CHAPTER 1

Introduction

The landscape of clinical trials is undergoing a profound transformation, driven by the rise of real-world evidence (RWE). As traditional randomized controlled trials (RCTs) remain the gold standard for establishing efficacy and safety, the integration of real-world data (RWD)—such as electronic health records, wearables, patient registries, and other sources—is reshaping how we design, conduct, and interpret clinical trials. In recent years, the explosion of digital health technologies, advanced analytics, artificial intelligence, and regulatory shifts has unlocked new opportunities to complement RCTs with RWE. These advancements promise to accelerate drug development, enhance trial inclusivity, and provide deeper insights into real-world patient outcomes. Yet, they also introduce complex challenges—methodological, ethical, and operational—that demand careful consideration.

1.1 MEDICAL PRODUCT DEVELOPMENT PATHWAY

The discovery and development of medical products is a complex process, encompassing preclinical research, clinical development, and post-approval life-cycle management. Preclinical research leverages biomedical innovations like next-generation sequencing to generate new insights into disease processes (Luh and Yen, 2018; Siu et al., 2015; Torshizi and Wang, 2018). It also applies novel biotechnologies, such as high-throughput screening, to identify lead compounds for further investigation (Carnero, 2006; Dahlin and Walters, 2014; Lloyd, 2020). Furthermore, it involves laboratory experiments, including in vitro and in vivo tests, to assess potential toxicity in cells, tissues, and animals (Pelkonen et al., 2011; Saeidnia et al., 2015; Wienkers and Heath, 2005).

When a compound demonstrates preliminary evidence of efficacy and an acceptable toxicity profile in preclinical studies, investigation advances to clinical trials in humans. These trials are designed to confirm whether the investigational product produces the intended effects in a predefined target population. Clinical development typically proceeds through three phases: Phase I trials (dose-finding studies) establish tolerability and identify a maximum tolerated dose; Phase II trials (proof-of-concept studies) gather preliminary data on efficacy to inform "Go/No-Go" decisions for larger trials; lower study doses to establish lower limit of dose range; and Phase III trials (confirmatory trials) definitively demonstrate the product's safety and efficacy in a broader patient group for the studied dose(s) (Friedman et al., 2010; Piantadosi, 2017).

If these trials generate substantial evidence of the product's favorable benefit-risk profile, the sponsor may submit a New Drug Application (NDA) to regulatory agencies for marketing authorization. Following approval, the product enters the market, and its safety and effectiveness are continuously monitored in the general population. A detailed description of the clinical development process is provided in Chapter 3.

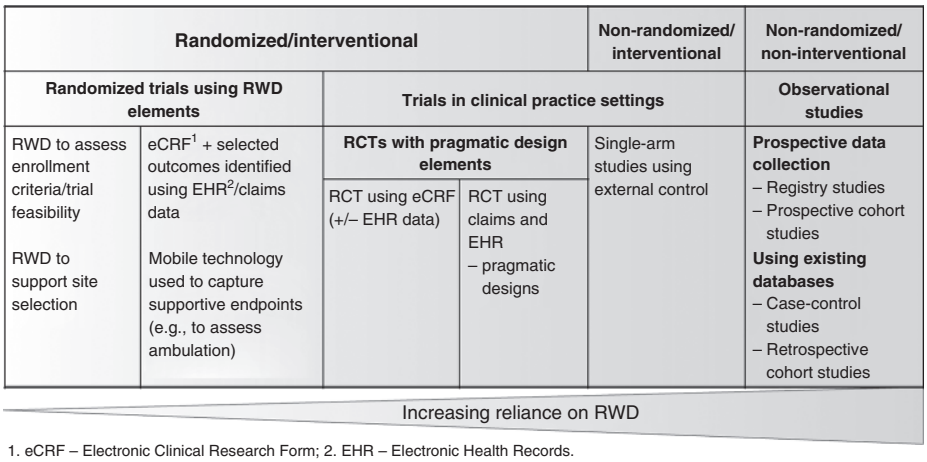

FIGURE 1.1 A wide spectrum of study designs and potential uses of RWD/RWE.
Source: Adapted from (Stein, 2019).

The drug development process is iterative, with each stage critically informed by evidence accumulated from all preceding steps. For instance, the design of a Phase II trial is grounded in data from Phase I and preclinical studies, just as a Phase III RCT is constructed upon the totality of evidence from earlier clinical and preclinical phases.

A prominent trend in modern clinical development is the growing integration of RWD and RWE across all stages. As illustrated in Figure 1.1 (Stein, 2019), RWE is now utilized in the design, conduct, and analysis of a wide spectrum of studies, from interventional RCTs to non-interventional, observational research. For example, RWD is increasingly leveraged for trial feasibility assessments—estimating patient population size, standard-of-care comparators, timelines, and costs (Rajadhyaksha, 2010)—as well as for planning eligibility criteria and enhancing patient recruitment (Evans et al., 2021b). See more discussion in Chapter 6.

1.2 DEVELOPMENT OF EVIDENCE-BASED MEDICINE

The foundations of evidence-based medicine (EBM) can be traced to the ninetieth century, a period marked by the systematic synthesis and dissemination of medical knowledge in textbooks and peer-reviewed journals (Claridge and Fabian, 2005). The core purpose of EBM is to guide clinical decisions for individual patients by integrating three key elements: the best available scientific evidence, the clinician's expertise, and the patient's values and preferences.

The definition of EBM has evolved over time. It was initially described by early proponents as "a systemic approach to analyze published research as the basis of clinical decision making" (Claridge and Fabian, 2005). This was later refined by Sackett et al. (Sackett et al., 1996) as "the conscientious and judicious use of current best evidence from clinical care research in the management of individual patients." The modern, more concise definition is "the integration of the best research evidence with clinical expertise and patient values and preferences" (Straus et al., 2019).

Archibald Cochrane is widely regarded as the father of the modern EBM (Stavrou et al., 2014). His seminal work, *Effectiveness and Efficiency: Random Reflections on Health Services* (Cochrane, 1972), profoundly influenced standards for reliably evaluating medical practice. Cochrane specifically championed the RCTs as the gold standard for assessing therapeutic effects and advocated for the systematic review and synthesis of RCTs to generate the most robust evidence on intervention outcomes. These principles formed a cornerstone of modern EBM and directly inspired the establishment of The Cochrane Collaboration (Levin, 2001; Shah and Chung, 2009).

While RCTs are generally considered the "gold standard" for establishing efficacy and occupy the highest tier in traditional evidence hierarchies (Figure 1.2) (Burns et al., 2011), they possess inherent limitations. These include under-representation of the general target population, limited generalizability (external validity), short duration, reliance on surrogate endpoints, and high costs (Frieden, 2017; Richesson et al., 2020); further details on these constraints are discussed in Chapter 3.

On the other hand, RWE studies, which generate "clinical evidence regarding the usage and potential benefits or risks of a medical product" from RWD, serve as a critical supplement to RCTs. They provide insights into a product's effectiveness and safety in settings that reflect routine clinical practice. An RWE study may leverage existing, fit-for-purpose RWD sources like electronic health records (EHRs), or be a dedicated observational study, either retrospective or prospective.

In the framework of EBM, the other two pillars—clinical expertise and patient values and preferences—can be viewed as forms of evidence generated from the "real-world" of clinical practice. While historically considered a lower level of evidence, RWE systematically captures and analyzes these very elements. Ultimately, it is the combination of rigorous evidence from RCTs with the practical, contextual evidence from RWE studies that creates the totality of evidence essential for informed regulatory and clinical decision-making throughout a product's life cycle; see Chapter 5 for details.

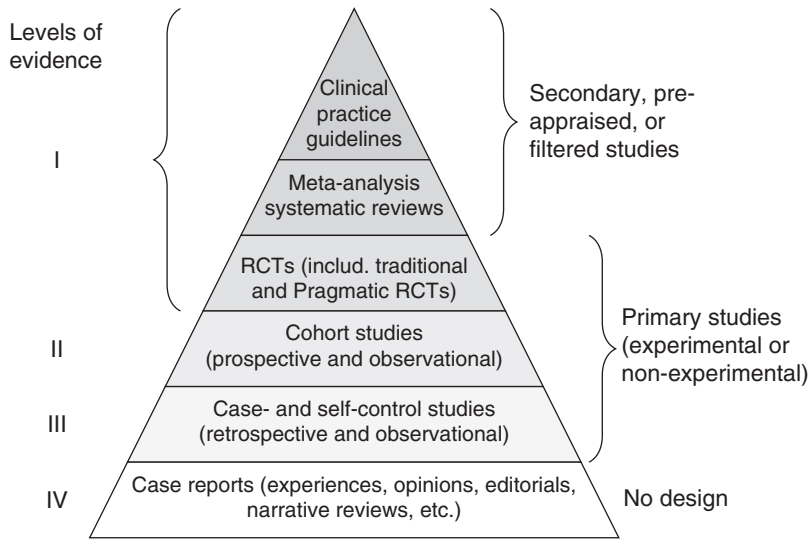

FIGURE 1.2 Level/strength of evidence generated from clinical practice guidelines, meta-analysis, experimental and nonexperimental studies, and case series and reports.

1.3 THE 21ST CENTURY CURES ACT

The 21st Century Cures Act (Cures Act), signed into law in December 2016, was designed to accelerate medical product development and bring innovative treatments to patients more rapidly and efficiently (US Congress, 2016). Building on the FDA's ongoing efforts to incorporate patient perspectives, the Act mandates that the agency modernize development paradigms, including the use of RWE, to expedite the review and approval of novel products.

The FDA's subsequent RWE Framework outlines how RWD can be leveraged in this endeavor, for instance, by assembling geographically distributed research cohorts to facilitate drug development for rare diseases (FDA, 2018f). Indeed, the agency has an established history of utilizing RWE to support regulatory decisions in this area, a practice that has been extensively documented in the literature (Chen et al., 2023a; Feinberg et al., 2020; Gross, 2021; He et al., 2023b; Jarow et al., 2017; Liu et al., 2022b; Purpura et al., 2022).

1.4 REGULATORY GUIDANCE AND RELATED DOCUMENTS

In recent years, regulatory agencies worldwide have launched numerous frameworks and initiatives and released guidance to support the use of RWD and RWE in drug development and regulatory decision-making. This section provides a summary of key guidance from major international agencies, including the International Council for Harmonisation (ICH), with a specific focus on rare disease drug development.

1.4.1 Guidance and Related Documents by the FDA

The FDA's 2018 *Framework for Its RWE Program* established the agency's foundational approach, defining the scope of RWD use, outlining an evaluation framework for regulatory decision-making, and highlighting initial demonstration projects (FDA, 2018f). These projects, conducted across multiple venues, are a key mechanism for the FDA to promote shared learning with external stakeholders (FDA, 2023n).

A significant subsequent initiative is the Advancing RWE Program, launched in October 2022. This program provides a forum for sponsors to discuss RWE with agency staff and is designed with three core objectives: (1) identifying approaches for generating RWE to support new effectiveness claims or fulfill post-approval study requirements; (2) developing consistent agency processes for RWE evaluation; and (3) clarifying the RWE characteristics that can inform regulatory decisions (FDA, 2023g).

Within this program, the Oncology Center of Excellence (OCE) has initiated a dedicated Oncology RWE Program (FDA, 2023q). Its strategic priorities are to:

- Optimize knowledge building through a centralized RWD research portfolio.
- Advance regulatory science and policy via methodological research and collaboration.
- Foster strategic partnerships for the pragmatic use of RWD.
- Accelerate the field through leadership, training, and rigorous methods development.

Building upon its RWE Program framework, the FDA has published numerous guidance documents on the use of RWD and RWE to support drug development and regulatory decision-making. Key examples of such guidance documents for drug and biological products include: (1) *Use of Electronic Health Record Data in Clinical Investigations* (FDA,

2018k), (2) *Real-World Data: Assessing Electronic Health Records and Medical Claims Data to Support Regulatory Decision-Making for Drug and Biological Products* (FDA, 2024b), (3) *Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products* (FDA, 2023e), (4) *Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products* (FDA, 2023i), (5) *Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drug and Biological Products* (FDA, 2022e), (6) *Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products* (FDA, 2023k).

In addition, the FDA has issued complementary guidance for medical devices (FDA, 2017c) and established data standards for regulatory submissions containing RWD (FDA, 2023d).

1.4.2 Guidance and Related Documents by the EMA

The European Medicines Agency (EMA) has established a strategic framework to advance the use of RWE, beginning with its Regulatory Science to 2025 strategy which promotes high-quality RWD in decision-making (EMA, 2018b, 2020). A key initiative under this framework is the Big Data Task Force, established with the Heads of Medicines Agencies (HMA) to leverage large data sources for regulatory innovation (EMA, 2019b). This includes maintaining a metadata catalog of RWD sources to facilitate their use in product development (EMA, 2022c).

A cornerstone of the EMA's RWE efforts is the Data Analysis and Real World Interrogation Network (DARWIN EU®). Launched in 2021, its mandate is to provide timely, high-quality RWE by: (1) cataloging European data sources; (2) delivering validated evidence on medicine use, safety, and effectiveness; and (3) conducting non-interventional studies to address specific regulatory questions (EMA, 2023a).

While the EMA has published various pharmacoepidemiology guidelines (EMA, 2013, 2017b), the following are particularly relevant for generating efficacy evidence in drug development: (1) the *Guideline on registry-based studies* (EMA, 2021a, 2021b): (2) the *Scientific guidance on post-authorisation efficacy studies* (EMA, 2017c), and the *Reflection paper on establishing efficacy based on single-arm trials* (EMA, 2024b).

1.4.3 Guidance and Related Documents by the NMPA

To foster innovation and improve the efficiency of pharmaceutical research and development, the China National Medical Products Administration (NMPA) has actively promoted the use of RWE to support drug regulatory decision-making. A cornerstone of this initiative is the development of a comprehensive series of guidance documents on RWE studies, marking a significant contribution to the field of RWE in China's drug development landscape.

Building upon a foundational framework of four core guidelines—covering RWE, RWD, RWE study design and protocol development, and regulatory communication—the NMPA has extended its guidance to address specific clinical applications in areas such as oncology, rare diseases, pediatric drugs, and traditional Chinese medicine. This section provides an outline of the core content and distinctive features for this RWE guidance series, elucidates its role in advancing drug development, and discusses the ongoing challenges in utilizing RWE to support regulatory decisions in China.

Examples of RWE-related guidance documents from the NMPA include: (1) the core *Guideline on Using Real World Evidence to Support Drug Development and Regulatory Decision-making* (NMPA, 2020b), (2) the *Guideline on Using Real-World Data to Generate Real-World Evidence* (NMPA, 2021), (3) the *Guideline on Real-World Study Design and Protocol Framework* (NMPA, 2023b), (4) the *Statistical Guideline on Clinical Trials for Rare Diseases* (NMPA, 2022a), (5) the *Guideline on Using Single-Arm Trials to Support Marketing Applications for Antitumor Drugs* (NMPA, 2023a), and (6) the *Guidance on Natural History Studies of Rare Diseases for Drug Development* (NMPA, 2023c). A broader perspective is offered by Wang et al. (2024a).

1.4.4 Guidance and Related Documents by the ICH

The ICH has taken steps to harmonize the use of RWD in regulatory decision-making. In March 2022, it issued a final concept paper establishing an internationally harmonized framework for the planning, design, and analysis of pharmacoepidemiological studies that utilize RWD for safety assessment (ICH, 2022b).

Building on this, a September 2023 reflection paper outlined a strategic approach to address persistent global challenges, including a lack of standardized RWD/RWE terminology, variable data quality, and diverse study designs (ICH, 2023c). This reflection paper aims to facilitate convergence on terminology and standardized reporting formats, while also guiding the regulatory assessment of RWD and RWE.

1.4.5 Guidance and Related Documents by the MHLW of Japan

In 2021, Japan's Ministry of Health, Labour and Welfare (MHLW) released the *Basic Principles on Utilization of Registry for Applications* (MHLW, 2021a). This guidance outlines five primary applications for registry data in drug development: (1) clinical study planning, (2) serving as an external control, (3) complementing or substituting for a clinical study, (4) supporting conditional approval, and (5) evaluating efficacy and safety in post-marketing studies.

The document specifically acknowledges the utility of registries for rare diseases and provides general considerations for their use, including data reliability, appropriateness, patient consent, and the importance of early consultation with regulators. It further details specific considerations for using registry data as an external control, such as the suitability of the patient population, endpoints, evaluation period, and statistical methods.

To supplement these principles, the MHLW has also issued several supporting documents: *Points to Consider for Ensuring the Reliability in Utilization of Registry Data* (MHLW, 2021b), along with question-and-answer documents for drugs (MHLW, 2022), and regenerative medical products (MHLW, 2023b).

1.4.6 Guidance and Related Documents by Other Regulatory Agencies

1.4.6.1 Canada

The Canadian Agency for Drugs and Technologies in Health (CADTH) has issued guidance to promote transparent reporting of RWE studies for regulatory decision-making (CADTH, 2023). This guidance explicitly addresses the unique challenges of rare disease

drug development, including the frequent infeasibility of RCTs due to small patient populations and the lack of available comparators. It further notes that RWD can be utilized to assess treatment effectiveness and estimate the population size of patients with a rare disease who might benefit from a therapy.

Complementing this guidance, CADTH—often in collaboration with other organizations—has launched initiatives like the Best Brains Exchange. This forum serves as a learning platform to support the optimal integration of RWE into decision-making processes for rare disease therapies (CADTH, 2024).

1.4.6.2 Australia

The Australian Government Department of Health released a National Strategic Action Plan for Rare Diseases in 2020, building upon the foundation of Australia's Orphan Drug Program (TGA, 2015). This plan emphasizes multi-stakeholder collaboration to ensure the high-quality collection and effective use of rare disease data (RVA, 2020). Its key priorities include advocating for broad epidemiological surveillance, improving data collection and utilization, developing a national research strategy for genomics and precision medicine, and fostering a supportive environment for clinical trials in Australia.

In alignment with this national strategy, the Therapeutic Goods Administration (TGA) of Australia has implemented initiatives to incorporate RWE and patient-reported outcomes (PROs) into regulatory decision-making. The TGA has also formally adopted international guidelines on the use of diseases (TGA, 2024).

1.4.6.3 South Korea

The Ministry of Food and Drug Safety of South Korea (MFDS) is actively promoting the use of RWD and RWE for regulatory decision-making, particularly for rare diseases where patient populations are limited. The agency has issued guidance on utilizing RWD from sources like electronic medical records (EMRs) to supplement or inform clinical trial data (Burns et al., 2023).

For instance, its guideline on medical information database studies outlines standards for the planning, execution, and reporting of regulatory-grade RWE to support drug approval applications, including those for rare disease treatments (MFDS, 2021).

In summary, regulatory agencies worldwide have issued guidance documents governing the use of RWD and RWE to support drug development and regulatory decision-making. These guidelines share several common principles: (1) defining the roles of RWD/RWE in general and rare disease drug development; (2) emphasizing RWD standardization and quality assurance; (3) outlining methodological approaches for generating RWE, such as the use of historical controls; and (4) promoting multi-stakeholder collaboration to advance the field (Burns et al., 2023; Vaghela et al., 2024).

Despite this convergence on core principles, the level of detail and specific focus in these guidelines vary significantly. Key factors driving this heterogeneity include: (1) differences in the epidemiology and definitions of rare diseases across regions; (2) divergent government policies and medical practices, leading to distinct national priorities; (3) varying levels of maturity, experience, and regulatory acceptance of RWD/RWE; and (4) diverse levels of engagement and collaboration among academia, industry, and government (Beaulieu-Jones et al., 2020; CIOMS, 2023; ICH, 2024a).

1.5 DISCUSSION AND SUMMARY

The landscape of clinical development is at a pivotal juncture. The RCT, long regarded as the undisputed gold standard for establishing efficacy, is no longer being asked to stand alone. As this chapter has outlined, we are transitioning from an era of *evidence hierarchies* to one of *evidence integration*. The driving force behind this transformation is the rise of RWE, which offers a complementary view of how medical interventions perform in the complex, diverse reality of routine clinical practice.

This chapter has traced the philosophical and regulatory foundations of this new era. The principles of EBM, championed by pioneers like Archibald Cochrane, have always called for the integration of best research evidence with clinical expertise and patient values. RWE provides the methodological bridge to systematically capture and analyze the latter two components, transforming anecdotal experience into analyzable data. It is the natural evolution of EBM, powered by the digital footprint of modern healthcare.

Importantly, this is not a story of replacement but of synergy. While RCTs excel at answering the focused question "Can this treatment work under ideal conditions?" (efficacy), RWE helps answer the equally vital question "Does this treatment work in everyday practice for a broad range of patients?" (effectiveness). This complementary relationship is essential for addressing the unique challenges of modern drug development, especially in areas like rare diseases, oncology, and chronic conditions where traditional trial designs face significant practical and ethical hurdles.

The global regulatory momentum, as demonstrated by frameworks and initiatives from the FDA, EMA, NMPA, and other major agencies, underscores that this integration is now a core strategic priority. The proliferation of guidance documents—from high-level frameworks to specific methodological recommendations—provides a clear signal: the use of RWE is transitioning from exploratory to foundational. These frameworks, initiatives, and guidelines consistently emphasize common pillars of data quality, methodological rigor, and stakeholder collaboration, even as they adapt to regional contexts and healthcare system variations.

However, the successful integration of RWE into the clinical trial ecosystem is not without its challenges. Key discussions that will permeate this book include:

- *Methodological rigor*. How do we design RWE studies to minimize confounding and bias to a degree that supports confident regulatory and clinical decision-making?
- *Data quality and fitness-for-purpose*. How do we ensure that RWD from sources like EHRs and registries are standardized, complete, and fit to answer specific research questions?
- *Bridging the evidence gap*. What are the optimal trial designs—such as pragmatic trials, hybrid models, and externally controlled trials—that leverage the strengths of both RCTs and RWE?
- *Regulatory acceptance*. How can sponsors generate RWE that meets the evolving standards of regulatory agencies for both safety and effectiveness claims?

In conclusion, the *era of real-world evidence* represents a paradigm shift toward a more efficient, generalizable, and patient-centric clinical development process. The goal is a future in which clinical trials are continuously informed by RWD—making them smarter, faster, and more relevant. The subsequent chapters of this book will delve into the methodologies, applications, and case studies that are turning this vision into a reality, providing a comprehensive guide for navigating the exciting and transformative integration of clinical trials and RWE.

1.6 SUPPLEMENTS

1. *Broader preregistration and transparency for RWE study protocols*. At its heart, preregistration and transparency for RWE studies involve publicly documenting the study's design, methodology, and analysis plan before the analysis is conducted and, in some cases, even before the data are accessed. This practice is a direct adaptation of the long-standing requirement for prospective registration of interventional clinical trials on platforms like ClinicalTrials.gov.

   The fundamental goal is to distinguish between hypothesis-generating (exploratory) and hypothesis-testing (confirmatory) research. For RWE to be used in high-stakes decision-making—such as supporting a new drug indication, informing a regulatory safety decision, or changing clinical guidelines—it must be generated with the same scientific rigor and freedom from bias as a Phase III RCT. Preregistration is a critical tool to achieve this. A comprehensive preregistration for a confirmatory RWE study should detail: (1) research question and its associated estimands, (2) data sources, (3) study design, (4) cohort definition, (5) primary and secondary endpoints, (6) covariates, (7) statistical analysis plan (SAP) (including at least methods to control confounding, prespecified sensitivity analysis, and strategies to address missing data), and (8) plans for deviations. Several platforms now support the preregistration of RWE studies such as ClinicalTrials.gov and OSF (Open Science Framework) Registries.

   In summary, broader preregistration and transparency are foundational pillars for establishing RWE as a reliable, confirmatory tool in clinical development and regulation.
2. *Global divergence*. The adoption of RWD and RWE in clinical trials and regulatory decision-making varies significantly worldwide. This divergence is driven by differences in regulatory frameworks, data infrastructure, healthcare priorities, and clinical practices. Regional emphases are distinct: the United States often prioritizes methodological rigor in emulated trials; the European Union focuses on building multi-database networks and generating evidence for the product lifecycle; China aims to enhance the efficiency and inclusivity of its drug development and approval processes; Japan frequently utilizes registry-driven evidence; while many emerging markets currently rely on RWE primarily for post-marketing surveillance. This heterogeneity presents a substantial challenge for global harmonization, particularly for multiregional submissions that leverage RWE.