# From Randomized Controlled Trials to the Real World: Putting Evidence into Context

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How often have you treated a patient with a medication for type 2 diabetes mellitus (T2DM) and found that the patient didn't achieve the benefits you expected based on the results of a phase 3 randomized controlled clinical trial (RCT)? Perhaps your patient had a 0.6% reduction in glycated hemoglobin ($HbA_{1c}$) instead of 1% as reported in the RCT. Or maybe you found that hypoglycemia occurs in 20% of your patients treated with a specific medication per month rather than the 3% reported in the latest RCT of that medication. Such differences between RCTs and real life are common.

A recent analysis of an observational cohort of 917,440 adults with diabetes in the Surveillance, Prevention, and Management of Diabetes Mellitus network showed that the rate of severe hypoglycemia ranged from 1.4 to 1.6 events per 100 person-years.[1] In contrast, a systematic review of 216 RCTs in patients with T2DM by Bolen et al found that few RCTs reported even 1 case of severe hypoglycemia for most classes of medications (except sulfonylureas or insulin for which hypoglycemia is very common) as mono-, dual, or triple therapy.[2]

Why are there differences between the results observed in RCTs and those achieved in real-world clinical practice? Do these different data sets serve different purposes? If so, what? What are the benefits and limitations of each? Before we begin answering these questions, it is important to become familiar with key terminology (**TABLE 1**).[3-5] The primary source for these definitions is the US Food and Drug Administration's (FDA) 2017 *Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices*; universal acceptance is not implied. Nonetheless, the definitions provided here can be used for a general understanding. Two particularly important terms are real-world data (RWD) and real-world evidence (RWE). RWD are data collected from a variety of sources outside of an RCT that relate to patient health status and/or delivery of health care. RWE is clinical evidence regarding the usage and potential benefits and/or risks of a medical product derived from analysis of RWD.[3]

## RANDOMIZED CLINICAL TRIALS

Traditional RCTs are the "gold standard" for clinical research because they enable a direct comparison of the impact of ≥2 interventions on ≥1 outcomes, often efficacy and safety. To do this, an RCT is designed to minimize the impact of external factors on outcomes by strictly controlling the study methods, ie, setting, characteristics of the patient population, interventions, the primary and secondary outcomes, as well as the statistical analyses. Typical—but not universal—

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DISCLOSURES

Dr. Blonde discloses that he is a speaker for AstraZeneca; Janssen Pharmaceuticals, Inc.; Novo Nordisk Inc.; and Sanofi US. He is a consultant for Intarcia Therapeutics, Inc.; Janssen Pharmaceuticals, Inc.; Merck & Co.; Novo Nordisk Inc.; and Sanofi US. He has received grant research support from AstraZeneca; Janssen Pharmaceuticals, Inc.; Lexicon Pharmaceuticals, Inc.; Merck & Co.; Novo Nordisk Inc.; and Sanofi US.

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**TABLE 1** **Glossary of terms[3-5]**

| Term | Definition |
|---|---|
| Average treatment effect | The average effect of treatment on those participants who received the treatment[5] |
| Effectiveness trial | Also called a pragmatic trial, measures the degree of beneficial effect under real-world clinical settings[4] |
| Efficacy trial | Also called an explanatory trial, determines whether an intervention produces the expected result under ideal circumstances.[4] Most randomized controlled trials are efficacy trials |
| Medical administrative claims data | Claims arising from a person's use of the health care system (and reimbursement of health care professionals for that care) |
| Observational study | A study that does not involve any interventions (experimental or otherwise) on the part of the investigator, eg, a population study in which changes in health status are studied in relation to changes in other characteristics. Most analytical epidemiologic designs (notably, case-control and cohort studies) are called observational because investigators observe without intervening other than to record, classify, count, and analyze results |
| Post-marketing surveillance | Collection, analysis, and interpretation of data or other information about a marketed device or drug |
| Propensity score | The probability of treatment assignment conditional on observed baseline characteristics. It allows one to design and analyze an observational (nonrandomized) study so that it mimics some of the particular characteristics of a randomized controlled trial. This is achieved by balancing the distribution of observed covariates between treated and untreated subjects so that they are similar at baseline[5] |
| Propensity score matching | The formation of matched sets of treated and untreated subjects who share a similar value of the propensity score. This enables the estimation of the average treatment effect for the treated. The most common is 1-to-1 pair matching, in which pairs of treated and untreated subjects are formed, such that matched subjects have similar values of the propensity score[5] |
| Prospective study | Also called a concurrent cohort study, defines the original population of interest at the start of the study and collects exposure/treatment and outcome data from that time point forward. The start of the study is defined as the time the research protocol for the specific study question was initiated |
| Randomized or traditional clinical trial | Typically conducted in specialized research settings with a specific population. These studies often utilize measures designed to control variability and ensure data quality, such as detailed eligibility criteria, detailed case report forms that exist apart from medical records, and intensive monitoring and auditing designed to ensure precise adherence to study procedures and rigorous precision in data collection. They typically also include substantial efforts to ensure compliance with treatments and to avoid concomitant treatments that might influence the randomized treatment effect |
| Real-world data | Data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources (outside of a randomized controlled trial) |
| Real-world evidence | Clinical evidence regarding the usage and potential benefits and/or risks of a medical product derived from analysis of real-world data |
| Registry | An organized system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure, and that serves ≥1 predetermined scientific, clinical, or policy purposes |
| Retrospective analysis | Also called an historical cohort study, defines the population and determines the exposure/treatment from historical data. The variables and outcomes of interest are determined at the time the study is initiated |

features of RCTs involving medications are[4]:

- prospective design
- randomization of study participants between/among treatment arms
- strict inclusion and exclusion criteria
- specific use and dose(s) of interventions
- extensive, regimented monitoring that often involves more frequent patient visits than would occur in usual clinical practice
- extensive patient support and education
- relatively short follow-up (weeks, months, 1 to 2 years)

RCTs or safety/efficacy trials often compare the interventions of interest, such as an investigational medication or biologic, with placebo or sometimes with an established drug to determine whether the medication produces the expected result under ideal conditions.[4] Although valuable for research and required for regulatory purposes, such a comparison might not be entirely helpful to a clinician who often is more

interested in the effectiveness and safety in patients who are more similar to those he or she sees and relative to best current or most common practice.[6]

Therefore, RCTs assess the efficacy and safety of the medication, whereas real-world studies evaluate the effectiveness of the medication, including the degree of beneficial effect under real clinical practice conditions.[4] Differences between efficacy and effectiveness might be larger for medications that produce benefits over many years such as for a chronic disease, but smaller for an acute disease where benefits are observed more quickly.[7] Differences between efficacy and effectiveness also might be larger for medications used in a diverse population because of the wide heterogeneity of patient characteristics that might impact outcomes.[7]

As noted above, a key characteristic of an RCT is the use of strict inclusion and exclusion criteria. This creates a well-defined patient population that generally is younger and healthier and whose sociodemographic characteristics are more homogeneous than patients treated with the medication in the real world.[4,6,8] Furthermore, non-white races, women, and older adults often are underrepresented in RCTs, while pregnant women and children often are excluded in pre-approval clinical trials. Previous and concomitant treatment often is limited. Consequently, the narrowly defined population in an RCT could represent only a small percentage of patients expected to be treated with the medication in the real world. Thus, the internal validity attained in RCTs often limits the generalizability or relevance of the RCT results to other patient populations.[9] Because of the highly selected population, careful clinical management, and relatively short trial period, patients in RCTs might be less likely to experience adverse events and clinical outcomes than real-world populations, which may lead to an underestimation of a medication's adverse outcomes in clinical practice.[4]

Another limitation of RCTs is that patients who elect to participate in RCTs often are highly motivated, although motivating factors can vary significantly by condition.[10-13] High rates of treatment adherence generally are observed in RCTs because of extensive patient support and education with frequent patient visits. For example, retrospective analysis of the Optum/Humedica claims database showed that only 29% and 37% of patients treated with a glucagon-like peptide-1 receptor agonist or dipeptidyl peptidase-4 inhibitor, respectively, were adherent over 1 year.[14] By comparison, investigators estimated the adherence rate to be 95% in RCTs of these agents.[14]

Historically, RCTs have not assessed health care resource utilization or direct and indirect costs because the types of primary clinical endpoints used are less likely to correspond with the optimal endpoint for economic evaluation, such as quality-adjusted life years, hospitalization or office visit costs, medication costs, and missed work time.[6] Moreover, the use of a composite of several endpoints as is sometimes done in an RCT, generally does not lend itself to cost per composite clinical endpoint. In contrast, clinical endpoints that focus on the treatment's impact on how a patient feels, functions, or survives are useful for economic evaluation.[6,15]

## SHIFTING FOCUS

Increasing recognition of the limitations of RCTs, particularly their limited generalizability to real-world clinical practice, has been paralleled by decades of concerns about escalating health care costs with only modest improvements in health care quality.[9] The shift from volume-based to value-based payment has stimulated further interest in estimating how a medication or intervention affects care quality and spending in the real world. It also has stimulated interest in treatment decision-making for and by an individual patient.

Making these value-based estimates is not new; they have been done for decades using population health data, usually on a national or regional level through the use of insurance claims databases or registries.[16] On a local level, hospitals and clinicians have used patient level data for quality and safety monitoring via chart audit.

Now the availability of patient-level data in electronic health records that includes data across the health care system has not only streamlined the collection and analysis processes, it often provides a more complete picture of the patient experience. When it doesn't, claims databases can be used to provide missing data elements. There has been expansion in the size and types of databases available; therefore, the term "big data" often is used when referring to some RWD sources.[17] Databases commonly used for real-world studies of patients with diabetes include Truven Health Analytics MarketScan, Optum Humedica SmartFile, GE Healthcare Centricity Practice Solution, IBM Explorys, and Kaiser Permanente. In some countries, health data of nearly the entire population is available for analysis from resources such as the United Kingdom Clinical Practice Research Datalink.

## REAL-WORLD EVIDENCE

The role of RWE in health care decision making, as well as regulatory affairs and drug development, is expanding. Current and evolving uses of RWE include changes in product labeling by the FDA, the development of a personalized treatment plan by patients and physicians, use as a tool for quality improvement, and measurement of health care resource utilization and associated costs.[17] RWE also can be used to provide information about clinical questions when RCTs would be impractical to conduct because they might require

**TABLE 2 Example of benefits and uses of real-world data[18]**

- Estimates of effectiveness in a variety of typical practice settings
- Comparison of multiple alternative interventions (eg, older vs newer drugs) or clinical strategies to inform optimal therapy choices beyond placebo comparators
- Estimates of the evolving risk-benefit profile of a new intervention, including long-term and rare clinical benefits and harms
- Examination of clinical outcomes in a diverse study population that reflects the range and distribution of patients observed in clinical practice
- Results on a broader range of outcomes, eg, patient-reported outcomes, health-related quality of life, and symptoms, than traditionally have been collected in RCTs, ie, major morbidity and short-term mortality
- Data on resource use for the cost of health care services and economic evaluation
- Information on how a product is dosed and applied in clinical practice and on levels of compliance and adherence to therapy
- Data in situations where it is not possible to conduct an RCT
- Substantiation of data collected in more controlled settings
- Data in circumstances where there is an urgency to provide reimbursement for some therapies because it is the only therapy available and might be life-saving
- Interim evidence—in the absence of RCT data—upon which preliminary decisions can be made
- Data on the net clinical, economic, and patient-reported outcome impacts following implementation of coverage or payment policies or other health management programs

**Abbreviation:** RCT, randomized controlled trial.



too many patients over too long a period of time and be too expensive. Other uses and benefits of RWD are shown in **TABLE 2**.[18]

There is no universally accepted definition of RWD. In its broadest terms, RWD refers to data obtained outside of an RCT.[19] RWD can be gathered retrospectively, as commonly used for health outcomes research, or prospectively, as may be used for safety monitoring or a pragmatic trial.[20]

As with RCTs, data quality is of paramount importance. The RWD used to develop RWE must be high quality. Because RWD often are taken from multiple but heterogeneous sources, it is important that RWD is refined before analysis and interpretation as RWE.[19,20] For example, a $HbA_{1C}$ level might be documented using a procedure code as well as in a clinician note. Steps must be taken to ensure the data are consistent. Another example is where information is absent in 1 data source, eg, electronic health record, and might need to be filled from another source, eg, claims database.

The length of an RWE trial sometimes is longer than an RCT so that accurate assessment of health outcomes can be made.[4] RWE trials generally involve a simple design and include a large sample size, often tens of thousands patients, from diverse settings. Application of exclusion criteria and techniques such as propensity score matching (see **TABLE 1**) could reduce the number of patients. Large datasets allow the use of novel data analytics such as machine learning and predictive modelling.

In RWE trials, standard treatment or current practice is a typical comparator, although new treatments could be used. Consequently, similar to RCTs, RWE trials of medications could include patient populations or indications not approved by the FDA. In contrast to RCTs, RWE trials allow patients and their clinicians to choose treatments based on clinician preference, as well as the patient's characteristics and preferences.[4]

There are many potential limitations to RWE trials.[18] Most RWE trials involve nonrandomized patients where it often is not known why patients were assigned to a particular treatment or intervention, which can introduce confounding. To correct for nonrandomization, patient groups might be matched using covariate adjustment, propensity scores, etc; nonetheless, selection bias and other confounders could remain. Patient accrual over a reasonable period of time might be difficult, particularly for a medication with low usage or rare condition. Data may be of poor or unknown quality or missing leading to random or systematic bias.[21] The collection and analysis of RWD can be costly.[17]

Limitations among RWD sources are common as well.[9] For example, electronic medical record data and patient registries could consist of variable types and quality of information. Some data elements might be missing from these sources as well as from claims data and there may be limited follow up of some patients.[21] Moreover, the reasons patients initiate or change treatments often are not available. These limitations should not exclude the use of these sources, but should be documented so that their impact on analysis and interpretation can be understood.[20]

The challenges presented with the limitations of RWD are a focus of active efforts by the FDA, National Institutes of Health, pharmaceutical manufacturers, and other stakeholders.[9,22,23]

## CASE EXAMPLES

### Beta-blocker therapy post-myocardial infarction

An early example of how RWD can lead to practice change

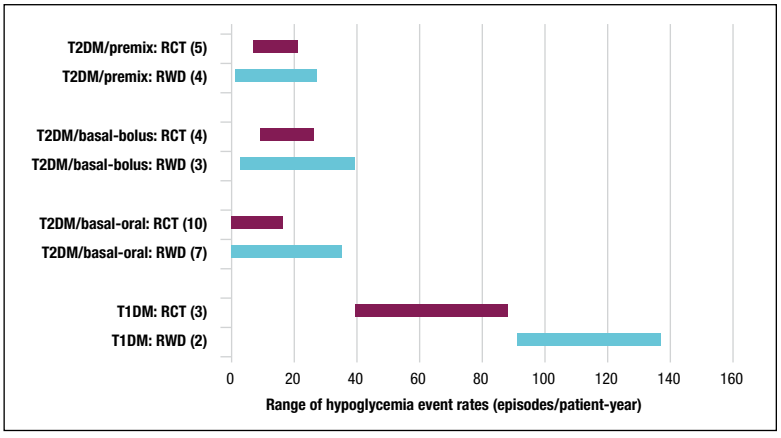
involves the use of beta-blockers in patients who had experienced a myocardial infarction (MI). In the 1990s, Medicare sponsored the Cooperative Cardiovascular Project, which analyzed medical records of >200,000 people who had experienced an MI. The analysis showed that patients who had vs those who had not received a beta-blocker following an MI, including those with a contraindication to beta-blocker therapy, experienced a substantial reduction in mortality (relative risk, 0.67; 95% CI, 0.62 to 0.72).[24] These results supported similar evidence from some earlier clinical trials, helping to make beta-blocker therapy standard care in patients with an MI.

### Insulin glargine 300 units/mL

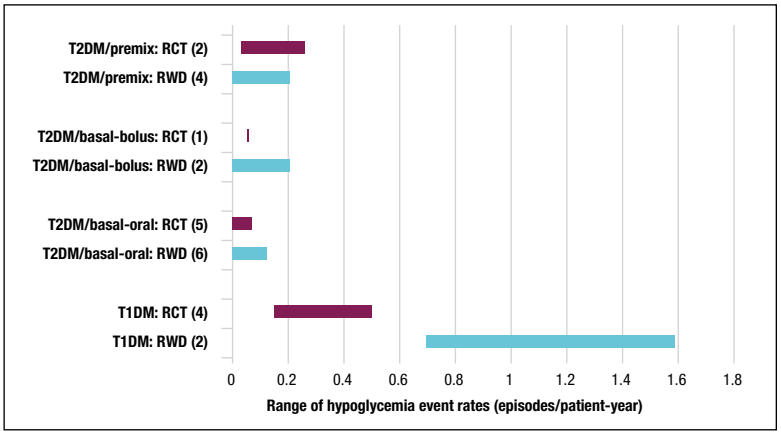
Differentiate Gla-300 clinical and Economic in reaL-world Via EMR Data study (DELIVER 2) was a retrospective analysis of the Predictive Health Intelligence Environmental database.[25] The purpose of the analysis was to evaluate clinical outcomes of patients with T2DM currently using basal insulin who were then switched to either insulin glargine, 300 units/mL, or other basal insulins in real-world practice. (The reason for the switch is not included in the dataset.) Patients who switched to insulin glargine, 300 units/mL, (N = 2196) or other basal insulins (N = 3837) were compared following 1:1 ratio propensity score matching (N = 1819 in each cohort). From a baseline of 8.95% and 8.93%, $HbA_{1c}$ reductions were comparable in both cohorts (–0.51% vs –0.51%, respectively; $P = .928$). At 6 months, fewer patients who switched to insulin glargine, 300 units/mL, experienced hypoglycemia compared with those who switched to other basal insulins (15.4% vs 18.1%, respectively; $P = .015$). After adjusting for baseline hypoglycemia, switching to insulin glargine, 300 units/mL, was associated with a significantly lower rate of hypoglycemia compared with switching to other basal insulins (difference between least squares means of 0.15 events/patient-year; $P = .041$ favoring insulin glargine, 300 units/mL). Incidence and event rates of hypoglycemia requiring hospitalization or emergency care also were significantly lower with insulin glargine, 300 units/mL, contributing to an overall savings of $1439 per patient per year. In a real-world setting, switching to insulin

**FIGURE Hypoglycemia event rates in randomized controlled trials vs real-world data studies[26]**

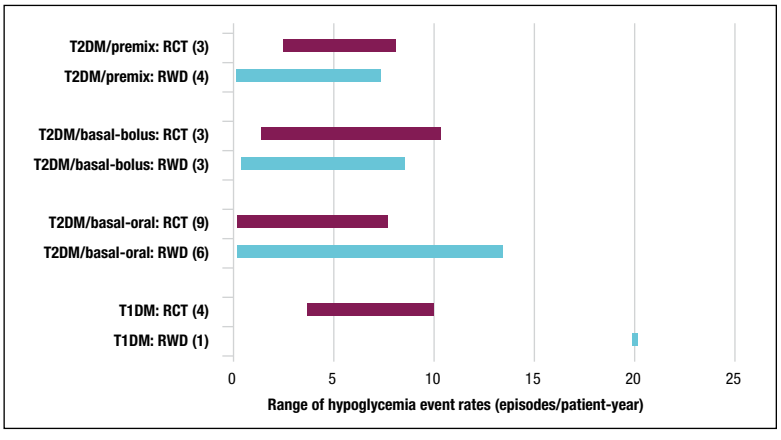
a. Nonsevere/confirmed




b. Severe




c. Nocturnal




**Abbreviations:** RCT, randomized controlled trial; RWD, real-world data; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

The number of studies in each subgroup is shown in parentheses.

glargine, 300 units/mL, was associated with a significantly lower risk of hypoglycemia, including hypoglycemia associated with hospitalization or emergency department visit, than switching to other basal insulins, while delivering comparable glycemic control.

### Hypoglycemia in insulin-treated diabetes

The frequency of hypoglycemia in patients with type 1 diabetes mellitus (T1DM) or T2DM has been compared in real-world settings vs RCTs.[26] A structured literature review of studies from 2010 to 2014 identified 6 involving patients with T1DM (4 RCTs, 2 RWDs) and 25 involving patients with T2DM (15 RCTs, 10 RWDs). The minimum study duration was 26 weeks for RCTs; there was no minimum for RWD studies. A minimum of 400 patients were required in each study. Case study reports and database studies were excluded from the RWD studies, the latter because the investigators felt they do not provide an accurate representation of overall hypoglycemia.

Higher rates of hypoglycemia generally were observed in RWD studies vs RCTs in patients with T1DM or patients with T2DM treated with basal-bolus or basal-oral therapy, although there was some overlap in the range of reported event rates (**FIGURE,** see previous page).[26] These findings indicate that the true burden of hypoglycemia might be underestimated in RCTs, probably resulting from carefully selected patients, carefully titrated dosing using a treat-to-target approach, closer supervision and blood glucose monitoring, and typically shorter duration. In interpreting these results, one must keep in mind that RWD studies also might underestimate the true burden of hypoglycemia because blood glucose monitoring from self-monitoring or continuous glucose monitoring might not be available or collected as frequently as occurs in RCTs.

## IMPLICATIONS OF REAL-WORLD DATA

RWE based on RWD is gaining importance as a complement to randomized controlled trials. The primary attribute that distinguishes RWE from other kinds of evidence is the clinical care and community settings as opposed to research-intensive or academic environments. The premise is that real-world data can be collected from multiple sources that include extremely large samples of patients in real-world clinical practice, then appropriately analyzed and evaluated to yield RWE that can be generalized to a broader population of patients treated with the medications, devices, or other interventions. This may include patient subgroups often excluded in RCTs, eg, older patients, children, those with renal impairment, etc. Therefore, RWE likely could facilitate improved management of patients. Barriers and limitations to RWE studies exist, however. But as these are increasingly addressed, RWE likely will have wider application in clinical research, regulatory review and approval, postapproval outcomes, and post-marketing surveillance. ●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