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Real-World Clinical Data: Shaping Evidence-Based Decision-Making In Diabetes Dosage Forms Powered By Natural Compounds

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Abstract

Real-world studies have emerged as a pivotal source of evidence for evaluating treatment effectiveness in clinical practice. While randomized clinical trials (RCTs) are the 'gold standard' for assessing the safety and efficacy of new therapeutic agents, the stringent inclusion and exclusion criteria in RCTs often limit the representativeness of trial populations vis-à-vis real-world patient cohorts. Real-world studies leverage electronic health records and claims databases, offering access to extensive datasets drawn from diverse patient groups. These studies can be observational, encompassing prospective or retrospective data collection over extended durations. Consequently, they offer insights into the long-term safety, especially concerning rare events, and the effectiveness of natural drugs in dosage forms in large, heterogeneous populations, shedding light on utilization patterns, healthcare outcomes, and economic implications. This review aims to elucidate the role of real-world evidence (RWE) studies in complementing RCT data, allowing for a more comprehensive assessment of the pros and cons of medications as they are practically used in clinical settings. We emphasize the importance of conceptualizing a target trial that RWE studies can emulate during the planning and execution phases. To facilitate understanding, we propose using graphical representations that underscore the temporality of crucial longitudinal study design choices. We also stress the need for transparent reporting of study elements to ensure reproducibility and recommend registering study protocols to enhance process transparency. These tools empower researchers, healthcare professionals, and stakeholders to efficiently comprehend each RWE study, assess its validity confidently, and make informed decisions based on its findings, particularly in diabetes research.

Keywords: Real-world evidence, Natural compounds, Diabetes, Dosage forms

Introduction

Real-world studies have become indispensable in complementing the evidence generated by randomized controlled trials (RCTs). RCTs are widely acknowledged for their ability to provide robust proof of medical intervention safety and efficacy. RCTs successfully mitigate bias and confounding by employing techniques like randomization and stringent patient selection criteria, thus establishing high internal validity. However, this often comes at the cost of external validity, as the trial populations may significantly differ from the broader patient populations encountered in real-world clinical practice. In response, real-world evidence (RWE) has emerged as a crucial means of assessing the practical effectiveness of medical interventions in a more diverse and representative patient population. RCTs' strict exclusion criteria frequently exclude most patients seen in routine clinical care, making RWE vital for understanding treatment effects in real-world, heterogeneous clinical settings, where patients often present with multiple comorbidities. Data from real-world studies can inform payers, clinicians, and patients' decisions regarding interventions outside the controlled research environment. It provides essential insights into drugs' long-term safety and effectiveness within larger patient populations, their economic performance in real-world scenarios, and their comparative effectiveness when measured against alternative treatments **[1-3]**.

Recent enhancements in the methodological rigor of real-world studies and the increased availability of higher-quality, comprehensive datasets have amplified the importance of findings from these investigations. Recognizing this, regulatory bodies like the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have acknowledged the significance of real-world data in supporting marketed products and contributing to product development and monitoring throughout their lifecycle. Moreover, national and regional healthcare bodies, such as the UK's National Institute for Health and Care Excellence (NICE) and Germany's Institute for Quality and Efficiency in Health Care (IQWiG), utilize real-world data for guiding clinical decision-making **[4,5]**. Payers also increasingly rely on such data to inform decisions, particularly in utilization management and formulary placement.

Transparency in real-world evidence in clinical therapies:

Given the growing number of real-world studies, more clinical evidence is now accessible for guiding treatment decisions and assessing the consequences of off-label usage. This review aims to

explore the impact of real-world clinical data and how its interpretation can assist clinicians in making informed decisions by appropriately assessing the clinical evidence available. Real-world data, as defined by the Association of the British Pharmaceutical Industry, refers to data collected outside the controlled confines of traditional randomized controlled trials (RCTs) with the aim of assessing real-world scenarios in clinical practice **[6]**. Real-world studies encompass both retrospective and prospective investigations, and when they incorporate prospective randomization, they are termed "pragmatic trial design" studies **[7]**. The primary distinction between RCTs and real-world studies can be attributed to (a) the research setting and (b) the source of evidence **[8]**. RCTs are typically conducted within a tightly controlled framework involving precisely defined patient populations. Patient selection frequently hinges on meeting stringent eligibility criteria for inclusion and exclusion. Participants in RCTs adhere to strict quality standards, with comprehensive monitoring, detailed case-report forms designed to capture additional information not found in regular medical records, and meticulous oversight by research personnel responsible for ensuring protocol adherence **(figure 1)**.

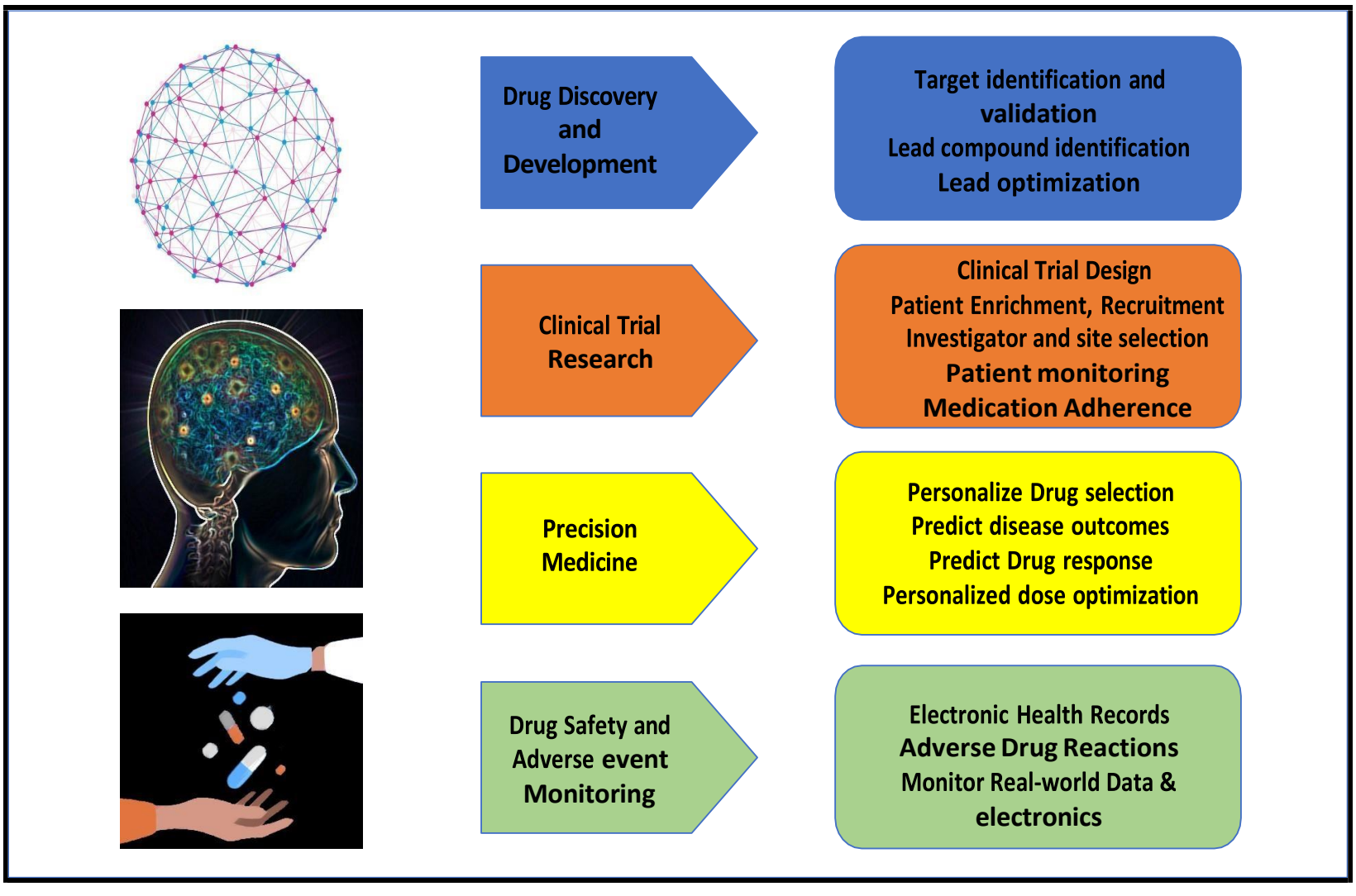

Figure 1: Application of real-world evidence in decision-making for natural compound delivery

In contrast, real-world evidence is often derived from diverse sources beyond the conventional clinical research setting. These sources may include non-research healthcare facilities, electronic health records (EHRs), patient registries, and administrative claims databases (often acquired from integrated healthcare delivery systems). Notably, real-world evidence can also be employed retrospectively as external control arms for RCTs to offer comparative efficacy data **[9-12]**. This article draws upon previous studies and does not involve research with human participants or animals performed by authors. A burgeoning source of real-world data is found in "pragmatic trials." These trials aim to demonstrate an intervention's practical, real-world effectiveness across a broad patient population **[13,14]**. They employ a prospective, randomized design and collect data on various health outcomes within a diverse and heterogeneous population, mirroring clinical practice **[15–17]**. Pragmatic trials unfold within everyday practice settings and include a population pertinent to the intervention. A control group receiving an acceptable standard of care (or placebo) is also incorporated, focusing on significant outcomes for the concerned population **[18]**. Pragmatic trials intentionally refrain from controlling aspects of care other than the intervention under study. This means clinicians can exercise their clinical judgment when selecting other medications **[19]**. These trials might center on specific patient types or treatments, with study coordinators choosing patients, clinicians, and clinical practices to enhance external validity, i.e., to ensure the results apply to routine practice **[20]**.

Consequently, pragmatic trials yield data about various clinically pertinent real-world factors, including different treatments, patient- and clinician-friendly dosing and treatment protocols, and cost-effectiveness. This information, in turn, contributes to addressing practice- and policy-relevant matters and prioritizes the outcomes most important to patients. It also takes into account real-world treatment adherence and compliance, directly assessing the impact of a medication or treatment regimen on patients.

Real-World Research: Enhancing General Applicability:

The natural progression of diabetes, particularly type 2 diabetes, poses challenges for researchers conducting Real-World Data (RWD) studies on diabetes treatment. One of the crucial pitfalls is the inadequate consideration of the heterogeneity in diabetes status. Diabetes is often treated as a binary condition, but this simplistic approach fails to capture the intricate aspects of the disease. Patients with diabetes share standard features but can be grouped into subcategories based on changing disease characteristics. Moreover, these characteristics can evolve differently in various patients, causing the definition of an 'average' patient to change over time. The wide range of available diabetes treatments, which can be used alone or in combination, further complicates the categorization and comparison of patients. Just as diabetes is dynamic, so are its treatments. A longitudinal perspective and analytical approaches respecting this temporal aspect are necessary **[21-23]**. Mistaken analytical approaches in dealing with the complexities of diabetes have led to incorrect inferences due to immortal time and associated bias in some instances. Eternal time is a period in which a patient, by definition, remains event-free. It often results from using future information to characterize a patient's status at study enrollment. This can create a group of 'immortal' patients who must have survived to meet the definition. Immortal time bias can affect either the treated group, the comparison group, or both. Since RWD often covers the entire study timeframe, it's easy to inadvertently introduce immortal time without the safeguards present in a Randomized Controlled Trial (RCT). Researchers using RWD must be aware of eternal time and take measures to prevent its introduction. Although it may be tempting to use future information to categorize patients when studying a condition like diabetes that changes over time, it opens the door to time-related biases.

In addition to the unique challenges posed by diabetes, Real-World Data (RWD) studies must grapple with issues of selection bias and information bias. Selection bias involves the characteristics of patients receiving the treatment under investigation and how they differ from the patients serving as comparisons. Unlike Randomized Controlled Trials (RCTs), where treatments are randomly assigned, the nonrandom allocation of treatments in RWD can introduce numerous differences between compared groups, collectively known as selection bias. These disparities can range from evident factors like age or gender to more clinical attributes such as comorbidities or concurrent medications. Furthermore, diabetes features can vary across comparison groups, including the duration of diabetes, laboratory results, or a history of hypoglycemia episodes. Yet, particular distinctions may remain hidden, like the treating physician's perception of the patient's likely adherence to treatment or monitoring. In protocol-driven RCTs, adherence and outcome documentation occur systematically at standard intervals after patient identification and treatment assignment **[24-28]**.

In contrast, RWD-based outcomes are identified, monitored, and documented based on the discretion of the treating physician(s). This can lead to the preferential documentation of more severe outcomes, as they involve interactions with the healthcare system, which are then recorded within the RWD. Many outcomes relevant to patients with diabetes encompass subtle changes in the spectrum of various indicators, including hypoglycemia, blood glucose, glycated hemoglobin A1C (HbA1C), renal function, and different stages of end-organ damage. Unless specific inquiries are made of patients or specific laboratory tests are ordered, these outcomes may remain unascertained. This article aims to illustrate how RWD can replicate and even extend Randomized Controlled Trial (RCT) evidence in the context of type 2 diabetes **[29].**

Natural Products in Diabetes Mellitus: A Systematic Review of RCT:

This review critically assesses a study that explores the role of natural products in managing the increasingly prevalent disease, type 2 diabetes mellitus (T2D) **[30]**. Upon an extensive review of the existing literature, it becomes evident that the concept of "natural products" lacks a precise boundary, as the line between what is considered natural and synthetic often blurs, owing to the ability to synthesize products from natural extracts. For instance, metformin is derived from a compound found in the French lilac, Galega officinalis **[31]**, while insulin can be synthesized from bacteria like E. coli, involving the transformation of a human insulin analog **[32]**. This ambiguity makes it challenging to narrow down specific keywords for an accurate search. The reviewed studies do not offer sufficient scientific evidence to warrant the widespread application of the investigated methods to the general population. More research is indispensable to assess the potential short-term and long-term side effects of these natural product-based treatments at both individual and collective levels **[33-38]**. Some studies **[39-45]** emphasize the need for further research to substantiate the beneficial effects associated with natural products.

These studies reveal that natural products can deliver more than one favorable outcome, extending beyond their insulin-sensitizing and hypoglycemic properties to include anti-inflammatory, antioxidant, and cholesterol-lowering effects **[46,47]**. For instance, a study by researchers involving Iranian propolis collected from beehives demonstrated many positive impacts on T2D patients. These results hint at the promise of long-term studies in unlocking the full potential of natural product-based treatments. Furthermore, studies like the one exploring insulin (SAR-Asp) highlight its effective glycemic control, which is nearly equivalent to various insulin options available on the market **[48]**. It is imperative to emphasize the importance of prolonged research to evaluate the substantial impact of this insulin comprehensively. Another study proposes the insulin-sensitizing effect of Scutellaria baicalensis (SB) as a complement to metformin in treating type 2 diabetic patients.

Additionally, it suggests that SB can enhance glucose metabolism by modulating the gut microbiota in patients with T2D, indicating its therapeutic potential **[49]**. This review encountered particular challenges when determining the inclusion of specific studies. As previously mentioned, the blurriness between the concepts of natural and synthetic products and the fine line between treatment and patient improvement posed complications. Moreover, many studies predominantly focused on the adjuvant role of natural products alongside conventional medications, making it difficult to establish the distinct benefits of these natural compounds. Nevertheless, it can be inferred that as an adjunct to metformin, several natural products such as Ginkgo biloba extract, pinitol, propolis, live probiotic L. Reuteri ADR-1 and heat-killed probiotic L. reuteri ADR-3, mixed berries, a Chinese plant extract, and resveratrol, hold promise in the treatment of T2D, offering distinct advantages when compared to metformin therapy in isolation **[49-53]**.

The examined studies have elucidated a strong connection between the diversity of microorganisms within the gut microbiota and the host's overall functioning and metabolism. Additionally, they have identified certain microorganisms that exhibit specific effects **[54-58]**. Notably, the investigations conducted by some researchers **[59-64]** present compelling evidence for the potential therapeutic advantages of enhancing the diversity and specific species within the intestinal microbiota in treating type 2 diabetes (T2D). This underscores the intestinal microbiota's potential as a promising target for managing this condition. Of particular interest is the in-depth exploration of the benefits associated with an increased abundance of butyrate-producing species, as well as the presence of Blautia spp. and Faecalibacterium spp., as these microorganisms have demonstrated a positive impact on carbohydrate and lipid homeostasis **[65]**. However, it's essential to acknowledge that not all studies reported beneficial effects in treating T2D, as some indicated no significant advantages **[66-71]**. In summary, the collective findings from the reviewed studies suggest that treatments and protocols employing natural products hold the most remarkable potential for improving insulin resistance in study subjects **[72-76]**. These interventions also exhibit a consistent positive influence on various biochemical parameters related to glycosylated hemoglobin, positively impact overall lipid profiles, and lead to a reduction in pre-prandial blood glucose levels.

Exclusion criteria in Randomized Controlled Trials (RCTs) might exclude a considerable portion of patients encountered in real-world scenarios. As previously indicated, individuals excluded from RCTs tend to be older, exhibit more medical comorbidities, and grapple with more complex social and demographic challenges than those included in these trials. Real-world studies offer the potential to gauge whether outcomes observed in RCTs hold relevance for broader populations of real-world patients. For instance, the EMPAREG OUTCOME RCT focused on Type 2 Diabetes (T2D) patients with established Cardiovascular Disease (CVD) and revealed in those treated with the sodium-glucose co-transporter-2 (SGLT2) inhibitor empagliflozin versus placebo, a significant reduction in the primary composite endpoint of a three-point major adverse cardiac event (MACE) encompassing CV death, non-fatal myocardial infarction, and non-fatal stroke, along with noteworthy reductions in CV death, all-cause death, and hospitalization due to heart failure **[77]**. Another RCT, the CANVAS trial, explored the SGLT2 inhibitor canagliflozin, and although it included a lower percentage of patients at high CV risk than EMPA-REG, it reported a marked reduction in the primary composite endpoint of a three-point MACE and the individual endpoint of hospitalization for heart failure. However, it did not demonstrate a significant benefit concerning CV or all-cause mortality alone **[78]**. Additional real-world studies could provide valuable reinforcement and expansion of the RCT findings. For instance, the CVD-REAL study, conducted with over 300,000 T2D patients, including those both with (constituting 13% of the total) and without established CVD, displayed a consistent reduction in hospitalization for heart failure, hinting at a tangible real-world advantage of the SGLT2 inhibitor drug class in T2D patients, irrespective of existing CV risk status or the specific SGLT2 inhibitor utilized **[79]**.

Criteria have been established to guide the design of observational studies, aiming to ensure higher-quality research outcomes. Guidelines such as STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) offer a standardized framework for reporting observational studies. Moreover, extensions of the CONSORT guideline specifically target pragmatic trials, outlining a reporting checklist encompassing various facets like background, participants, interventions, outcomes, sample size, blinding, participant flow, and the generalizability of findings. Adhering to these criteria not only enhances the quality but also bolsters the validity of real-world study data applicable in clinical practice. To mitigate confounding effects in observational studies, several methodologies have been developed, among which is Propensity Score Matching (PSM). PSM aims to enable comparison of treatment or management outcomes among similar patients by condensing multiple covariates into a single score, referred to as the propensity score. This technique allows for comparing outcomes across treatment groups of matched patients, potentially minimizing issues like selection bias **[80]**.

However, despite being a widely used and potent tool, there are limitations to the extent to which propensity score adjustments can control for bias and confounding variables. An illustration of this limitation arises in a comparison between RCT and real-world data concerning mortality in severe heart failure patients treated with the aldosterone inhibitor spironolactone **[81]**. While RCT data consistently demonstrated reduced mortality, a real-world study employing PSM indicated a seemingly heightened risk of death associated with spironolactone **[82]**. However, the authors caution against hastily concluding that spironolactone is hazardous based

solely on real-world data due to potential unknown biases and confounding factors, such as confounding by indication (i.e., biases stemming from unmeasured or unaccounted-for factors) **[83]**. This scenario underscores a notable limitation of PSM: it can only incorporate variables available within the existing data **[84]**.

Conclusion

In conclusion, real-world studies are invaluable complements and potential expansions of the insights derived from Randomized Controlled Trials (RCTs). While RCTs are the gold standard for minimizing bias when assessing medication efficacy and safety, their applicability to the diverse population of patients with diabetes in natural clinical settings is limited. Real-world studies, being conducted within actual clinical practices, offer a more accurate assessment of medication effectiveness and safety in the real-world context, involving both patients and clinicians. As study designs and methodologies continue to improve and data sources become more comprehensive, the potential for real-world evidence keeps growing. Furthermore, a better understanding of the limitations of real-world studies has paved the way for more effective mitigation strategies. Real-world evidence generates hypotheses that may warrant further investigation through RCTs and provides answers to research questions that are often impractical to address solely through RCTs. This dual role of real-world evidence can significantly enhance our understanding of healthcare interventions, ultimately leading to better-informed decision-making and improved patient care in the field of diabetes treatment.

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