Harnessing the power of RWD in clinical trials

Clarivate™

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Introduction

From high seas to high tech: 250 years of clinical trials

When James Lind conducted the first recognizable controlled clinical trial to rid sailors of scurvy, little did the Scottish naval surgeon know that in 1747 he was setting the blueprint for the future of clinical study for the next 250 years. With a theory that citrus fruits may be the key to curing the disease that was decimating the seafaring population, Lind divided 12 sailors into six pairs with each pair given a different dietary supplement such as oranges, lemons, or sulfuric acid. It is reported that within a week, the sailors given citrus fruits were able to recover. We do not know what became of those in the control group.

Fast forward to 2023, and clinical investigators still follow this model when conducting controlled clinical trials. While protocols have morphed and been augmented over the years, the division of patients into control groups with placebo or active comparator, while half the patients are given a novel therapy, remains the same.

However, industry, patients, and regulators are increasingly concerned about clinical trial equity and ensuring that patients enrolled in clinical trials represent the populations set to benefit the most from novel therapies. These populations include marginalized communities which have been historically underrepresented within clinical trials. Of the 53 novel drugs that were approved by the FDA in 2020, 32,000 people took part in supporting clinical trials. Within that number, on average, 75% of trial participants were White, 11% Hispanic, 8% Black, and 6% were Asian. Women made up an average of 56% of that number.[1]

It's a similar story in Europe. The E.U. Clinical Trial Regulation No. 536/2014, which went into force in 2022, emphasized the diversification of clinical trials to include a fairer representation by gender and age. In addition, it includes prescriptive rules on the inclusion of pregnant and breast-feeding women.

Diversity in clinical trials in the U.S. is now mandated by law through the Food and Drug Omnibus Reform Act of 2022. Couple this drive for better representation with phase 2 and 3 failure rates hitting 73% and 29%, respectively and costing on average $28 million for a phase 3 study, according to Clarivate's Centre for Medicines Research International program, and the need for new ways to improve outcomes and support unmet data needs becomes clear.

This is where real world data (RWD) enters the conversation.

53

novel drugs approved by the FDA in 2020.

Source: FDA

32K

people took part in supporting clinical trials.

Source: FDA

While clinical trials are the gold standard for studying the safety and efficacy of novel therapies, the controlled environment is not conducive to the need for equality within clinical studies. Gathering data from electronic health records (EHRs), pharmacy and insurance claims, wearable technologies and patient apps enables clinical investigators to see through a real world window that informs their knowledge of how patients respond to drug regimens in their daily lives.

The types of information gleaned from clinical studies and real world evidence are, of course, different. The FDA defines real world data as "data relating to patient health status and/or the delivery of healthcare routinely collected from a variety of sources." Examples of RWD include data derived from EHR medical claims data, data from product or disease registries, and data gathered from other sources (such as digital health technologies) that can inform on health status. Real world evidence is the clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of RWD.

Figure 1: Real world and other extra-clinical data sources.

Sources of information healthcare companies are using to gain an holistic picture of their patient:

Claims
Medical and pharmacy claims including submissions, remittances and denials.

Electronic Health Records (EHR)
Patient health records sourced from health systems and practices e.g. Diagnoses, vitals, assessments, vaccines, prescriptions, diagnostics ordered/results and provider notes.

Registry Data
Information sourced from registries including demographics, disease characteristics, patient/ physician reported outcomes and lab measures.

Social Determinants of Health
Information sourced on the patient's environment (i.e. economic stability, climate, pollutants, diet, education access, etc).

Family History
Personal and family medical history including health conditions, allergies, alcohol/cigarette use etc.

Literature
Information derived from literature sources like medical journals including burden of disease, incidence and prevalence, quality of life measurement, etc.

Genomic Data
Data related to the structure and function of an organism's genome e.g. RNA, DNA, Proteins.

Social/Digital Data
Information sourced from patient communities, social media and biometric monitoring devices.

Clarivate provides and connects many of these sources to help companies with activities like patient journey mapping and unmet need discovery.

While RWD alone cannot facilitate approvals, these data can supplement clinical data to enhance our understanding of conditions and treatments in a real world setting.

Challenges also lie in wait for physicians keen to collect, analyze, and aggregate data from sources outside of the clinic. The lack of efficient and reliable data standardization in existing processes creates barriers for use, while disparate regulatory approaches also block a global research strategy for trial sponsors.

With these obstacles in mind, plus the knowledge of the huge gains that can be made by using real world evidence, what is the best way to harness the power of real world data in clinical trials?

Methodology

This report incorporates Clarivate data from the following sources:

Cortellis Clinical Trials Intelligence™ is a comprehensive source of detailed insights on clinical sites and trial protocols including biomarkers, targets and indications.

Cortellis Competitive Intelligence™ provides access to data such as drug pipeline, deals, patents, global conferences and company content, along with the latest industry news and press releases. The Cortellis Competitive Intelligence Drug Timelines & Success Rates methodology is a patented analytic tool that applies statistical modeling and machine learning to more reliably and accurately forecast drug development milestones, timelines and probability of success.

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Integrating RWD in clinical studies

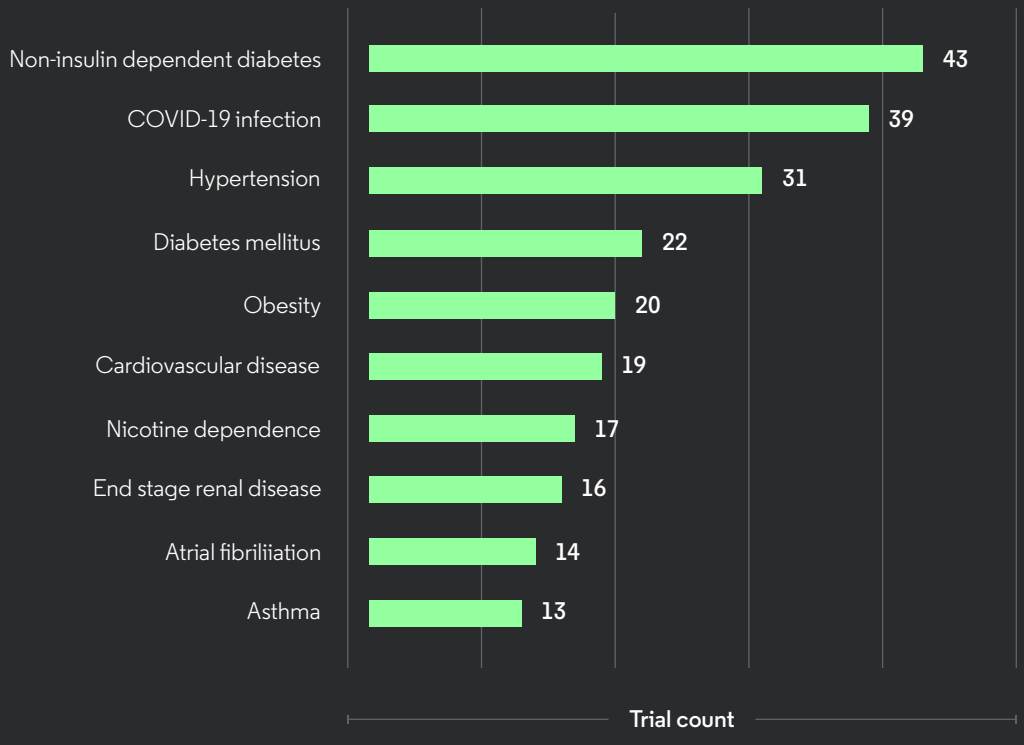
Trial recruitment and site selection

"The application of RWD to optimize clinical trial planning is the current sweet spot for use", said Samantha Chesney, Lead Consultantat, Clarivate.

"There are a lot of different ways that we can use real data in research," said Chesney. "That ranges from understanding which patients the drug is going to benefit most in the early stages, to choosing which sites and investigators we want to use in the later stages of trial planning."

Patient recruitment remains one of the most expensive, limiting, and time-consuming elements of clinical trials. Data show that 18% of patients drop out of studies after enrolling, with difficulty attending clinics cited as a major factor. Overall, 86% of trials do not meet enrollment timelines and 30% of phase 3 trials fail due to enrollment challenges. Patient recruitment is the largest cost driver of clinical trials, accounting for 32% of overall expenditure.[2]

Figure 2: Top 10 Conditions with EHR/EMR in Clinical Trial Inclusion.



Source: Cortellis Clinical Trials Intelligence

Finding a large and representative sample of patients is an even larger problem. Overly optimistic recruitment targets, narrow eligibility criteria, and lack of engagement with a disease community are all factors that can stop a phase 3 trial from a successful lift off. Identifying patient candidates through EHRs has become a powerful addition to trial recruiters' armamentarium though. For the reasons cited above, investigators are now able to look outside the traditional healthcare parameters. Insurance claims, disease registries and device-collected health data combine to create a fuller picture of the patient investigators are trying to reach, recruit, and retain in clinical trials.

"Prior to real world data being readily available, site selection was validated by looking at which hospitals and sites had previous clinical trial experience," explained Angela Weidner, Product Manager, Cortellis at Clarivate. "Now, you can overlay that clinical data with real world data . You can not only see if the hospital or site has the experience from running previous trials, but in addition if they also have the patient pool to pull from."

This type of patient data is not only used for recruitment. It can be used to validate a hypothesis, write a clinical development plan, support study design, validate study protocols and collect data on trial feasibility.

"RWD gives you a good idea of what your market size is going to be before pushing your asset forward. It also gives you an idea of what your struggle is going to be like, because you understand how many patients are walking through the doors with this disease. Epidemiological data is useful, but real world data gets to a more granular level than that."

Samantha Chesney,
Lead Consultant, Clarivate

Unmet need

According to the European Commission, 4.8% of the E.U. population in 2021 had unmet needs for medical care because healthcare services were too expensive, too far away or waiting lists too long.[3] The latest data from the Centers for Disease Control and Prevention (CDC) showed that in 2019, 8.5% of U.S. citizens delayed or did not receive needed medical care due to cost involved.[4]

4.8%

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Source: European Commission

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of U.S. citizens delayed or did not receive needed medical care due to cost involved.

Source: CDC

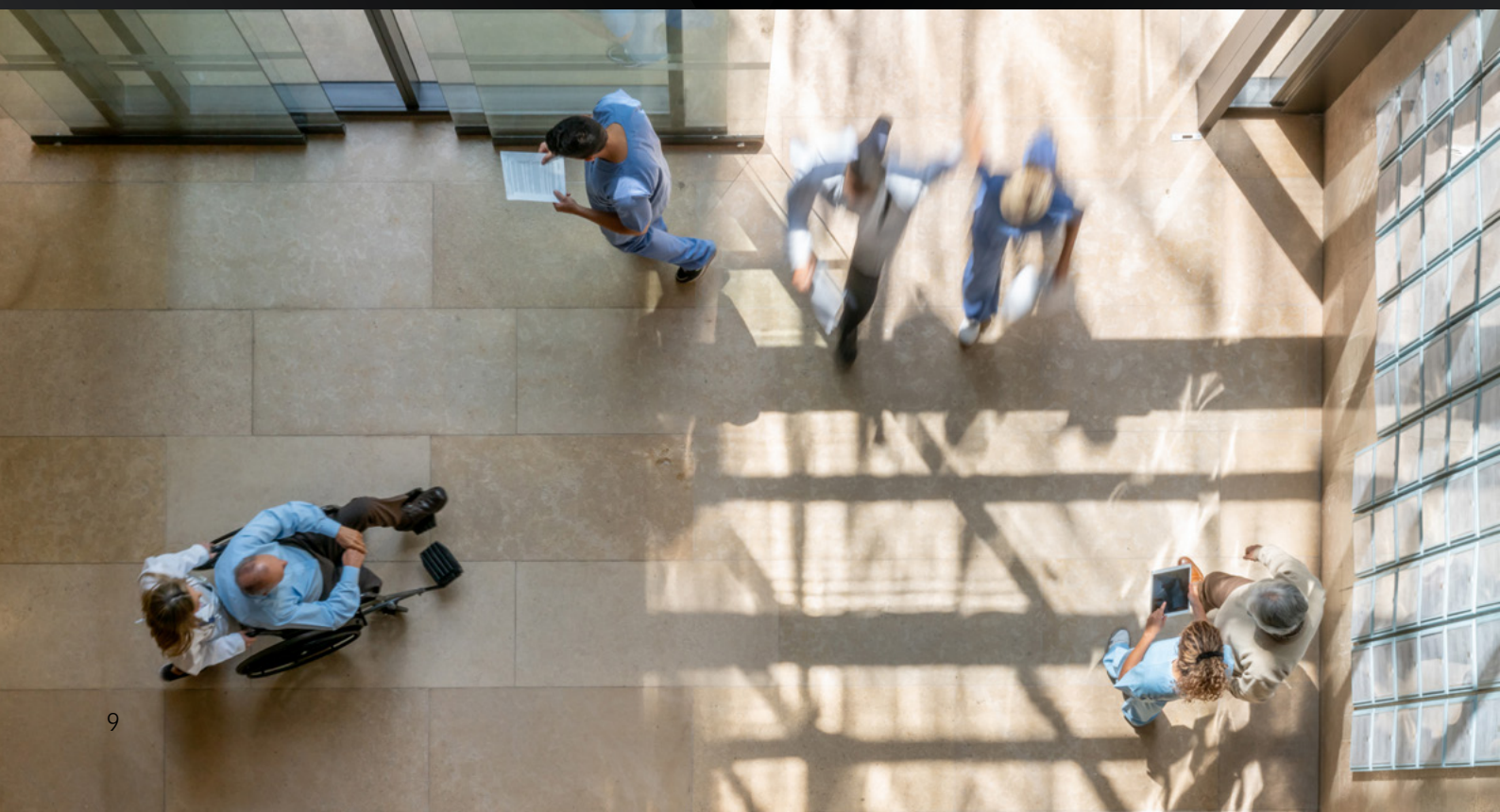


Figure 3: Clinical patient journey.

Identify unmet needs and opportunities for your brand in diagnosis and treatment protocols

How long does it take for a patient to receive **accurate diagnosis and treatment?**

What are current lines of **therapy, adherence, switching trends, and drug shares** for this indication?

Which HCPs do patients encounter throughout their care journey?

What are the key **unmet needs, delays, and pain points** in the patient experience?

Map HCP decisions and patient outcomes across their diagnosis, treatment, and referral journeys	Pinpoint gaps and delays brands can seek to mitigate in diagnostic and treatment protocols	Identify gaps, HCP and patient unmet needs, and opportunities to intervene
Medical and pharmacy claims	**EHR and registry data**	**Supplementary: Primary research and social listening data**
• Who, what, where and when around patient *diagnosis* • Who, what, where and when around patient *treatment* • Line of therapy, adherence, and switching patterns • Referral pathways by HCP type and site of care	• Correlate patient vitals and lab measures to diagnostic and treatment activities • Benchmark patient reported outcomes and adverse events by treatment received	• Identify HCP and patient unmet needs across the journey • Understand HCP treatment selection criteria • Unearth patient experiences and decision criteria by drug

Figure 4: Patient segmentation.

Segment and characterize patients to refine your positioning

What are key patient populations **segmented by comorbidities?**	What are the key patient groups **segmented by procedures and lab tests?**	What are they key patient groups **segmented by treatments received?**	Which patient segments present **the best market opportunity** for my product?
Size the total patient population, then drill down to size and profile priority segments	Segment patients by demographics, disease characteristics, treatments and procedures, etc.	Characterize patient segments to identify opportunity by segment
Medical and pharmacy claims	**EHR and registry data**	**Additional: Epidemiology data**
Segment patients by: • Demographics (e.g., age, gender, region) • Disease diagnosis • Procedures and treatments	Segment patients by: • Vitals • Personal health metrics • Lab test measures Benchmark patient reported outcomes and adverse events by segment	Identify key patient segments and subsegments to size and characterize

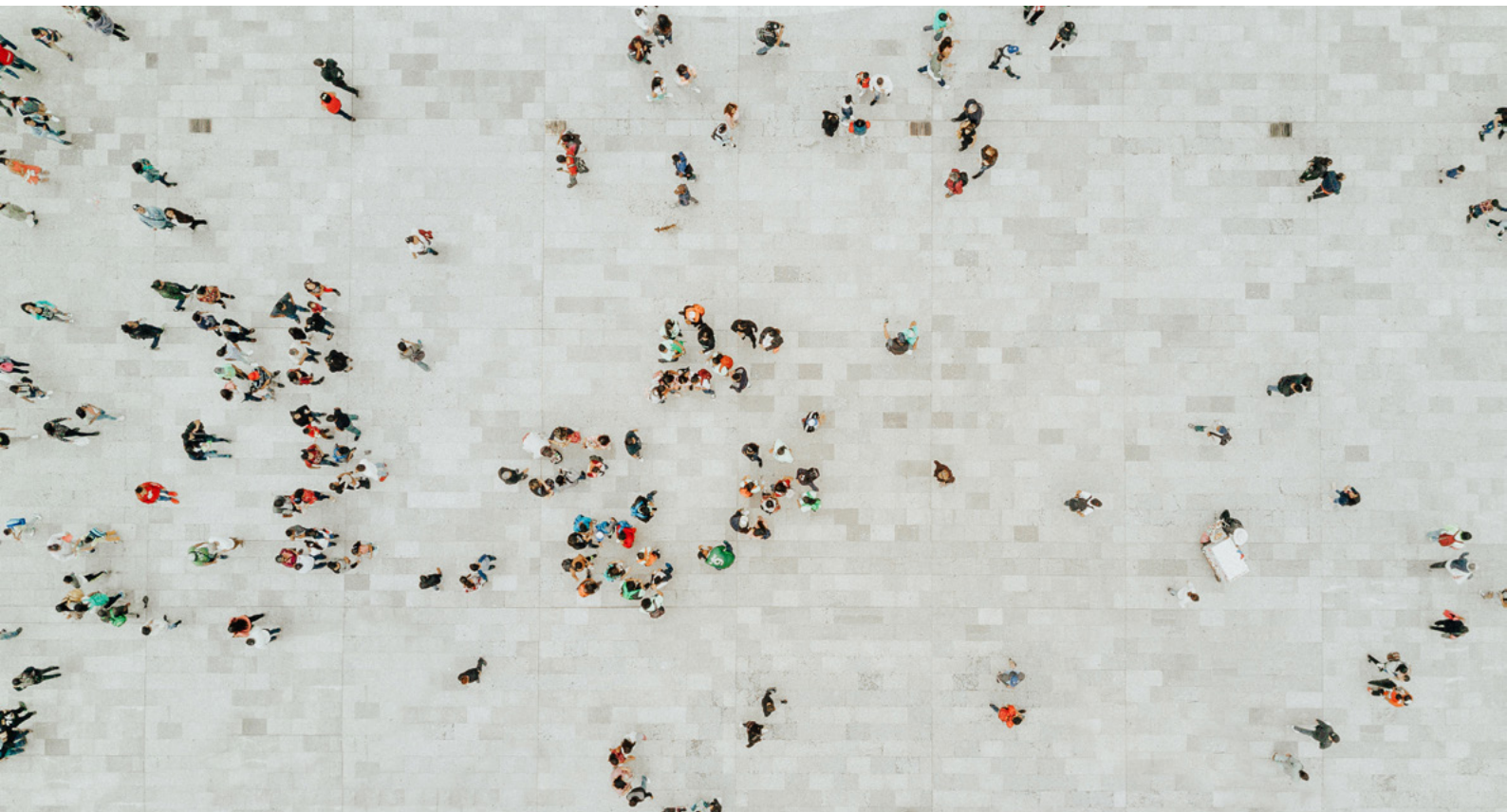
There are many underserved populations that could benefit from novel new therapies. Rare disease patients often struggle to find clinical studies that are targeted to their specific needs and are accessible.

PatientsLikeMe is a personalized healthcare network known for its extensive data on the amyotrophic lateral sclerosis (ALS) community. ALS is a rare neurological disease that affects motor neurons, those nerve cells in the brain and spinal cord that control voluntary muscle movement. Within this platform's database, researchers discovered that 9% of ALS patients reported using lithium carbonate, an off-label medication that exhibited promising results in a small-scale study involving 16 treated patients and 28 control subjects.

Based on this patient-reported data, researchers conducted a more expansive observational study using the data collected from these patients, which could be compared to multiple control groups.

Ultimately, the study revealed no discernible variance in disease progression after a 12-month period between the overall study group and the subset of patients receiving lithium carbonate treatment. Subsequent randomized studies corroborated these findings, demonstrating that the treatment exhibited no clinical effect within the broader population.

Chesney explained: "Real world data can show unmet need as part of a control group. Or when you find a similar drug that's on the market it can help to prove the statistical power of your safety or efficacy data, especially if you have the same or similar mechanism as another drug on the market. It can change the way that you're targeting patients, even though your drug is slightly different."



Regulatory considerations of real world data

There is an enormous volume of patient-reported data available to clinicians that is generated throughout clinical trials, and from social media networks, wearable devices and smartphone apps (Fig. 1). Electronic health records are increasing daily. In the U.S., the share of physicians reporting that their practice uses an EHR/EMR system has risen from 75% in 2013 to 87% in 2023.[5]

While the use of this type of data is a hot topic for many in clinical trials, and a tantalizing body of evidence for use in clinical studies, regulators are still a little cautious about how it is used. "It is not replacing the data produced in controlled clinical trials, but more so adding," said Chesney. "It is adding more power and more meaning behind the analysis."

The FDA's Real World Evidence Program, released in 2018, provides a framework for its multi-faceted approach to the use of RWD to develop RWE to support regulatory decisions. The Agency has already incorporated the use of RWE into safety evaluations through the Sentinel System, but more guidance is needed on RWE use cases for the demonstration of RWE in product efficacy.

In Europe, the Big Data Steering Group, the European Medicines Agency, and the European Medicines Regulatory Network are working to establish a sustainable framework to establish the use and value of RWE across different regulatory use cases.[6]

In the U.S., the FDA has a long history of using RWD and RWE to monitor post-market safety of approved drugs. While no novel drug has been approved based solely on RWD, between 1998 and 2019 there were 17 cases in which RWD were used as supplementary information in a new drug application (NDA), and 10 for line extensions, based on Clarivate Analytics data.[7] Applications were mostly applied in oncology and metabolism. The NDAs of all 17 products were approved.

According to Clarivate, Cortellis Competitive Intelligence, there were 42 drugs withdrawn from the market post-approval in the past 10 years based on post-marketing studies and/or RWD.

Real world evidence played a crucial role in the authorization of Merck KGaA and Pfizer's Bavencio (avelumab), a monoclonal antibody for metastatic Merkel cell carcinoma (mMCC), a rare and aggressive form of skin cancer. Given the absence of established treatment standards for mMCC, investigators leveraged data derived from EHRs to examine the actual clinical outcomes among a patient population receiving chemotherapy.

This allowed investigators to create a benchmark to gauge the effectiveness of chemotherapy in a real world context. By identifying patients who exhibited positive responses to avelumab and comparing their outcomes to the benchmarked data, researchers were able to document the therapeutic benefits of the treatment. The FDA granted accelerated approval to avelumab in 2017 based on these findings.

As in this case, and in most cases, RWD were used either as primary data, when noncomparative data were available to demonstrate tolerability and efficacy, or as supportive data when validating findings. Common sources of RWD were health or medical records (16 cases) and registries (8 cases).[7]

42

drugs withdrawn from the market post-approval in the past 10 years based on post-marketing studies and/or RWD.

Source: Cortellis Clinical Trials Intelligence

Barriers to regulatory utility

Lack of harmonization

While there are many ways to produce evidence based on RWD that inform pharmaceutical strategy and patient access, there are also multi-layered ceilings that limit the effectiveness of the data, and therefore the impact of that data on NDAs. Foremost among these is a lack of harmonization among health technology assessment (HTA) bodies and regulators.

Numerous HTA organizations acknowledge the significance and function of real-world evidence in assessing medicinal products. The Health Technology Assessment International (HTAi) has formed a dedicated group focused on RWE and artificial intelligence. Noteworthy initiatives like NICE's RWE Framework offer guidance and structure for utilizing RWE, while also exploring ways to incorporate it more extensively into their HTAs.

Despite the growing interest in using RWE for healthcare evaluations, there remains a lack of standardization across different regions regarding this guidance. This lack of harmonization creates uncertainty about the effective implementation of RWE. Moreover, it is important to highlight that not all HTA bodies currently possess the necessary resources to fully integrate RWE into their evaluations. Consequently, some organizations exercise caution in adopting RWE due to resource constraints.

Variability of data collection methods

Data collection methods vary significantly across different care settings and countries. Moreover, HTA authorities often request additional data late in the HTA process, creating a challenge as there are no established processes in place to gather the required information.

To assist researchers in meeting the standards set by decision-makers, it is crucial for HTA bodies to provide clear guidance on the characteristics of high quality RWE right from the outset. This should include defining the circumstances that warrant the use of RWE and outlining the evaluation criteria for such justification. The need for comprehensive guidelines is becoming increasingly urgent, particularly considering initiatives like the European Health Data Space (EHDS), which aims to facilitate easier data collection and sharing to enhance healthcare quality, research, innovation, and policymaking.

Unreliable RWD quality and transparency

Not all real world data is considered clinical grade by regulators, noted Chesney. "The regulatory authorities are still very cautious about what you can and can't use real world data for," she added.

To rely on RWE, it is essential for current data sources such as national cancer registries to collect data in a consistent and systematic way with an appropriate level of detail. Variable lifestyle factors are often not routinely documented, which limits the potential to transform real world data into evidence. Enabling adequate data transparency also empowers HTA bodies to gain increased confidence in the data and better comprehend its origins and collection methods.

"The regulatory authorities are still very cautious about what you can and can't use real world data for."

Samantha Chesney,
Lead Consultant, Clarivate

Key takeaways

RWD is, at present, most extensively used for clinical trial planning, site feasibility, and patient recruitment. Data can be overlayed on clinical data to validate site selection based on location and patient population.

Regulators are cautious about how RWD is used within the regulatory process. Novel drugs have not been approved with the use of RWD alone, but it's a potential differentiator to data generated in randomized clinical trials.

Standardization and harmonization is required within the respective regulatory systems to ensure global clinical strategies can be rolled out. In addition, there are questions about using data from varying sources, and data collection infrastructures will be of increasing importance in the future as the use of RWD continues.

The Salford Lung Study is renowned for its innovative approach using RWE to serve as a prime illustration of its effectiveness.

Sponsored by GSK, this groundbreaking study aimed to assess the safety and efficacy of a novel treatment for Chronic Obstructive Pulmonary Disease (COPD).

The study encompassed a vast cohort of 2,802 patients who received treatment from their own general practitioners within real world clinical settings. Notably, the study adopted inclusive criteria, incorporating 90% of screened patients to ensure a representative sample mirroring everyday medical practice.

The primary objective of the study was to gather data that accurately reflected patients' medication adherence and behaviors, while minimizing disruption to their routine care. Simultaneously, the study strived to enroll a substantial and diverse portion of the eligible population, allowing for generalizability of the findings. With a retention rate of 93% throughout the study duration, it can be deemed a resounding success.

Moreover, the study yielded several decisive clinical outcomes. It found that 100/25 mcg of Relvar Ellipta (Fluticasone furoate/vilanterol) achieved a superior reduction in exacerbations versus "usual care", in patients with COPD, in an everyday clinical practice setting.[8]

2.8K

patients within real world clinical settings.

93%

retention rate throughout the study duration.

References

1. Food and Drug Administration (2021) 2020 Drug Trials Snapshots Summary Report. Available at: https://www.fda.gov/media/145718/download (Accessed: 19 July 2023)

2. Deloitte University EMEA CVBA. (2020) Deloitte Insights, Intelligent Clinical Trials. Available at https://www2.deloitte.com/content/dam/insights/us/articles/22934_intelligent-clinical-trials/DI_Intelligent-clinical-trials.pdf (Accessed 19 July 2023)

3. European Commission (2022) Unmet Health Care Needs Statistics. Available at: https://ec.europa.eu/eurostat/statistics-explained/index.php?title=Unmet_health_care_needs_statistics#Unmet_needs_for_health_care (Accessed 20 July 2023)

4. Centers for Disease Control and Prevention (2022) Unmet Need for Health Care. Available at: https://www.cdc.gov/nchs/hus/topics/unmet-need.htm (Accessed 20 July 2023)

5. Clarivate (2023) Taking the Pulse® U.S. 2013-2023 and Re-taking the Pulse U.S. 2022. Available at: https://clarivate.com/products/research-reports/multichannel-engagement/taking-the-pulse/ (Accessed August 2023)

6. European Medicines Agency (2023) Real world Evidence Framework to Support EU Regulatory Decision-Making. Available at: https://www.ema.europa.eu/en/documents/report/real world-evidence-framework-support-eu-regulatory-decision-making-report-experience-gained_.pdf (Accessed 21 July 2023)

7. Bolislis, WR., Fay, M., Kühler, TC. 2020. 'Use of Real world Data for New Drug Applications and Line Extensions', Clinical Therapeutics, May, 42(5), pp 926-938. Available at: https://pubmed.ncbi.nlm.nih.gov/32340916/

8. Albertson, TE., Murin, S., Sutter, ME., Chenoweth, JA. 2017. 'The Salford Lung Study: A Pioneering Comparative Effectiveness Approach to COPD and Asthma in Clinical Trials'. Pragmatic and Observational Research, September, 20(8), pp 175-181. Available at: https://pubmed.ncbi.nlm.nih.gov/29033625/

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