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# Regulatory Fit-for-Purpose Considerations for Patient-Generated Health Data


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### Disclosures

Rachele Hendricks-Sturrup served as an independent executive with the National Alliance Against Disparities in Patient Health and is presently an independent director on the board of Public Responsibility in Medicine & Research (PRIM&R).

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## Executive Summary

Patient-generated health data (PGHD) are health-related data created, recorded, or gathered by or from patients, or their family members/other caregivers, to help address a health concern. PGHD complements information captured in other health care data sources and has the potential to alleviate challenges existing in pharmacoepidemiology data collection, such as misclassification, representativeness, and missing information. PGHD remains of interest to regulators, as insights gleaned from real-world evidence (RWE) generated using PGHD can help fill important gaps in clinical trial data and observational studies. This white paper summarizes key indicators of relevance, reliability, and quality to determine if PGHD is fit-for-purpose and offers practical considerations to support the initial development of medical products using PGHD collected in real-world settings, as well as subsequent development and surveillance of medical products using PGHD derived from regulatory-approved medical devices. Currently, the utility of PGHD to support drug and/or treatment applications remains unclear. Duke-Margolis proposes that regulators build a common framework based on present and evolving notions of fit-for-purpose PGHD.

## Background

Stakeholders generally define patient-generated health data (PGHD) as health-related data created, recorded, or gathered by or from patients, or their family members/other caregivers, to help address a health concern. The types of data collected in PGHD include medical and health history, treatment history, signs and symptoms, biometric data, and lifestyle choices.

The creation and use of PGHD offers multiple benefits to patients, caregivers, health care systems, and researchers as it complements information captured in other health care data sources and offers communication channels for greater patient care, involvement in health practice, and research. It has the potential to alleviate challenges existing in pharmacoepidemiology data collection, such as misclassification, representativeness, and missing information. When collecting PGHD, researchers can gather data on drug adherence, non-serious adverse events, quality of life, and pain and/or depression scales. Researchers can also collect additional covariates from patients which may not be present in an electronic health records (EHRs).[1]

PGHD comprises a wide and diverse array of health-related data generated directly (actively or passively) by patients. Examples of devices that generate PGHD include smart wearable devices, passive home monitoring devices, and digital mobile apps capable of recording physiological and/or behavioral data from persons of all ages. Self-reported symptoms in patient surveys (i.e., patient reported outcomes [PROs]), patient-driven registries, and direct-to- consumer (D2C) genetic testing, can also be considered as PGHD if the data is used or considered within a real-world clinical setting or is documented within clinical data infrastructure. In prior work, Duke-Margolis also describes PGHD as person-reported data, task-based

measures, active sensor data, and passive sensor data, all of which can be and have been used individually or in combination with clinical trial data to support the development and implementation of health research.[2]

PGHD generated in real world or uncontrolled study settings reflect a patient's lifestyle and is characterized as real-world data (RWD) within the regulatory science community. Thus, PGHD remains of interest to regulators, as insights gleaned from real-world evidence (RWE) generated using PGHD can help fill important gaps in clinical trial data and observational studies collected to assess medical product safety and efficacy beyond the clinical setting and based on the patient experience.

Digital devices, apps, and other medical device products that are used or developed to collect and/or generate PGHD possess unique and multifaceted characteristics. They can be utilized as a medical product themselves, incorporated into an existing product (i.e., combination products), used to develop or investigate a separate product, and/or used as a companion diagnostic. The Food and Drug Administration (FDA) considers many apps, wearables, and other sensors not expressly created as medical devices, such as direct to consumer tests or smartwatches, as devices. For example, the FDA Center for Devices and Radiological Health (CDRH) published an extensive report highlighting 90 examples of RWE generated from product and disease registry data, PGHD, and device-generated data that informed regulatory approval decisions for a diverse array of medical devices, including D2C genetic tests and other digital health devices, during fiscal years 2012 through 2019.[3] Two of these, the NaturalCycles™ app and the Dexcom™ glucose monitoring system used de-identified patient generated health data to fulfill premarket and/or post-marketing requirements. FDA's latest draft and updated guidance on the "Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices," cited the report to describe instances where RWE could support premarket and post-market regulatory decisions for medical devices.

Today, regulatory science discussions and literature only partially contextualize the regulatory acceptability and fit-for-purpose characteristics of the diverse array of PGHD collected in real-world settings. Many wearable devices, such as the Oura ring™, the Apple™ AI-powered coaching service, and a wearable air pollutant sampler remain experimental and not FDA-approved.[4] Continuous glucose monitors, like Dexcom™, however, are FDA approved and have been incorporated into clinical care"

The regulatory science community continues to explore whether PGHD generated in real-world settings can be reliable on its own to influence regulatory decision-making or can serve only as a supplement to other sources of RWD for that same purpose. Here, we summarize characteristics of fit-for-purpose PGHD collected in real-world settings, with a focus on data relevance, reliability, and quality both generally and across specific PGHD sources. We also offer practical considerations to support the initial development of medical products using PGHD collected in real-world settings as well as subsequent development and surveillance of medical products using PGHD derived from regulatory-approved medical devices (see **Table 1** in Appendix). We aim to inspire the regulatory science community to engage in further discussions and consider the development of practical guidance around what constitutes fit-for-purpose RWD with a specific focus on a growing and diverse array of PGHD.

## Overall Considerations

Generally, key indicators of relevance, reliability, and quality are sought when determining whether PGHD is fit-for-purpose. Duke-Margolis' prior work and recent guidance published by the FDA describe relevance metrics for PGHD as data availability, timeliness, generalizability, and linkages.[5, 6] That is, sponsors should ensure that their stated scientific objectives are adequately supported by PGHD and confirm that the PGHD source contains a sufficient number of representative patient data for its intended use.

**There are two main approaches to linking data: deterministic linkage and probabilistic linkage.**

There are two main approaches to linking data: deterministic linkage and probabilistic linkage. In deterministic linkage, a unique personal identifier, such as a social security number, is used in all data sources, which raises privacy concerns. In probabilistic linkage, multiple non-unique and less-sensitive identifiers are used, such as month of birth and gender. However, although this alleviates some of the privacy concerns, probabilistic linkage is less reliable and its quality is dependent on the types of data available for linkage.[1] Sponsors also should confirm that any data linkages within or from a PGHD source and across other RWD sources use a predefined linkage methodology that is scientifically valid, protects the privacy of individuals whose data will be used, supports interoperability, and accounts for differences in coding and reporting across sources. Stakeholders should also consider the clinical significance of the measurements, including whether or not the data is correlated with disease courses or has clinical significance that will determine whether it will be fit for regulatory decision-making. Some patient-generated health data measures serve as surrogate endpoints (steps), while others serve as clinical endpoints (e.g., number of falls, reported pain levels). In both cases, the need to identify what change would be clinically significant exists.

Duke-Margolis prior work and recent guidance published by the FDA also describe PGHD reliability as measures or indicators of data accrual, quality, and integrity.[5] While self-measured PGHD collected on behavior, such as physical activity, can have greater accuracy as compared to questionnaires and recall bias, PGHD collected from self-measured blood pressure and body temperature, for example, is likely to have lower reliability than provider led collection.[7] To ensure reliable data accrual, sponsors should confirm that they collect and process PGHD in a consistent and methodological manner.

**In cases of rare disease, delays in diagnosis and treatment are common and can be attributed to varied symptoms or clinical presentations across patients who are biologically diverse.**

In cases of rare disease, delays in diagnosis and treatment are common and can be attributed to varied symptoms or clinical presentations across patients who are biologically diverse and who encounter varied degrees of diagnostic testing availability, and time spent waiting for appointments and test results. Limited foundational disease-specific knowledge of rare diseases exacerbates these factors. Therefore, consistent and methodologically sound PGHD collection that takes these considerations into account is necessary to successfully evaluate medical product safety and effectiveness within and across a target population, which would be of interest to both the study sponsor and patient population. Leveraging PGHD for the variety of concretely explored and potential purposes it can serve

yields several important considerations and challenges. For example, primary limitations of PGHD use with rare diseases involve reconciling data from different devices, replicating data collection and accrual methods, protecting patient privacy, and standardizing protocols for data quality, reliability, and validity. Clinical uses of wearable devices and other digital modes of gathering data remains under development, and real-world experience using biometric data to address rare diseases warrants even further exploration.

All forms of PGHD are subject to three quality considerations: accuracy, completeness, and transparency. Researchers should routinely collect documentation of the accuracy of measures for all sources of PGHD data, but especially wearables and sensor data. There are several factors to consider as measures to ensure the robust quality of PGHD generated and collected in real-world settings. For instance, patients may become motivated to collect quality, timely, and consistent PGHD depending on if they are well or unwell (e.g., rare disease patients feeling variably motivated to contribute high quality PGHD to a patient registry to support drug development) or if financial or reward incentives are available (e.g., patients feeling motivated to contribute their fitness data to save money on health insurance premium costs though a wellness program). All of these factors influence the completeness of patient-generated health data.

Mental health care contexts pose specific challenges for data quality, as mental health terminology tends to vary across real-world settings, which can lead to potential misuses or inaccurate uses of mental health terms that can affect the accuracy and validity of PGHD.[8]

These challenges are especially true for social media data, where slang, emojis and false IDs are widely used, calling into question the validity of the data. Similarly, variability in the format, transmission, and storage of PGHD poses challenges for PGHD usability and integration across data systems. Therefore, sponsors seeking to collaborate with generators of PGHD collected in real-world settings must design and implement appropriate strategies, techniques, protocols, and measures to monitor and control the quality, timeliness, and consistency of PGHD. Learning health systems that provide patients with options or opportunities to upload their PGHD into their patient portals need to consider this aspect, thereby integrating PGHD into their medical records.

**In addition to the primary limitations of PGHD for rare disease, challenges within the scope of data ownership, privacy, security, and integration also exist.**

In addition to the primary limitations of PGHD for rare disease, challenges within the scope of data ownership, privacy, security, and integration also exist. Sponsors should transparently disclose the provenance of PGHD, while safeguarding patient privacy. Patient protections are especially needed in the instance of PGHD since many forms of it are not afforded Health Insurance Portability and Accountability Act (HIPAA) protections unless it becomes part of health system records, thereby allowing wearable and mobile app companies to legally collect and sell health data to third parties without a user's knowledge or consent. Before PGHD is used to support regulatory decision-making, stakeholders need to consider all of these challenges, especially for exceptionally sensitive PGHD related to mental/behavioral or reproductive health.

## Considerations for Wearables and Mobile App Data

Wearable and mobile app data hold exceptional promise to evaluate disease progress and/or interventions. For instance, one study explored the use of wearable devices for pediatric rare disease patients, evaluating ambulation of children with Niemann-Pick C (NP-C), Juvenile Idiopathic Arthritis (JIA), Duchenne Muscular Dystrophy (DMD).[9] All three of these conditions are neuromuscular illnesses, and patients downloaded disease-specific smartphone apps that were Bluetooth-paired with a wearable device. They then provided PGHD in the form of 30-minute episodes that measured average daily maximum steps, average daily steps, and average daily steps per 30-minute episodes. This evaluation demonstrates opportunities for child-friendly progress monitoring solutions for rare diseases through the use of PGHD. Beyond steps, a separate study investigated the use of a wearable device to better understand rest-activity disruption in DMD patients.[10] The study's findings support PGHD utility in describing sleep impairment as wrist actigraphy provided an efficient method of monitoring both sleep and motor impairment in children with DMD.

The feasibility of collecting RWD from social media has been demonstrated in several studies and social media's attraction as a data source can be attributed to the large volumes of data available, the velocity of the data, and the ability for real-time monitoring.[7] Using social media data can call into question the generalizability of PGHD, how well the PGHD can be applied to a broader population, one of the considerations for evaluating relevance of the data, as most social media users are younger women who are less acutely ill. Follow-ups with patients also can be a challenge. Although data from social media are advancing, a gap between technology and regulations exists. More guidance is needed on the role that social media can play in the pre-approval stage of drug development by generating hypotheses on patient conditions, experiences, and beliefs, which can aid in conventional clinical development.

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Wearable and mobile app data relevance considerations require evaluation of the state of data availability, timeliness, generalizability, and linkages. Generalizability connects to availability in that devices and apps must be available to a broad enough portion of the population for any RWD collected for research and analysis to reflect the needs and state of those that a new medical innovation serves as accurately as possible. Data availability and timeliness contain the imperative to ensure that wearables and mobile apps are accessible can collect data in a manner that efficiently, and quickly turns around the data for analysis. It also is important to consider data linkages across different devices that collect the same biometrics, such as rapid eye movement (REM) cycles as measured by different smart watches, and efforts to standardize measurement of these kinds of information across mobile data collection modes is necessary for a dataset to be considered relevant.

When evaluating wearable and mobile app data quality, it is important to focus on accuracy, completeness, and transparency. For instance, individuals using wearable devices or mobile apps to monitor aspects of their health may not wear their device(s) or activate their apps at all times or at times consistent with other users, creating a critical consideration when reporting data. Additionally,

many devices do not to count steps but instead, merely report overall cumulative activity (any activity) and call it "steps per day". This reality creates challenges for data uniformity and collection consistency across one or more users that may undergo comparison in a clinical study. Therefore, wearable and mobile app developers should continuously check and improve the collection and processing of biometric data they collect, as well as describe how health data are measured, whether in discrete or passive settings, via wearable devices and mobile apps.

Device, app, and software developers also should ensure that PGHD collection methods are accurate, consistent, and systematically processed across users and technological models. Transparency is especially an issue with consumer grade sensor data. Sensor company algorithms may be proprietary, making it difficult or impossible to ensure that what a FitBit™ reports as "steps per day": is actually the same (or equivalent) as what an Apple Watch™ reports a "steps per day." In order to use PGHD from wearables, the need exists to be able to ensure that data aggregated across multiple devices is measuring the same metric with the same criteria.

## Considerations for Direct-to-Consumer Genetic Testing Data

Direct-to-consumer genetic tests can be purchased directly by patients seeking to inform themselves, their families, and their clinicians about their genetic status. One notable example of a direct-to-consumer genetic test with FDA-market authorization and approval, based on RWE as a primary evidence source, is the 23andMe PGS Genetic Health Risk Test™.[11] Different direct-to-consumer tests have different regulatory pathways; however, the most relevant one to this discussion is the pharmacogenomic (PGx) test. Companies that offer direct-to-consumer pharmacogenetic tests are required to consult FDA for premarket review and clearance. The FDA has not authorized any direct-to-consumer pharmacogenetic tests to predict whether an individual is likely to respond to or have adverse reactions for any specific therapeutic drug. That is, the FDA has explicitly stated that reports from pharmacogenetic tests are only informative and are only to be used to describe if a person "has variants associated with metabolism of some therapeutics, but do not describe if a person will or will not respond to a particular therapeutic, and does not describe the association between detected variants and any specific therapeutic."[11] Therefore, it remains to be determined whether RWD generated by the test itself could be used to assess whether an accompanying therapy is safe and/or efficacious.

This determination is important since a lot of controversy exists regarding the reporting of genetic variants that have uncertain or no clinical significance, pushing researchers to investigate the possibility of FDA-approved tests for genetic variants to have clinical significance. The growth of self-directed testing raises the risks of patient confusion, and the FDA stating that reports from PGx tests are only informative and cannot predict how a person responds to a particular therapy helps reduce this confusion. However, this challenge also raises questions regarding the value and actionability of pharmacogenomic tests. How valuable are direct-to-consumer pharmacogenetic tests if consumers cannot take action based on results? Preliminary considerations to examine the effectiveness of direct-to-consumer tests include: the ease of use of the test, assessing the appropriateness for the clinical need of the test being offered, verifying the accuracy of test results, examining the linkage of the test to care, and assessing the cost of the test.[4]

In the FDA's draft guidance, "Use of Real-World Evidence to Support Regulatory Decision Making for Medical Devices," relevance, reliability, and quality were identified as factors that need to be considered before evidence from direct-to-consumer genetic tests is used in regulatory decision making. Focusing specifically on direct-to-consumer genetic tests and PGHD reliability, FDA further considers reliability as whether or not a test can accurately and reliably measure what it claims to measure (analytical validity), whether the measurement is predictive of a certain state of health (clinical validity), and what a company says about their test and how well it works (claims).[11] To ensure reliability, direct-to-consumer genetic testing companies must clearly define what variants are being tested, information on the health care settings/environment, and purpose of data collection and timeframe (including the timeliness of data entry, transmission and availability).[5] Data accrual methods must also be carefully considered. Such processes include data cleaning and cross-referencing procedures, methods for data retrieval, and efforts to minimize missing data extraction, and data quality checks in data captured at the point of care.

**Data quality dimensions include accuracy, completeness, and transparency.**

Data quality and integrity considers systems used to ensure sufficient data quality, revolving around completeness, accuracy and consistency across sites and over time. Direct to consumer test results should be evaluated with data quality assurance plans and procedures developed for the data source itself. The quality of the data element population, adherence to source-established data quality assurance, and quality control policies and procedures are all factors to consider. With regards to direct-to-consumer tests, large numbers of tests need evaluation over a long period of time before they are used in regulatory decision making. However, since patients conduct direct-to-consumer tests, it could be challenging to track measures of data accrual, such as timeliness and environment/health care systems information.[5]

Data quality dimensions include accuracy, completeness, and transparency. Surrogates of accuracy include testing the validity of the data elements, the logical plausibility of the data (if the result points to a specific genetic variant), the completeness of collected data, and whether or not the provenance and transformations performed on the data are transparent as the data moves from the collection to storage stages.[6] The logical plausibility is the primary consideration for direct-to-consumer test data. If the results do not point to a specific biomarker, then they cannot influence regulatory or therapeutic decision making.

Relevance considers data availability, timeliness, linkages, and generalizability. The FDA also states in their most recent guidance "Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices" that "if the RWD source is insufficient on its own, the sponsor should determine whether supplemental data sources are available and sufficient to provide any missing information necessary to address the study question." Whether results from direct-to-consumer tests can stand alone is still a point of contention; therefore, it is best if these results are submitted with any relevant supplemental material such as "covariates that may impact exposure or outcomes of interest (patient and family history, pre-existing conditions, labs, demographics)." Similarly, because of the uncertainty around direct-to-consumer tests being able to stand alone, integrating direct-to-consumer test results into electronic health care systems and registries would make the tests results more acceptable for regulatory purposes as they will be integrated with other data, as opposed to being evaluated independently.

## Considerations for Patient-Powered Registry and Platforms for PGHD

Patient-powered registries can be considered as a form of PGHD, and, if possible, sponsors are encouraged to review patient perspectives submitted to the FDA in response to their draft guidance on "Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products." For the purposes of this paper, "patient powered registries" refer to registries "powered" by patients and family members that manage or control the collection of the data, the research agenda for the data, and/or the translation and dissemination of the research from the data.[12]

According to the FDA, registries may have advantages over other RWD sources in that they collect structured and predefined data elements and can offer longitudinal, curated data about a defined population of patients and their corresponding disease course, complications, and medical care. In addition, registries may systematically collect data that medical claims datasets or EHR datasets may lack (e.g., patient-reported outcomes, treatment adherence, measures of disease severity, etc.). In the December 2023 final guidance "Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products," the FDA encouraged sponsors to facilitate and prioritize the collection of outcomes and data that are important to patients. The guidance discusses considerations regarding a registry's fitness-for-use in regulatory decision-making, focusing on attributes of a registry that support the collection of relevant and reliable data.[5]

**Data relevance considerations for patient-powered registry PGHD include ensuring a sufficient quantity and representativeness of registry participants, data linkage capabilities of the registry, and data generalizability.**

Sponsors should ensure that registries are adequately relevant for the scientific objectives. Data relevance considerations for patient-powered registry PGHD include ensuring a sufficient quantity and representativeness of registry participants, data linkage capabilities of the registry, and data generalizability. Sponsors should confirm that a sufficient number of representative patient data is present in the registry for its intended use. Sponsors should also confirm that any data linkages within a patient-powered registry and across other RWD sources use a predefined linkage methodology that is scientifically valid, protects the privacy of individuals whose data will be used, supports interoperability, and accounts for differences in coding and reporting across sources. This methodology is a particularly important relevance consideration as the ability to link between patient-powered registry data and other data sources/types can further supplement PGHD data for regulatory fit-for-purpose use. Patient-powered registry PGHD should be generalizable to the larger target population with characteristics or conditions of interest to the sponsor.

**Reliability considerations for patient-powered registry PGHD include accrual, data quality and integrity, accuracy, completeness, and traceability.**

Reliability considerations for patient-powered registry PGHD include accrual, data quality and integrity, accuracy, completeness, and traceability. Sponsors should ensure that registry data is collected and processed in a consistent and methodological manner. With patient registry data, patients providing their data must follow defined processes and procedures for data collection. This requirement may involve education to

ensure data is collected uniformly and sponsor quality control processes to assess for completeness, accuracy, and consistency.

To further ensure data reliability, sponsors should establish data dictionaries to provide common definitional frameworks for both researchers and patients who will input their data into the registry. A data dictionary should define common data elements, allowable values and format for the data elements with data standards and terminologies used, and information regarding the origin of the data for each data element. Sponsors should take steps to promote the use of common data elements to promote standardized, consistent, and universal data collection.

Patient registry data is reliable if it is also accurate and complete and if data acquisition and management practices around a patient registry are transparent. It is critical to maintain access controls and audit trails to demonstrate the provenance of the registry data and to ensure the data is traceable from a given source. Sponsors seeking to leverage PGHD from a patient registry should be transparent about registry data provenance and whether algorithms were used to transform the data beyond its original or raw form.

The FDA mentioned in the December 2023 final guidance "Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products," that patient-reported data may be inputted into a registry. For instance, wearable biometric monitoring devices can capture detailed patient data that holds great potential to close rare disease research and knowledge gaps efficiently. Technologies most equipped for this goal may possess a multimodal sensing for disease monitoring and the ability to contribute collected data to patient registries. In a diagnostic context, these data collection devices would passively monitor aspects of human health that could correlate with disability and detect anomalies in ambulation, mobility, sleep duration, heart rate, and other physical symptoms. They would factor in a constellation of symptoms in concert with one another to provide a holistic depiction of disease indicators in real time and give quicker insight to users, prompting them to seek definitive diagnosis, treatment, and/or specialty care. These data could continually feed patient registries to make this process more expedited and helpful over time. Studies are exploring this multimodal sensing method for infectious disease monitoring; this model could translate to rare diseases as well. This approach also holds true for mental and behavioral data, where there is great potential to safely and securely integrate mobile mental health data into registries and electronic health record data systems to monitor therapeutic outcomes.

**In a diagnostic context, these data collection devices would passively monitor aspects of human health that could correlate with disability and detect anomalies in ambulation, mobility, sleep duration, heart rate, and other physical symptoms. They would factor in a constellation of symptoms in concert with one another to provide a holistic depiction of disease indicators in real time and give quicker insight to users, prompting them to seek definitive diagnosis, treatment, and/or specialty care.**

## Considerations for Patient-Reported Outcomes Data

Patient-reported outcome (PRO) data collected in real-world settings is a strong source of PGHD. PRO data can help construct a personalized endpoint, which then reflects what is important to individual patients enrolled in trials or real-world studies, especially for diseases with variable clinical manifestations that impact patients differently. PRO data can be collected through a variety of PGHD modalities (e.g., EHRs, mobile apps). FDA's April 2023 draft guidance "Patient-Focused Drug Development: Incorporating Clinical Outcome Assessments into Endpoints for Regulatory Decision-Making" describes the use of a "most bothersome symptom" approach where patients identify, at baseline, the one disease-related symptom that is most bothersome to them, and the patient's status on that symptom post-randomization then becomes the analyzed outcome.[13] The "most bothersome symptom" endpoint, therefore, most reflects a patient's real-world experiences with a health condition. This endpoint can serve as a relevant and reliable source of real-world evidence if collected in real-world settings, processed in a consistent and methodological manner, and integrated into a clinical trial as a control arm. Digital health technologies used to collect these endpoints can undergo special and/or common development, testing, and deployment to ensure the privacy, security, quality, and integrity of data collected. PRO data are an important PGHD source as they can measure directly patient's experiences with disease management, symptoms, and other meaningful information. One such example is a 2023 study where researchers had patients with Parkinson's disease complete surveys and interviews to qualitatively understand the relevance of digital PRO measures to people with Parkinson's disease.[14] The researchers mapped, using "most bothersome symptom" as one metric, digital measures back to personal symptoms to assess relevance from the patient perspective. The study found that patients rated electronic measures of tremor and hand dexterity as most meaningful and relevant in early stages of Parkinson's disease.

**Data relevance considerations for PGHD from patient-derived PRO data include data availability, linkages, timeliness, and generalizability.**

Data relevance considerations for PGHD from patient-derived PRO data include data availability, linkages, timeliness, and generalizability. Sponsors should ensure that available PRO data that can meet study objectives. As with patient-powered registry PGHD, sponsors should confirm that any data linkages from PRO data and across other RWD sources use a predefined linkage methodology that is scientifically valid, protects the privacy of individuals whose data will be used, supports interoperability, and accounts for differences in coding and reporting across sources. The time period when patient-derived PRO data were collected also should be relevant to meet scientific objectives and patients should be provided with education or other support to ensure their data is inputted safely and accurately. Patient-derived PRO data should be generalizable and inclusive of a target population with characteristics or conditions of interest to the sponsor.[5]

## Conclusion

The diverse nature of and ambiguity in standards for PGHD presents both challenges and opportunities for RWE researchers and policy stakeholders. Currently, PGHD has been used solely to support regulatory applications for medical devices. Yet, the utility of PGHD to support drug and/or treatment applications remains unclear or not fully contextualized. Therefore, to maximize the potential of PGHD as sources of valid scientific evidence in drug and medical device applications, Duke-Margolis proposes that regulators, like the FDA, build a common framework based on present and evolving notions of fit-for-purpose PGHD that are described herein. Doing so would be useful to support regulatory decision-making, including approval of new treatments, labeling updates, and post-market surveillance, and such action would benefit RWE policy stakeholders, especially patients. To our knowledge, minimal international guidance exists regarding the regulatory acceptability of patient-generated health data. The Medicines and Healthcare Products Regulatory Agency (MHRA) states that "the relevance, objectivity and practicality of [PGHD] measurements should be considered, taking into account the disease, age, and potential functional abilities of the user. Some devices may be regulated as a medical device and advice can be sought from MHRA when required."[15] Swiss Medic writes that "current developments in the field of mobile/wearable devices may enable market authorization holders to extract valid data for pharmacovigilance, the challenge with this data is applying statistical methods that help avoid misinterpretation and wrong conclusions with regard to therapeutic measures."[16] Therapeutic Goods Administration says that increasingly patient-generated data including from home-use settings and data gathered from mobile devices will become increasingly important. The introduction of a medical device Unique Device Identifier, for example will also significantly increase the ability to monitor specific medical devices and patient outcomes globally.[17]

How these types of new data sources and identifiers work and their use for RWE and PROs will need to be more clearly set out. The information from these regulators echoes Duke-Margolis' conclusions that a) PGHD supporting regulatory decisions has only been used/conceived in medical devices, b) age, disease, and functional abilities all impact PGHD measurements and need consideration and c) certain metrics like relevance, objectivity, practicality, clinical utility, and quality need to be evaluated to determine patient-generated health data's regulatory acceptability.

## Appendix A

### Table 1 | Operational Considerations for Regulatory Fit-for-Purpose PGHD

| PGHD Source | Operationalizing Fit-for-Purpose PGHD | | |
|---|---|---|---|
| | **Relevance**<br>*Data availability, timeliness, generalizability, and linkages* | **Reliability**<br>*Data accrual, quality, and integrity* | **Quality**<br>*Accuracy, completeness, and transparency* |
| **Wearables and Mobile App Data** | Sponsors should consider data linkages across different wearable and mobile devices that collect the same forms of biometric data, and attempt to standardize related measures. | Developers should ensure that collection methods are accurate, consistent, and systematically processed across users and technological models. | Developers should continuously monitor and improve upon the collection and processing of biometric data, and be transparent about how various pieces of health data are measured, either in discrete or ongoing settings, via wearable devices and mobile apps. |
| **Direct-to-Consumer Genetic Testing Data** | Sponsors should provide any relevant and linked supplemental data, such as preexisting conditions, labs, and demographic information to regulatory agencies. | Sponsors and/or the FDA need to discern the clinical validity, a component of reliability of direct-to consumer tests identified by the FDA, before the tests are used in regulatory decision making.<br>Companies should implement verifiable methods to ensure that genetic data are collected in the most reliable and accurate way possible. | Sponsors must consider the logical plausibility of the direct-to-consumer data (whether a data point corresponds to/with a specific genetic variant).<br>Sponsors should evaluate direct-to-consumer tests in accordance with specified data quality assurance plans and procedures. |
| **Patient-Powered Registry Data** | Sponsors should identify and confirm preexisting data linkages between a patient-powered registry and other RWD sources, apply a predefined and scientifically valid linkage methodology where needed, describe system interoperability features where they exist, and account for differences in coding and reporting across sources.<br>Sponsors and registry owners should describe measures taken to ensure individual-level privacy in the presence of data linkages. | Sponsors may find value in educating patients who input their data into registries to ensure uniform data collection.<br>Registry owners should establish data dictionaries to provide common definitional frameworks for both researchers and patients who will input their data into the registry. | Sponsors should be transparent about the provenance of data within patient-powered registries, as well as algorithmic transformations to the data. |
| **Patient-Reported Outcomes (PROs) Data** | Patient advocates should ensure PRO data are generalizable and inclusive to the target population and/or subpopulation of interest. | Sponsors should confirm PRO data are collected and processed in a consistent and methodologically sound manner. | To ensure data accuracy and completeness, sponsors should ensure data is collected in a thorough and clear manner.<br>Sponsors and patient advocates should provide patients with education and other support needed to accurately capture and report their PRO data.<br>Sponsors should balance the need for data transparency with patient privacy and discretion. |

## Appendix B
## Regulatory Acceptability of Patient Generated Health Data Workstream Members

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