

COVID-19 Research Comparative Outcome Looking Through Real-World Evidence Vs. Clinical Trials

Niveditha Hariharan

PhD, Medical Writer, THB™: Technology | Healthcare |
Big Data Analytics, Premises No. 7(2 Bays) Sector 32
Opposite Jet Airways Training Centre
Institutional Area, Sector 32, Gurugram, Haryana 122001

Betina Chandolia

MDS, Medical Writer, THB™: Technology | Healthcare |
Big Data Analytics, Premises No. 7(2 Bays) Sector 32
Opposite Jet Airways Training Centre
Institutional Area, Sector 32, Gurugram, Haryana 122001

Farah Iram

PhD, Senior Medical Writer, THB™: Technology | Healthcare |
Big Data Analytics, Premises No. 7(2 Bays) Sector 32
Opposite Jet Airways Training Centre
Institutional Area, Sector 32, Gurugram, Haryana 122001

Saurav Deka

MBBS, MD, FCCM, AVP-Real World Evidence, THB™:
Technology | Healthcare | Big Data Analytics
Premises No. 7(2 Bays) Sector 32, Opposite Jet Airways Training Centre
Institutional Area, Sector 32, Gurugram, Haryana 122001

Aparajita Dubey

M.Sc, Senior Medical Writer, THB™: Technology | Healthcare |
Big Data Analytics, Premises No. 7(2 Bays) Sector 32
Opposite Jet Airways Training Centre
Institutional Area, Sector 32, Gurugram, Haryana 122001

Lavina Yadav

M.Sc, Executive Vice President, THB™: Technology | Healthcare |
Big Data Analytics, Premises No. 7(2 Bays) Sector 32
Opposite Jet Airways Training Centre
Institutional Area, Sector 32, Gurugram, Haryana 122001

ABSTRACT

Randomized controlled trials (RCTs) are considered the gold standard because of their conventional study design, accurately defined endpoints, and high-quality evidence to define any cause-effect relationships. On the other hand, Real-world

Data (RWD) relates to the collection of data pertaining to health status of the patient and/or delivery of routine health care. As the sources of RWD are becoming vast, Real-World Evidence (RWE) studies are gaining increasing attention. RWE can emerge as the backbone for regulatory decision-making in clinical research by providing adequate scientific evidence. A lot of RWE studies have been conducted in COVID-19, where a variety of repurposed drugs have been tested in real-world settings for the treatment and management of COVID-19. The current need is to work on a Hybrid trial methodology combining the most important parts of traditional RCTs and observational study designs to infer the RWE.

Keywords: RCTs, RWD, COVID-19, regulatory decision

INTRODUCTION

Randomized control trial (RCT) and Real-world evidence (RWE) studies are interdependent. The clinical practice guidelines are mainly based on published results from carefully designed RCTs. They provide evidence for bias control, collection of detailed data, and patient populations selection, which reduces variation that could affect study results. RWE correlates to the usage and potential benefits or risks evaluation using real-world data, including the status of patient health, health care, and patient outcomes using sources such as electronic health records. However, both have their advantages and disadvantages for various variables. The most critical factor in both studies is the protection of data privacy¹. This review aims to cover all the aspects of RCT and RWE in detail.

Randomized Controlled Trials

Randomized Controlled Trial (RCT) is a prospective, comparative, quantitative study/experiment performed under controlled conditions with random allocation of interventions to comparison groups. It is the most meticulous research method of determining whether a cause-effect relationship exists between an intervention and an outcome. When evaluating the effectiveness and safety of an intervention by performing RCT, high-quality evidence can be generated. RCT capitulates effectively to systematic review and meta-analysis, providing a solid base for synthesizing evidence generated by such studies. The clinical practice based on evidence helps to improve patient outcomes and safety and is generally cost-effective. Designing and conducting an RCT, analyzing data, interpreting findings, and disseminating results require time and can be challenging as several practicalities are considered².

RCT is carried out by randomly assigning subjects to one of two groups: one is the experimental group that will receive the intervention being tested, and the other is the comparison group or control group that will receive an alternative or conventional treatment. The difference between the outcome of these groups is noted. The results are analyzed and are used to assess the effectiveness of the intervention, which will determine the extent to which a treatment, procedure, or service can be beneficial to the patients².

RCTs are the gold standard because they are blinded, concealed, and unbiased. Blinding helps in minimize the bias and maximize the validity of the results, concealment helps minimize both performance and assessment bias, and unbiased sampling helps to accurately represent the entire population^{3,4}. Ideally, while at the time of recruitment, it is not known to which group the participant will be allocated. This is known as concealment. This is done so by using automated

randomization systems with the help of a computer. They are blinded to minimize the bias as the participants and the medical staff, including doctors, nurses, and researchers, do not know what treatment each participant is receiving⁵.

The advantages of RCTs are that they provide internal validity, precise measures of efficacy, and acute toxicity of new therapies under ideal conditions. Due to randomization, the bias is minimized. They allow exploratory measures of secondary endpoints, which include patient-reported outcomes. They can help to evaluate prognostic and predictive properties of new biomarkers and therapies. They provide a mechanism where whether the treatment is new or potential toxic can be studied carefully in the centers of excellence⁶.

The disadvantages of RCT can include the comparatively higher costs in terms of time and money, issues with generalizability, and loss of follow-up⁶. The patients enrolled in RCT are usually not similar to those in routine practice because applicability to clinical practice can be limited. The patient pool, the eligibility criteria, the trial attractiveness, and network adequacy of clinical sites may influence enrollment in RCT⁶. The elderly and comorbid patients are usually under-represented in RCTs. The RCTs may not apply to smaller sample size. It uses a surrogate primary endpoint, which might not be a valid measure of patient benefit. RCTs have limited ability to detect chronic and rare toxicities⁷.

Real-World Evidence

RWE is the investigation of Real-world data (RWD) from a study developed with a high degree of pragmatism. According to the 21st Century Cures Act, RWE is evidence developed from “data regarding the usage, or potential benefits or risks, of a drug derived from sources other than randomized clinical trials⁸.” Conclusions drawn from observations of patients in healthcare settings are referred to as RWE (rather than subjects in a research environment). Real-world data (RWD) is information obtained from numerous sources through observations of regular clinical practice and connected to produce significant patterns. RWD is based on patients and their providers selecting therapies based on the clinical characteristics and preferences of the patients^{9,10}.

In September 2013, the Ministry of Health & Family Welfare (MoH&FW) released guidelines for Electronic Health Records (EHR) in India. This was done based on recommendations made by the EMR Standards Committee organized under the MoH&FW. This document recommended the developing a uniform system for the creation and maintenance of electronic health records by healthcare providers. A revision of these standards was notified in December 2016^{11,12}. Wearable devices and smartphones generate billions of user-specific data points every day, but over 99% of this newly created digital data remains unanalyzed. New open data policies, such as the Open FDA and academic data-sharing initiatives, are increasing the amount of searchable data available to RWE researchers. New software based on emerging artificial intelligence, machine learning, and natural language processing capabilities is streamlining the mission of combing through large databases to assess associations between patient characteristics, health care professional characteristics, diseases, and treatments^{13,14}.

RWE Sources

Real-world data sources generally fall into four categories¹⁵. Figure 1 depicts the various sources of RWE data:

How to conduct an RWE study? (RWE Plan and Design)

To conduct an RWE study like any clinical test involves an ethics committee, and prospective participants must provide informed consent for access to individual medical records, regardless of whether interventional or non-interventional. An assessment methodology that considers risk and a medical monitoring strategy are essential to ensuring data integrity. Monitoring of the site should include consent procedures, randomization integrity, safety, and follow-ups^{16, 17}.

RWE Design

RWE study designs are categorized as follows¹⁸

- a. **Retrospective design:** studies gather data over a short time, rely on clinical records of good quality, and are generally low-cost studies. These studies, however, have limitations such as incomplete or inaccurate data. Examples include Clinical/hospital record/chart review, administrative data/insurance claim data, electronic medical records (EMRs).
- b. **Prospective design** these studies include patient-specific information and clinical details that are not regularly collected, and they provide information on the long-term natural history of a patient's condition. These studies may have uncertain timelines, as they are dependent upon the rate of presentation of eligible patients, and they are likely to be expensive. Examples include Registries, health surveys, prospective observational studies, post-authorization safety studies.

RWE Planning

A standardized data collection is essential to ensuring high-quality data in pragmatic trials that are conducted in real-world usual care settings. To accomplish this, it would necessitate using special capturing software or modifying EMR to acquire disease-specific data. Propensity scoring can significantly reduce bias for long-term prospective studies or retrospective data collection. Propensity scoring considers the classification of the relationship between treatment assignment and baseline characteristics¹⁶. Participants are matched across two treatment groups using the propensity score. Participants who are matchable are compared, while those who are not are eliminated from the analysis. Bias and nonrandomization issues necessitate adhering to acceptable research practices. To confirm the validity of the RWE study strengthening the reporting of observational studies in epidemiology for general cohort studies, good research for comparative effectiveness checklist or pragmatic explanatory continuum indicator summary (precis) tool is recommended¹⁹.

Strength and Limitations of RCTs and RWE

The differences between RCTs and RWE are provided in table 1. The strength and limitations of RCTs and RWE are discussed in table 2.²⁰⁻²²

RWE for Regulatory Decision Making

The major disadvantages of using the RCT approach for regulatory decision-making include cost, labor dependence, and generation of data with limited or restricted applicability in real-world clinical practice.

To ensure regulatory-grade data quality RWE, both retrospective and prospective, should fulfill a defined checklist. It includes high-quality, auditable datapoint, with complete information following transparent study designs and analysis plans critical for robust RWE. RWE is based

on a broad range of patients, which can be translated into superior generalizability. RWE should be recent and timely with higher scalability in terms of the data model, patient population, and defined endpoints²³.

Measures to improve the Value of RWE

Six methods for improving the value of RWE discussed by the clinical trial experts includes²⁴

- i) Stakeholders to develop methodology standards for RWE trials to improve the quality of these studies
- ii) A mandatory national registry for RWE trials
- iii) Establishing formal restrictions on submission or publishing of data from an unregistered RWE for regulatory purposes
- iv) Designing of a synthetic control arm for fatal diseases such as cancer to accurately predict mortality outcomes in patients not receiving an investigational intervention in an RWE prospective study
- v) RWE to collaborate with networks such as the Patient-Centered Outcomes Research Institute (PCORI) and the National Patient-Centered Clinical Research Network (PCORNET) and
- vi) Data collection by researchers using a secure FDA mobile app was released in November 2018.

USFDA and Real-World Evidence Drugs

In December 2018, the FDA announced the launch of a Real-World Evidence Program to apply across its drug and biologic review process according to the 21st Century Cures Act (Cures Act). The main objective for RWE programs was to support the approval of a new indication, its expansion, and post-approval study. It includes prospective noninterventive clinical trials where intervention is identified at the start of the study, e.g., pragmatic trials, and retrospective observational studies where the intervention is studied from historical data for the trial population.

RWE is gaining momentum at the Center for Drug Evaluation and Research (CDER) with multiple ongoing randomized and observational studies for the prevention and care of diabetes-related outcomes. For example, Sanofi (2018) RWE study, compares clinical outcomes in insulin-naïve adults with type 2 diabetes initiating insulin glargine or Insulin Degludec. The results in improvement in glycemic control and hypoglycemia outcomes were similar to those of the first completed RCT. Another example is using RWE from randomized pragmatic trials to evaluate major adverse cardiac events (MACE) to address both the safety and benefit of diabetes therapies. In Indian settings, similar RWE studies to assess management and real-world outcomes of diabetes mellitus are in progress, and similar results are expected. Hence, RWE trials can certainly expedite and improve clinical research efforts and approve drugs and devices for diabetes care²⁴.

Hybrid designs and their advantages

The hybrid design includes randomization and using pragmatic or realistic outcomes based on practical rather than theoretical considerations. Other hybrid designs include single-arm trial data and other comparable real-world data (RWD) or by applying novel data collection approaches to capture long-term outcomes in a real-world setting. The major objective of these hybrid design approaches is to support the regulatory decision making by demonstrating the

effectiveness of drugs without opting for the traditional RCTs. RWE obtained from observational studies is useful in fulfilling post-approval safety monitoring requirements.

Hence, specific hybrid study designs considered for regulatory decision-making by the FDA are basically classified into three broad categories (a) Investigational new drug submissions for RCTs using RWD to capture clinical outcomes or safety data, which includes pragmatic and large simple trials, b) protocols for single-arm trials using external controls and (c) clinical trials using RWE to fulfill a post-marketing requirement for evaluating the safety to support the regulatory decision²⁵.

Pragmatic and large simple trials have many features similar to very large RCTs, including randomization, enabling a broader patient group to participate. These trials are designed to demonstrate effectiveness in a daily clinical practice setting and study more clinically meaningful outcomes for patient's benefit. For example, the feasibility of pragmatic trials was tested by the label expansion achieved for Janssen's INVEGA SUSTENNA (Case study)²⁶.

External controls: Non-randomized clinical trials with comparison against external controls are used to demonstrate effectiveness in increasing number, mostly related to rare diseases. These types of trial designs are very useful with a limited number of patients with a particular condition, with randomization not being a feasible or ethical. Trials with external controls have emerged as recent innovation with RWE has been recently used to support decisions which have led to accelerated approval, full approval, or label expansion⁸.

The RWE approvals mainly fall under three broad categories: (a) based on data from registry-like case series; (b) external control data that are mostly obtained from registries, medical records, scientific literature, etc. and (c) based on data from expanded access programs (EAP) which allows physicians and patients access to pre-approval, investigational drugs outside of the actual clinical trial setting²³.

Long-term follow-up studies using RWD: Observational designs and methods are crucial for providing post-marketing evidence of drug safety. The regulatory framework for RWE has offered new opportunities for conducting streamlined safety and efficacy studies, supported with new technology and data²⁷.

Methodologies such as decentralization, direct-to-patient approaches or databases could be used to capture RWD and long-term outcomes. This can be considered as a step towards the adoption of hybrid study designs to improve clinical efficiencies. These innovative approaches can be beneficial for conducting long-term studies of pre-approval, investigational drugs, which require longer follow-up duration to attain the required safety and effectiveness outcomes. Machine learning techniques are used to enhance the prediction accuracy of algorithms for various RWD studies. Hence, if negating some of the drawbacks, the potential these hybrid study methodologies offer by combining the best features of RCTs and studies with RWD is extraordinary. This approach can even replace RCTs for regulatory decision-making in certain situations. It would be widely used and accepted by researchers, clinicians, and regulators after gaining more experience with these types of study designs²⁸.

RWE STUDIES ON COVID-19

RWE Studies on Diagnostic methods of COVID-19

Several RWE studies have been conducted in the context of finding accurate diagnostic tools for COVID-19. RT-PCR is the widely used and accepted method for the diagnosis of SARS-CoV2 infections. Scientists have also tried exploring the role of radiological techniques that help in the diagnosis of COVID-19. The findings of a few RWE studies are described below.

There was a great debate whether computerized tomography (CT) can be an adjunct or replacement to reverse transcriptase PCR in the screening and diagnosis of COVID-19 pneumonia. Studies²⁹ that were conducted to analyze the role of CT in the diagnosis of COVID-19 pneumonia were retrospective analysis and case series, and hence definite conclusions cannot be drawn in the use of CT as a diagnostic test for COVID-19.³⁰

Real-world data points out that chest X-ray can be used as a first-line examination in suspected COVID-19 patients. Cozzi et al.³¹ reported an overall accuracy of 76-86% for chest X-rays.

RWE Studies on the association of Comorbidities with COVID-19 Severity

COVID-19 patients with comorbidities are at a higher risk of undergoing mortality than others. A few examples of RWE studies that explored the association of comorbidities are described here.

Wang et al.³² conducted a systematic review and meta-analysis and identified that hypertension is the most prevalent comorbidity in severe COVID-19 patients. Hypertensive patients had a 2.5-fold increased risk of having severe forms of COVID-19 than non-hypertensive individuals³³. In a recent meta-analysis³², it was identified that the prevalence of diabetes in severe cases was 14.4% vs 8.5% in non-severe cases. Cardiovascular risk factors were found to be associated with disease severity and mortality. A study conducted by Guan et al.³⁴ identified that 13.7% of COVID-19 positive patients had elevated creatine kinase levels and 37.2% had elevated levels of LDH.

RWE Studies on various Drugs used in the management of COVID-19

A lot of repurposed drugs were used for the treatment and management of COVID-19.

1. Corticosteroids

Corticosteroids as anti-inflammatory agents may be used to reduce the inflammatory responses in COVID-19.³⁵ The use of dexamethasone in the treatment of COVID-19 in different contexts is summarized in Table 3.

2. Antiviral agents of COVID-19

As COVID-19 shares 79.5% of sequence identity with SARS-CoV, several antivirals have been tested to treat COVID-19.³⁶ This includes arbidol, chloroquine, HIV protease inhibitors like lopinavir/ritonavir, new nucleoside analogues like remdesivir and convalescent plasma.³⁷ Some broad-spectrum anti-virals like oseltamivir were also tested.³⁸

1. Arbidol

Several retrospective studies with a small sample size have yielded controversial results regarding the use of arbidol in the treatment of COVID-19.³⁹⁻⁴⁰ Larger RCTs are required to clarify the role of arbidol.

2. Chloroquine

CQ/HCQ has immunomodulatory and anti-viral properties and has been used for the treatment of COVID-19. There are several randomized clinical trials carried on finding the efficacy of HCQ in COVID-19. The results are highly conflicting.

Million et al.⁴¹ conducted a meta-analysis between the big data and the real world to evaluate the clinical efficacy of chloroquine derivatives in COVID-19 infection. They conclude that chloroquine derivatives are effective in improving clinical and virological outcomes and reduce mortality. Also, their observations point out that big data (electronic registry data analysis) lack basic treatment definitions.

Singh et al.⁴², in a large retrospective cohort of hospitalized COVID-19 patients, identified that HCQ had shown no benefits in mortality rate or the need for mechanical ventilation. Annie et al.⁴³ observed no significant differences in the 30-day mortality rate between HCQ and no-HCQ group in a retrospective cohort of patients.

Becerra et al.⁴⁴ evaluated the real-world effectiveness of HCQ, azithromycin (AZIT), and ivermectin (IVM) among hospitalized COVID-19 patients. The study reports no beneficial effects of HCQ+AZIT+IVM. Instead, HCQ+AZIT increased the risk of all-cause mortality.

3. Favipiravir

A retrospective observational study involving hospitalized adult patients with COVID-19 in Thailand identified that favipiravir was effective in treating COVID-19 patients. Also, no life-threatening adverse events were reported.⁴⁵

4. Remdesivir

Intravenous remdesivir did not improve the clinical outcomes or mortality in a randomized, double-blind placebo-controlled multicenter study involving 237 patients.⁴⁶

In a retrospective real-world observational study involving 333 adult patients receiving anti-viral drugs for COVID-19 treatment, it was identified that remdesivir showed higher clinical improvement rates than lopinavir/ritonavir (LPV/r) (15% vs 10%).⁴⁷

5. Lopinavir/ritonavir (LPV/r)

Lopinavir/ritonavir (LPV/r) has been shown to inhibit viral replication invitro and has been tested for treating SARS-Cov.⁴⁸

In a real-world observational study conducted in Mexico, the efficacy of repurposed antivirals and antibiotics in the treatment of COVID-19 was analysed. No significant benefits were seen for the repurposed anti-virals. Oseltamivir increased the risk of mortality in the general population, ambulatory, critical, non-critical, pregnant, and hospitalized patients. Antibiotics increased the mortality risk in the general population and pediatrics. They offered protection for hospitalized and critical patients.³⁸

3. Convalescent plasma

Before the advent of COVID-19 vaccines, convalescent plasma has been a viable therapeutic option for treating COVID-19. A few reports documented that convalescent plasma saved lives

with no serious adverse events. As the sample size was small in most of the studies, large scale clinical studies are warranted.⁴⁹⁻⁵⁰

4. Monoclonal antibodies

Bamlanivimab

Bamlanivimab is an anti-spike monoclonal antibody that was shown to be effective in treating SARS-Cov2 infections in RCTs. Kumar et al. conducted a retrospective case-control study to find the efficacy of bamlanivimab in RW settings. It was identified that the 30-day hospitalization rate was significantly lower among patients receiving bamlanivimab.⁵¹

Tocilizumab

As “cytokine storm” is documented in critically ill patients infected with COVID-19, monoclonal antibodies like tocilizumab that target IL-6 has been explored in treating COVID-19 patients.⁵² In a study involving 21 patients receiving tocilizumab during the hospital stay, and it showed short-term survival benefits in patients with severe COVID-19 illness.⁵³

Studies with larger sample size and randomization are needed to determine the efficacy of tocilizumab in patients hospitalized with COVID-19. As adverse serious events like candida infection, lipid metabolism disorder, and intestinal perforation are associated with the use of tocilizumab, caution is required during its usage.⁵⁴⁻⁵⁵

5. Anti-platelet drugs

COVID-19 is associated with high incidences of thrombosis and mortality. Anti-coagulants are used to treat thromboembolism. However, the timing, dosage, and duration of anti-coagulants in the management of COVID-19 is yet to be elucidated.⁵⁶

RWE studies on the Efficacy of COVID-19 Vaccines

According to the large phase 3 clinical trials, the FDA approved mRNA vaccines mRNA-1273 (Moderna) and BNT162b2 (Pfizer/BioNTech) had shown 94.1% and 95.1% efficacy respectively.^{57,58} Pawlowski et al.⁵⁹ conducted a study to unravel the efficacy of mRNA vaccines in the real-world settings and identified that the administration of two COVID-19 vaccine doses was 88.7% effective in preventing SARS-Cov2 infections with onset at least 36 days after the first dose. Compared with the propensity-matched unvaccinated COVID-19 patients, vaccinated patients who were subsequently diagnosed with COVID-19 infections had significantly lower hospital admission rates.

Chodick et al.⁶⁰ analyzed the first dose of BNT162b2 vaccine in reducing the SARS-Cov2 infections in the RW settings. The first dose of vaccine was associated with a 51% reduction in the incidence of PCR-confirmed SARS-Cov2 infections at 13-24 days after immunization. The differences in the current study results with RCTs might be due to the timepoints in which the vaccine efficacy was tested and the differences in the characteristics of the study population.

Jabal et al.⁶¹ evaluated the immunogenicity of the BNT162b2 vaccine 21 days post the first dose among 514 Israeli healthcare workers. It was identified that immunogenicity was similar by ethnicity and sex, and it decreased with age. Regardless of detectable IgG antibodies pre-vaccination, people with prior infection had antibody titers higher than naïve individuals. The

first dose of the vaccine was found to be effective in 92% of the study cohort, 21 days of post-vaccination.

CONCLUSION

RWE is increasingly gaining importance with an exponential increase in the availability of electronic data and improved analytical tools for researchers. Compared to RCTs, RWE has higher advantages in terms of cost and performance causing change in the preference of researchers towards RWE instead of RCT. The changing regulatory opinions, guidance frameworks, and evolving RWD methodologies, using RWE for regulatory decision-making is gaining recognition. This can be revolutionized by setting higher standards, better rules, more reliable databases, and superior methods for eliminating confounding factors. The focus on the development of hybrid study designs will have the benefits associated with both RCTs and RWD. In such designs, the limitations of RCTs and RWD will be minimized, which could be attained by establishing a cross-disciplinary team and involvement of pharmacoepidemiologists.

References

- [1]. Villines TC, Cziraky MJ, Amin AN. Awareness, Knowledge, and Utility of RCT Data vs RWE: Results From a Survey of US Cardiologists: Real-world Evidence in Clinical Decision Making. *Clin Med Insights Cardiol*. 2020 Sep 2;14:1179546820953410. doi: 10.1177/1179546820953410. PMID: 32952404; PMCID: PMC7476349.
- [2]. Bhide A, Shah PS, Acharya G. A simplified guide to randomized controlled trials. *Acta Obstet Gynecol Scand*. 2018 Apr;97(4):380-387. doi: 10.1111/aogs.13309. Epub 2018 Feb 27. PMID: 29377058.
- [3]. Karanicolas PJ, Farrokhyar F, Bhandari M. Practical tips for surgical research: blinding: who, what, when, why, how?. *Can J Surg*. 2010;53(5):345-348.
- [4]. Sil A, Kumar P, Kumar R, Das NK. Selection of Control, Randomization, Blinding, and Allocation Concealment. *Indian Dermatol Online J*. 2019;10(5):601-605. Published 2019 Aug 28. doi:10.4103/idoj.IDOJ_149_19
- [5]. Hariton E, Locascio JJ. Randomised controlled trials - the gold standard for effectiveness research: Study design: randomised controlled trials. *BJOG*. 2018;125(13):1716. doi:10.1111/1471-0528.15199
- [6]. Haidich AB, Ioannidis JP. Patterns of patient enrollment in randomized controlled trials. *J Clin Epidemiol*. 2001 Sep;54(9):877-83. doi: 10.1016/s0895-4356(01)00353-5. PMID: 11520646.
- [7]. Booth CM, Tannock IF. Randomised controlled trials and population-based observational research: partners in the evolution of medical evidence. *Br J Cancer*. 2014;110(3):551-555. doi:10.1038/bjc.2013.725.
- [8]. Blonde L, Khunti K, Harris SB, Meizinger C, Skolnik NS. Interpretation and impact of real-world clinical data for the practicing clinician. *Adv Ther*. 2018; 35:1763-1774.
- [9]. Nicholls SG, Carroll K, Brehaut J, et al. Stakeholder views regarding ethical issues in the design and conduct of pragmatic trials: study protocol. *BMC Med Ethics*. 2018; 19:90.
- [10]. Jarow JP, LaVange L, Woodcock J. Multidimensional evidence generation and FDA regulatory decision making defining and using "real-world" data. *JAMA*. 2017; 318:703-704.
- [11]. Ozair, FF, N Jamshed, A Sharma, and P Aggarwal. 2015. "Ethical Issues in Electronic Health Records: A General Overview." *Perspect Clin Res* 6 (2): 73–76.
- [12]. <https://www.itu.int/net4/wsis/archive/stocktaking/Project/Details?projectId=1515593078>. Mantri, Manisha. 2016. "Electronic Health Record (EHR) Standards for India (2016)," 57. Ministry of Health & Family Welfare, and Government of India. 2018. "Digital Information Security in Healthcare, Act [Draft for Public Consultation].
- [13]. Data sharing and the future of science. *Nat Commun*. 2018; 9:2817.

- [14]. National Academy of Sciences. Sharing Clinical Trial Data. Available at: <http://www.nationalacademies.org/hmd/Activities/Research/DrugForum/Sharing-Clinical-Trial-Data.aspx>. Accessed February 20, 2019.
- [15]. U.S. Food and Drug Administration, "Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices," August 31, 2017, <https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm513027.pdf>
- [16]. Ziemssen T, Hillert J, Butzkueven H. The importance of collecting structured clinical information on multiple sclerosis. *BMC Med* 2016; 14:81.
- [17]. Association of the British Pharmaceutical Industry. Demonstrating Value with Real World Data: A Practical Guide. Association of the British Pharmaceutical Industry; 2011. Available from: <http://www.abpi.org.uk/our-work/library/guidelines/Pages/real-world-data.aspx>.
- [18]. Sherman RE, Anderson SA, Dal Pan GJ, Gray GW, Gross T, Hunter NL, et al. Real-world evidence – What is it and what can it tell us? *N Engl J Med* 2016; 375:2293-7.
- [19]. Mentz RJ, Hernandez AF, Berdan LG, Rorick T, O'Brien EC, Ibarra JC, et al. Good clinical practice guidance and pragmatic clinical trials: Balancing the best of both worlds. *Circulation* 2016; 133:872-80.
- [20]. Klonoff DC. The Expanding Role of Real-World Evidence Trials in Health Care Decision Making. *J Diabetes Sci Technol*. 2020 Jan;14(1):174-179. doi: 10.1177/1932296819832653. Epub 2019 Mar 6. PMID: 30841738.
- [21]. Lyman GH, Kuderer NM. Randomized Controlled Trials Versus Real-World Data in the COVID-19 Era: A False Narrative. *Cancer Invest*. 2020 Nov;38(10):537-542.
- [22]. Kim HS, Lee S, Kim JH. Real-world Evidence versus Randomized Controlled Trial: Clinical Research Based on Electronic Medical Records. *J Korean Med Sci*. 2018 Aug;33(34):e213. <https://doi.org/10.3346/jkms.2018.33.e213>
- [23]. Baumfeld Andre E, Reynolds R, Caubel P, Azoulay L, Dreyer NA. Trial designs using real-world data: The changing landscape of the regulatory approval process. *Pharmacoepidemiol Drug Saf*. 2020 Oct;29(10):1201-1212. doi: 10.1002/pds.4932. Epub 2019 Dec 10. PMID: 31823482; PMCID: PMC7687110.
- [24]. Klonoff DC. The New FDA Real-World Evidence Program to Support Development of Drugs and Biologics. *J Diabetes Sci Technol*. 2020 Mar;14(2):345-349. doi: 10.1177/1932296819832661. Epub 2019 Mar 12. PMID: 30862182; PMCID: PMC7196856.
- [25]. Zhu M, Sridhar S, Hollingsworth R, Chit A, Kimball T, Murmello K, Greenberg M, Gurunathan S, Chen J. Hybrid clinical trials to generate real-world evidence: design considerations from a sponsor's perspective. *Contemp Clin Trials*. 2020 Jul;94:105856. doi: 10.1016/j.cct.2019.105856. Epub 2019 Oct 24. PMID: 31669449.
- [26]. Patsopoulos NA. A pragmatic view on pragmatic trials. *Dialogues Clin Neurosci*. 2011;13(2):217-24. doi: 10.31887/DCNS.2011.13.2/npatsopoulos. PMID: 21842619; PMCID: PMC3181997.
- [27]. Martina R, Jenkins D, Bujkiewicz S, Dequen P, Abrams K; GetReal Workpackage 1. The inclusion of real world evidence in clinical development planning. *Trials*. 2018 Aug 29;19(1):468. doi: 10.1186/s13063-018-2769-2. PMID: 30157904; PMCID: PMC6116448.
- [28]. Jahanshahi, M., Gregg, K., Davis, G. et al. The Use of External Controls in FDA Regulatory Decision Making. *Ther Innov Regul Sci* 55, 1019–1035 (2021). <https://doi.org/10.1007/s43441-021-00302-y>
- [29]. Fang Y, Zhang H, Xie J, Lin M, Ying L, Pang P, Ji W. Sensitivity of chest CT for COVID-19: comparison to RT-PCR. *Radiology*. 2020 Aug;296(2):E115-7.
- [30]. Raptis CA, Hammer MM, Short RG, Shah A, Bhalla S, Bierhals AJ, Filev PD, Hope MD, Jeudy J, Kligerman SJ, Henry TS. Chest CT and coronavirus disease (COVID-19): a critical review of the literature to date. *American Journal of Roentgenology*. 2020 Oct;215(4):839-42.

- [31]. Cozzi A, Schiaffino S, Arpaia F, Della Pepa G, Tritella S, Bertolotti P, Menicagli L, Monaco CG, Carbonaro LA, Spairani R, Paskeh BB. Chest x-ray in the COVID-19 pandemic: Radiologists' real-world reader performance. *European journal of radiology*. 2020 Nov 1;132:109272.
- [32]. Wang Z, Deng H, Ou C, Liang J, Wang Y, Jiang M, Li S. Clinical symptoms, comorbidities and complications in severe and non-severe patients with COVID-19: A systematic review and meta-analysis without cases duplication. *Medicine (Baltimore)*. 2020 Nov 25;99(48):e23327.
- [33]. G. Lippi, J. Wong, B.M. Henry, Hypertension and its severity or mortality in Coronavirus Disease 2019 (COVID-19): a pooled analysis, *Pol Arch Intern Med* (2020), <https://doi.org/10.20452/pamw.15272>.
- [34]. W.J. Guan, Z.Y. Ni, Y. Hu, W.H. Liang, C.Q. Ou, J.X. He, L. Liu, H. Shan, C.L. Lei, D.S.C. Hui, B. Du, L.J. Li, G. Zeng, K.Y. Yuen, R.C. Chen, C.L. Tang, T. Wang, P. Y. Chen, J. Xiang, S.Y. Li, J.L. Wang, Z.J. Liang, Y.X. Peng, L. Wei, Y. Liu, Y.H. Hu, P. Peng, J.M. Wang, J.Y. Liu, Z. Chen, G. Li, Z.J. Zheng, S.Q. Qiu, J. Luo, C.J. Ye, S.Y. Zhu, N.S. Zhong, Clinical Characteristics of Coronavirus Disease 2019 in China, *N Engl J Med* 382 (2020) 1708–1720, <https://doi.org/10.1056/NEJMoa2002032>.
- [35]. Group TR. Dexamethasone in hospitalized patients with Covid-19—preliminary report. *The New England journal of medicine*. 2020 Jul 17.
- [36]. Zhou P, Yang X-L, Wang X-G, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature*. 2020;579(7798):270–273.
- [37]. Tao Y, Tang LV, Hu Y. Treatments in the COVID-19 pandemic: an update on clinical trials. *Expert Opinion on Emerging Drugs*. 2020 Apr 2;25(2):81-8.
- [38]. Mancilla-Galindo J, García-Méndez JÓ, Márquez-Sánchez J, Reyes-Casarrubias RE, Aguirre-Aguilar E, Rocha-González HI, Kammar-García A. All-cause mortality among patients treated with repurposed antivirals and antibiotics for COVID-19 in Mexico City: A real-world observational study. *EXCLI journal*. 2021;20:199.
- [39]. Zhu Z, Lu Z, Xu T, et al. Arbidol monotherapy is superior to lopinavir/ritonavir in treating COVID-19. *J Infect*. 2020. DOI:10.1016/j.jinf.2020.03.060
- [40]. Deng L, Li C, Zeng Q, et al. Arbidol combined with LPV/r versus LPV/r alone against corona virus disease 2019: a retrospective cohort study. *J Infect*. 2020. DOI:10.1016/j.jinf.2020.03.002.
- [41]. Million M, Gautret P, Colson P, Roussel Y, Dubourg G, Chabriere E, Honore S, Rolain JM, Fenollar F, Fournier PE, Lagier JC. Clinical efficacy of chloroquine derivatives in COVID-19 infection: comparative meta-analysis between the big data and the real world. *New microbes and new infections*. 2020 Nov 1;38:100709.
- [42]. Singh S, Khan A, Chowdhry M, Chatterjee A. Outcomes of hydroxychloroquine treatment among hospitalized COVID-19 patients in the United States-real-world evidence from a federated electronic medical record network. *MedRxiv*. 2020 Jan 1.
- [43]. Annie FH, Sirbu C, Frazier KR, Broce M, Lucas Jr BD. Hydroxychloroquine in Hospitalized Patients with COVID-19: Real-World Experience Assessing Mortality. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy*. 2020 Nov;40(11):1072-81.
- [44]. Soto-Becerra P, Culquichicón C, Hurtado-Roca Y, Araujo-Castillo RV. Real-world effectiveness of hydroxychloroquine, azithromycin, and ivermectin among hospitalized COVID-19 patients: results of a target trial emulation using observational data from a nationwide healthcare system in Peru. *Azithromycin, and Ivermectin Among Hospitalized COVID-19 Patients: Results of a Target Trial Emulation Using Observational Data from a Nationwide Healthcare System in Peru*. 2020 Jan 1.
- [45]. Rattanaumpawan P, Jirajariyavej S, Lerdlamyong K, Palavutitotai N, Saiyarin J. Real-world experience with favipiravir for treatment of COVID-19 in Thailand: Results from a multi-center observational study. *MedRxiv*. 2020 Jan 1.
- [46]. Wang Y, Zhang D, Du G, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. *Lancet*. 2020. 395(10236):1569–1578.

- [47]. Flisiak R, Zarebska-Michaluk D, Berkan-Kawinska A, Tudrujek-Zdunek M, Rogalska M, Piekarska A, Kozielowicz D, Klos K, Rorat M, Bolewska B, Szymanek-Pasternak A. Remdesivir-based therapy improved recovery of patients with COVID-19 in the SARSTER multicentre, real-world study. medRxiv. 2020 Jan 1.
- [48]. Yao TT, Qian J-D, Zhu W-Y, et al. A systematic review of lopinavir therapy for SARS coronavirus and MERS coronavirus-A possible reference for coronavirus disease-19 treatment option. J Med Virol. 2020;92(6):556–563.
- [49]. Shen C, Wang Z, Zhao F, et al. Treatment of 5 critically ill patients with COVID-19 with convalescent plasma. JAMA. 2020;323(16):1582–1589.
- [50]. Duan K, Liu B, Li C, et al. Effectiveness of convalescent plasma therapy in severe COVID-19 patients. Proc Nat Acad Sci. 2020;117 (17):9490–9496.
- [51]. Kumar RN, Wu EL, Stosor V, Moore WJ, Achenbach C, Ison MG, Angarone MP. Real-World Experience of Bamlanivimab for COVID-19: A Case-Control Study. Clinical Infectious Diseases: an Official Publication of the Infectious Diseases Society of America. 2021 Apr 13.
- [52]. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395 (10223):507–513.
- [53]. Ramaswamy M, Mannam P, Comer R, Sinclair E, McQuaid DB, Schmidt ML. Off-label real world experience using tocilizumab for patients hospitalized with COVID-19 disease in a regional community health system: a case-control study. medrxiv. 2020 Jan 1.
- [54]. Vikse J, Henry BM. Tocilizumab in COVID-19: beware of risk of intestinal perforation. Int J Antimicrob Agents. 2020. DOI:10.1016/j.ijantimicag.2020.10.6009.
- [55]. Antinori S, Bonazzetti C, Gubertini G, et al. Tocilizumab for cytokine storm syndrome in COVID-19 pneumonia: an increased risk for candidemia? Autoimmun Rev. 2020. DOI:10.1016/j.autrev.2020.102564. Epub ahead of print.
- [56]. Tritschler T, Mathieu ME, Skeith L, Rodger M, Middeldorp S, Brighton T, Sandset PM, Kahn SR, Angus DC, Blondon M, Bonten MJ. Anticoagulant interventions in hospitalized patients with COVID-19: A scoping review of randomized controlled trials and call for international collaboration. Journal of thrombosis and haemostasis. 2020 Nov;18(11):2958-67.
- [57]. Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 Vaccine. N Engl J Med. 2021;384(5):403-416.
- [58]. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and efficacy of the BNT162b2 mRNA COVID-19 Vaccine. N Engl J Med. 2020;383(27):2603-2615.
- [59]. Pawlowski C, Lenehan P, Puranik A, Agarwal V, Venkatakrishnan AJ, Niesen MJ, Horo JC, Badley AD, Halamka J, Soundararajan V. FDA-authorized COVID-19 vaccines are effective per real-world evidence synthesized across a multi-state health system. MedRxiv. 2021 Jan 1.
- [60]. Chodcik G, Tene L, Patalon T, Gazit S, Ben-Tov A, Cohen D, Muhsen K. The effectiveness of the first dose of BNT162 b 2 vaccine in reducing SARS-CoV-2 infection 13-24 days after immunization: real-world evidence. Medrxiv. 2021 Jan 1.
- [61]. Jabal KA, Ben-Amram H, Beiruti K, Batheesh Y, Sussan C, Zarka S, Edelstein M. Impact of age, ethnicity, sex and prior infection status on immunogenicity following a single dose of the BNT162b2 mRNA COVID-19 vaccine: real-world evidence from healthcare workers, Israel, December 2020 to January 2021. Eurosurveillance. 2021 Feb 11;26(6):2100096.

Table 1: Differences between RCTs and RWE

Variables	RCTs	RWE
Purpose	Efficacy	Effectiveness
Protocol vs. care driven	Protocol, compliance with GCP mandatory	Usually care, results derived from clinical practice.
Setting	Experimental setting	Real-world setting
Follow up	Designed, Short-term follow-up durations	In actual practice, long-term follow-up
Treatment	Fixed pattern	Variable pattern
Study Group	Homogeneous	Heterogeneous
Attending Physician	Investigator	Many practitioners
Comparator	Placebo/selective alternative interventions	Many alternative interventions
Randomizing and blinding	Required	Not required
Patient Monitoring	Continuous, per protocol	Changeable
Result	Lower external validity and higher internal validity	Higher external validity and lower internal validity

Table 2: Strength and Limitations of RCTs and RWE²⁰⁻²²

RWE	RCTs
Strength	
Less time and cost	More time and cost
Duration of clinical research can be shortened	Duration of clinical research cannot be shortened
No period is required for patient recruitment/enrollment	Time period is required for patient requirement/enrollment
Research can be safely carried on high-risk groups	Research cannot be safely carried on high-risk groups
RWE can uncover rare unforeseen problems better for low event rate outcomes	It's not much better than RWE
Limitations	
Massive amount of data is required for correct analysis	A massive amount of data is not required
More time is required for data quality management.	Comparatively, less time is required for data quality.
Lack of privacy/confidentiality/lost data	Privacy/Confidentiality is maintained, and lost data can be retrieved
Patients are highly diverse.	Limited by strict inclusion and exclusion criteria
High possibility of bias due to unrecognized confounders	Low possibility of bias

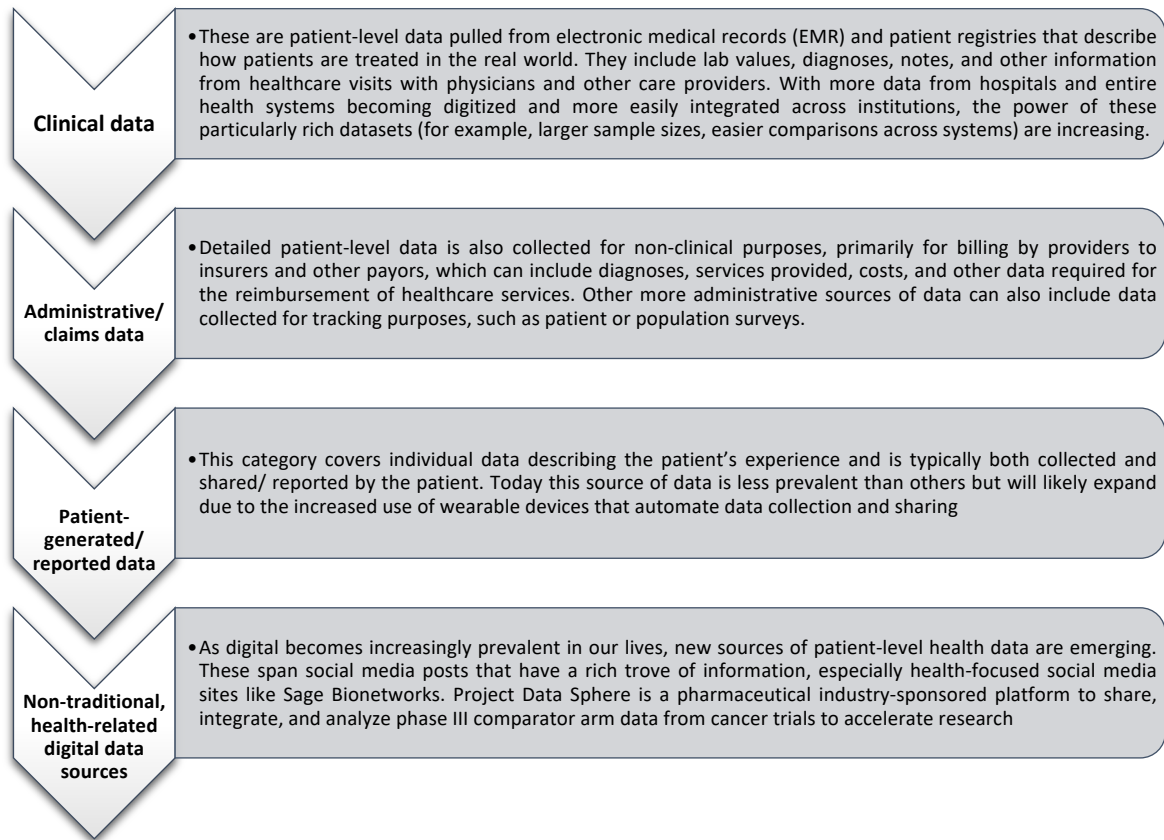


Figure: 1 Various source of RWE data

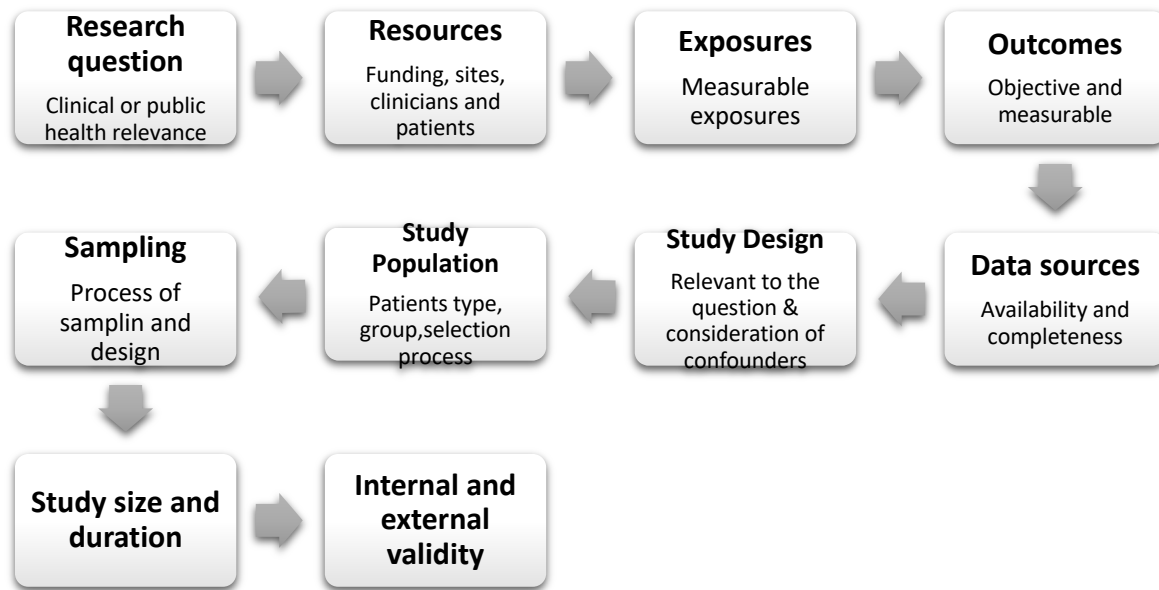


Figure 2: Plan of real-world evidence study