The evidence gap

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Why digitally powered real-world evidence is the fix needed for our broken clinical trials system.

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In September, at the US National Academies of Science (Washington, DC), Scott Gottlieb, the newly appointed US Food and Drug Administration (FDA) commissioner, and Janet Woodcock, long-time director of the Center for Drug Evaluation at the FDA, declared an urgent need to fix the broken clinical trials system by ushering in a new way of thinking about clinical trial design and execution.

"We need to close the evidence gap between the information we use to make FDA's decisions and the evidence increasingly used by the medical community, by payers, and by others charged with making healthcare decisions," Gottlieb told attendees of the National Academy of Sciences workshop on the impact of real-world evidence (RWE) on medical product development. These ideas aim toward a more seamless alignment between how we test new treatments and how healthcare providers and payers use and pay for them, are potentially game-changing. They point to an emerging era of real-world data and evidence generation that will usher in a new paradigm for determining not only a treatment's efficacy, but also its effectiveness in the population at large.



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US FDA Commissioner Scott Gottlieb has highlighted the need to close the evidence gap between the information used in regulatory decision making and RWE increasingly used by the medical community, payers, and others charged with making healthcare decisions.

Real-world data and RWE

Turning real-world data (RWD), a vast repository gathered from multiple sources, into usable RWE requires the use of methodologies that appropriately fit the purpose. For healthcare providers, RWE can inform tangible actions to be taken to better manage efficiency and effectiveness of healthcare delivery. For biotech and pharma, RWE collected either before or after marketing can lead to valuable information to support better product life-cycle management. For regulatory purposes, RWE will increasingly be used to inform and supplement product labels, provide historic controls, understand patient-reported adverse effects (risks) and effectiveness (benefits) to support legislated patient-centered drug development, and will become part of the body of evidence to support combination therapies.

Mobile platforms and digital technology will be an integral part of RWE strategies, as they offer the means to understand patient comorbidities associated with disease, patient adherence and compliance to drug treatment, and the differences between drug provision in the population and in the context of a clinical trial.

The limits of randomized controlled clinical trials

The world of RWE will be profoundly shaped by information technology that has made available access to large amounts of clinical data. Data from electronic medical records (EMRs) and mobile technologies are converging with patient demands that they and their interests be placed front and center in clinical research, regulatory approvals and healthcare delivery decisions. The accumulation and analyses of large amounts of data by multiple players present an opportunity for interpreting the many important factors driving patient outcomes (**Fig. 1**). This stands in stark contrast to the historical clinical research approach where drug efficacy has

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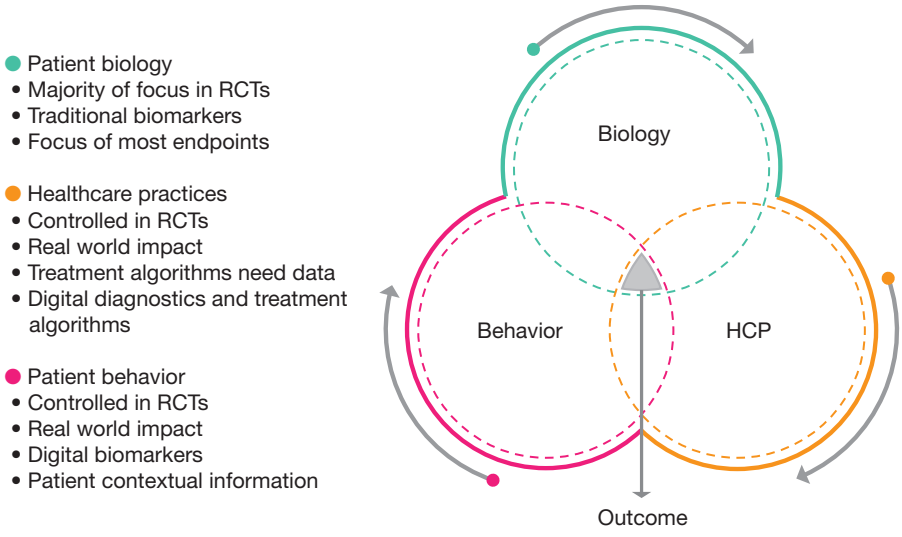


Figure 1 Three influencers of response to therapy: biology, healthcare practices (HCPs) and behavior. RCTs mostly focus on biology in a controlled setting, yet HCP use of medications and patient behavior also have a profound influence on treatment outcome.

almost exclusively been tested using randomized, controlled clinical trials (RCTs).

The RCT is and has been the gold standard for assessing treatment efficacy and safety in premarket clinical trials used to gain regulatory approval. Because RCTs are driven by creating an ideal experiment to test underlying biology in as controlled a manner as possible, they emphasize the goals and interests for the researcher or sponsor, but they often miss key considerations of importance to patients and healthcare providers. Most RCTs enroll highly selective selected patient populations, to meet well-defined inclusion and exclusion criteria that enhance the opportunity to evaluate the drug effect on as clean a background as possible; those chosen are often not reflective of typical patients. These studies are usually conducted in research-intensive clinics not typically found in many standard healthcare settings. Therefore, there is a critical gap in the knowledge needed to determine and predict real-world effectiveness and outcomes of treatment interventions.

Many issues not often studied in clinical trials can have a profound impact on the real-world effectiveness of a drug (**Fig. 1**). These include comorbidities, medication adherence and persistence, healthcare management, economic factors (e.g., insurance restrictions or lack of insurance), side effects, stigma and psychosocial factors. Thus, to truly understand the patient-centered benefits and risks of a drug, these factors must be studied and better understood. The efficacy–effectiveness gap between RCTs and the real world is largest for drugs that are used in treating chronic diseases, such as cardiovascular disease, diabetes, many infectious diseases and, more recently, cancer, which has often moved from acute care to chronic disease management. In these cases, drug benefits and risks accumulate over many years, as opposed to the benefits and risks for therapies used to treat acute illnesses. For chronic disease, the impact of comorbidities, patient adherence and persistence with drug regimens, and affordability and education on real-world effectiveness are greatly underestimated.

Real-world data

Recently, myriad startup data-mining companies, biotech and pharma, and academic medical centers have begun using the emerging health IT layer and the wave of big data analytics to try to fill these gaps, analyzing data relating to a patient's health status or healthcare delivery and generating RWD. RWD encompasses data mined retrospectively from EMRs, insurance claims, governmental data on socioeconomics or demographics, traditional observational studies, and, more recently, data coming from in-home monitoring devices or even wearable devices worn by patients.

An illustration of RWD in action is found in a recent study by Carls and colleagues[1] who compared the reduction in HbA1c levels in response to two different anti-diabetic drug classes in pooled large data sets from RCTs (efficacy) and EMRs and claims data (effectiveness, RWD). In this case, they showed that HbA1c level reduction for patients taking either glucagon-like peptide 1 receptor agonist (GLP-1RA) or dipeptidyl peptidase 4 inhibitor (DPP4) drugs was, in the real world, about half that reported in the RCT. The most important finding of this study, however, was the cause—approximately 75% of the reduction observed in the RWD set is attributed to poor medication adherence.

Studies directly using patient data captured from wearable devices or mobile technologies are another informative source of RWD, but, as currently collected, such data often lack contextual information to truly understand what the inputs say. For example, did a patient walk less because they were depressed, hurt their ankle or had a flare-up of their arthritis? Without context, the data can be misleading. Additionally, many of the direct-to-consumer devices or apps used to collect information have not been validated as diagnostic tools, and have not undergone the regulatory approval necessary to support new drug applications when used in clinical trials.

Although RWD studies like these are illuminating, the use of RWD to draw conclusions about effectiveness has its limitations and challenges. Many of these data sets, even within the same EMR vendor's system, are not interoperable, are driven by billing codes and give an incomplete, fragmented picture of data based on in-clinic patient encounters. Selection bias is also a critical issue in RWD analyses, as patients are not randomized to treatment, potentially leading to over- or underestimates of treatment effects.

RWE and clinical trials

RWE can be thought of as evidence generated from RWD using research methods or study designs that test treatment effects on outcomes in the context of how treatments will typically be used. For the biotech and pharma industry, the emerging importance of RWE means redefining much of how they think about product development and commercialization. RWE has become a new topic of great interest in biotech and pharma, but many questions remain about how RWE will fit into the highly regulated process of drug approval and post-market testing and support. Many companies are taking a stepwise approach to RWE where retrospective data and pilot studies are used to capture valuable information to drive the design of prospective RWE studies.

Choosing the right clinical trial design and methods for a study is also dependent on many factors including the expected size of the effect, the nature of the disease (e.g., chronic versus acute, rare versus common), and importantly, how much intervention is acceptable or feasible within the infrastructure of a typical healthcare setting. Additionally, different study methods may be required to generate a level of evidence that is acceptable. For example, a drug label or clinical practice guideline change will likely require randomization to be used as part of the study design.

The types of studies employed to generate RWE can be thought of as a continuum

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between RCTs and purely observational studies (retrospective or prospective). Important observations can be made with retrospective observational data about the order of events in a natural context but with significant caveats. Prospective observational studies, on the other hand, do collect data in the natural context and follow patients through time, and therefore provide a view of the temporal relationship between exposure and outcome variables using purposeful data collection. Recent developments in data analysis methods are overcoming issues like bias and confounding factors that have historically been problematic in observational study data interpretation.

To truly establish cause and effect, one must take an interventional approach so that randomized schema can be used to compare treatment interventions or to compare treatments to controls, typically an RCT. Because RCTs don't give the complete picture of real-world effectiveness, pragmatic clinical trial approaches are gaining interest. Although RCTs test a hypothesis under ideal experimental conditions, pragmatic clinical trials (PCTs) test and compare treatments in everyday clinical use. PCTs employ randomization in routine clinical care and are an incremental step toward fully embedding clinical trials into clinical practice. PCTs represent an important step in the continuum between RCTs and observational studies and will likely be a major source for generation of RWE.

Technology-enabled clinical studies for RWE

A well-designed RWE study should bring convenience to patients and allow direct patient data capture to gather critical information about individual perspectives and experiences beyond the clinic. This is where the power of digital technologies will play an ever-increasing and important role. Typically, the patient experience is captured in the clinic during a study visit using interviews, complex questionnaires or written journals to capture the symptoms experienced, such as pain, swelling and rhinitis. Methods for in-clinic data collection from patients often consist of long, paper-based questionnaires, journals or web-based surveys. These tools are inconvenient, time-consuming and burdensome to patients. They also do not reflect the daily life of a patient. The use of in-home, web and mobile-based technologies are changing that, bringing convenience to patients and capturing data in real time as events are happening.

Large technology companies, such as Apple (Cupertino, CA, USA) and Verily (S. San Francisco, CA, USA), have been involved with many such studies, providing tools such as ResearchKit and wearable sensors as part of these observational studies. Apple partnered with the University of Rochester and Sage networks to help researchers understand how Parkinson's disease symptoms are correlated with factors such as sleep, exercise and mood, using features available on the iPhone. Since 2015, the mPower app has enrolled over 10,000 participants, making it the largest Parkinson's study in history—engaging a large number of participants who never took part in clinical research before[2]. The app has helped researchers better understand Parkinson's disease by using the gyroscope and other iPhone features to measure dexterity, balance, gait and memory. Researchers have gained greater insight into the factors that make symptoms better or worse.

Another example of direct patient data capture is the use of mobile tools to diagnose and follow the progression of autism. Previous research has shown that early treatment of developmental issues associated with autism can lead to higher IQs and better social skills, making early detection and diagnosis critical. The "Autism & Beyond" app uses the front-facing high-definition (HD) camera in iPhone, along with innovative facial recognition algorithms, to analyze emotional reactions to videos in children as young as 18 months. Children can be screened without having to see a specialist in person, allowing earlier diagnosis and treatment. The app successfully enrolled more people in the first month than a related study did in nine months[2].

The use of digital tools in randomized studies, however, has been more limited. Recently, mobile tools were integrated into a large randomized, controlled clinical trial by the pharmaceutical company GlaxoSmithKline (GSK; London). GSK collaborated with Apple and ResearchKit on PARADE (Patient Rheumatoid Arthritis Data from the Real World Study). The purpose of this study was to investigate the feasibility of using a mobile app to recruit and enroll patients and to gain insights about rheumatoid arthritis in a real-world setting[3]. GSK reported close to 200 downloads within the first 48 h alone.

As a key symptom for arthritis sufferers is morning stiffness, this made getting up, showering, dressing and traveling to the clinic for interviews by staff a burden. By the time many patients got to the clinic, morning stiffness symptoms had dissipated. Using the mobile app, participants were able to track their morning stiffness symptoms as they occurred and answer interview questions via their phone in their own homes. These data then reflected their experiences more accurately in real time.

In many instances, digital approaches are still being piloted to address various challenges associated with RWE and pragmatic clinical trials. The most important consideration for mobile tools is that they be simple and meaningful to the patients and their families. Patients and/or clinical study participants must derive value and self education from the information and tools provided and be able to easily use it within their normal lives. As the technology for self-management shifts responsibility for disease management from social institutions that are paid to manage patients to the patients and families themselves (unpaid caregiving), patients may view the mobile technology as

Box 1 Connecting the clinical and digital worlds at My Own Med

My company, My Own Med (Bethesda, MD), has created a connected digital system for clinical studies that is proving to be a powerful tool for RWE generation and for streamlining implementation. Our RWE study platform is connecting multiple data streams, including those coming from patient input, from mobile and other database application interfaces, such as EMRs, biorepository databases and/or clinical trial databases. In each instance, real-time data are seamlessly pushed or pulled from multiple data sources, using a permission-based system, such that each healthcare professional, study personnel, investigator or sponsor has access to the appropriate data for their role in the study. Direct-from-patient data are integrated with other data streams and visualized through customizable dashboards.

Our RWE study platform is enabling a collection of RWE across a broad array of diseases and questions, including the following: first, testing remote hepatitis C management of high-risk intravenous-drug-using patients by connecting a central infectious disease management team to remote teams at methadone clinics across the state of New York; second, assessing health education and monitoring interventions for HbA1c management in a large cohort of type 2 diabetes patients in western Texas; third, evaluating the impact of enhanced communication tools to drive compliance of dual antiplatelet therapy for risk of secondary myocardial infarction; and finally, comparing different medical and/or antibacterial products on control of community-acquired infections done almost exclusively using in-home clinical trials.

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burdensome rather than empowering, leading to attrition and patient dissatisfaction[4]. In patient group interviews and presentations, they often report that they want help managing their conditions, but they don't want their lives defined by them.

Unresolved issues

Although there are many opportunities to use wearables and digital technologies for health and disease management and clinical research, many social and behavioral issues inherent to people remain challenges. Persistence with these tools, like persistence with many behaviors, has been shown to be problematic, with drop-offs of use within a few months[5,6]. The promise of direct-to-patient mobile technology as a means to change health management behavior is still early in its exploration, lacking large studies demonstrating the impact of mobile applications on health outcomes or effectiveness. To date, most of the work has been done in pilot studies, with very few randomized studies demonstrating the effectiveness of these interventions[6].

Another important consideration of using technology to support RWD studies is the subject of privacy and bias. With more and more scrutiny on how and where our data are being used, clinical studies using RWD walk a fine line between gathering the largest data set possible and assuring the patient feels that their data are safe and secure. It is not entirely clear which entities are responsible legally and ethically for interpretations and follow-up from patient data[4]. Thus, it is possible that the technology will bias studies to people who feel more confident about using technology and the security of their personal health information. It is critical therefore, to ensure security and to thoroughly discuss privacy and how data will be managed, maintained and shared with all potential participants, specifically as it relates to the incorporation of electronic data capture. The consent process is an important component to ensure participants understand all components of a study, including those that use digital.

In a recent article in *Clinical Leader*, Murray Stewart, chief medical officer at GSK notes, "Even after patients agree to the trial, there is concern about what will happen to their data if they use the app. There has to be clear consent there"[7]. In this regard, technology can be used both to secure a patient's participation, and to help a patient understand what is required of them, as graphic user interfaces can be incorporated in links to additional information and allow the consent to be broken up into sections with embedded survey questions to ensure that the participant fully understands the goals and requirements of the study. Another major advantage is the ability to maintain consent information in a database that can be queried as opposed to on paper in filing cabinets.

The PARADE study also incorporated eConsent technology. Stewart goes on to say that the consent process is not only important to securing participation in a study, but also to helping patients understand what will be required of them[7]. He points out that pharma companies have historically been very conservative about using innovative approaches for obtaining patient consent, which has resulted in consent forms mostly remaining on paper and getting longer (and often more confusing) for patients.

Yet another important consideration is the integration of patient-facing data captured by a mobile tool with EMR and other in-clinic data. This integration is often necessary to give a more complete picture of RWE study participants. Use of the digital tools in RWE studies needs to mesh with workflows used in typical healthcare system patient support and management. Ideally, this means building a digital infrastructure that captures and standardizes these workflows with intuitive, easy-to-use tools and interfaces. In fact, mobile and web-based tools can be used to capture the perspectives of healthcare or study personnel as well. This gives real-time insight into the study or care management strategies being employed at each site, as well as the frequency and types of communications between the clinic and patients.

Building these digitally powered systems requires flexibility in the IT layer combined with suites of easy-to-use tools and interfaces that connect healthcare or study personnel with patients or study participants seamlessly and in real time. Once established, these digital systems can be further developed to create networks of patients and clinical sites that can be built upon, iterated, reused and scaled up for support of ongoing and new clinical studies. Within our company, My Own Med (Washington, DC) we have developed such models (**Box 1**) and have found flexibility and the ability to iterate and integrate data from multiple streams in real time to provide a powerful means for RWE studies and patient management strategies. Having a holistic data set fills in gaps of knowledge about the impact of study or care coordination, care transitions and out-of-clinic management factors that impact a patient's response to therapy.

The use of technology to support RWE studies enhances patient engagement and participation, allows real-time data capture, reduces participant burden associated with in-clinic study visits and provides much richer insights into participants' experiences and outcomes. It also improves participant retention, critical for long-term observational studies. Real-time data exchange provides sponsors with greater visibility into the study and mitigates the risk of study-site bias.

Toward a technology-enabled RWE future

Future RWE studies will incorporate a 360° view of the patient based on loops of real-time communication, input from stakeholders around the patient and incorporation of data from many sources (e.g., EMRs, laboratories, genetics, environment, sensors, retail, grocers and pharmacies). These data will enable the early detection of symptoms, such as medication side effects, changes in health status (e.g., life events with an impact on health) and capture of information (e.g., about home environment, employment, social support networks, and access to healthcare), all factors that contribute to, and can be predictive of, health outcomes (**Fig. 1**). Real-time capture of patient-reported outcomes will dramatically inform time-to-event measures, and allow clinical or laboratory assessments to be conducted at the time of a reported change. For instance, bio-specimens can be obtained the day the first symptom is experienced, as opposed to months later based on scheduled clinical visits.

Enabling RWE for the future will require a confluence of expertise from physicians, clinical researchers, healthcare professionals, community health workers, sociologists, epidemiologists, technology developers and policy makers. As we move toward a technology enabled health system a few principles must be addressed as follows:

- Establish a 'social contract' with our patients and participants. In exchange for their participation in RWE we need to give them value back. This means sharing results and study progress with them, using the technology to start conversations and learn with them, and not dismissing their input. We need to acknowledge the value of their time, effort and data while respecting their privacy.

- Use technology to flip in-clinic visits (whether study or healthcare management) to home engagement or engagement at places more convenient for patients. Much of this can be enabled through technology from in-home visits, to tele-health and easy information exchange between patients and their healthcare provider or study managers.

- Advance regulatory policy to help shepherd RWE clinical study designs and evidentiary

standards for regulatory actions spanning approval, expanded indications, label changes and post-market requirements. This will require input from academia and industry working with regulatory agencies to establish new paradigms.

- Build models to support digitally captured RWE as a means to establish the value of these interventions to payers for reimbursement decisions and population health management.

- Devise tools focused on enabling community outreach to attain better healthcare quality, enhance clinical research participation, and drive better health outcomes in low-resource communities.

- Develop digital tools and RWE studies that are culturally sensitive and relevant to drive broader participation and deeper understanding of health, disease, and therapies of diverse populations and under-represented minorities.

- Build learning-based healthcare provider and patient networks that can provide study-ready test beds for innovative therapies to be tested in typical real-world care settings.

- Establish framework for when RWE is useful and when it's not. Like anything, it will be good for some things but not for all. How can we prospectively define the best-use cases for RWE, and when is it appropriate to conduct a traditional clinical trial?

It is clear the healthcare world is changing. Mobile technologies are becoming a ubiquitous part of society and are a part of our everyday life. But digital technology's impact on clinical research and healthcare is still in its infancy. On balance, digital technologies are going to fundamentally change how we conduct clinical trials and how we engage patients. Digital technologies, combined with RWE studies, have the potential to transform the current clinical trials paradigm. The question is, Will we be ready to embrace the change?

COMPETING FINANCIAL INTERESTS
The author declares competing financial interests: details are available in the online version of the paper.

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