Paper RE02

The Real Benefit to Using Real-world Evidence Studies" Using RWE to Revamp Clinical Trials

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ABSTRACT

In past decade the amount of clinical data generated outside of clinical trials has hit an unseen level. Having that data on hands enabled clinical researchers to step into new era of clinical trials based on real world evidence that could potentially be a game changing in pharmaceutical industry.

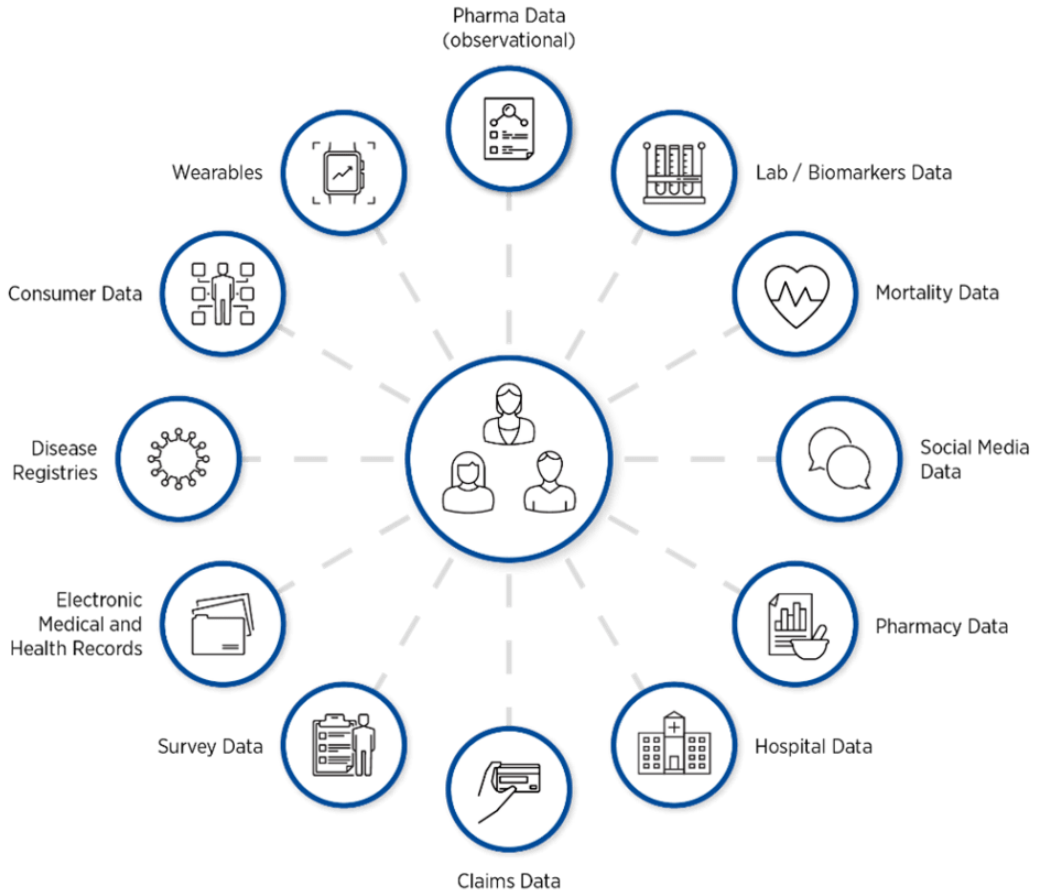
This paper is intended to provide a brief discussion about the benefits of Real-World Evidence Studies conducted to enhance traditional Clinical trials.

INTRODUCTION

In order to understand what real-world evidence is, we should identify the data that serves as a driving power for

REAL-WORLD DATA (RWD)

According to CDER RWD are the data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources that include Electronic Health Records (EHRs), claims and billing activities, product and disease registries, Patient Generated Health Data (PGHD), Prescription data etc.



Electronic Health Record (EHR) is a digital version of a patient's paper chart that contains a patient's medical history, diagnoses, medications, treatment plans, immunization dates, allergies, radiology images, laboratory and test results, etc.

Patient Generated Health Data (PGHD) is health data created by Patient, Family members or other Caregivers Contain a patient's health history, treatment history, Biometric data, Symptoms, Lifestyle choices etc. It provides information directly from the patient about what happens outside of visits such as Types and Frequency of symptoms, Nature and severity of disability, Impact of disease/condition on the daily life, Perception regarding the treatment given.

Nowadays when most of the population uses smartphones, smart watches and bands the collection of Patient generated data become more robust, continuous and accurate.

REAL-WORLD EVIDENCE(RWE)

FDA defines Real-world evidence as the clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD.

RWE clinical trials are to complement the knowledge gained from traditional clinical trials, whose well-known limitations make it difficult to generalize findings to larger, more inclusive populations of patients, providers, and health care delivery systems or settings that reflect actual use in practice.

Unlike randomized clinical trials, where data elements collection process is strongly directed and managed mandated, the creation of RWE requires assessing, validating and aggregating various sources of data available through routine clinical practice.

Conducting RWE trials require adequate and accurate analysis of RWD coming from variety of sources which makes researchers to deal with series of challenges.

The first challenge that we should deal with is bringing data collected from different sources and that are in different forms into a unified database that will enable further analysis. As PGHD generated mostly by patients who are not clinical specialists is not always accurate and complete that is why it's quality needs to improved prior including it into RWE trials.

Missing data handling was always a big deal. In RCTs this topic is being addressed in SAP as the source of missing data is well known there. RWD is whole another story as here we should identify the reason why certain data is missing and only after that we can take known steps in handling it.

Analysis tool selection plays a Significant role in analyzing RWD and it may depend on the size of the data and the nature of the analysis. If the data to be processed is complete, accurate, well structured, small scaled and, what is important, the analysis of it is limited to some basic calculation the simplest Microsoft Excel could be enough. If it comes more of complex analysis and inferential statistical models then conventional Software like SAS, R or Python steps in to give wider functional of validated procedures, formulas and data processing techniques.

FDA GUIDANCE

On September 2021 FDA released draft guidelines called ***"Real-World Data: Assessing Electronic Health Records and Medical Claims Data To Support Regulatory Decision Making for Drug and Biological Products Guidance for Industry"*** that is meant to help sponsors to avoid common mistakes conducting RWE trials.

The 21st Century Cures Act (Cures Act), signed into law on December 13, 2016, is intended to accelerate medical product development and bring innovations faster and more efficiently to the patients who need them.

Guideline provides recommendations on various aspects of submitting protocols to FDA as well as selecting data sources to maximize the completeness and accuracy of the RWD. Protocols submitted to FDA should identify all data sources proposed for the study maximize the completeness and accuracy of the RWD.

FDA recommends specifying how all relevant populations, exposures, clinically relevant outcomes, and covariates will be captured during the study period, particularly in situations where data availability varies greatly over time.

Sponsors should consider whether validating the variable to a greater extent is necessary and discuss with the relevant review division.

FDA recommends clearly defining the various time periods pertinent to the study design in the protocol

Special attention should be paid to handling missing data.

Guidelines for RWD and RWE data document submission could be found at:

Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drug and Biological Products | FDA

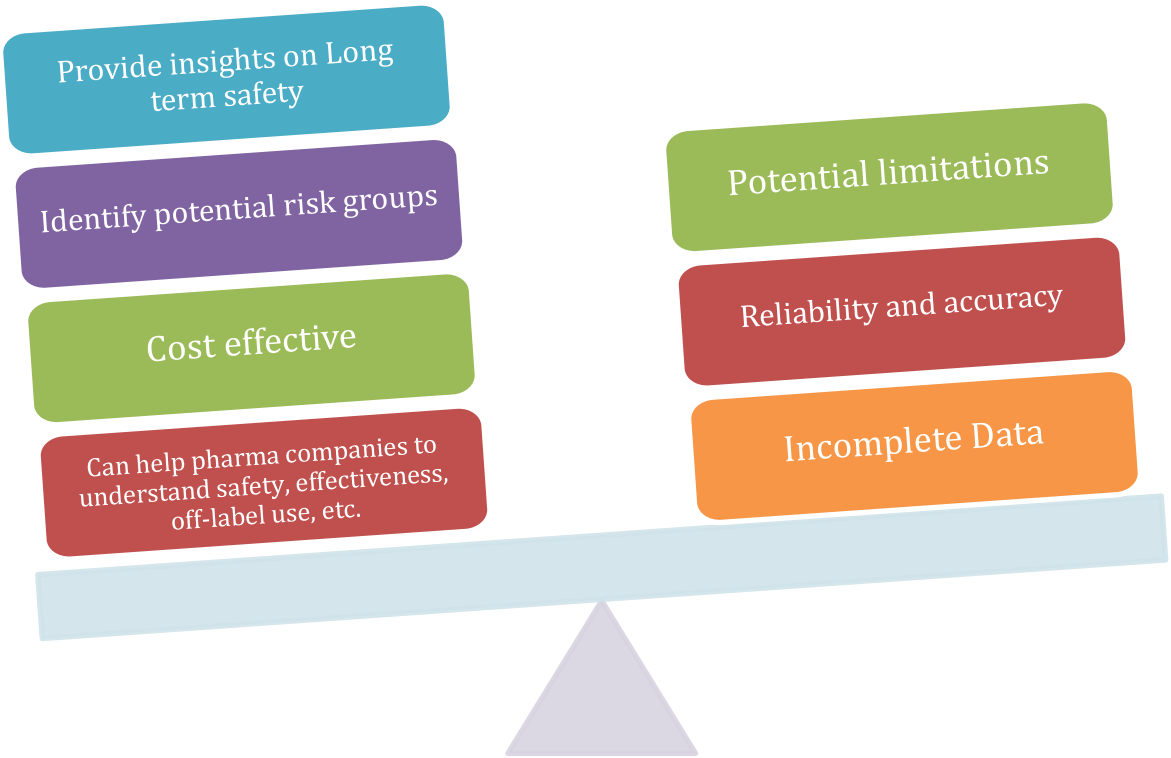
PROS AND CONS

Speaking of advantages and disadvantages RWE have we can freely say that even though RWD can be incomplete, have a poor quality, it's accuracy may be questionable or even it may have certain level of limitations it still owns the most crucial characteristic for drug development that is comparably low cost.

Safety follow up in RCT usually don't last long due to limited resources and high costs. RWE, on the contrary, can hold patient data for lifetime as it is gathered during routine clinical activities or collected by healthcare applications autonomously over the period of their usage.

Due to larger scale and variety of population analysis conducted on RWD could lead to identifying potential risk groups of people prescribed to certain treatment.

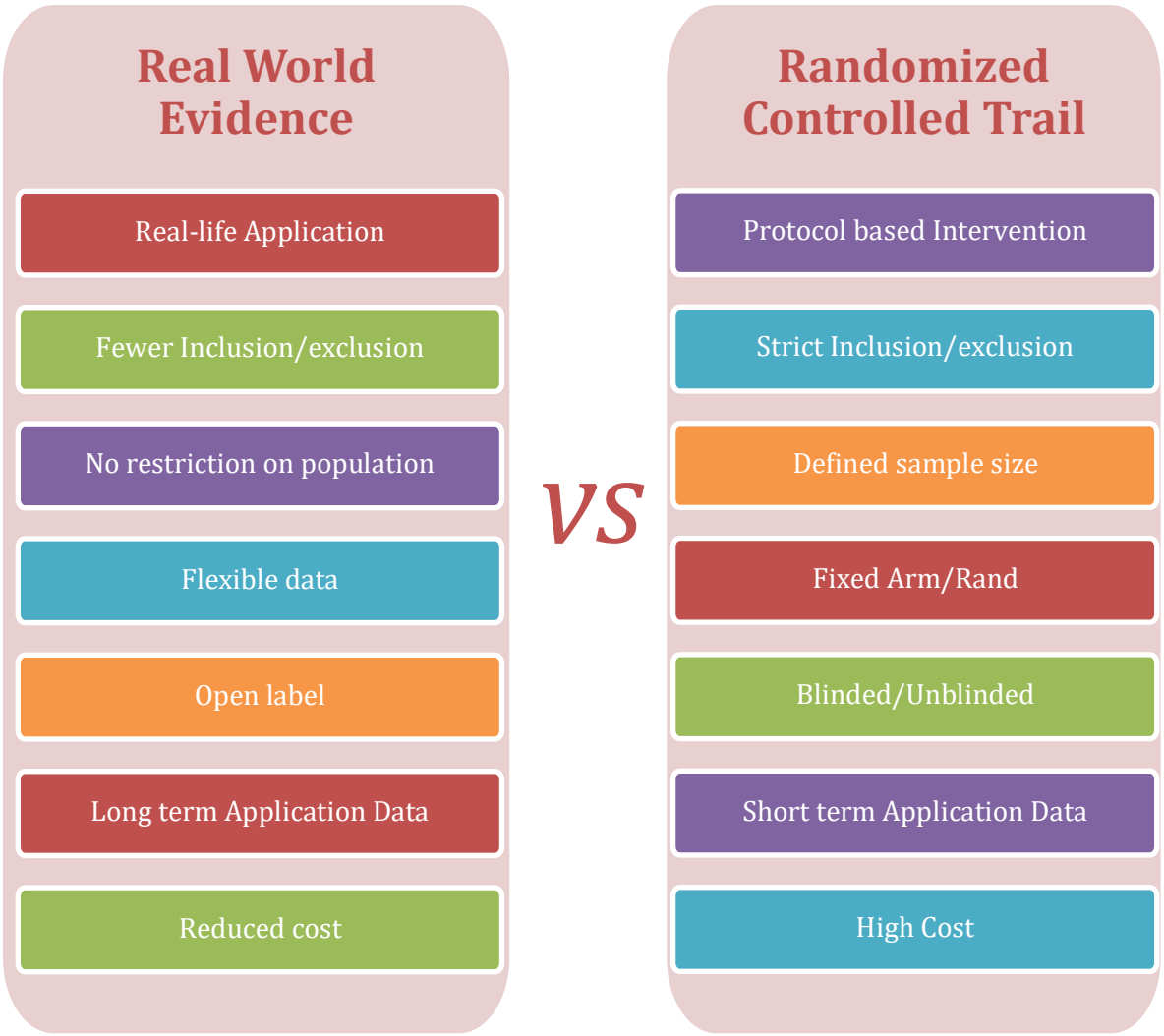
As a result, RWEs contribute into understanding of safety, effectiveness of a treatment and potential of off-label usage that could lead to extended application of a treatment in healthcare with minimum expenses.



PARALLES BETWEEN RWE AND RCT

Closer look at some key aspects of clinical trial will show pictorial differences between conventional RCT and RWE intended studies.

TABLE 1



RCTs are based on pre-designed protocol with limited sample size selected by very specific, strict inclusion and exclusion criteria whereas RWE protocol is being developed based on real life application of treatment. Population of treated subjects could be huge due to lot lesser selection criteria.

Conventional trials could be both Blinded or unblinded, but in RWE subjects already know what medications they are taking and due to exposure to a specific treatment they are being selected as a part of RWE trial.

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Finally, RCTs are always High Cost and for large scale trials can hit up to $50 million that will include recruiting, stuffing, data analysis and reporting expenses.

APPROVED BY FDA

Ibrance (palbociclib)

In April 2019, the FDA expanded the approval of Ibrance (palbociclib) to treat certain types of breast cancer in men. Before the approval, Ibrance was only approved for use in women. In this case, the manufacturer used real-world data from three databases to provide evidence for approval. Real-world evidence was useful in this instance since

breast cancer isn't as common in men. So, recruiting enough participants for RCTs would be difficult. Now, men with certain types of breast cancer have an approved treatment option.

Orencia (abatacept)
In December 2021, the FDA approved Orencia (abatacept) to prevent graft versus host disease (GVHD). GVHD occurs when a stem cell or bone marrow donor's immune cells attack the recipient's body. Orencia became the first FDA-approved medication to prevent GVHD. Researchers reviewed real-world data from a registry. They looked at outcomes of stem cell transplant recipients. People who received Orencia with standard treatment had a better survival rate 6 months after transplant than those who didn't receive Orencia.

CONCLUSION

RWE is difficult, but effective way to enhance RCT with analyzing data collected outside of the RCT scope. It is cost effective way to assess safety and effectiveness of treatment available market to larger extent. The target of improving reliability and acceptability of RWE trials could be improved in near future by unifying and standardizing the ways of RWD collection through variety of sources widespread worldwide.

REFERENCES

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(https://www.fda.gov/regulatory-information/search-fda-guidance-documents/submitting-documents-using-real-world-data-and-real-world-evidence-fda-drug-and-biological-products)

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