# Drug regulatory decision-making: Evidence and real-world data as allies of randomized controlled trials

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**ABSTRACT**
With the Covid-19 pandemic, the world has been faced with the pragmatic search for effective treatment and highlighted the importance of real-world evidence and data as valuable for decision-making by different stakeholders. This evidence has brought new insights into efficacy, safety, and quality of drugs with patient-centered clinical outcomes. This paper describes some important elements of real-world evidence and data: 1) they are related to the patient's health status and/or the provision of health care routinely collected from various sources; 2) although, controlled clinical trial results are the basis for clinical decision-making, they can currently incorporate real-world evidence and data; 3) there is increasing use to support regulatory decision-making; 4) are underutilized sources to assess the impact on public health in risk minimization, health technology assessment, costs, and clinical decisions.

**Keywords:** Evidence, real-world data, controlled clinical trial, system of records.

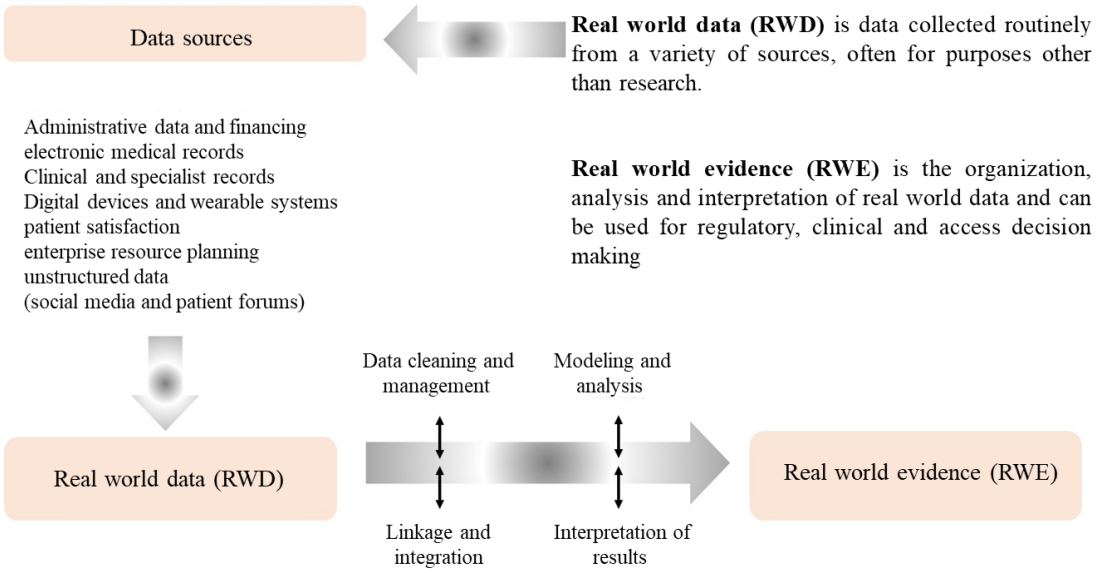
## 1 INTRODUCTION

### 1.1 THE POTENTIAL OF REAL-WORLD EVIDENCE AND DATA

With the Covid-19 pandemic, Real World Evidence (RWE) and Real-World Data (RWD) have contributed to broadening the view of patients and drugs excluded or not implemented in randomized controlled trials (RCTs) (KACIROTI *et al.*, 2021). It showed the world the need to maximize responses from stakeholders (researchers, funders, health systems, regulators, health professionals and patients) and the importance of scientific cooperation initiatives, data sharing and transparency.

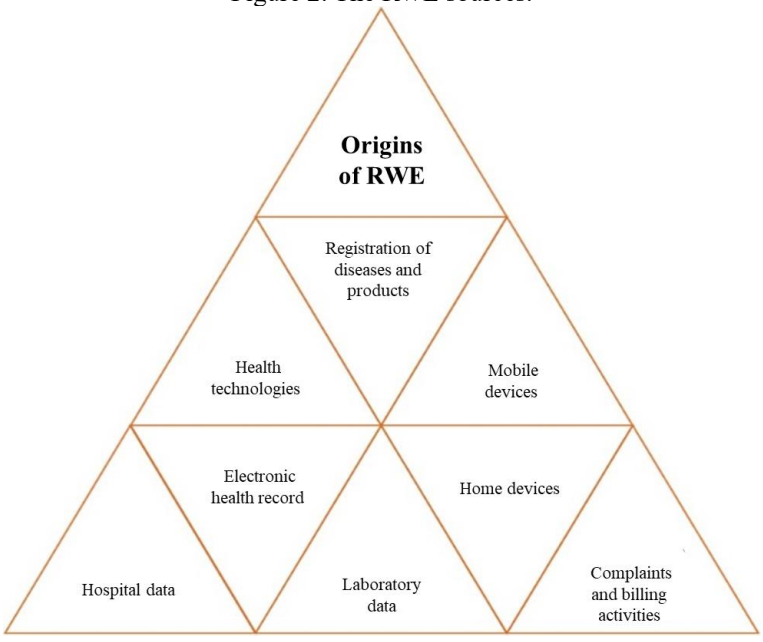
RWE studies rely on RWD (health records, data captured by mobile phones, other devices, data mining by Data Mining, Big Data, social media monitoring) Figure 1. They detect cost, benefits and risks, side effects and other long-term outcomes (DREYER, 2022; LIU; PANAGIOTAKOS, 2022).

Figure 1. Data fundamentals and real-world evidence.




In December 2016 the Food and Drug Administration (FDA) released the 21st Century Cures Act (Cures Act), accelerating the development and innovation of medical products. And in 2018, the FDA released guidance for evaluating RWE Figure 2 sources. RWE and RWD have become part of life sciences industry decisions by adopting methodology that meets the agency's regulatory standards in terms of efficacy and safety (FDA, 2020).

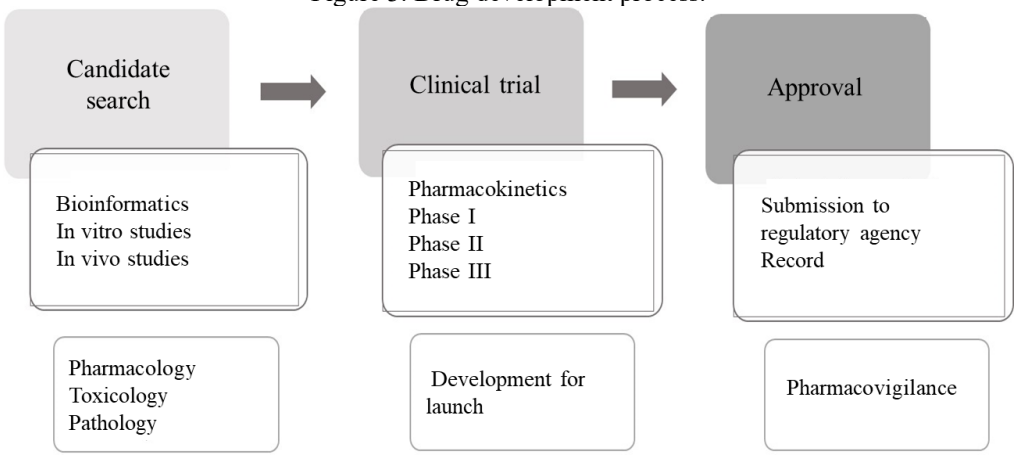
Figure 2. The RWE sources.




Much of the RWE and RWD literature expressed regulatory aspects (approval of new products for rare diseases). Currently, they are in the Research and Development (R&D) of biopharmaceutical companies applying RWD in: 1) pipeline strategy; 2) new sources of RWD to develop products; 3)

clinical development; (4) "big" RWD analysis; and (5) support for internal decisions (SCHUHMACHER; GASSMANN; HINDER, 2016) Figure 3.

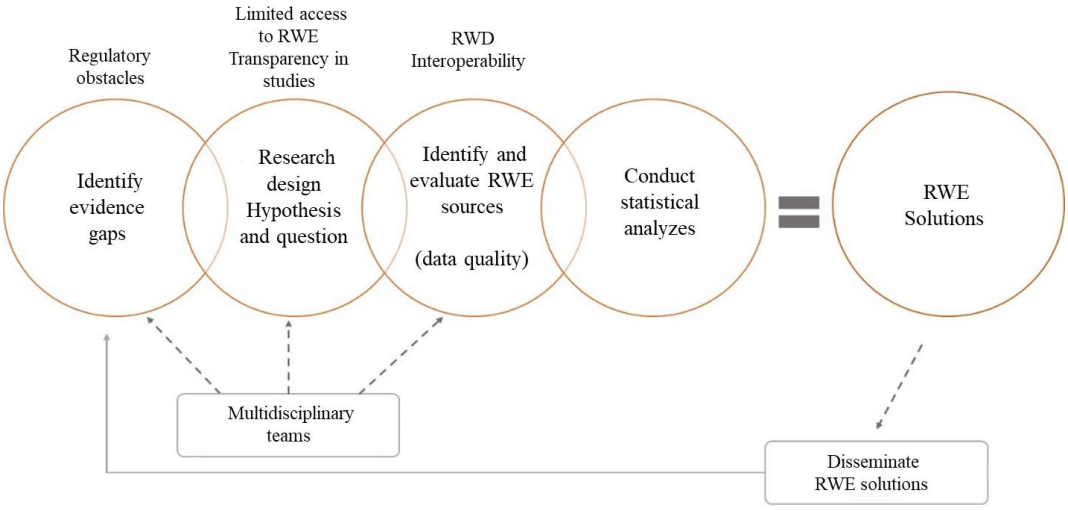
Figure 3. Drug development process.




A close look at the risks and benefits of an RWE drug is clinical evidence derived from the analysis of real-life data. And RWD are routinely collected data relating to the patient's health or clinical condition, captured from a wide variety of sources from part of routine care (SINDUSFARMA, 2022)

Understanding the scientific structure of RWE is a key factor and may start with drug treatment evidence gaps. This identification needs to include various perspectives of patients, stakeholders, healthcare professionals, and managers and policymakers. Failure in this step may result in the formulation of an incorrect research question, which may affect the rest of the RWE steps, generating evidence of little utility in decision making (Figure 4).

Figure 4. The challenges of structuring the RWE steps.

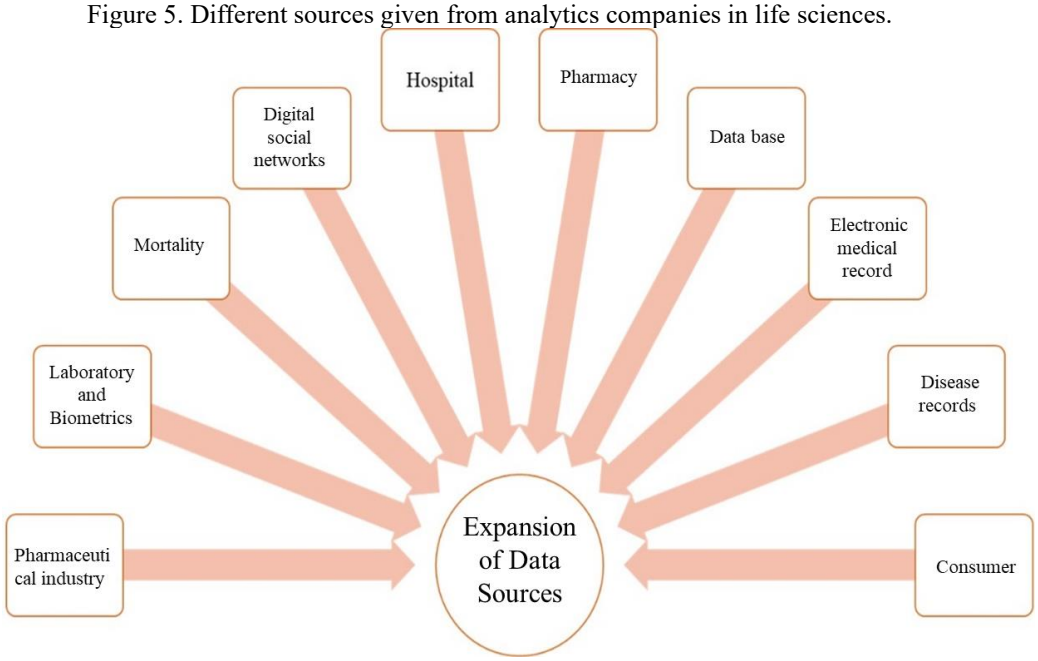


Another crucial step is the identification and evaluation of RWD. The quality of RWD sources varies significantly and there is limited research to understand this aspect. It is essential to structure a quality assessment model of the available RWD sources. Periodic evaluations are necessary to ensure the accuracy of the data (SINDUSFARMA, 2022).

Currently faced with regulatory pressures of care costs, stakeholders (researchers, funders, health systems, regulators, healthcare professionals and patients) are being guided by the right treatment to the right patient as measured by real-world outcomes. Some questions are among these actors: a) how to identify patients with lower risk and greater benefit of treatment "X"? b) how to manage the patient population, with a view to a policy, to promote the balance between clinical and financial outcomes? c) how to predict, identify, minimize, monitor and measure drug safety problems? d) how to ensure high standards of treatment adherence, patient education, support and follow-up to maximize the best outcome?

The life sciences industry (pharmaceutical, medical devices, biotechnology, digital therapy companies, and other innovators) works on investing in quality RWD and RWE to meet the demands of health management and health care outcomes. Today's analytics companies are growing to meet the demands of integrated data that have the breadth of patient health Figure 5.

Figure 5. Different sources given from analytics companies in life sciences.




Observing the exposed scenario goes through the pragmatism of Covid-19 in using research designs, in addition to RCT, in producing patient-centered evidence. It showed research advances (e.g. genomics, proteomics, gut microbiome, epigenomics, big data science, computational biology and artificial intelligence). It revealed flaws in the production and synthesis of evidence in medicine, public health and factors that influence clinical research (LONDON; KIMMELMAN, 2020). And it

reinforced the paradigm shift in how RCTs are designed, conducted, monitored, adapted, reported and regulated (SUBBIAH, 2023).

## 1.2 THE RELEVANCE AND CONSIDERATIONS OF RANDOMIZED CONTROLLED TRIALS IN DRUG R&D

The drug R&D and RCT scenario has a high cost to stakeholders (researchers, funders, health systems, regulatory bodies, health professionals and patients) around 1.5 to 2.5 billion dollars and inefficiencies and deficiencies of the health system (DIMASI; GRABOWSKI; Hansen, 2016; WOUTERS; MCKEE; LUYTEN, 2020). During the Covid-19 pandemic a number of scientific questions to be answered exceeded the responsiveness of RCTs. So, RWE studies were the main sources of evidence of symptoms, influence of patient characteristics, and the risk of morbidity and mortality (KACIROTI *et al.*, 2021; PETRILLI *et al.*, 2020; SULEYMAN *et al.*, 2020).

Since the 1960s, RCT has been the foundation for demonstrating the efficacy and safety of drugs for regulatory approval. However, after approval, patient outcomes may differ in clinical practice with no guarantee of safety to adverse effects. Given safety limitations, after the 90s, the FDA and EMA (European Medicines Agency) began using clinical practice evidence in terms of RWE and RWD and continue to establish legal aspects of nonrandomized trials in supporting evidence of RCT or assisting in clinical decision-making (EMA, 2023; FDA, 2023).

RCT researchers express concern that RWE may not be reliable in establishing causal relationships because it is neither randomized nor blinded, and RWD is outside strict quality control (EICHLER *et al.*, 2021). However, factors intrinsic to this design may limit the generation of evidence: a) rigid selection criteria that reduce external validity; b) certain conditions the design is not feasible; c) the duration is not always sufficient to evaluate long-term treatment or identify rare side effects; d) it is not always possible to perform in populations with specific diseases due to the difficulty of recruiting patients and e) they tend to take longer than real-life studies (SINDUSFARMA, 2022). And this may fail to generate evidence for practical decisions by stakeholders (researchers, funders, health systems, regulators, health professionals and patients) (CORRIGAN-CURAY; SACKS; Woodcock, 2018; SHERMAN *et al.*, 2016).

The RCT information vacuum is of interest to regulatory agencies, especially for certain patient groups. Although RCT plays a central role in determining treatment efficacy, there is little evidence on vulnerable subgroups. RWE and RWD are often the only source of information about treatment outcomes for patients with complications and vulnerabilities (high-risk family history, lifestyle factors, limited access to health care, and economic hardship) (DREYER, 2022).

RWD as a patient-centered research modality will become a routine source of data for RCT (ABERNETHY, 2023). This shows that it is necessary to advance in studies with non-interventional

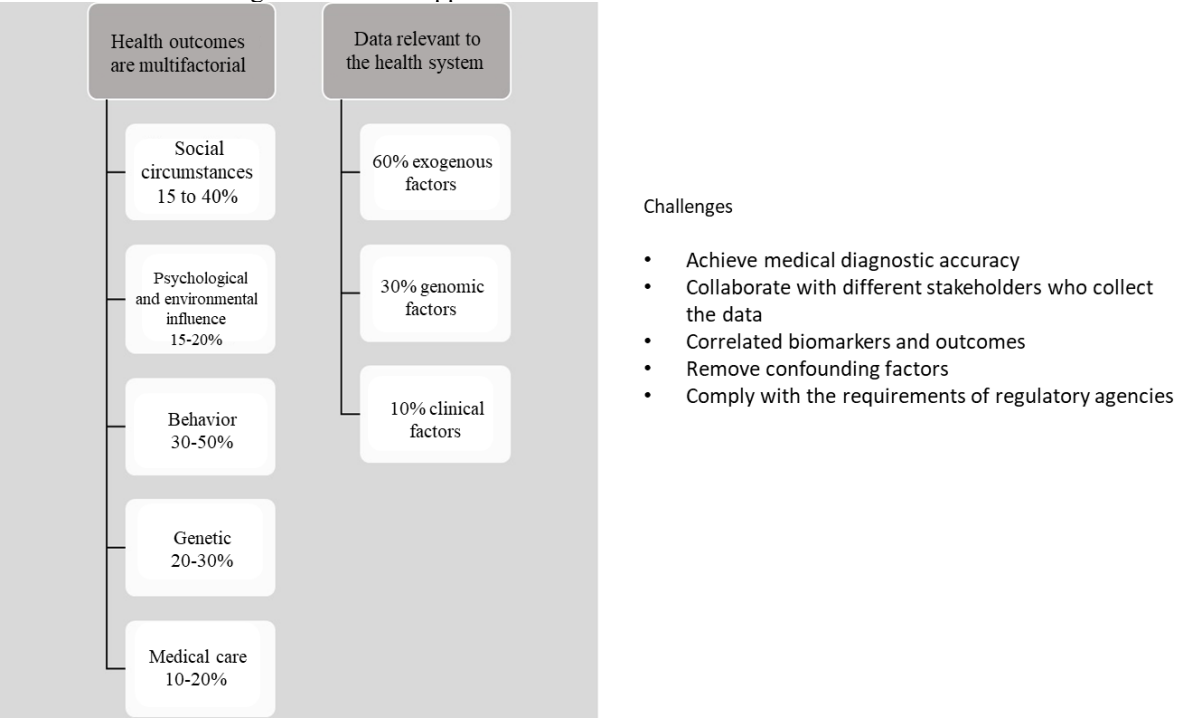
methodology of comparative efficacy, as they provide indispensable information on the risks and benefits of treatment in patients with complications. To do so, stakeholders (researchers, funders, health systems, regulatory bodies, health professionals and patients) interested in evidence should identify the specific health status or clinical phenomenon of interest and consider each step between clinical phenomena within the research database. Propose specific questions about possible errors or biases that affect each of the steps (SIMON *et al.*, 2022; VELENTGAS *et al.*, 2013).

The RWE and RWD are aggregated values to the RCTs. Tan et al (2022) showed proportions of those excluded from these studies and the importance of data collected during routine care. They studied electronic records of prescriptions and medical visits to quantify the proportion of people with a certain condition who were excluded from RCTs due to vulnerabilities such as multimorbidity, polypharmacy and age (adolescents or elderly). The exclusion rate was higher than 50% in adolescents who use several medications and similar values in the elderly over 80 years. Multimorbidity was excluded by 91.1% and concomitant medications by 52.5%. They identified gaps for cardiovascular disease and psychiatric conditions with implications for RCT outcomes. (TAN *et al.*, 2022).

The duty to care with concrete benefits to patients depends on the ability of different stakeholders the duty to learn. The requirement in the clinical process ensures that the research progresses without compromising the interests of patients (LONDON; SEYMOUR, 2023). This question is written in the work of Naggie *et al (2023) report the results of the RCT of the Accelerating Covid-19 Therapeutic Interventions and Vaccines 6 (ACTIV-6), in which 1,206 participants with mild and moderate cases of Covid-19 were not benefited with Ivermectin* (NAGGIE et al., 2023). Not all medical decisions are difficult, some care situations medical knowledge is sufficient and are straightforward. They become complex as the number of diagnoses, treatment options, risk of complications, and amount of patient data increases.

Healthcare is transitioning with a focus on value and outcomes when delivering patient care. Several factors play a role in this process and technology allows incorporating studies of RWE and RWD as a demand of the health ecosystem by recognizing that clinical decisions reflect the diversity of the population, contexts that people live and receive this care (CAVLAN, OLÍVIA *et al.*, 2018) Figure 6.

Figure 6. Holistic approach to healthcare with vision to RWE and RWD.




The scope of these studies has changed in the health value chain (pharmaceutical companies, biotechnology and health system). They have moved from monitoring the safety of post-marketing drugs, to supporting RCT outcomes and improving the treatment approach through observational studies. And the health system has recognized management and outcomes as principles in coverage decisions (EMA, 2023).

Investment is needed in the interface infrastructure between research and care, because the success of RWE and RWD will depend on robust, scalable data from different sources. Prospective RCTs may benefit from data collection in routine clinical settings. For example, by collecting accurate movement information from Parkinson's patients, temporal assessment will be longitudinal with support from electronic records, sensors, and environmental information. These sources can inform the history of patients before the start of RCT, allow monitoring of safety and efficacy after the end of the trial (ABERNETHY, 2023).

The real impact of this trend line involves: 1) strong engagement between science and policy; 2) more open, reliable and responsible scholarly communication practices among policymakers and 3) increasing digitization and visualization of scholarly communication. That will result in the availability and sharing of basic research data in scholarly communication as part of the Open Data movement (SHAHIN *et al.*, 2020).

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