UBC

WHITE PAPER

Modern Approaches and Considerations for Designing Real-World Studies 2025

Novel study designs and emerging approaches to incorporate real-world data are helping to shape compelling value stories.

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Modernized Real-World Evidence Study Designs

In recent years, the proliferation of real-world data (RWD) — such as electronic health records, insurance claims, and patient-reported outcomes — coupled with advances in tokenization and data linkage, has created significant opportunities for the life science and the biopharmaceutical industries. As a result, real-world evidence (RWE) — the clinical insights derived from analyzing RWD — has gained increasing recognition for its value across the product life cycle. Today, RWE plays a critical role in supporting early clinical development, facilitating regulatory approval, guiding post-market surveillance, and sustaining value beyond the patent exclusivity period.

As RWE becomes more integrated into regulatory and development strategies, researchers are adopting a broader range of study designs that effectively leverage RWD. Typical RWE study designs include externally controlled trials, pragmatic studies, and non-interventional (observational) cohort studies.[1] Among these, external control arms are gaining particular traction in clinical research settings in which randomized, placebo-controlled trials may not be feasible due to practical or ethical constraints, such as in rare disease populations.

In response to the growing use of externally controlled trials, UBC published an article titled External Controls in Research: The "What, Why and How," which outlines key methodological considerations for designing and analyzing externally controlled trials. The article addresses validity concerns to minimize bias resulting from a lack of comparability between treatment and control arms.[2] It also provides examples of U.S. Food and Drug Administration/European Medicines Agency approvals that incorporated external controls in study designs used as supporting evidence.[2]

Beyond externally controlled trials and the other established RWE study designs briefly mentioned above, modern approaches are emerging that enable more robust data integration, broader patient representation, and more flexible study execution. These include tokenizing patient data and linking these data across datasets, which may encompass a variety of real-world sources, as well as clinical study data. When planning such studies, sponsors must first define the research questions they wish to answer and then determine the most appropriate study design, data sources, and analysis plans.

Building on these evolving approaches to RWE design and data integration, this white paper briefly revisits topics UBC explored in its 2023 version, including decentralized (direct-to-patient) study elements and registry-based studies enriched with additional RWD. In this updated edition, we present two new case studies that reflect more modern approaches: The first highlights a pragmatic study in which patient data were linked to RWD, while the second demonstrates the utility of linking a patient support program to RWD.

Definitions

- **Data analysis plan** is a structured framework outlining methods, statistical techniques, and procedures to process and analyze real-world data from sources such as registries or electronic health records to answer research questions, ensuring rigorous evidence generation for real-world evidence studies like cohort studies or pragmatic trials.
- **Decentralized (direct-to-patient) studies** collect data via digital tools (e.g., wearables, mobile apps) or remote methods, incorporating patient-reported outcomes and real-world data with flexible designs that align with modern real-world evidence approaches such as data linkage and diverse data sources.
- **Externally controlled trials** use control groups that either come from a different source population, are not observed concurrently, or both. In contrast, randomized clinical trials use control groups that are concurrently observed and randomly assigned from the same source population.[10]
- **Non-interventional (observational) cohort study** is a protocol-based investigation when the intervention of interest is given during routine clinical care, according to the clinician's judgement.[10]
- **Patient registries** are organized systems that use observational study methods to collect standardized clinical and other data from a population defined by a specific disease, condition, or exposure, followed over time to evaluate specified outcomes, including the safety of medicines.
- **Patient support programs** are sponsored by pharmaceutical companies to improve patient access and adherence to prescribed therapies.
- **Payers** are the groups that pay for or manage payment of medical care, medications, and patient support services. They typically include insurance companies, government health programs, employers, and other entities responsible for paying for healthcare.
- **Pragmatic studies** are often embedded within clinical practice and incorporate some secondary use of data collected as part of patients' routine clinical care.[10]
- **Providers** are healthcare professionals or healthcare organizations that are involved in the care of patients enrolled in patient support programs. They typically include physicians, nurses or home healthcare providers, clinics or hospitals, and pharmacists.
- **Randomized clinical trial** is a prospective study that randomly assigns participants from the same source population to intervention and control groups, conducted under controlled conditions to evaluate the efficacy and safety of a medical intervention, with concurrent data collection.[10]
- **Real-world data** are data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources[11] and may include claims, electronic health records, data from wearable devices, and other sources.
- **Real-world evidence** is the clinical evidence about the usage and potential benefits — or risks — of a medical product derived from the analysis of real-world data.[11]
- **Sponsor** is an entity — typically a pharmaceutical company, research institution, or government agency — responsible for initiating, funding, and overseeing a clinical study or real-world evidence research, ensuring compliance with regulatory and scientific standards.
- **Stakeholder** is an individual or group, such as patients, payers, providers, or sponsors, with an interest in the outcomes of real-world evidence studies, impacted by or contributing to the design, execution, or application of clinical research and data integration efforts.

Case Study 1: Incorporating Direct-to-Patient (decentralized) Study Design Elements

At the Summit for Clinical Ops Executives (SCOPE) in February 2023, UBC presented a case study on incorporating direct-to-patient, or decentralized, study design elements[3] — an approach that significantly expands the addressable patient population beyond the geographic limitations of traditional brick and mortar sites, and supports more diverse enrollment Figure 1 (below). Additional detail on decentralized approaches has been published in UBC's Decentralized Research Playbook to help sponsors plan, prioritize, and educate internal stakeholders on the design and execution of studies incorporating these elements.[4]

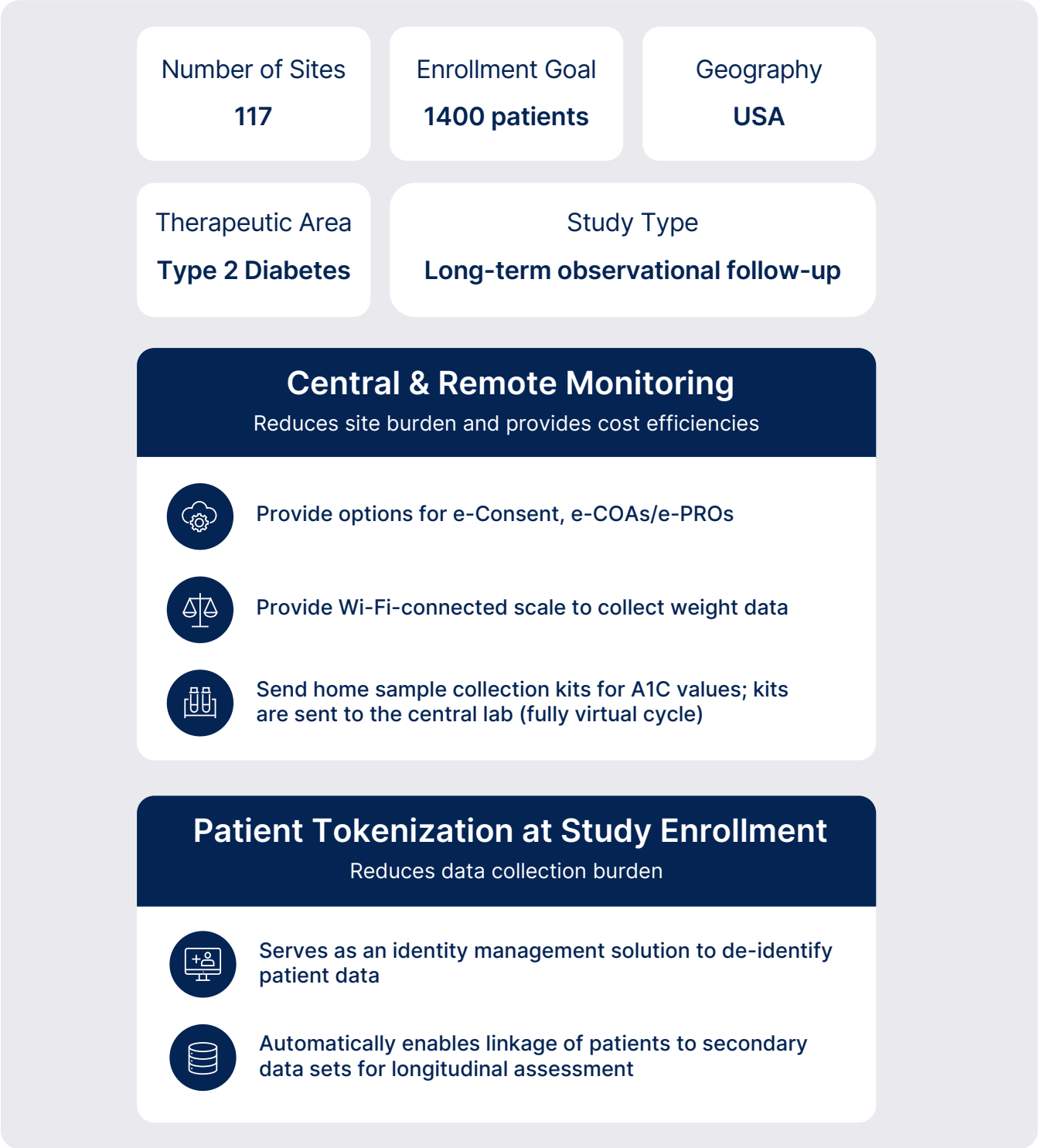

Figure 1. Case Study 1: Direct-to-Patient Study Design

Case Study 2: Integrating and Enriching Registries

Registries become significantly more powerful when integrated with other data sources. This approach is especially invaluable in rare disease research, in which small patient populations[5] make it challenging to gather comprehensive insights. Figure 2 (below) illustrates how four separate registries for a rare disease were combined into a single, universal registry enriched with other sources of RWD.

When integrated effectively, registries provide opportunities to better understand a disease's natural history, real-world care patterns, safety profiles, and treatment outcomes. Incorporating RWD sources — such as patient-reported outcomes, electronic health records, wearables, and claims data[6] — creates value for patients, payers, providers, and pharmaceutical sponsors.

Realizing these benefits requires careful technical execution and specialized expertise. Deduplicating patients is a necessary first step, followed by creating a common data model that accounts for coding structure, data sources, and level of data completeness. Equally critical are the enabling technologies — including data linkage, tokenization, ingestion, and the standardization of data from disparate sources into a common data model — that make robust data integration and harmonization possible.

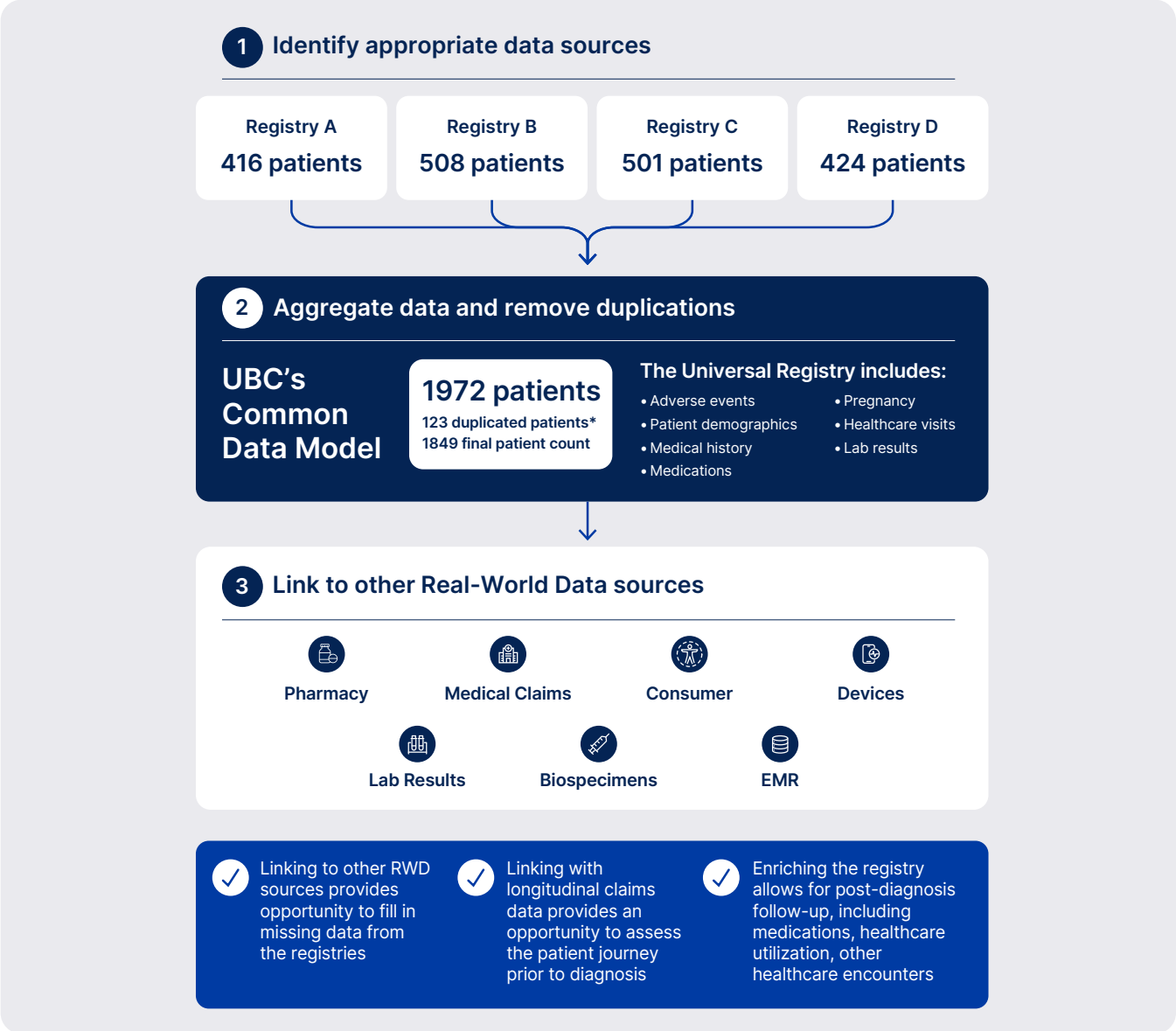

Figure 2. Case Study 2: Integrated registry enriched with RWD. This figure has been adapted from a presentation at SCOPE 2023.[7]

Case Study 3: Enriching a Pragmatic Study with RWD

In 2024, UBC presented the concept of real-world data (RWD) linkage to pragmatic studies at the Summit for Clinical Ops Executives (SCOPE) and the Professional Society for Health Economics and Outcomes Research (ISPOR). Linking clinical study data to RWD allows researchers to understand participants' pre-trial healthcare status, contextualize adverse events and discontinuation during the trial, and track patients post-trial — illuminating a rich longitudinal view of each participant's healthcare journey.

Producing a more comprehensive, longitudinal dataset that links RWD with clinical study data requires a well-designed and thoughtfully executed data strategy — including appropriately managed patient consent and tokenization, carefully planned data sourcing and standardization, and robust data management. UBC has explored these components in detail in a previously published case study titled, Enriching Clinical Studies with Longitudinal Real-World Data.

This current case study, Figure 3 (below), focuses on a separate effort to enrich an ongoing pragmatic trial with RWD. In this instance, UBC partnered with a European study sponsor to design and implement a robust data strategy that linked RWD to the study. This allowed researchers to examine patient history prior to the trial, use study participant data to contextualize clinical events during the trial, and follow patients after the trial ended. The post-trial follow-up, in particular, yielded strategic insights — most notably, the opportunity to help close the efficacy-effectiveness gap, and to track real-world outcomes such as effectiveness, safety, healthcare utilization, comorbidities, and concomitant medication use.

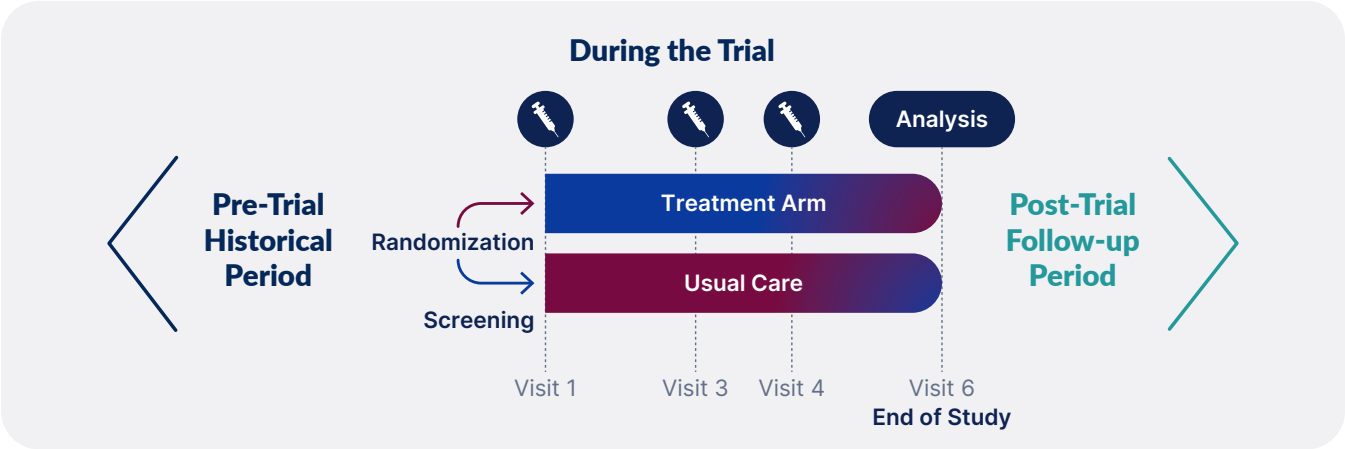

Figure 3. Linking pre- and post-trial longitudinal RWD to clinical trial data. Additional details can be found in the recently published case study (see above).

Case Study 4: Linking Patient Support Programs to RWD

At the 2025 Professional Society for Health Economics and Outcomes Research (ISPOR) Conference, UBC introduced a novel approach to linking patient support programs (PSPs) with real-world data sources, demonstrating how this strategy allows sponsors to better evaluate the impact and effectiveness of their PSPs.[8] Specifically, sponsors can explore potential factors that influence patient participation and identify contributors to poor adherence, such as comorbidities, insurance type, and adverse outcomes. With linked data, sponsors can gain a complete view of the patient journey, enabling them to understand behavior patterns before patients enroll in a PSP, as illustrated in Figure 4 (below). Moreover, sponsors can identify providers (e.g., physicians, clinics, pharmacies or other healthcare professionals) who are participating and those who are not. These insights may lead to additional options for patients participating in a PSP — such as personalized engagements, education or home nursing services — as well as targeted education initiatives for providers, including medical science liaison outreach.

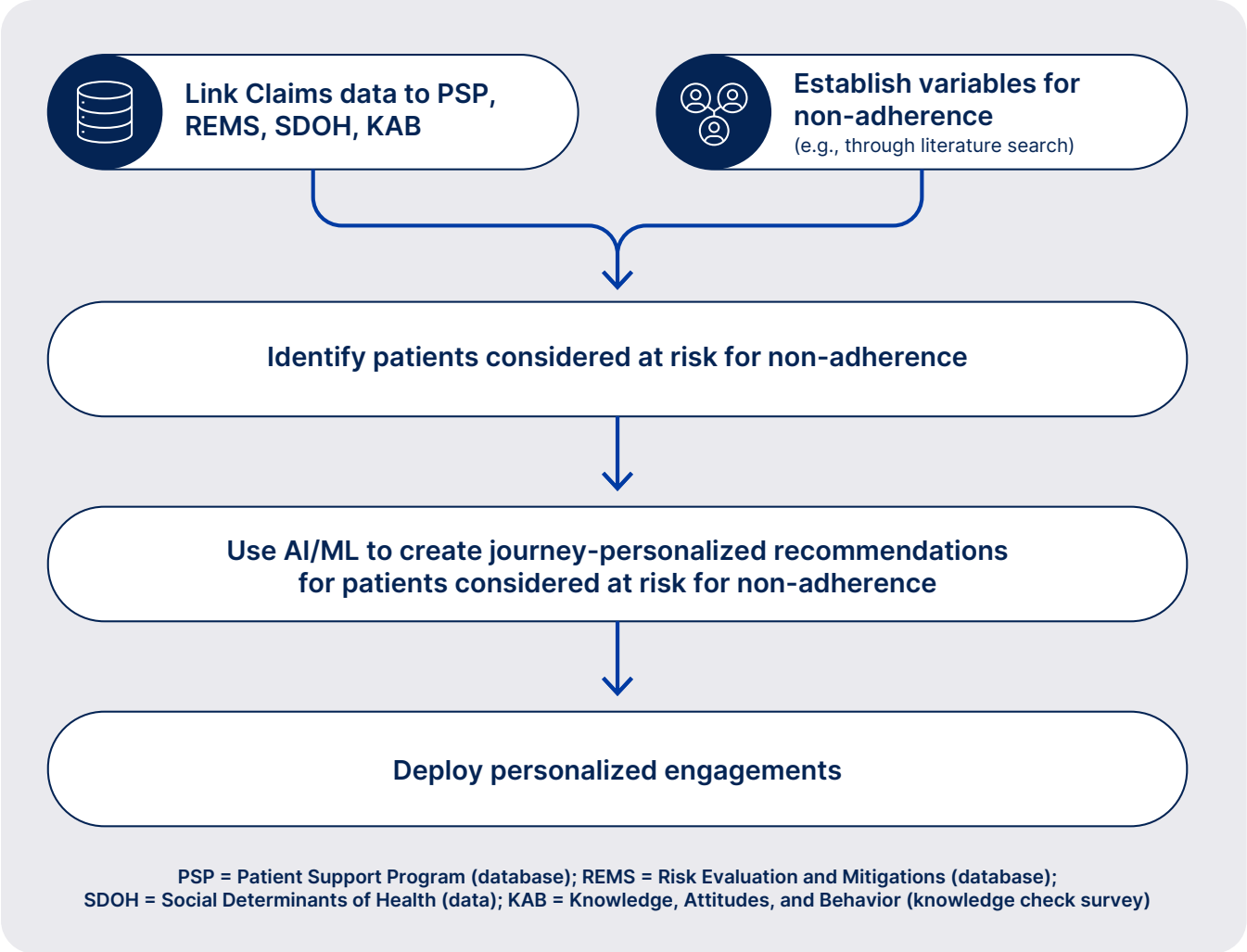

Figure 4. Case Study 4: Linking Patient Support Programs to RWD

Data Analysis Plan

A data analysis plan is a structured framework that outlines how data will be analyzed to address a study's research objectives. In the context of RWE studies, it helps ensure that analytical methods are prespecified, transparent, and aligned with regulatory and scientific expectations.

A well-designed data analysis plan for RWE studies should detail how primary and key secondary endpoints will be analyzed; how confounding factors will be addressed; and how follow-up periods will be defined. It should also specify the approach to handling intercurrent events, missing or misclassified data, and issues relate to multiplicity.[1] Together, these elements ensure the analysis is transparent, reproducible, and aligned with the study's objectives and data characteristics.

In any RWE-based study, it is critical that sponsors prespecify how they will assess the effects of confounding factors, address potential sources of biases, and evaluate data quality.[9] Doing so strengthens the credibility of the findings by reducing the risk of post hoc manipulation and supports regulatory and payer confidence in the results. These planned analyses also help evaluate the robustness of the results and provide insights into uncertainties. Throughout this white paper, we described some steps to consider when addressing the statistical analysis for RWE studies. In brief, sponsors should proceed as follows:

- Define the research questions
- Plan your study design and data collection
- Prepare and clean data
- Address confounding, bias, and sensitivity analysis
- Interpret and report statistical analysis results clearly

RWE Study Strategy

A key takeaway for sponsors is to plan real-world studies *a priori* and engage the U.S. Food and Drug Administration early in the process. As the regulatory landscape continues to evolve, sponsors are adopting modern approaches in real-world evidence (RWE) study design and data analysis that can demonstrate product value not only to regulators, but also to other external stakeholders, including patients, payers, and providers.

Sponsors are adopting modern approaches in RWE study design and data analysis that can demonstrate product value not only to regulators, but also to other external stakeholders, including patients, payers, and providers. Such approaches include direct-to-patient (decentralized) study design elements, tokenization, linkage, and secondary data integration, including RWD sources not traditionally used (e.g., patient hubs). Each approach enriches the view of the patient healthcare journey. Having a partner at the forefront of such novel study designs can drive value story creation and strategy development.

Meet the Author

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Evidence generation strategies, powered by rigorous science, designed to demonstrate value.

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About UBC

United BioSource LLC (UBC) is the leading provider of evidence development solutions with an expertise in unifying evidence and access. UBC helps biopharma mitigate risk, address product hurdles, and demonstrate safety, efficacy, and value under real-world conditions. With over 30 years of experience, UBC is uniquely positioned to develop end-to-end integrated evidence generation strategies, identify fit-for-purpose data sources, operationalize planned studies and ensure regulatory-grade, publishable outputs.

To learn more about how UBC can help you modernize your RWE study design, reach out to us at **contact@ubc.com**

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