WHITE PAPER

Transforming clinical trial design and execution

Harnessing the power of real-time technologies and data

Part two of a three-part series on decentralized clinical trials

Contents

The paradigms of clinical trial execution are evolving rapidly as pharma companies embrace the ideas of decentralized, remote and virtual clinical trials. These concepts are explored in Part 1 of this series and play an increasingly important role in the current paradigm of trial execution – and will continue to do so in the future.

In Part 2 of this series, we explore the concept of real-world data in clinical trials. As noted by **Mark Lambrecht, PhD**, Director of the EMEA and APAC Health and Life Sciences Practice at SAS, "This next wave of clinical trial design will combine the best of both worlds: the gold standard randomized controlled trials (RCTs) and the ability to adapt the design based on real-world data."

The **FDA defines RWD** as "… the data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources." Another way to understand RWD is that it's all health-related data that doesn't come from an RCT. RWD can come from electronic health records, claims, bills and digital patient-generated data from sensors – both in the office and remotely when patients are at home and work. The evidence generated from this data regarding using a medical product and its potential benefits or risks is called real-world evidence (RWE). RWE can come from many sources, such as randomized, simple and pragmatic trials and observational studies – all of which can include wearable sensors.

Real-world data and real-world evidence play a greater role in health care decisions than ever before. For example, according to the **FDA**:

- The FDA uses RWD and RWE to monitor post-market safety and adverse events of drugs. This data is used to make regulatory decisions for drugs.
- The health care industry uses RWD and RWE to make insurance coverage decisions and to create guidelines and decision support tools for physicians and other direct care providers.
- Developers of medical products are using RWD and RWE to design clinical trials, from large simple trials and pragmatic clinical trials to observational studies used to develop novel treatments.

RWE is powerful but not a panacea

RWE is not a magic formula that solves all the information gaps in clinical trials. But when collected to gather more meaningful and observational data about the trial recruits, it can help advance the understanding of a therapy. Digital technology such as wearables or adherence-measuring techniques might tell us whether the patient dose is correct, provide greater confidence about the optimal dose or shed light on possible adverse events and interactions with concomitant medications. In the case of COVID-19, RWD from sources such as electronic health records, claims, patient forums and digital technology is used to **monitor vaccine safety and effectiveness** by the **US FDA**, **EMA** and other regulatory authorities such as the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan and the National Medical Products Administration (NMPA) in China.

RWE: An important tool to improve the planning and conduct of clinical trials

Designing effective clinical trials is a complex process that starts with generating a hypothesis and defining the target patient cohort for the trial. This process can be lengthy and iterative, requiring inputs from many stakeholder groups and data sources. RWD has become essential to more accurately exploring target patient populations and informing robust initial trial hypotheses.

When used effectively during trial feasibility assessments, RWD enables organizations to create more patient-centric protocols. As a result, they can identify and reduce operational risk and development costs while increasing the likelihood of regulatory approval. This, in turn, accelerates the successful launch of new treatments to patients.

The primary tools used to generate a clinical trial hypothesis include:

- Published findings from previous trials conducted in the patient population of interest.
- Primary chart review studies that may be costly and resource-intensive.

While these tools can be useful, their depth and breadth are limited, especially when focusing on a rare disease or subpopulation. This will likely become even more challenging, given the increasing movement toward precision medicine and targeted cohorts. Using RWD enables researchers to explore actual populations and their behavior and outcomes in near-real time. They can also test hypotheses rapidly to determine clinical relevance along with the care and treatment pathways of the desired cohort. Expanding on those capabilities, researchers can even model a clinical trial by applying predictive analytics. Machine learning removes the need for researchers to test hypotheses manually and shortens the time from hypothesis generation to optimized trial design.

The expanded availability of RWD sources – and encouragement by regulators to use it – suggests that using RWD to optimize eligibility criteria and recruitment may become the "new normal" across the clinical trials enterprise. The benefits include:

- Increasing efficiency in clinical trials.
- Expanding clinical trial access by broadening eligibility criteria.
- Reducing patient and site burden.
- Improving diversity and representation in clinical research.
- **Speeding** up the development and availability of new medical treatments.

Clinical Trials Transformation Initiative (CTTI)

Based on research and the collaboration of experts and key stakeholders across the clinical trials ecosystem, the CTTI created recommendations, resources and case studies for using RWD to evaluate trial eligibility criteria and recruit potential research participants. The work promotes greater awareness and appropriate use of RWD sources in clinical trials planning. **This approach** is often a low-risk, high-reward way to bring increased efficiency, shorter timelines and better patient access to research efforts.

Using RWE as synthetic control arms

In the context of an **RCT**, a control group is used to understand how patients with similar characteristics and experiences within a treatment group will fare without receiving the experimental treatment. However, in some cases, ethical concerns or feasibility challenges make RCTs impossible. In these cases, external control arms, where RWD is used to create the control arm, are increasingly accepted.

What are synthetic control arms?

According to the report, **Real-world evidence to support regulatory decision-making for medicines: Considerations for external control arms,** "External control arms are also called 'synthetic' control arms as they are not part of the original concurrent patient sample that would have been randomized into the experimental or the control treatment arms as in a traditional RCT. External controls can take many forms. For example, external control arms can be established using aggregated or pooled data from placebo/control arms in completed RCTs or using RWD and pharmacoepidemiological methods."

When standardized control data is pulled from historical RCTs to create an external control arm, the result is still a nonrandomized comparison. This can impact the diversity of the trial since clinical trial participants may share similarities. For this reason, using RWE can improve the representation of more diverse patient populations and help increase the external validity of the trial. "Depending on the regulatory and clinical context, RWE generated from external controls can serve as real-world benchmarks (rather than as 'formal' comparators) or real-world comparators," **the report** concludes.

Realizing the benefits

Using synthetic control arms helps pharmaceutical companies conduct clinical trials when feasibility and ethical concerns prevent RCTs. They can also be used to support marketing claims and label expansions, as noted in a **recent report**. It concludes, "By reducing or eliminating the need to enroll control participants, a synthetic control arm can increase efficiency, reduce delays, lower trial costs and speed lifesaving therapies to market."

A new regulatory framework?

The growing emphasis on the role of RWE in regulatory agency decision making has fueled a new optimism to achieve these goals and provided an impetus for a **new regulatory framework** and the **HMA/EMA Big Data Task Force**. In the APAC region, Japan PMDA published ***Basic Principles on Utilization of Registry for Applications*** in May 2021 to discuss registry data used as an external control. China NMPA issued the ***Guidelines for Real-World Evidence to Support Drug Development and Review*** in January 2022 to guide and standardize the use of real-world evidence in drug development.

Regulatory agencies' acceptance of external control arms to support specific regulatory decisions may differ across therapeutic areas and clinical contexts. Several disease areas can uniquely benefit from using RWD in establishing external controls, given the randomization-based challenges associated with investigating rare diseases or diseases with high unmet needs. Given the ever-increasing number of patient subpopulations defined by specific genetic mutations or biomarkers, using RWD to establish external controls is particularly important. For example:

- The drug, blinatumomab, received label expansion for patients with MRD-positive acute lymphoblastic leukemia based on RWD.
- Eteplirsen received **accelerated approval** for patients with Duchenne muscular dystrophy.

Traditional versus pragmatic: Changing the trial model with RWE

Over the last 50 years, we've seen an amazing increase in the number of therapeutic agents available to the clinician. The randomized, controlled trial has been the anchor to proving a new drug's initial efficacy and safety during this period.

The RCT attempts to reduce variability between groups, decrease confounders and ensure equipoise. This has resulted in the need for smaller sample sizes to show a positive drug effect. A randomized controlled trial is a well-controlled efficacy trial designed to determine, under experimental conditions, whether an intervention (such as a drug) produces a reproducible result under optimal conditions.

Since the mid-2000s, we've seen an exponential increase in smaller clinical trials used to assess a medical treatment's clinical efficacy and safety. Still, this increase has come at a cost. RCTs are **time-consuming, expensive and may not accurately represent** the entire patient population.

In contrast, the pragmatic RCT (pRCT) is a type of effectiveness or pragmatic trial that measures the potential beneficial result of an intervention, such as a drug, in real-world conditions. When testing the RCT (efficacy) and pRCT (effectiveness) of an intervention or drug, the intervention is evaluated in a pragmatic-explanatory continuum that expands the potential generalizability of a positive response.

Instead of just more or larger RCTs, more real-world experience and analysis before and at the time of drug approval might detect adverse events earlier (even before the release of the drug). Drug adherence is another important variable that can affect the actual efficacy of a drug when used in a real-world setting. The RCT may have higher drug adherence rates than would be seen in real-world use because the drug is provided, and a kind of "Hawthorne effect" could occur with the constant encouragement of investigators and research staff.

Real-world data, such as that from a pRCT, is another layer of effectiveness data; the intent is not to replace the RCT or efficacy data but rather to provide a more comprehensive evaluation of a drug. Before or after drug approval, real-world observational studies can also help address efficacy and side effects, including potential disease-drug and drug-drug interactions. If designed correctly, they can evaluate drug-use adherence and provide a comprehensive side effect profile.

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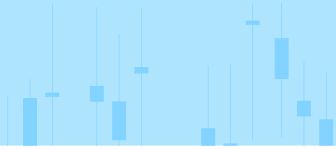

Real-world examples of success

The world's first large-scale pragmatic trial and well-published example of pRCT is the Salford Lung Study (SLS) for COPD and asthma. According to the report, ***The SLS: a pioneering comparative effectiveness approach to COPD and asthma in clinical trials***, the study "evaluates a therapy in a 'real-world' setting with drug-use adherence rates, side effects, comorbidities and effectiveness that reflect use in a real population."

Similarly, **Johnson & Johnson's long-acting antipsychotic Invega Sustenna®** was part of a randomized, pragmatic, **real-world trial**, known as the PRIDE study, that used measures collected in clinical practice. Participants who received this long-acting injection typically saw a six-month delay in the relapse of their schizophrenia symptoms compared to those who were given a mix of seven antipsychotic pills.

Pragmatic trials are gaining traction with researchers

Pragmatic trials (such as the SLS study) are becoming more popular for several reasons. First, the generated data helps ensure that the trials are relevant, include the right patients and gather evidence from clinical aspects, patient outcomes, economic relevance and impact on quality-of-life parameters. And second, the RWE captured during a pragmatic trial contains a treasure trove of insights about the subjects, which can aid in closing the RCT implementation gap.

The real-world pRCT is likely to become more common in large, organized health care systems built around integrated pharmacies and EMR systems. The pRCT provides evidence of drug safety and effectiveness outside an RCT. When primary and secondary caregivers, pharmacies, hospitals, home nurses and social workers are all on the same electronic record, studies become relatively inexpensive when evaluating a drug therapy or other interventions in a real-world environment.

Don't force the pragmatic approach

Pragmatic trials have clear advantages in certain environments, but the approach is unrealistic for many trials.

According to Ian Ford, PhD and John Norrie, M. Sc., authors of the New England Journal of Medicine article, "**Pragmatic Trials**," "Some trials need not be forced to be pragmatic, and others will naturally have pragmatic features because of the nature of the intervention and the health care context in which the trials are conducted. Very few trials can be fully pragmatic. Trials of truly novel interventions can be game changers without being particularly pragmatic. No single trial, pragmatic or otherwise, is likely to answer all potential questions about the value of any health care technology."

To illustrate, consider one particular study type identified in the US FDA RWE framework: **the hybrid design**, which integrates a traditional, randomized controlled trial with pragmatic design aspects to collect real-world patient data. This design preserves the benefit of randomization, provides real-world outcome data while potentially accelerating product development, and lowers the cost of data collection and patient follow-up.

Learn more

Want to learn more? We invite you to read the other papers in this series:

- **Part 1:** ***Decentralized clinical trials: From evolution to revolution.***
- **Part 3:** ***The connected patient in decentralized clinical trials: Harnessing the power of real-time technologies and data.***

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