evidation

Five-Step Action Plan to Implement Your PGHD Strategy

Leveraging person-generated health data (PGHD) to deliver actionable insights

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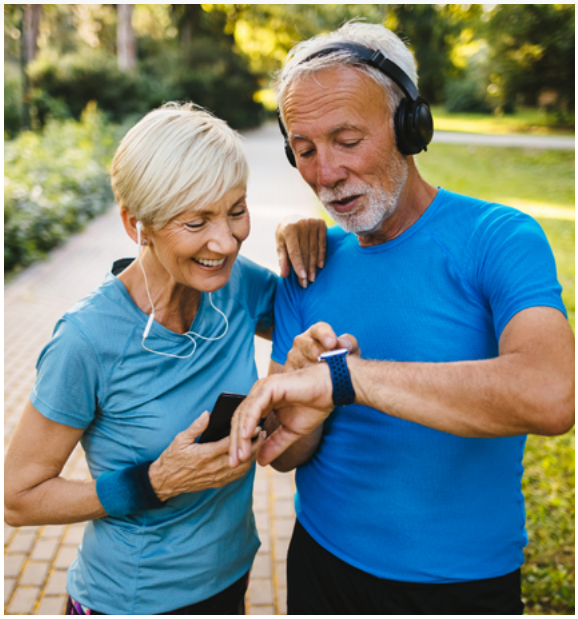

2022

Summary

As stakeholders across clinical development as well as healthcare providers increasingly embrace measurements of health outside the clinic, it is becoming increasingly critical to incorporate person-generated health data (PGHD) into clinical research and development programs. Given the novelty of PGHD, healthcare systems also must determine how best to mobilize around PGHD and initiate relevant research. A joint FDA-industry meeting identified five key takeaways for organizations seeking to implement the use of PGHD to enhance their clinical product development programs: provide value to research participants, use evidence-based study designs, apply proven tools from traditional clinical research when appropriate, leverage PGHD to identify what matters most to participants, and deploy PGHD methods to identify gaps in knowledge obtained from clinical trials.

In this publication, we describe and expand on these ideas and draw inspiration from real-word examples that demonstrate the potential of PGHD.

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INTRODUCTION:

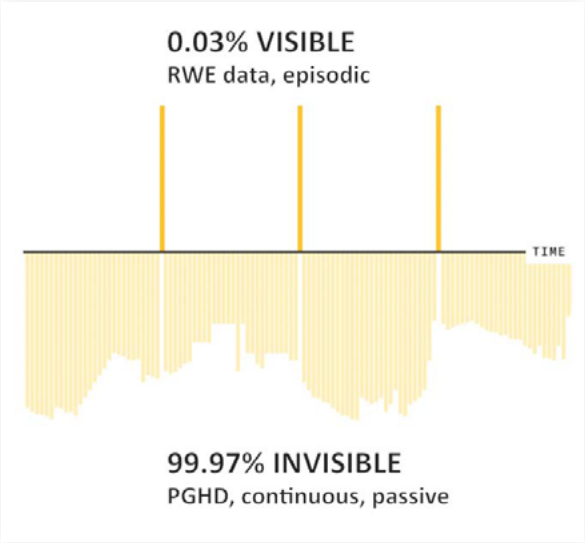
Context for Regulatory Discussions of PGHD

Data from randomized, controlled clinical trials (RCTs) are the hallmark of medical research. These data are critically important for development of safe, effective medical interventions and regulatory decisionmaking. However, RCTs suffer from limitations that result in knowledge gaps. These include delays in recruiting large cohorts, difficulties in enrolling diverse and representative populations, slow accrual of rarer outcomes, the need for an extensive infrastructure with resultant high costs, and only limited data on individual behavioral and physiological variables outside of the healthcare and research environments. While these issues are not unique to RCTs, they are a significant bottleneck to developing actionable data for regulatory decision making.

The COVID-19 pandemic, in particular, has highlighted our need for more patient-centric data in general and a deeper understanding of patient behaviors and perspectives specifically[1]. As the death toll approaches 5 million people worldwide[2], how best to prevent transmission of variants within specific populations, treat their various manifestations, and motivate people to receive vaccinations remains unclear. Technologies that can provide real-time interactions with patients might offer a unique way to streamline collection of real-world data and thereby shorten the time to effective interventions.

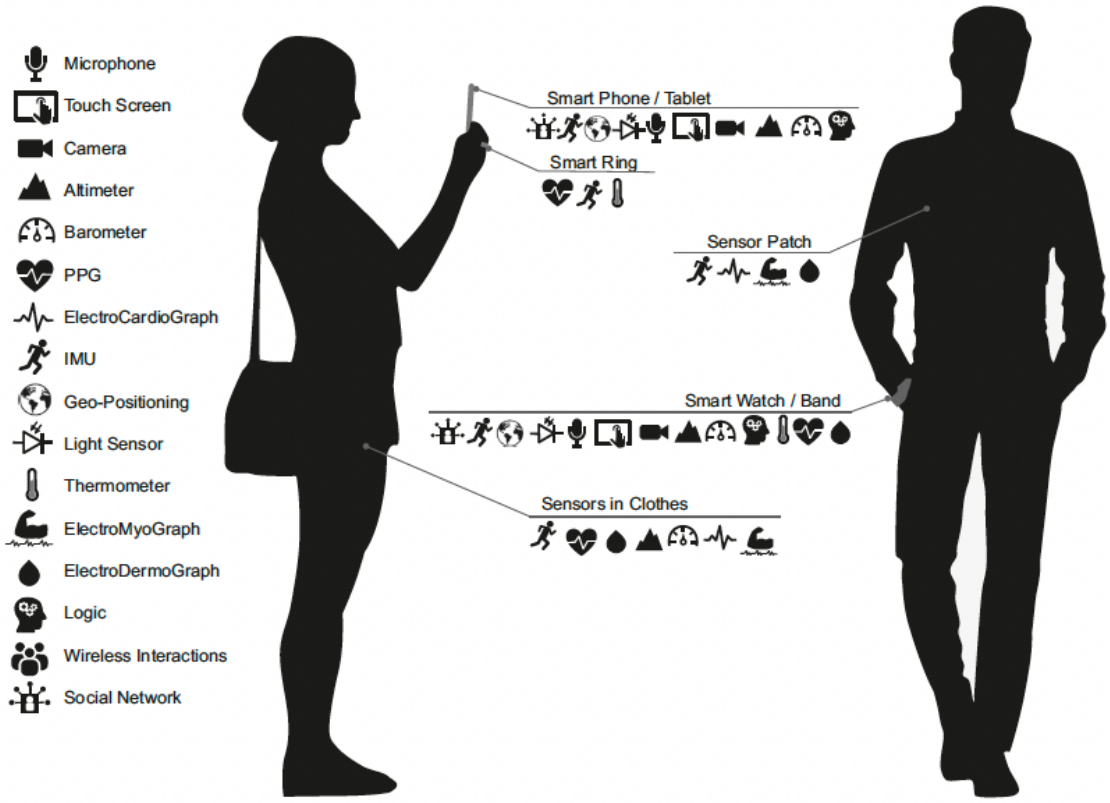
The US Food and Drug Administration (FDA) signaled its support of the use of such real-world evidence (RWE) in the 2012 FDA Safety and Innovation Act (FDASIA), which formally established a Patient-Focused Drug Development (PFDD) initiative to incorporate patient voices in drug and biologic development. The FDA defined PFDD as "a systematic approach to help ensure that patients' experiences, perspectives, needs, and priorities are captured and meaningfully incorporated into drug development and evaluation." Real-world evidence recently served as the basis for approval of a new use for an antirejection drug[3]. Still, RWE can offer only episodic snapshots of a person's overall condition. Person-generated health data might offer a morecomprehensive picture of an individual's health, environmental, and behavioral situation.

Real-World Evidence versus Person-Generated Health Data (PGHD)



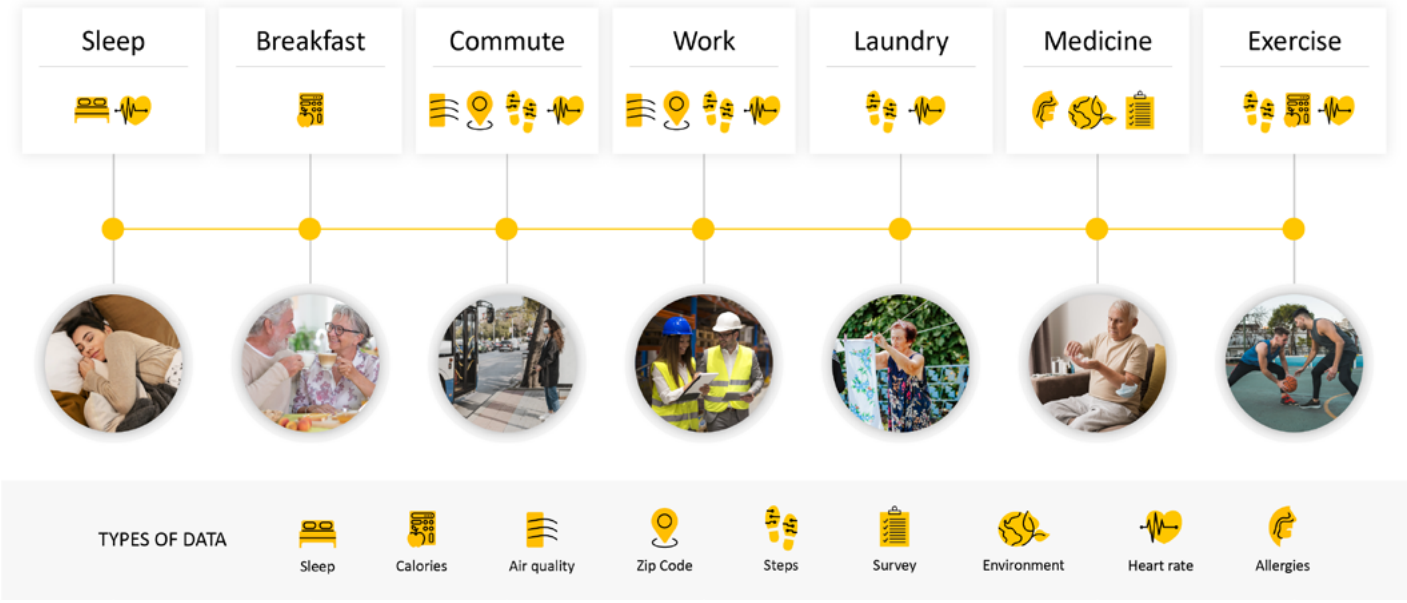
Technological advancements in wearable devices and other sensors have enabled the continuous, passive collection of PGHD. Such technologies offer significant opportunities to close knowledge gaps and increase our understanding of health and specific conditions in unprecedented ways, by measuring previously invisible physiological and behavioral activities in participants' own environments, not just in research or clinical settings.

Potential Sources of Person-Generated Health Data (PGHD)



Source: Kourtis LC, Regele OB, Wright JM, Jones GB. Digital biomarkers for Alzheimer's disease: the mobile/ wearable devices opportunity. NPJ Digit Med. 2019;2:9. doi: 10.1038/s41746-019-0084-2. Epub 2019 Feb 21. PMID: 31119198; PMCID: PMC6526279.

Person-Generated Health Data in Everyday Life



Agencies such as the FDA have recognized the importance of incorporating patient perspectives into regulatory decision-making, and that PGHD can play a critical role in collection of relevant data in this regard. The FDA's Patient Engagement Advisory Committee (PEAC) was established to "help assure that the needs and experiences of patients are included as part of the FDA's deliberations on complex issues involving the regulation of medical devices and their use by patients."[3] It is the first and only advisory committee whose members are all patients, caregivers, or representatives of patient organizations.

The FDA and PEAC have long acknowledged the potential role of PGHD in incorporating RWE into regulatory activities, particularly in the post approval phase, as well as the need for methods to aid in integration of PGHD across product lifecycles.[4] These and other issues were considered during a November 2018 meeting,[5] which called for additional discussions about the critical elements of these data and how they could best be used throughout the lifecycle of medical devices. As a result of this meeting, the FDA's Digital Healthcare Center of Excellence (DHCE)[6] and the US Department of Health and Human Services began partnering to form coordinated registry networks[7] facilitate the collection of interoperable, person-generated RWE to improve the quality, effectiveness, and safety of medical interventions.

These efforts have already resulted in approvals for digital therapeutic applications for insomnia, substance use disorders, attention deficit/hyperactivity disorder (ADHD), diabetes management, and heart rhythm abnormalities.[8] And as previously mentioned, the FDA recently approved a new use for a drug to prevent organ transplant rejection on the basis of strong RWE of effectiveness.[4] There is still work to do, however: a recent analysis found that only 30% of approved labels for new drugs and biologics mentioned patient experience data in their applications, even though patient-reported outcomes were included in 84% of the FDA's reviews.[9]

On May 4, 2021, the FDA held a public session online that covered PGHD and its potential uses throughout the healthcare ecosystem.[10] Discussions covered sources of PGHD, data quality measures, interoperability, and potential impacts of the data in regulatory and healthcare settings. What emerged were five features of PGHD valuable to researchers and patients alike, listed in the table below:

KEY FEATURES OF PGHD

Provides a real-world perspective

Captures patient perspectives

Enables precision medicine

Includes people who may not be typically included in clinical trials, such as women, people of color, rural residents, etc.

Provides novel clinical opportunities, including real-time physiological and behavioral monitoring

The FDA is committed to determining the best ways to incorporate PGHD data into regulatory decision-making.[11] As medical stakeholders increasingly embrace PGHD, it will therefore become increasingly critical to incorporate PGHD methods into clinical research and development programs. In addition, given the novelty of PGHD, healthcare systems must determine the best ways to mobilize around PGHD and initiate relevant research.

The May 2021 FDA webinar yielded actionable insights to facilitate the collection and use of PGHD. In this article, we describe and expand upon these insights, and illustrate the potential of PGHD through real-life examples.[12]

Five Actionable Insights to Aid in Collection and Use of PGHD

1. Provide value to research participants to improve retention
2. Use evidence-based study designs to ensure collection of high-quality data
3. Apply tried-and-true tools from traditional clinical research when appropriate
4. Leverage PGHD to gain unique insights into what matters most to participants
5. Deploy PGHD methods to identify what isn't being learned from clinical trials

1 Provide Value to Research Participants to Improve Retention

There are two main strategies for improving retention of study participants: minimizing the burden of data collection and sharing, and increasing the value of participation.

To minimize burdens associated with participation, researchers must make providing data as easy as feasible, incorporating this activity into patients' daily lives to the extent possible. Ideally, data would be collected via passive means, such as through wearable devices. Any application or platform used for research likewise should be easy to use but also secure.

Two strategies can increase the value of research to participants: 1) making participants feel like they are part of a community, and 2) developing meaningful content that helps individuals manage their conditions. One established method for achieving both aims is the patient-driven registry, which the International Medical Device Regulators Forum defines as an organized system with a primary aim to improve the quality of patient care that continuously collects relevant data, evaluates meaningful outcomes and comprehensively covers the population defined by exposure to particular device(s)at a reasonably generalizable scale (e.g. international, national, regional, and health system)[12]

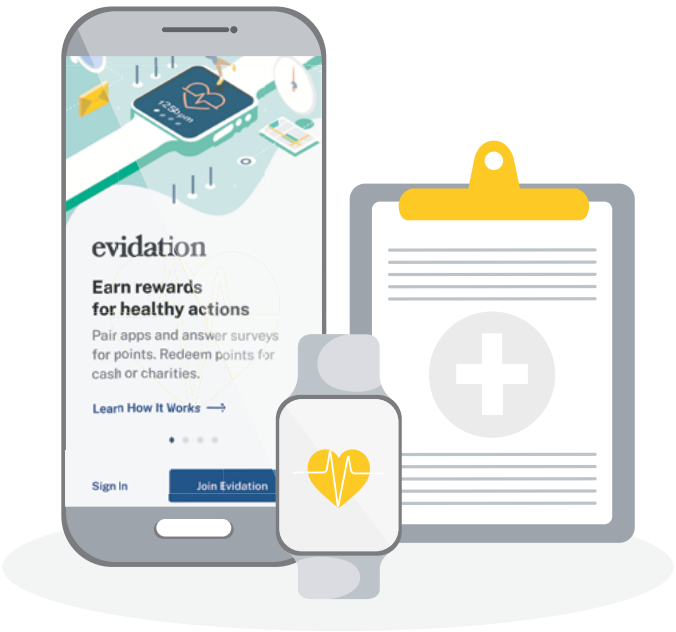
Differences Between a Patient-Driven Registry and a Typical Clinical Study

REGISTRY	CLINICAL STUDY
→ Usually observational	→ Often but not always interventional. Well defined and pre-specified protocol.
→ More broad inclusion criteria related to condition or product, minimal exclusion.	→ Strict set of inclusion, exclusion criteria to select patients
→ Results are generalizable to a broader patient population	→ Focused on a relatively homogeneous group

As shown in the table, registries can offer advantages compared with clinical studies. Expanding the concept to Coordinated Registry Networks (CRNs), which build on existing national or regional registries, allows strategic harmonization and linkage of data elements, and greatly increases the power to detect correlations and conduct other analyses.

Many patient-driven registry networks (defined by patients and intended to measure what matters to patients) have shown great success at engaging relevant cohorts and answering questions important to them. These include the Michael J. Fox Foundation for Parkinson's Research Fox Insight project[13], the ArthritisPower network[14], the National Organization for Rare Disorders (NORD),[15] and the Foundation Fighting Blindness.[16]

Another method to achieve the goals of community and generation of meaningful content may be the use of wearable technologies. One study in patients with atrial fibrillation showed greater engagement with the healthcare system among users of smartwatches and other wearable technologies compared with nonusers.[17] In particular, users of these technologies underwent ablation significantly more often than did nonusers, possibly reflecting the devices' ability to generate continuous, actionable data for both users and providers.



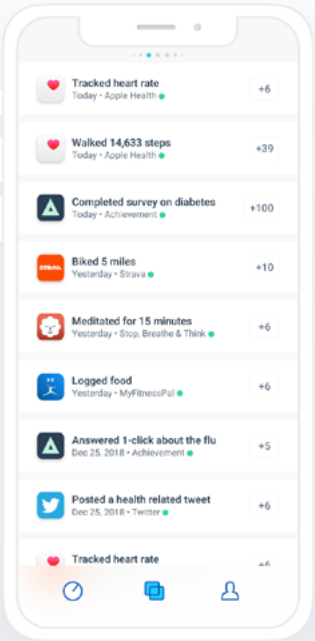
INSIGHT IN ACTION

Evidation's health and research platform, trusted by a community of over 4 million individuals, enables users to join remotely conducted virtual studies and research, sharing PGHD captured on smartphones and wearable devices and patient-reported outcomes in an effort to provide a more holistic view of the patients' lived experience outside clinic walls. These contributions help further Evidation's understanding of human and behavioral health with a goal of providing actionable insights to patients and the industry to enable them to deliver better health outcomes.

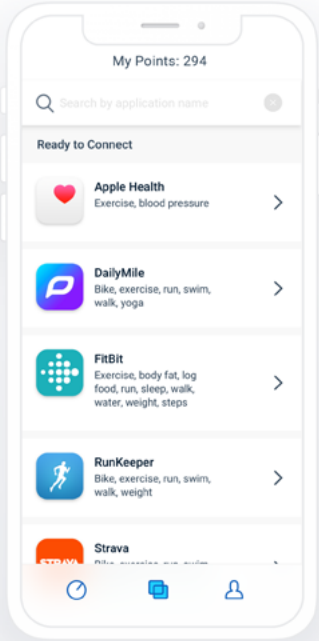
The app is easy-to-use and allows people to earn rewards for healthy actions, receive personalized content about relevant health conditions, and participate in cutting-edge research all from the comfort of their homes. Deidentified and summarized insights are shared back to the population of users or published in peer-reviewed medical journals.

THE EVIDATION HEALTH AND RESEARCH PLATFORM

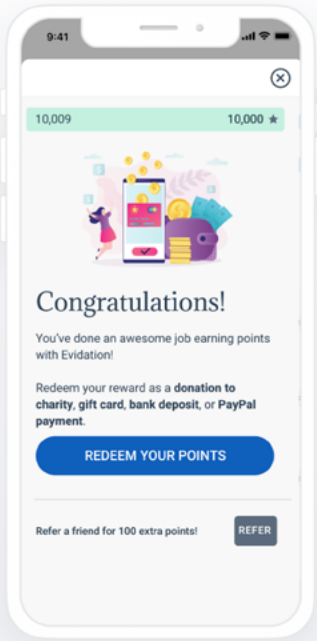
Earn Points for Healthy Actions



Connect Apps and Earn Points



Redeem Your points for Cash or Charities



2 Use Evidence-Based Study Design to Ensure Collection of High-Quality Data

In addition to retention, researchers must also ask participants the right questions and collect the right data to ensure the generation of high-quality, useful data. A primary method for achieving this goal is to develop specific research questions and define and collect ONLY the data and endpoints needed to test the hypothesis. There are four key concepts to evidence-based, participant-centered study designs:

- **Selecting objectives and asking questions that are important to patients.**[18] Having one or more representatives from the specific cohort involved in the design of the study is highly desirable in this regard. Barring this, researchers should use whatever previous data are available to generate relevant research questions.

- **Designing studies and technology to be patient-centric,** to be focused on the research question, and to minimize patient burden. For example, the most effective questions are those that can be answered easily and meaningfully, such as asking "Did you miss work due to your illness?" rather than "How did you feel that day?" Gamification can also assist with engagement and retention.[19] Finally, device-based studies must balance security with ease of use.

- **Applying thoughtful data cleaning and quality checks**; anticipating oddities or discrepancies (patient reports are not clinical records). These can include using smart pickers for medications, using logic tests for variables such as dates, accounting for typographic errors, strategies for dealing with missing data, etc.

- **Actively monitoring data quality and listening to patient feedback.** A dynamic study design allows adjustments to be made if needed. For example, active monitoring of data might identify survey questions that are unclear, based on the responses. Missing data could also indicate that participants might not want to share data OR that the information may not need to be collected because it is not relevant.

Before, during, and after the study, researchers should be transparent about participants' data use and rationale. This consists of communicating how and why their data will be used, as well as disseminating the findings in a manner interesting to most participants.

3 Leverage Tried-And-True Tools from Traditional Clinical Trial Research when Appropriate

Clinical trials have several strengths that can be leveraged for PGHD; the wheel need not be reinvented for every aspect of PGHD research. Experts can successfully be deployed similarly in clinical trials and PGHD research through, for instance, study leaders, working groups, cores, etc. working together to determine aspects of study design and data collection, storage, and analysis. In fact, clinical investigations have been successfully nested within registries,[20] and guidelines have been generated for this purpose.[21]

Traditional strategies that have worked in clinical research can work for PGHD as well. In some cases, existing approaches can be enhanced by leveraging technology to remove barriers to participation. Some examples from across the end-to-end process include[22]:

- **Widening the enrollment funnel.** Inclusion and exclusion criteria should be as nonrestrictive as possible, to maximize the candidate pool.

- **Understanding key stakeholders.** Patients are interested in new research opportunities, the ability to easily sign up or prescreen (ideally online), and minimal disruption to their lives. Clinical trial sites want eligible patients appearing at a steady rate, a system to organize and track them, and support from sponsors to arrange for transportation or in-home testing. Research sponsors likewise want steady progress toward complete enrollment and to know — in real time — the study's enrollment status.

- **Harnessing digital targeted advertising.** Patients often never find out about clinical trials, especially if their physician is not participating. Every clinical trial should now be advertised on mass channels that have sophisticated targeting, such as Facebook. Studies are currently falling short, however: only 11% of organizations currently recruit patients through social media.[23]

- **Conducting online prescreening.** In addition to informing patients about a clinical trial, researchers must provide actionable ways to prescreen, sign up, and opt-in for contact. Databases such as **clinicaltrials.gov**, although they provide comprehensive listings of trials, suffer from two key problems: complex study descriptions that use clinical language, and no actionable

way to prescreen. Eventually, all studies should have an online prescreening tool that allows people to find out if they are eligible and, if so, to continue the enrollment process. This is a benefit in all studies, even traditional ones, as it can improve the quality of participants that end up at the site.

- **Consolidating and transferring medical records.** Once a patient has passed a screening visit, the next major barrier to participation is the consolidation and transfer of medical records. For patients with complex histories or severe conditions, this process can take months, and it often becomes the study site's responsibility. A central, secure repository of electronic medical records (EMRs) that can be accessed by patients or caregivers is critical for easy transfer and use by trial sites.

- **Facilitating in-home testing.** Patients are often burdened by the number of study visits, blood tests, and other assessments required for trials. If visits not requiring a clinical environment could occur in patients' homes, participation would increase dramatically. In-home testing could be conducted via apps, wearable technologies, or diagnostic devices specifically designed for given visits. Expedited regulatory review of such tracking systems would help substantially in such efforts.

4 Leverage PGHD to Gain Unique Insights into What Matters Most to Participants

By providing participants with choices and observing how they engage, researchers can learn what matters most to them, which has critical implications for the development and optimization of interventions and management of symptoms and diseases. For example, observing which self-reported outcomes participants choose to track provides insight into which symptoms are of greatest importance.

Evidence supports the incorporation of PGHD in efforts to improve healthcare outcomes. The Agency for Healthcare Research and Quality (AHRQ) systematically reviewed automated-entry PGHD devices and mobile apps for prevention or treatment of 11 chronic conditions, specifically looking for evidence of their impact on often-unmeasured health outcomes such as quality of life and symptom improvement.[24] They included 114 controlled studies that used 118 unique devices and 26 mobile apps.

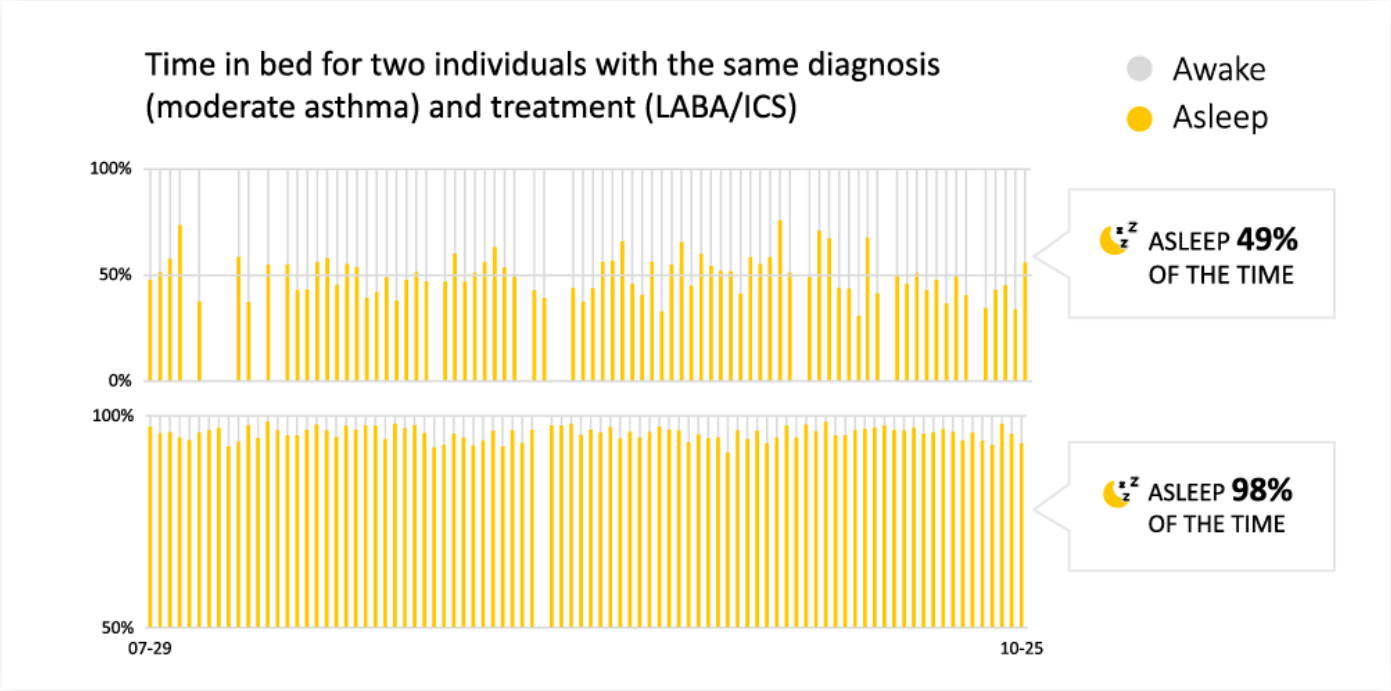
For three conditions — coronary artery disease, heart failure, and asthma — they found a possible positive effect of PGHD technologies on outcomes. There were also positive effects on the time to detection of cardiac arrhythmias and the surrogate outcome of blood pressure. But for conditions such as obesity, chronic obstructive pulmonary disease (COPD), diabetes prevention, sleep apnea, stroke, and Parkinson's disease, the effects of PGHD were unclear.

The study also revealed deficiencies in underlying study enrollment: <20% of the participants in the cardiac disease studies were women, only 8% of studies enrolled rural populations, and many of the studies enrolled nonrepresentative populations generally (in terms of race, sex, or age). This study thus identified targets for future research to determine the specific impact of PGHD in more diverse cohorts, to improve the measurement of important health outcomes, and to study the long-term effects of PGHD.

In healthcare settings, it would be ideal to have PGHD entered and stored in the same record and using the services as other patient data. The provenance of the PGHD (the metadata) would be the key to its successful integration into EMRs. Data provenance (also referred to as "data lineage") is metadata paired with records detailing the origin, changes to, and information supporting the confidence or validity of the data. Using metadata allows the user to control

and filter the information for specific use cases. Its use would thus overcome much of the resistance to the use of PGHD in EMRs, which stems from the perceptions that they are less reliable, that they are too "noisy," and that providers would be liable for the data.

INSIGHT IN ACTION



**LABA = Long-acting beta-adrenoceptor agonist; ICS = inhaled corticosteroids.*

In a survey of 14,000 individuals with asthma, Evidation identified real-world behaviors and disease impact measures that diverged based on condition severity and treatment choice. These distinct differences in control of symptoms evidenced through PGHD would not be found in traditional RWE.[25]

5 Deploy PGHD Methods to Identify What *Isn't* Being Learned from Clinical Trials

PGHD research offers opportunities to reach underrepresented groups in clinical trials and answer patient-centric questions that are not being adequately addressed in such studies. As an example, the Fox Insight project collects longitudinal information directly from people with and without Parkinson's disease through a web-based, mobile-optimized platform.[26] Volunteers can contribute many different types of data, such as health-related surveys, genetic information, and telemedicine visits. Most important is the fact that the worldwide volunteers also have input into the development and execution of research projects.

This platform removes many of the typical barriers to research participation: narrow eligibility criteria, mobility restrictions, transportation challenges, and lack of access to medical and research institutions. To date, more than 50,000 people have enrolled, and more than 600 researchers around the world are accessing and using these data to power relevant research.

Publications from this project[27] have provided insights not only relevant to people with Parkinson's disease but also concerning research in general. In one case study alone, the project collected the largest sample to date (more than 10,000 responses) of patient-reported problems for any neurological disorder.[28] Several disease-specific research questions also have been answered through this registry, such as characterizing the course of neurological disease through direct patient reports,[29] identifying whether and how people with Parkinson's disease talk about the experience of "off" symptoms[30], and better understanding the economic burden of disease.[31]

This project demonstrates several advantages over attempting to recruit participants via traditional means. First, the registry consists of study participants whose age matches that of persons participating in clinical trials in this space. The database also includes a higher proportion of men than typically recruited to clinical trials, pointing to the potential for PGHD to capture more male-relevant data on the disease. Specific strategies are being explored to enhance the diversity of PGHD participants, given that lack of diversity in clinical trials has been an ongoing challenge. Finally, the Fox Insight study has also shown how online studies are more nimble than clinical trials and can adapt quickly to new contexts. During the COVID-19 pandemic, Fox Insight has been able to investigate the impact of the disease and its vaccines on people with and without Parkinson's disease much faster than clinical trials could.

INSIGHT IN ACTION

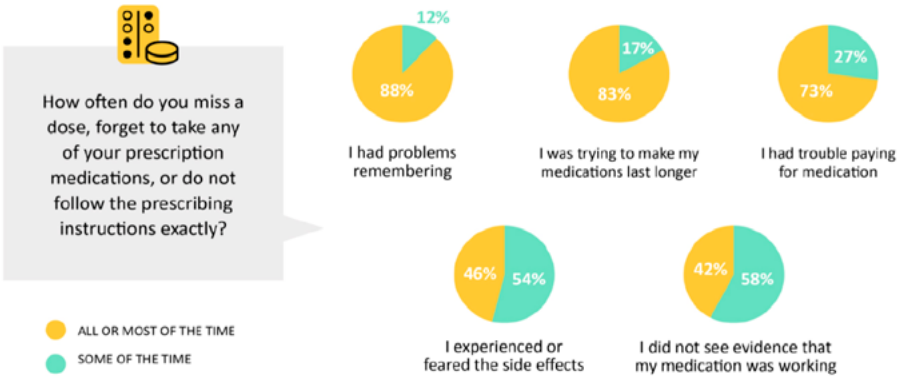
In collaboration with the American College of Cardiology (ACC), Evidation launched a nationwide initiative focusing on individuals living with heart failure.[33] Over 1,000 participants with heart failure and other chronic conditions shared their particular needs and sources of value that could improve engagement and health outcomes.

For example, 14% of individuals report not taking medications for heart failure[32], and the majority of this group describe high burden-over 70% report having symptoms, and more than 40% report frequent daily life limitations. These data are important because most people living with heart failure are not receiving guideline-directed therapy, and this type of data will help researchers and providers identify suboptimally treated individuals.

Missing a Dose of Medication

We asked patients how often they miss a dose of their medications and why. The most common reason for occasionally missing a dose was simply because they forgot, but we also saw that many patients reported having trouble paying for medications or tried to stretch their medications to limit costs. In addition, patients who avoided or stopped taking their medications reported having concerns about the medication, experienced side-effects or believed the medications did not work on them.

- Why it matters: Non-adherence can have serious consequences. In the simplest cases, patients need help managing their medications, but we also need to help patients work with their care team to transition to the best medications for them so that they feel the benefit of taking them.



Insights from the ACC/Evidation program can be found **here**.

Case Study

Evidation has built products and tools that work to characterize the vast majority of an individual's lived health experience, which occurs outside the clinic. Incorporating such additional PGHD can shift the industry towards understanding patient perspectives on a more representative level and tailoring therapeutic options based on how patients feel and function in everyday life.

In the May 2021 webcast, the FDA discussed the importance of incorporating patient-centric approaches into regulatory decision-making and the critical role PGHD plays in moving the needle in developing safe and effective medical products that provide meaningful benefit to patients. This paradigm shift is the future of healthcare as stakeholders agree that we need to invest in strategies that yield more value, and measuring what matters most to patients from bench to bedside is key. Incorporating PGHD can help complement ongoing research, improve regulatory positioning, and close the gap between patients and providers.

In collaboration with Eli Lilly, Evidation assessed the feasibility of collecting data for 12 weeks from multiple smart devices, including iPhones, iPads, Apple Watches and in bed sensors, of 113 older adults with and without cognitive impairment, and tested whether the data from these devices can differentiate between healthy individuals and participants with cognitive impairment.[33]

Symptomatic participants with mild cognitive impairment or mild Alzheimer's disease tended to type slower, receive fewer text messages, and spend more time using helper apps than did the healthy controls. After controlling for age, the device derived features showed good ability to differentiate between participants who did and did not have cognitive impairment. Thus PGHD has the potential to monitor for and detect early symptoms of cognitive impairment, which would allow accelerated development and testing of new therapies.

CONCLUSION

Incorporating PGHD can shift the life sciences industry and healthcare ecosystem toward understanding patient perspectives on a more representative level, to tailor therapeutic options based on how individuals feel and function in everyday life. It also can move the needle in developing safe and effective medical products that provide meaningful benefit to patients. Arguably, PGHD-driven approaches have an important role in healthcare's future, and there is a gathering consensus that evidence generation must encompass measuring what matters most to patients to yield more value from all perspectives. Early efforts at incorporating PGHD are promising, and require more concerted effort from all stakeholders to ensure that this value is realized.

For more information about Evidation and its products, visit **evidation.com** or email **partner@evidation.com**

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