# Hybrid studies and other approaches to generate real world evidence

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**Abstract**

*Real world evidence (RWE) studies serve many purposes and are creating new opportunities for evidence generation in drug development. The demand for RWE is growing and is unlikely to subside as healthcare decision makers become increasingly aware of what it offers. With the rise of electronic medical records (EMRs), new hybrid approaches are evolving to cross-link data and close knowledge gaps. The landscape for RWE studies will be changing dramatically over the next few years as EMRs become more accessible. There are numerous hybrid designs to generate RWE insights. This article explores some of these, with a focus on hybrid EMR and database studies.*

## Introduction

Real world evidence (RWE) research is an important component of biopharmaceutical product development and commercialisation. RWE of safety, effectiveness, and value is necessary to achieve successful market access and product uptake. In addition to robust early development clinical trial programmes, payers and other key stakeholders, such as patients, physicians and caregivers, demand evidence of benefits and risks in a real-world setting. A regulatory authority may require post-approval research or monitoring to determine real-world safety, due to concerns about a product's safety when it becomes widely prescribed, while payers may require validation of a product's real-world clinical value and cost-effectiveness to determine optimal formulary positioning.

Compared with clinical trial data, RWE data more closely describe how the product will perform in a broader, more representative population over a longer timeframe, and provides information on comparators and outcomes that are not part of a clinical trial protocol.[1] With the growing need for information on real-world effectiveness and safety, real-world research has become an area of methodological innovation to reduce cost and facilitate time-efficient gathering of information. This article will focus on hybrid RWE studies.

## Understanding real world evidence

RWE studies serve many purposes and are creating new opportunities for evidence generation in drug development. With the European Medicines Agency guidance requiring the collection of risk-benefit data in post-authorisation safety studies[2], pharmaceutical companies must take a more granular approach, examining different subpopulations to determine their respective risk– benefit balance. There is also an increasing demand from payers to conduct observational studies on a new product's effectiveness, and payers and clinicians are eager for more detailed health outcomes data to inform prescribing and reimbursement decisions.[3]

RWE studies are most common in peri- and post-approval settings. Peri-approval designs contribute to the characterisation of burden of illness and unmet need, which are essential to better understand the potential clinical, humanistic, and health economic impact of a novel treatment or device. These studies also serve as important inputs to health economic models and evaluations necessary for reimbursement. Post-approval studies are important for ongoing value demonstration, evaluations of comparative effectiveness and monitoring of drug safety.

Traditional methods of evaluating real-world data include, but are not limited to, retrospective analyses of administrative claims, review and abstraction of medical records and prospective longitudinal studies, such as disease and treatment registries. Although each of these methodologies is associated with a unique set of strengths, practical challenges may be encountered, and data gaps may remain due to certain associated methodological limitations. For example, administrative claims databases have not typically been developed for research purposes and often do not contain clinical variables of interest. Moreover, site-based reviews of medical records can be labour-intensive, especially in the absence of electronic medical records. Registries, although comprehensive in data collection scope, typically require years to complete and are expensive to set up and run.

RWE can be divided into primary data, collected specifically for research purposes, and secondary data, collected for other purposes. Primary data are generally obtained from study-specific case report forms, electronic medical and health records, or clinical outcome assessments. These data are collected in interventional phase IV studies and in non-interventional prospective studies, patient registries, and health surveys. Meanwhile, secondary data are often obtained from medical record reviews, registries or insurance claims databases, and are used in retrospective database studies or as an input into prospective or hybrid studies.[4]

Trials of interventions are described as either pragmatic or explanatory. Explanatory trials generally measure efficacy, the benefit a treatment produces under ideal conditions, often using carefully defined subjects in a controlled research setting. These specialised studies recruit as homogeneous a population as possible and aim primarily to further scientific knowledge.[5]

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By contrast, pragmatic clinical trials measure effectiveness, the benefit the treatment produces in routine clinical practice, and are carried out after product approval. A pragmatic trial reflects variations between patients that occur in real clinical practice and aims to inform choices between treatments. These trials should represent patients to whom the treatment will be applied, and test whether an intervention works in real-world circumstances. Pragmatic trials offer a scientific method of research for policymakers and clinicians, and serve as RWE sources for decisions, such as for funding, regulations, policy, and organisational changes.[6]

### Rise of hybrid RWE studies

To understand outcomes fully, traditional data collection will only take us so far. Often, there is no single truth standard when it comes to the evidence used to support medical decisions. In today's drug development environment, sound clinical choices can only be made based on a 'mosaic' of information of various precision and certainty. The evidence continuum includes RWE, findings gleaned from rigorous trials, and a lot of evidence constructs in between.

Hybrid study designs that aim to generate high quality data, collected in a rapid and time-efficient manner, may be an option when more traditional approaches are not suitable. They require a strategic approach for the development of optimal study designs to address research questions that warrant multiple data sources to combine retrospective and prospective data, including primary or secondary sources of RWE. With the rise of electronic medical records (EMRs), new hybrid approaches are evolving to cross-link data and close knowledge gaps. For example, secondary data from anonymised EMRs can be enriched with primary data from physicians and patients. There are numerous hybrid designs to generate real-world evidence insights. We explore some of these herein, with a specific focus on hybrid EMR and database studies.

### Hybrid studies using EMRs and databases

Drug developers have long considered randomised controlled trials (RCTs) to be the gold standard in clinical research. However, RCTs are simply not well suited to answer all research questions. Although RCTs provide the strongest evidence for efficacy of a treatment, real world studies provide an ideal way to study effectiveness, i.e., how a treatment works in actual practice. With the recent upsurge of EMRs, real world studies that leverage existing medical and healthcare administrative data have become practical tools for getting actionable answers to clinical questions, including safety outcomes and many other endpoints.

Hybrid study designs that examine both EMR data and survey data are an innovative way to maximise the potential of real world databases. Such approaches incorporate not only passive data collection via EMRs, but also active data collection via other studies, eg, cross-sectional (survey) and prospective studies. Such designs have broad application, such as the assessment of practice patterns, patient experiences, and outcomes in physician offices.

In the hybrid model, patients can be identified in the EMR database and invited to participate. As these patients go online to register and provide consent, baseline survey information can be collected from sites about characteristics of the patients and providers. Prospective information can be gathered via surveys from healthcare providers, and EMR data can be continually assessed to determine if new patients qualify for study inclusion.

One key advantage of this approach over registries is that it reduces the research burden at the site and provides cross-validation of what the patient reports and what the physician reports, therefore enhancing the strength of EMR data. Furthermore, a "look-back" period can be incorporated to lessen overall study duration and facilitate time and cost efficiencies. Data about real world patient experience also has the potential to improve the quality and delivery of medical care, reduce overall costs, and improve outcomes by accelerating the understanding of how best to incorporate new therapies and technologies into everyday clinical practice. Essentially, these data help fill the knowledge gap between clinical trials and actual clinical practice.

Access to existing high quality clinical data is increasingly in demand. However, there are a number of issues that confound the collection of these data. Payers are increasingly asking for more evidence of cost-effectiveness that applies to the real world. Availability of these data is, however, contingent upon a product being reimbursed and prescribed. In addition, the quality of real world databases from country to country is also mixed. Those that exist are often incomplete across different healthcare sectors. For example, many are focused on general practitioners or hospitals, but rarely does one database cover all the different settings that play a role in medical treatment. Moreover, a database may not be available for the specific research objectives of interest or the existing data may be incomplete. Another challenge is free-form text entry, which often makes key information difficult to extract from a database. As such, EMR databases may show medicines that have been prescribed, but were not necessarily dispensed, or a database may include the start date of a treatment, but not the end date.

Still, even given these limitations, it is expected that these data sources will be increasingly available globally over the next decade as interest in real world databases continues to grow. This growth is driven by a number of factors. First, there is a recognised need for more timely and cost-effective research approaches, and it is now widely understood that real world data is an essential component of evidence-based medicine. Further, technological advances and common data standards are enabling integration of disparate data sets. Scientific methods are growing in their sophistication to allow valid conclusions from real world database studies. Adoption of EMRs to support healthcare is accelerating, and much of this will be driven by government financial incentives and legislation. New standards evolving out of these acts will allow for common data elements across EMR systems.

With the expected surge in EMR growth globally, we can expect to see increased interest in novel approaches to use real world data to supplement RCT data, providing a more holistic perspective on a drug's true efficacy and effectiveness. The landscape for real world studies will be changing dramatically over the next decade as EMRs become more accessible, and it may be that we can execute most of our studies by recruiting patients via social media and online patient

communities, obtaining informed consent online, and combining EMR data with patient/provider surveys and so forth.

### Cluster clinical trials

Although not purely RWE, in a cluster randomised trial (CRT), groups of subjects, rather than individual subjects, are randomised to receive one of the interventions being studied. Clusters may include provider practices, families, schools, clinics, health plans, towns, and others. An example of the application of a CRT is in the assessment of health promotion programmes, where it is problematic to design a study in which one member of a cluster (eg, a town, a community, or a patient in a group practice) can be exposed to the full impact of a programme while another member would have no exposure. A CRT can provide a way to better approximate the real world setting for drug or programme combinations. With the increased interest in pragmatic clinical trials, comparative effectiveness research and community health promotional activities, the use of CRTs has been growing.[6]

### Roll-over registries

In roll-over registries, patients who participated in clinical trials used for regulatory submissions are "rolled over" into post-approval registries. Roll-over studies provide continued treatment and assessment of long-term effectiveness and safety follow up in patients receiving recently approved drugs.

### Registry-based prospective RCTs

There are specific issues inherent to observational studies. In an observational database study, the assignment of treatment is not random. This means there may be varying severity of illness between patients who receive different treatments, which limits what we can infer in terms of treatment comparisons and outcomes. Although randomisation controls known and unknown differences between groups, databases do not. Statistical methods, such as propensity score matching and instrumental variable analysis can help provide balance and compare like-to-like patients, but there is still work to be done in this area.

Database or registry-based prospective randomised clinical trials (RRCTs) combine the advantages of randomisation and observational study methods. With a 'pragmatic' goal, these studies aim to ensure high generalisability of the results, ie, external validity, while the explanatory aspect of the design, through randomisation to reduce bias, confounding and effect modification, enhances internal validity. Compared with RCTs, RRCTs afford simplified regulatory procedures and ethics committee approval, are inexpensive to conduct, and promote the adoption of evidence into practice.

### Conclusions

Database analysis has its own unique set of challenges but, when used appropriately, is an excellent tool that supplements RCT and prospective observational study data to provide a more comprehensive picture of efficacy and effectiveness. Innovative hybrid study designs that leverage routine data sources are quickly capturing the interest of drug developers. Healthcare providers, and national and local payers are using real world databases to provide quality and outcomes measurement to drive the most value for their patient populations.

The outlook for RWE generation – standalone or in conjunction with clinical trials – is promising, with the potential to improve health outcomes and cost-effectiveness of new therapies. The demand for RWE is growing and is unlikely to subside as healthcare decision-makers become increasingly aware of what it offers. Biopharmaceutical companies and clinical research organisations (CROs) need to stay at the forefront of developments in RWE, data sources, analytic techniques and study methodologies to ensure they are able to optimise patient access and formulary placement of new products.

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Optimal product positioning and market uptake requires a thoughtful multi-year and multi-dimensional strategy that culminates in an evidence base, which will facilitate product coverage, reimbursement, and adoption. To meet the increasing demand for RWE studies, sponsors and CROs are ramping up their capabilities in this growing area of interest. Many are forming partnerships and building capabilities to leverage the opportunities offered by RWE. Novel study designs and methods are critical in sponsors' ability to adapt, and complementary approaches to evidence development are necessary to gaining the bigger picture of a product profile and to address different stakeholder requirements. Hybrid designs bring new opportunities for robust, more rapid evidence development at lower cost. Each approach (RCTs, prospective observational and retrospective database studies) has unique strengths and weaknesses. By using a combination of these approaches and leveraging the ability to supplement any missing information with existing data from routine sources such as EMR, researchers can fill evidence gaps more efficiently and effectively.

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