

# The Missing Reality of Real Life in Real-World Evidence

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Reality is defined as a real event, a real thing, or state of affairs. Reality exists in the places where we live our daily lives, in the relationships we have with others, and in our experiences, circumstances, and situations that occur across the lifespan. As the everydayness of our lives becomes increasingly digitized, data generated from the reality that exists outside of our healthcare encounters holds much promise to fill recognized gaps in real-world evidence (RWE). In the past decade, many factors have converged to uniquely position person-generated data for use in health care delivery, payment reform, product development, and regulatory decision making. Yet, real-world data will fall short of its promise to fill gaps in RWE if what we learn does not reflect the real lives of real people from across the spectrum of social, economic, and cultural experiences.

## PERSON-GENERATED DATA: THE EVERYDAYNESS OF REALITY

The notion that value can be derived from understanding how people feel and function in their everyday lives is finding its way to health care delivery, payment reform, product development, and regulatory decision making. There is clear evidence that when people have the opportunity to give voice to their experiences better outcomes can result.<sup>1</sup> In oncology care among patients receiving chemotherapy for advanced cancer, systematic monitoring of patient-reported data was associated with improved symptom control, better quality of life, fewer emergency department visits, longer endurance and tolerability of chemotherapy, and higher overall survival.<sup>2</sup> Despite the potential benefits of patient experience, data challenges remain for integrating it into systems designed for clinical data collection and use. There are signs of progress, including a recently published guide that provides best practices for administrators, clinicians, researchers, information technologists, and others seeking to integrate patient-reported outcomes into the electronic health record.<sup>3</sup>

## CONFLUENCE ACROSS MULTIPLE DOMAINS

Internet-enabled devices with sophisticated technology and capabilities are commonplace in our daily lives and can generate real-time data from a full range of experiences real people have each day—including the experience of living with and managing illness. After a research paper published in 2008 reporting lithium slowed the progression of amyotrophic lateral sclerosis (ALS), patients living with ALS suggested an idea for a new study to researchers at PatientsLikeMe, a pioneering patient-powered research network. The result was a rigorous observational study that used patient experience data along with clinical measures to refute the findings of the original study, findings that were later corroborated in a conventionally run study.<sup>4</sup> This patient-led ALS study demonstrated the unique capabilities of a novel online environment to collect

and analyze patient-generated data in a methodologically sound manner fit for comparative effectiveness research.<sup>5</sup>

Opportunities to be actively engaged in one's care have evolved, with many patients now accessing and reviewing their doctors' notes in real time.<sup>6</sup> Patient advocacy organizations and rare disease groups are leveraging their learned expertise to advance innovative partnerships for drug development.<sup>7</sup> Life sciences and pharmaceutical companies are establishing C-suite level positions and real-world evidence (RWE) departments to support patient input into the design, implementation, and evaluation of their clinical trials.<sup>8</sup> In addition, patient preference data demonstrated its unique value to the totality of evidence US regulators considered in their assessment of benefits and risks for drugs and devices.<sup>9</sup> The approval of a weight loss device in 2015 by US regulators marked the first approval of a new device that was based in part on qualitative data from those expected to use the device, obese individuals, about their benefit–risk trade-off if the device resulted in what they deemed a sufficient amount of weight loss.<sup>10</sup>

Congress provided legislative clout to bring the voice and perspective of real people to the forefront in health care, research, and regulatory decision making. The Patient-Centered Outcomes Research Institute (PCORI) was established as a nongovernmental organization in 2010 to support research that helps people make better informed health decisions.<sup>11</sup> PCORI created a national patient-centered clinical research network along with 18 clinical partners that includes 20 patient-powered research networks, which is part of the People-Centered Research Foundation.<sup>12</sup> The Prescription Drug User Fee Act (PDUFA) for fiscal years 2018–2022 ensured that the US Food and Drug Administration (FDA) reauthorized commitments to its patient-focused drug development activities initiated under the 2013–2017 PDUFA V legislation.<sup>13</sup> Among its many provisions, the 21st Century Cures Act passed in December 2015 requires the FDA to develop a framework and guidance

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for evaluating data collected from outside randomized clinical trials to support approvals of new indications for previously approved drugs, and to support or fulfill postapproval study requirements.<sup>14</sup> In addition, the Cures Act directs the FDA to develop a plan to issue draft and final versions of one or more guidance documents regarding the collection of patient experience data and the use of such data and related information in drug development.

Technology companies, application developers, and citizen scientists continuously iterate on functionalities that enable smart phones, digital devices, and wearables and even ingestible sensors to actively and passively capture a diverse array of qualitative, quantitative, and algorithmically driven personal data in real time, all the time. The spread of these technological advances is influencing how people think about their health and wellness—ranging from simply counting the number of steps taken each day to creating rich longitudinal and personalized profiles across multiple variables. Sleep patterns, mood, physical activity, and biometrics, such as weight, pulse, and blood pressure, can easily be tracked, synced, and visually displayed in smart phones, tablets, and other Web-based environments. For people living with health conditions, digital technologies, social media, and patient networks have opened up opportunities to learn, track, and share their personal experience data leading to better health and improved outcomes.<sup>15,16</sup> There exists untapped potential for regulators to learn from data collected in patient networks and communities about treatment-related experiences, including the use of regulated products for unapproved purposes, often referred to as off-label use. A research-based patient network studied the use of amitriptyline, a drug approved in the 1960s for depression. The findings indicated that off-label uses were more commonly reported than on-label use. Interestingly, patients living with ALS who frequently experience the distressing symptom of excessive saliva reported using amitriptyline to intentionally take advantage of the drug's most commonly reported side effect of dry mouth.<sup>17</sup> There is much more to learn about the postapproval characteristics of regulated products that goes beyond adverse event reporting, prescribing patterns, and claims data. Patients are uniquely positioned to advance knowledge about the tolerability of products over time, what the safety and effectiveness profile looks like for unapproved purposes or populations, and how patients balance the benefit–risk trade-offs of using products in their daily lives.

A new frontier of person-generated data is gaining momentum—biospecimens for genomic and multi-omic analyses designed to more deeply explore the molecular basis of disease and better understand the unique characteristics of an individual's past, current, and future health.<sup>18</sup> Reality in the context of molecular data has been described as “that which is actually occurring in a specific patient, which, if understood and appropriately treated, will achieve an expected outcome with little variation.”<sup>19</sup> Yet, real-time knowledge of individual's behaviors, actions, and decisions coupled with biological characteristics leave vulnerable the right to privacy and self-determination especially when data from multiple sources is associated with complicated algorithms that make it difficult to track back to the data's original intent and provenance.<sup>20</sup>

## CLARITY MATTERS

Along the way, a lexicon has emerged to represent health-related data not collected in randomized clinical trials and clinical care. Terms such as “real-world data,” “real-world evidence,” and “patient experience data” are now integrated into the vocabulary of the healthcare ecosystem, although definitional and operational variability exists.<sup>21</sup>

In December 2018, the FDA acted on two of its directives from the Cures Act. It released a draft of the first of four separate guidance documents implementing a patient experience data program.<sup>22</sup> It also released a framework for an RWE program.<sup>23</sup> Upon the release of this RWE framework, the FDA Commissioner Scott Gottlieb stated, “Today's data comes from a broader variety of sources than ever before. And we have more tools to leverage this information to inform patient care.”<sup>24</sup> Importantly, both documents support the inclusion of person-generated data in regulatory decision making and provide definitional clarity:

- *Patient experience data* includes data that are collected by any persons (including patients, family members and caregivers of patients, patient advocacy organizations, disease research foundations, researchers, and drug manufacturers) and are intended to provide information about patients' experiences with a disease or conditions including (i) the impact (including physical and psychosocial impacts) of such disease or condition, or a related therapy or clinical investigation, on patients' lives, and (ii) patient preferences with respect to treatment of such disease or condition.
- *Real-world data (RWD)* are data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources. Examples include data derived from electronic health records, medical claims and billing data, data from product and disease registries, and patient-generated data, including from in-home use settings and data gathered from other sources that can inform on health status, such as medical devices.
- *Real-world evidence* is the *clinical* evidence about the usage and potential benefits or risks of a medical product derived from analysis of RWD.

Certainly, the diversity of novel sources that are not yet fully understood requires ongoing study.<sup>25</sup> However, work to codify patient voice and align it with data familiar to regulators has begun.<sup>26</sup> The implications of increased transparency into the reality and real-world experiences of individuals pose risks. However, we should not let risks that can be mitigated impede progress toward integration of person-generated data into regulatory decision making and more broadly across the healthcare ecosystem. Additionally, we must accept responsibility to translate what we learn into reality-based RWE that is fit for care, research, and regulatory purposes, but more importantly is useful, meaningful, and actionable for each of us in the everydayness of living our lives.

The elements to close recognized gaps in RWE are available. When brought together we can address the fundamental questions each of us have when it comes to the real world of our health and the decisions we face to manage it: “What treatment is best for

me?” “How do people treated in the real world perform on this therapy?” and “What is the value of this therapy relative to other treatment options?”<sup>27</sup>

The answers to these questions and more are within reach. In our quest to answer them, we must ensure that the data generated from the real lives of real people represent all voices and not just those most advantaged to be heard.<sup>28</sup> RWD will fall short of its promise to fill gaps in RWE if what we learn does not reflect the real life of real people from across the spectrum of social, economic, and cultural experiences.

### SYNERGY IS NOW POSSIBLE

The term *synergy* has its roots in the Greek word *synergia*, which means “working together.” Together, let us step up to the challenge of harnessing the power of the lived experiences of real people that are grounded in the reality of their real worlds. Let us commit the necessary resources to expand the development of scientific methods and analytics for data that truly reflect the worlds within which we live and the outcomes we actually experience—there is little standing in our way to close the gaps that persist in RWE.

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