence and persistence can help set expectations about prescriber and patient behaviors during the trial. Lastly, although there is growing emphasis on designing clinical trials to be more inclusive of patient groups likely to receive the commercial product post-approval, challenges remain due to the need for homogeneity within the trial in order to observe clear treatment effects. As a result, trial participants do not always fully represent the commercial treatment population. Natural history data can help identify those patient subgroups that were not studied in clinical trials, and can evaluate their similarities and differences.

SITE IDENTIFICATION AND PATIENT RECRUITMENT

Authors of clinical trial protocols often grapple with this crucial question: What is the real world prevalence of the patients defined by the inclusion and exclusion

criteria? RWE represents an opportunity to gain predictive insights into this essential consideration that oftentimes will play a decisive role in the successful execution of a study.

If a clinical trial fails to meet the initial enrollment projections, serious delays in patient recruitment timelines and costly protocol revisions can result. According to a recent Deloitte survey, the pharmaceutical industry is prioritizing trial patient recruitment as an extremely valuable RWE application. With many healthcare providers investing in health information technologies that allow them to better track and connect with their patients, information available from real-time electronic systems within ambulatory healthcare settings and hospitals offer insights into patient profiles that can help refine the design of inclusion and exclusion criteria. This approach requires new partnership models, access to the right data, and innovative technology.

Data on the natural history of disease can be helpful in understanding which HCPs/specialists are treating these patients and in which settings, as well as assessing the impact of key trial eligibility criteria on patient enrollment or even the subsequent product labeling (e.g., by understanding what relevant patient groups may be excluded from study).

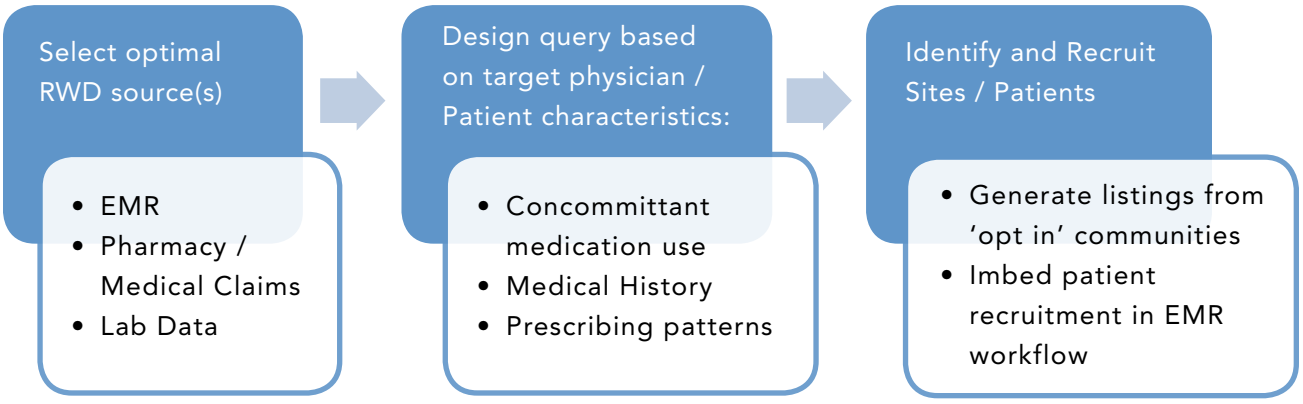
A recent study using EMR to evaluate the effect of change in blood pressure guidelines in diagnosing hypertension is one such example[2]. This retrospective study analyzed the change in prevalence of hypertension in the ambulatory patient population resulting from a recent revision to treatment guidelines. Enriched insight like this into the prevalence and characteristics of patients with a given condition enables protocol writers to design inclusion and exclusion criteria with an informed point of view on projected patient accrual velocity.

RWD allows researchers to go further by detecting where patients are clustered and pinpoint sites that are appropriate for participation in research projects. RWD derived from EMR, claims databases and other RWD sources provide a distinct advantage for site recruitment, HCP referral programs, and patient-directed recruitment campaigns in the U.S. This data-driven approach (*see figure 2*) to clinical trial site and patient recruitment is bringing innovative drugs to market faster by accelerating patient accrual across sites.

The first step in applying RWD to a specific project is selecting the appropriate data asset(s) that possesses

2 https://www.practicefusion.com/new-real-world-evidence-ispor/

Figure 2



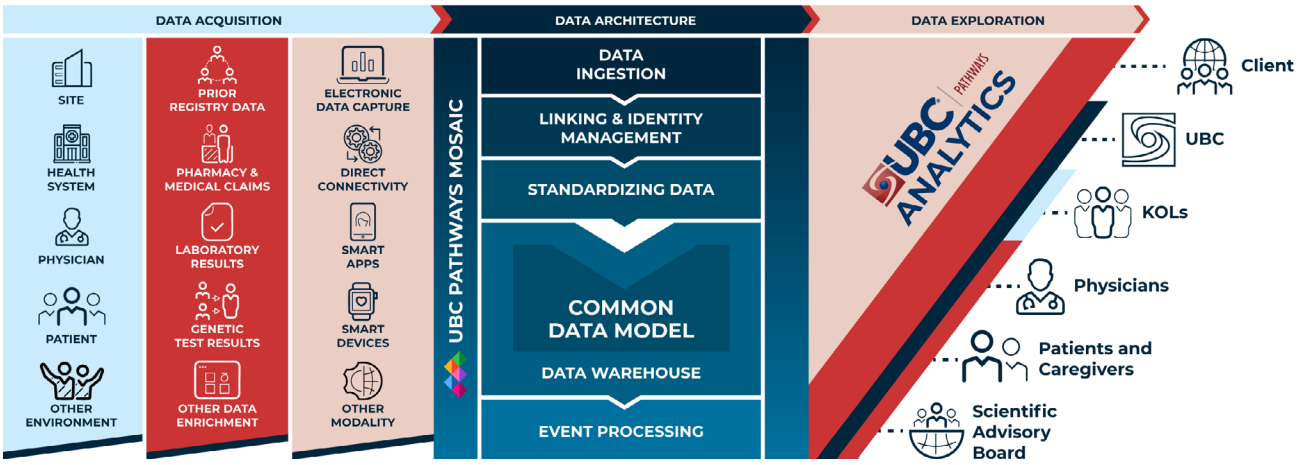
relevant pharmacy and healthcare claims data as well as EMR sources that contain robust patient profiles that will drive the identification of appropriate sites and patients for the study. These data sources often possesses 'opt in' communities of prescribers and patients that allow for direct engagement for potential participation in research opportunities. Patients of interest are matched to the specific physicians who treat them, identifying optimal investigative sites and areas to conduct direct to patient outreach. Opportunities are also emerging to streamline this workflow by imbedding enrollment processes into the EMR.

DATA COLLECTION / INTEROPERABILITY:

What exactly is meant by the term "interoperability" and how will this concept be implemented in actual practice to enhance data collection in clinical studies? The data that researchers are seeking to evaluate on new treatments reside in fragmented and disparate systems and formats. Interoperability enables different information technology systems and software applications to communicate and exchange data. These solutions bring transformative improvements to the accuracy and velocity of data collection for clinical trials. Clinical trials are enriched through the efficient acquisition of RWD from medical /pharmacy claims, lab data, wearables, biomarkers and other sources (*figure 3*).

This transformation will not be easy. Bringing RWE into clinical trials requires integrated technology solutions that solve the fragmented data landscape. These technical solutions must be able to normalize and integrate data from many sources including EMR, connected devices, ePRO and others. This is accomplished through standards based data exchanges, EDI, SML, HL7, FHIR, JSON as well as flat-file data feeds, advanced APIs and Web Services. Implementing these new practices for data collection requires expertise

Figure 3



in data linkage and the intricacies of data privacy.

Data linkage and privacy are essential considerations for the implementation of RWE strategies to support clinical trials. The ability to unite disparate, de-identified data sets from multiple sources is critical; however, robust tactics to ensure data privacy must be in place. A HIPAA compliant de-identification and matching engine to support longitudinal patient record linkage is an important component of an effective strategy.

A combination of experience in traditional research competencies (i.e., site identification, patient recruitment) and technical expertise will be required to advance this new age of research that will rely heavily upon the concept of interoperability.

FINDINGS / CONCLUSIONS

The adoption of RWD and RWE applications presents an opportunity to positively impact the primary cost drivers and minimize the reasons for failure in the conventional controlled clinical trial paradigm by informing optimal study design, facilitating faster patient recruitment and modernizing data collection in a digital world. Expertise in identifying the right data for the right purpose and executing practical solutions is an essential requirement for capitalizing on the promise of RWE. UBC's unique expertise employing transformative tactics for clinical study design and execution creates significant value for life sciences companies that are embracing the potential of RWE. ●