healthverity®

WHITE PAPER

The secret to expediting drug approval: Synchronizing clinical trial and real-world data

A better understanding...

The COVID-19 pandemic brought to light many of the challenges clinical trials face in urgently addressing new and rapidly evolving diseases and answering questions about long-term safety and efficacy. Clinical researchers and government agencies quickly learned that incorporating real-world data (RWD) from sources such as medical and pharmacy claims, electronic medical records (EMRs), labs, and more can overcome these challenges.

At the height of the pandemic, HealthVerity worked alongside agencies such as the **National Institutes of Health (NIH)** and the **Centers for Disease Control and Prevention (CDC)** to help track and better understand the virus through the analysis of RWD. Additionally, we worked with a leading pharmaceutical company to conduct the largest real-world evidence (RWE) vaccine effectiveness study, which ultimately led to its emergency use authorization (EUA).[1]

This experience taught us much on incorporating RWD into clinical trials, which we will cover in this white paper, including:

- **The benefits of synchronizing RWD and randomized clinical trials (RCTs)**
- **The value of RWD at each stage of the clinical trial lifecycle**
- **The challenges and solutions for incorporating RWD into clinical trials**
- **Guidance for sponsors when using RWD for regulatory submission**

Contents

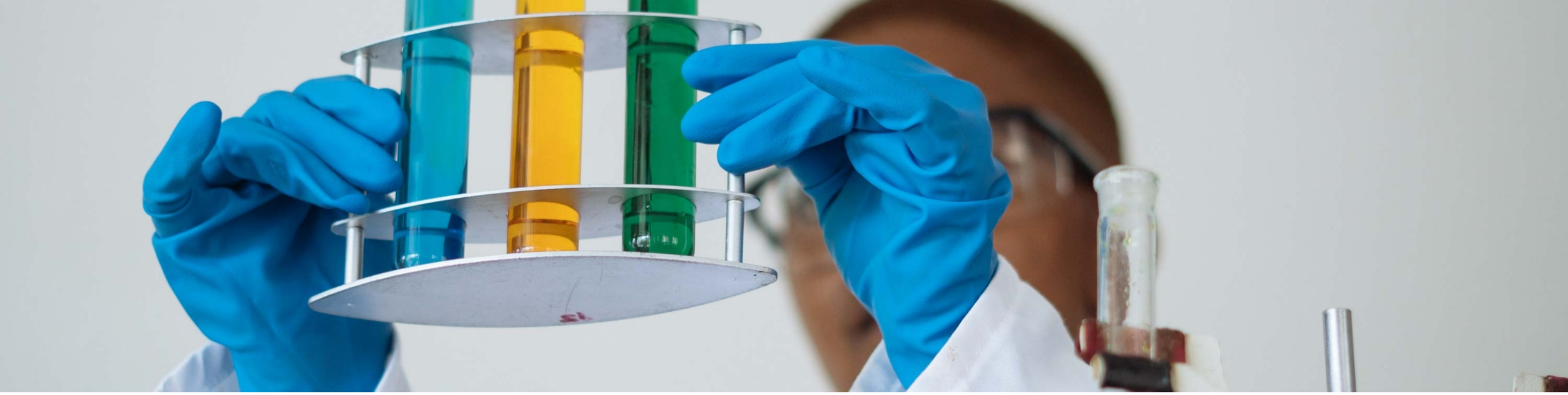
The benefits of synchronizing RWD and RCTs

RCTs have been used to demonstrate the efficacy of new therapies since 1948 and were first dubbed the ‘gold standard’ in 1982 by the *New England Journal of Medicine*, but they are not without their challenges.[2] Due to limitations in trial sizes and inclusion and exclusion criteria, RCTs may not represent use in a real-world setting or include patients with comorbidites.[3] Most studies are also unable to show long-term outcomes.[3] The study is designed to get to an event or endpoint, such as a heart attack two years post treatment, but may not be designed to capture long-term outcomes 10 years later. Additionally, with the cost of developing a new drug ranging from $314 million to $2.8 billion and 85% never achieving FDA approval, it’s important to optimize RCTs to overcome these limitations.[4,5]

LIKELIHOOD OF DRUG LAUNCH

89%	**68%**
with the support of RWD	without the use of RWD

The volume of RWD that exists in today’s digital world can provide clinical researchers with relevant insights, contextualize and build upon results from RCTs, and help drive more informed RWE that supports regulatory approval. This ultimately gets safe and effective medications into the hands of the patients who need them faster. In fact, one study found that drugs developed with the support of RWD had an 89% likelihood of launch, compared to drugs developed without the use of RWD, which had a 68% likelihood to launch rate.[6]



The value of leveraging RWD across the clinical research stages

RWD can be leveraged as part of the clinical development program to help achieve important clinical research goals, answer questions and address regulatory concerns that could not be answered without the combination of data sources.

BEFORE TRIAL:

Before a trial begins, there are several ways that RWD can address and overcome challenges long observed in RCTs:

Study design: Study design often accounts for RCT failures, but RWD can reduce the uncertainty that contributes to design characteristics, like endpoints and sample sizes, that often lead to these failures.[7] Using real-world historical data, researchers can gain deeper insight into patient demographics and optimize RCT designs and protocols.

Recruitment: Clinical trial recruitment is a major challenge in clinical research and many RCTs are canceled due to a failure to meet participation thresholds or study costs are increased due to delayed recruitment. Several factors contribute to clinical trial recruitment success, including understanding how many patients may be eligible at a given site, how to reach those patients, how to compel patients to participate and how to ensure that relevant physicians are aware of trials so that they can refer patients.

The value of leveraging RWD across the clinical research stages

Several types of data can provide sponsors with a deeper understanding of study participants, which can help to improve both recruitment and site selection for clinical trials.

Patient recruitment: RWD can improve the effectiveness and efficiency of trial recruitment strategies by identifying cohorts with a greater likelihood of benefiting from a particular treatment.[8,9] Additionally, RWD can be used to find untapped pools of patients who are promising candidates for participating in RCTs, as well as for identifying target patient populations that can help to diversify clinical trial participation.

Site recruitment: RWD can also help to determine how many patients could potentially enroll at certain sites, which contributes to site feasibility decisions.

Enrollment screening and qualification: Using RWD, researchers can gain a robust understanding of the representative population and develop flexible criteria that is most likely to capture enough participants to achieve desired endpoints, such as limiting age restrictions.[4] For participating patients who have provided consent, RWD can also facilitate patient screening, validate patient-reported data, and provide a deeper view into participants' health with information on current and historical treatments, diagnosis, and hospitalizations.

DURING TRIAL:

While RCTs are underway, there are further opportunities to draw on RWD to extract more information out of trials faster. Using real-time RWD, safety can be assessed and studies can be contextualized to help in the preparation of regulatory submissions.

Responder characterization: Clinical trial data often reveals that certain sub-populations of patients are more likely to respond in specific ways to a given treatment, such as experiencing adverse effects or better outcomes. Once these trends have been recognized, new research questions arise. Trial design, however, usually precludes adequate investigation of these new questions, whereas RWD may be able to provide answers.

Demographic data and medical history, available in RWD sources such as EMRs, can help researchers better understand these differential responses to treatment. In addition, RWD can reveal non-reported information and provide clarity on patients who were lost to follow up.

Contextualization studies: The COVID era has illustrated how quickly the standard of care can change or a condition can produce new potential comorbidities, such as cardiovascular impact post COVID. Concurrent safety contextualization studies allow researchers to understand the changing treatment environment and provide robust data as part of the full regulatory submission package.

External control arms: There are cases in which RCTs are impractical, such as in the cases of rare or deadly diseases where it is difficult to justify, from an ethical perspective, withholding treatment from a subset of patients.[5,10] Single-arm studies are thus sometimes advised in cases where the benefits of the investigational treatment are expected to be substantial or rapid and where there is a pre-existing deep knowledge of the course of the untreated disease. In these cases, regulatory-grade RWD can provide crucial control arm information.

In 2020, three out of every four new drug applications and biologic license applications included RWD.[12]

Regulatory approval: Accompanying clinical trial data with RWE in submissions to regulatory bodies has been shown to reduce, and in some cases, entirely remove post-marketing commitments.[11] As such, in 2020, three out of every four new drug applications and biologic license applications included RWD.[12]

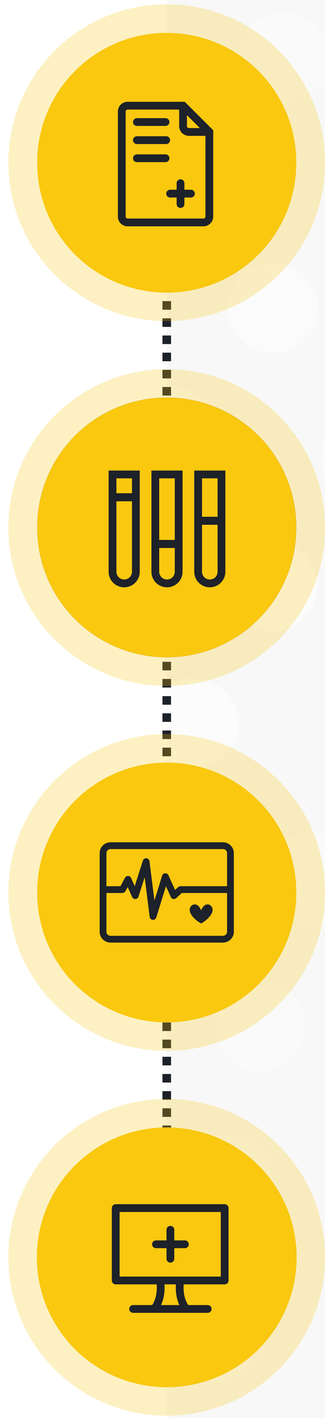
FOLLOWING TRIAL:

After the trial concludes, there is enormous potential to integrate RWD to support new knowledge, as well as the approval process. Additionally, RWD can be leveraged to get longer-term insight on the population itself, which can drive several aspects of research, development and marketing strategies.

Surveillance monitoring: With RWD from sources such as claims data, lab, mortality and EMR, surveillance monitoring can provide insight on long-term outcomes and survival.[5] Additionally, RWD can be leveraged to support post-marketing commitments, assessing adverse events and overall safety.

Research on vulnerable populations: RCTs fail to capture information on vulnerable populations, such as pregnant women, because these groups are frequently excluded from trials.[5] The resulting evidence gap can be filled with RWD from a variety of sources.

Comparator studies: Comparator studies are increasingly being used due to pressure from both payers and regulators. RWD can meet this need by enabling more efficient evaluation of the relative efficacy of investigational products with respect to drugs that are already on the market.



Payer evidence: RWD on costs can be used to support comparative effectiveness research, which can provide value evidence required by payers to cover the costs associated with new treatments.[5]

Part of the value of incorporating RWD into clinical trials is the capability of future proofing not only the clinical trial, but the entire research program.

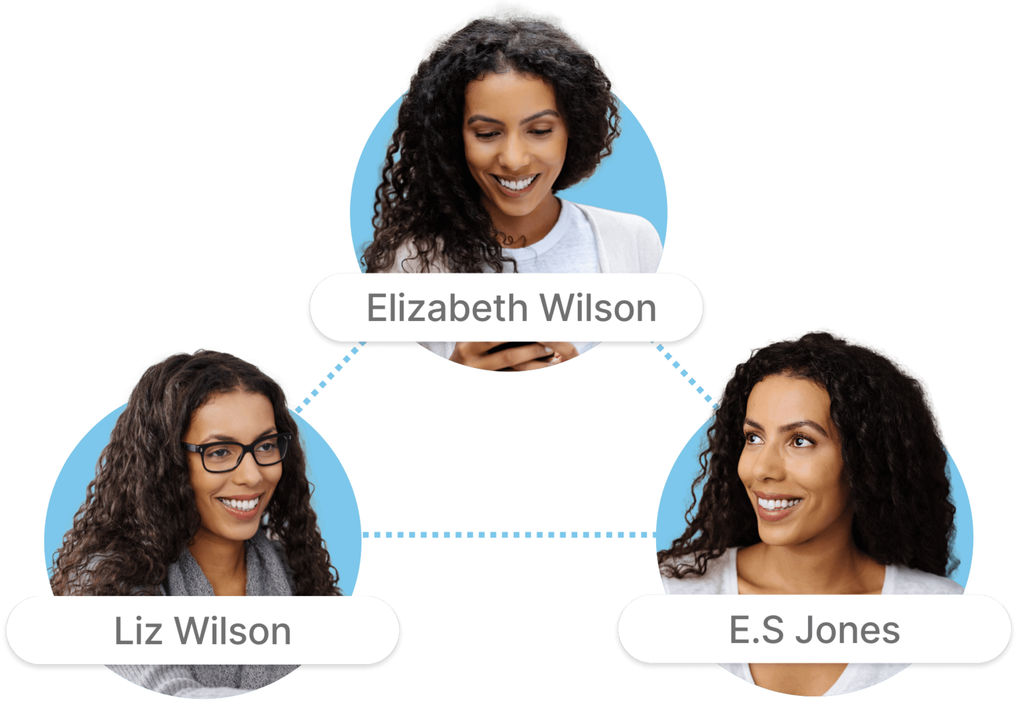
Combining RWD with RCT data can deepen knowledge of the entire patient journey rather than relying on fragmented data captured at a specific moment in time. Part of the value of incorporating RWD into clinical trials is the capability of future proofing not only the clinical trial, but the entire research program.

Challenges and solutions to incorporating RWD

Despite accumulating evidence of the value RWD can bring to the clinical trial landscape, research suggests that this approach of combining RCTs with RWD has far from reached its potential.[9]

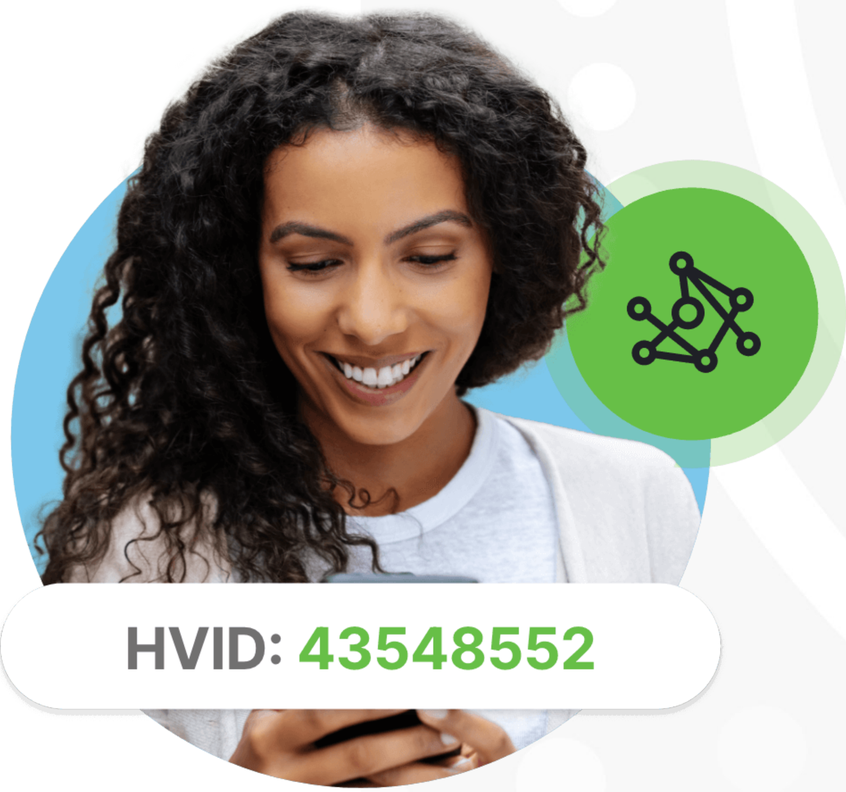
Challenge: Accurately linking RCT data and RWD

The de-identification that currently occurs in clinical trials to protect patient privacy can limit accurate matching of individual patients' RCT data to their RWD. Additionally, RWD is inherently inconsistent (e.g., misspellings, nicknames, address changes, missing fields), making accurate linking even more of a challenge. Inaccuracies can fragment patient journeys, overlook comorbidity information, and limit visibility into off-trial events and safety signals, while leading to less comprehensive findings.



Solution: Patient identity resolution

The HealthVerity patient matching and identity resolution technology synchronizes patient identities over time and across data sources with algorithms and techniques that excel at accurately resolving patient identities despite the noise in RWD. Beyond simply replacing personally identifiable information (PII) with an alphanumeric string, or token, HealthVerity matches identities to a continuously updated referential database of over 200 billion healthcare and consumer transactions and leverages machine learning techniques to ensure the highest accuracy rate when assigning a universal and persistent HealthVerity ID (HVID) from our master patient index. Additionally, we utilize probabilistic matching techniques, which can better handle the inherent noise in RWD, as opposed to legacy techniques that require an exact match or create a new token by default, resulting in higher patient counts.



HEALTHVERITY PATIENT IDENTITY RESOLUTION

The transformation of patient information into universal, de-identified HVIDs to accurately synchronize patient records over time and across data sources, enabling **longitudinal patient journeys** while creating a single source of truth for identity.

PATIENT TOKENIZATION

Hashing and encrypting patient information to create a "token" that **can be use once** to link data across datasets.

Figure 1. Patient identity resolution versus patient tokenization.

Challenge: Siloed data

Healthcare data has historically existed in siloes, with medical claims from one source, EMRs from another, and pharmacy and hospital data from other sources, making it difficult for researchers to efficiently define and find a patient cohort with all the needed data elements for the research question at hand. Additionally, as new questions arise, new data may be needed to maximize researchers' understanding of the efficacy, safety and indications of investigational therapies.

Solution: Vast, interoperable RWD ecosystem

HealthVerity partnerships enable broadscale access to the nation's largest ecosystem of healthcare and consumer data, including EMR, medical and pharmacy claims, lab results, and more. Comprised of more than 200 billion de-identified transactions, the HealthVerity data ecosystem is unparalleled and continually expanding, providing an enormous amount of interoperable, HIPAA-compliant data that can be leveraged to rapidly support wraparound research needs as clinical trials move through their natural stages. With so much data ready to be used, programs built upfront with identity resolution can flexibly evolve based on new insights or changes in the healthcare environment.

Challenge: Informed consent & Institutional Review Board (IRB) submittals

With both RCT data and RWD de-identified, there is some uncertainty as to if consent is needed to synchronize de-identified data sources, if it should be separate from the trial consent form, and ultimately, how to manage it through the IRB approval process.

Solution: A thoughtful approach

In our experience, HealthVerity has found that it is best to get informed consent for RWD synchronization and to do so upfront, otherwise, it can be an additional burden and more difficult to seek consent later in the trial. While the consent form can be separate or incorporated into the trial consent, an advantage to using a separate form is that a participant can opt to participate in the trial, but not in RWD synchronization. We have found that approximately 80% of participants do consent to connecting their RCT data and RWD. Many CROs and other organizations have suggested language to assist with developing the appropriate consent forms, which should be included as part of the IRB review. We also suggest a custom HIPAA certification to combine RCT data and RWD and can guide you through this process.

Challenge: Meeting FDA guidelines

The ultimate goal of an RCT is to receive approval from the FDA so it is important to ensure that the incorporation of RWD into your trial meets FDA guidelines.

Solution: *Guidance to help meet FDA requirements*

The FDA has provided significant draft and final guidance for consideration when preparing to submit RWE for regulatory approval. In addition to ensuring the study is designed appropriately to provide adequate scientific evidence, there are several considerations related to the RWD itself. Primarily, is the RWD fit for use or purpose. Both relevance and reliability should be a part of that consideration:

Relevance: Did the RWD include key elements (patient characteristics, exposures, outcomes) and was there a sufficient number of representative patients for the study? Consider demographic and clinical information, treatment information for the disease of interest (as applicable), and health-related outcome information.

Reliability: Was the data accurate and complete? Did it have provenance and was it traceable? Submissions should include a data dictionary with well defined elements and ranges, etc., data accrual and audit trails, and defined processes for data integrity/ collection and transformation.

RWD unlocks significant potential for clinical trial research, but these challenges related to data interoperability, consent and regulatory requirements can prevent evidence generation from being a seamless process. HealthVerity is revolutionizing the durability of disparate healthcare data and demonstrating how discovery can be accelerated by synchronizing siloed datasets in a seamless, privacy-protected and HIPAA-compliant manner.

About HealthVerity

HealthVerity synchronizes transformational technologies with the nation's largest healthcare and consumer data ecosystem to power previously unattainable outcomes and fundamentally advance the science. We offer a comprehensive, yet flexible approach, based on the foundational elements of Identity, Privacy, Governance and Exchange (IPGE), that synchronizes unparalleled Identity management with built-in Privacy compliance and Governance, providing the ability to discover and Exchange a near limitless combination of data at a record pace. Together with our partners in life sciences, government and insurance, we are Synchronizing the Science.

To learn more about the HealthVerity, visit healthverity.com

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