



Harnessing safety data from wearable devices

Pharmacovigilance professionals propose how to capture, evaluate, and report information across a medicine’s lifecycle

About the Pharmacovigilance Innovation Forum

Deloitte's Pharmacovigilance Innovation Forum (Pi) is an industry-led collaboration among pharmacovigilance (PV) thought leaders to explore potential solutions to address challenges and drive innovation. Through open dialogue and idea-sharing, Pi seeks to: 1) identify topics, define scope, and align industry leaders to areas of interest; 2) explore pre-competitive (i.e., freely shared for everyone's benefit) solutions; and 3) establish ownership using a co-chair model between industry leaders and Deloitte to drive practical and actionable steps that drive real value to the industry.

Introduction

Several industry leaders from Deloitte's Pharmacovigilance Innovation Forum (Pi) (see sidebar) collaborated to open the dialogue on the potential impact of wearable technology in pharmacovigilance (PV) – the monitoring, assessment, reporting, and prevention of the adverse effects of medicine¹. This paper, which proposes principles for consideration and discussion among stakeholders, focuses on wearables used in the clinical study setting in the United States to capture measures for specific purposes. Examples include electrocardiography (ECG) devices and apps to monitor heart-related conditions and insulin monitors, such as special contact lenses to measure for HbA1C diabetes. It does not include general activity monitors, such as step counters, that are linked to cell phone apps.

In a health care environment that has greater availability of technology and information, it is possible to collect an increasing variety and volume of data. This data spans a medicine's lifecycle and can lead to better understanding of benefits and risks for patients. Stakeholders have a responsibility to discuss and ultimately agree on principles to guide the appropriate and ethical collection and use of this data, all the while underpinning the scientific integrity of the analyses it generates.

¹ http://www.who.int/medicines/areas/quality_safety/safety_efficacy/pharmvigi/en/

The promise and challenge of wearables-generated safety data

Biopharmaceutical manufacturers already collect information from patients taking medicines through clinical trials, spontaneous adverse event reports and, increasingly, through real-world evidence (RWE) data collection and observational studies. Wearable technology ("wearables") can allow collection of additional information such as physical functioning, activity level, and vital signs². Wearable devices on patients and/or consumers can measure biometrics³ (unique body measurements or characteristics, such as fingerprints), biotelemetry⁴ (the remote and continuous assessment of physical and physiological characteristics), performance, and general well-being (see infographic). Wearables include a broad spectrum of technologies, ranging from insulin pumps to applications (apps) to devices with motion sensors designed to take photos and synchronize with mobile devices. One of the most significant features of wearables is the ability to connect to the internet, thus facilitating data exchange between the source and the network.^{5,6} Wearables can address the scarcity of data that exists in between health care provider visits to drive new insights and outcomes. This data could offer a broader view of the patient experience before, during, and after dosing, or as a more general study of disease.

2 Piwek L, Ellis DA, Andrews S, Joinson A. The rise of consumer health wearables: promises and barriers. *PLoS Med*, 2016; 13(2): e1001953. doi:10.1371/journal.pmed.1001953.
3 <https://www.dhs.gov/biometrics>
4 <http://www.gsk.com/en-gb/about-us/corporate-partnerships/mclaren-partnership/>
5 http://www.webopedia.com/TERM/W/wearable_technology.html
6 <http://www.investopedia.com/terms/w/wearable-technology.asp>

If the potential merits of mining safety data from wearables are worth exploring, so are the associated challenges⁷ of managing a potentially large increase in data volume. Without appropriate guidance and some level of alignment among stakeholders concerning how and when wearables data is useful and informative, its benefits could be nullified. Early analysis concerning the potential value and management of this data is prudent, based on the experience of our forum bearing in mind the following:

- **Not all data is equally informative.** There is a hierarchy of evidence⁸ which indicates the usefulness of information in understanding disease burden, health improvement, or other patient experiences with medicines, including those that are adverse. Well-controlled studies with findings replicated by more than one researcher are considered the most trustworthy. Single case studies are at the other end of the spectrum—they are neither robust nor generalizable in the same way that randomized clinical trials are nor do they provide statistically significant results. However, in a post-launch/real-world setting—the majority of a medicine's lifecycle—spontaneous reports are an important and necessary source of safety information. In the realm of patient care, the goal is not only to characterize the medicine by determining its effects on the patient, but also to address the needs of individual patients. Large quantities of pharmacovigilance data is collected over a period of years from clinical trials and post-approval, the latter mostly from the uncontrolled settings of everyday patient care. Wearable devices and health care applications such as data monitors or activity trackers may provide an opportunity to collect richer

data in studies and in real-world settings. They enable the data to be continuously collected, as opposed to the previously sporadic data collection, providing an opportunity for early post-launch surveillance of the time and context of an adverse event. Data from wearables or apps needs to be understood within the hierarchy of information.

- **More ubiquitous data is not necessarily more instructive.** More sources of less robust data could lead to a signal-to-noise ratio that may quickly outstrip the resources available for analysis. When collecting and combining diverse sources of information, it will be important to create appropriate frameworks to outline the questions and issues to be addressed. Appropriate filters must be applied to capture and analyze useful data—usefulness being defined by purpose.
- **Diverse data combined correctly can lead to better insight.** Given the long lifecycle of a medicine that moves through development into clinical practice and/or over-the-counter availability, the hierarchy of evidence, as described by Daly et al., may need further examination to include additional qualitative studies⁹. While case studies may still sit at the lower end of these hierarchies, they can be an important contributor to pharmacovigilance. Medicine development professionals are familiar with cases of rare events that may appear only after many years of a medicine's use in the clinical setting. Wearable devices may offer an opportunity to collect much more detailed information, if not about the initial occurrence of a rare event, then at least about the event's duration and course of recovery or chronicity.



7 Kohlmann M, Gietzeit M, Haux R, Song B, Worf K, Marschaollek M. A methodological framework for the analysis of highly intensive, multimodal and heterogeneous data in the context of health-enabling technologies and ambient-assisted living. *Inform Health Soc Care*, 2014; 39(3–4): 294–304. Informa UK Ltd. ISSN: 1753-8157 print / 1753-8165 online DOI: 10.3109/17538157.2014.931847

8 Evans, D. Hierarchy of evidence: a framework for ranking evidence evaluating healthcare interventions. *Journal of Clinical Nursing*, 12: 77–84. doi:10.1046/j.1365-2702.2003.00662.x

9 Daly, Jeanne et al. A hierarchy of evidence for assessing qualitative health research. *Journal of Clinical Epidemiology*, 2007; 60 (1): 43 – 49.

Exploring the use of wearables alongside the use and development of medicine has already begun. Biotelemetry¹⁰ is seen as one exciting opportunity to assess and improve the effectiveness of medicines. In clinical studies, patient data can be collected in real time, in a real-world setting, rather than waiting for the traditional tests performed at a study visit. Biotelemetry gives a much more robust, complete, and meaningful set of measures which may, for example, help determine stages of disease progression.

Apps are available for a variety of diseases and conditions, or more generally, to measure activity level. Some of them complement treatment by motivating patients' behaviors¹¹. Others track symptoms through a mixture of surveys and sensor-enabled tests. Initial uptake of these apps may be high, but analyses have suggested that use can wane quickly¹², implying the need to develop data collection that patients find as compelling and useful as do researchers. It will be advantageous for patients, researchers, regulators, health care providers, payers, and other interested stakeholders to work together toward meeting these logistic and scientific challenges.

Wearables can encompass a broad range of technologies, including the ability to:



Connect to the Internet



Facilitate data exchange between the source and the network



Address the scarcity of data that exists in between health care provider visits to drive new insights and outcomes

Interoperability challenges in using wearables data

Despite the wealth of valuable data potentially captured by wearable technology, a number of challenges exist around its collection—some of which may be addressed through clinical trial study design.

- **Linkability to other data sources.** Biometric data generated by wearable technology has limited value when evaluated in isolation. However, meaningful correlations often occur when the data is interpreted in the context of the disease, the therapeutic intervention, and the patient's medical history. Still, a limitation often exists with regard to availability of the information in real time. To facilitate comprehensive data evaluation, information needs to be accessed from multiple, disparate sources, including electronic health records (EHRs). Unique patient identifiers across those data sources are needed for data integration. However, patient data privacy laws governing access to such identifiers and access to data sources may differ by country, potentially limiting a global approach for gleaning data from wearables.

In a clinical study setting, wearables data would be linked only to patient data from other sources collected within the study for purposes as outlined in the study protocol. This limited scope allows for testing in a controlled setting while limiting confounding influences on the data.

- **Representativeness of population/demographics.** Challenges exist in consistently measuring patient demographic and socioeconomic factors that influence individuals using wearable technology. There may be further sensitivities within different cultures about sharing information gathered through wearables use. Additionally, data generated by wearable technology may not represent the broad population due to affordability and/or accessibility issues associated with medical care. Insufficient understanding or impaired cognition/mobility could also impact a patient's ability to use the wearable technology as directed.

¹⁰ <http://www.gsk.com/en-gb/about-us/corporate-partnerships/mclaren-partnership/>

¹¹ http://www.fiercepharma.com/marketing/pfizer-s-new-moodivator-app-meant-to-help-people-monitor-mental-health?utm_medium=nl&utm_source=internal&mrkid=645969&mkt_

¹² <http://www.fiercebiotech.com/it/gsk-starts-ra-trial-apple-researchkit-advancing-industry-use-iphone-run-studies>

- **Data reliability and trustworthiness.** There are a number of factors when using wearable technology that can lead to falsified or missing data, minimizing the information's usability and reliability. For example, patients may not want to wear the technology or may feel as if they are being coerced into wearing it. Some patients may have concerns about how the data will be used (although others may see the value of collected data; for example, as insurance companies begin to explore the use of wearables to collect client data)¹³. Further, individuals may have concerns about others' perceptions of their health status if they are seen wearing the technology. Some patients simply may not wish to focus on their condition or draw attention to it, and may feel that a device could impact their independence and/or quality of life. Any of these or other factors may cause users to influence the data that is collected, such as wearing the device inappropriately or sharing it with others to contribute false data.

Ultimately, control of wearing the device, using it appropriately, and keeping it linked to centralized data collection will belong to the patient. As noted previously, patients will need to perceive some benefit to remain motivated to use the device. For example, a wearable may be more appealing if it is viewed as providing a better sense of disease control or enhancing patient care and well-being rather than simply being a data collection device for research.
- **Sustained use for longitudinal data collection.** Motivating users to wear technology consistently and correctly for a sustained period of time may be challenging. For example, if the device malfunctions or if a new version is released, maintaining longitudinal data already collected should be a consideration for longer-term data collection. Cross-platform compatibility also should be considered if a user is able to switch devices from one manufacturer to another. Utility or aesthetic preferences also may affect duration and consistency of use, thereby undermining the reliability and quality of data collected.
- **Lack of standards for data comparison and synthesis.** A comprehensive data set that includes wearables comprise diverse sources that may lack consistency and standards across data types. This data may be difficult to consolidate, analyze and/or interpret. In a study setting, the initial difficulties may stem from integrating very frequently collected endpoints with those collected retrospectively at scheduled study visits. In uncontrolled settings, larger challenges may exist, such as an inability to link an individual's information to his patient identifiers, or no agreed upon ontology or lexicon. These factors and others could make data coding and analysis difficult.

13 "Wearable technology: gathering data from tooth to toe: Workplace health schemes have spotted opportunities for gathering information about employee 'wellness.'" Geof Wheelwright. Financial Times. 21 November 2016. <https://www.ft.com/content/9b00b05c-70fe-11e6-a0c9-1365ce54b926?sharetype=share> Piwek L, Ellis DA, Andrews S, Joinson A. The rise of consumer health wearables: promises and barriers. PLoS Med, 2016; 13(2): e1001953. doi:10.1371/journal.pmed.1001953.

Thresholds for valid cases

Pi Forum leaders suggest that digital devices follow many of the same principles used by social media¹⁴ concerning thresholds for valid cases and reportability which, in turn, should be aligned with the earlier guidelines for reportability. Guidance from various worldwide regulatory authorities exists on this topic which indicate that at least four identifiable elements are required to qualify the validity of an individual case¹⁵:

1. An identifiable patient
2. An identifiable reporter
3. A suspect drug or biological product
4. An adverse experience or fatal outcome suspected to be due to the suspect drug or biological product

Valid individual cases will have identifiable information that contributes to a better understanding of product and patient safety. A controlled environment, especially in the context of interoperability, provides an opportunity to explore the ways in which devices can add richer safety information.

Data management and analytics considerations

The growth of digital device use and interoperability of resulting data provide vast opportunities for harnessing information from wearables for pharmacovigilance purposes. These opportunities are matched by methodological and analytic challenges to manage and interpret the data; challenges that can be met, in part, by building a framework for representation, analysis, and inference from incongruent, multi-source and multi-scale biomedical data¹⁵.

For the pharmacovigilance and medical community to leverage meaningful information from wearable devices, stakeholders need to consider how to (1) encode these diverse, multi-modal, often unstructured data; (2) aggregate, harmonize, and fuse encoded data into a structured format that will facilitate analytics; (3) formulate efficient methods of extraction; and (4) develop appropriate analysis methods.

The existing PV ecosystem has relied largely on structured spontaneous and clinical trial safety datasets housed in databases with controlled dictionaries (e.g., MedDRA, WHO-Drug dictionaries) for safety signal detection and analytics. The emergence of innovative health care data sources such as wearables and mobile health (mHealth) technologies has posed some challenges in terms of characterizing multi-modal, multi-scale, heterogeneous data (sometimes called big health care data) that could be structured or unstructured. There is a need to develop data standards, controlled vocabularies, and ontologies for structural or semantic representations of data and metadata from wearable devices and fuse them into existing PV dictionaries. Foreseeably, a new representation platform to harmonize these data standards and ontologies would be developed to assist extraction and analyses.

How we harness the power of data from wearable and mHealth technologies will depend on the degree to which we successfully manage the raw data, extract valuable information, transform that information to knowledge, and enable clinical decision making and action that are evidenced-based; not just for PV but for the entire medical community.

Because wearables technology renders an increase in the volume of data, companies should consider the following:



Not all data is equally informative



More ubiquitous data is not in and of itself more instructive



Diverse data combined correctly can lead to better insight

14 Powell et al., Drug Saf (2016) 39:443–454

15 Dinov, ID. Methodological challenges and analytic opportunities for modeling and interpreting Big Healthcare Data. GigaScience (2016): 5:12. DOI 10.1186/s13742-016-0117-6.

Delivering actionable insights from wearables data

Wearable technology enables the collection of additional patient information and offers a broader view of the patient experience throughout the study of a disease, thus promoting actionable patient insights. It empowers patients and health care providers alike with accurate and timely data to promote understanding of disease states and the use of medicinal products. However, as we look to the future, the topic of how wearables data should be evaluated in the PV context must be addressed. In controlled clinical trial settings, the answer to this challenge is straightforward from a PV perspective: medical-grade wearables are effective in supplying data, and relevant information provided by the investigator should be reported in accordance with established regulations.

A more challenging aspect to address is how wearables data should be captured and evaluated in a spontaneous setting. The key tenet to keep in mind for PV is reasonableness. Remember that an information hierarchy exists—not all data is equally informative, more data is not necessarily better data, and increased volume does not equal quality. Wearable applications must be better understood to best leverage the data and avoid information overload.

Wearables data can enhance established PV technology by acting as an additional data source to identify potentially new or underreported safety risks¹⁶. However, linking wearables to other systems (e.g., EHRs) may be a challenge in terms of patient representativeness, data reliability, data privacy, and lack of standard ontologies. Data and classifications need to be standardized across real world data to deliver actionable insights for PV stakeholders. Looking ahead, machine learning and other technologies could provide valuable opportunities to improve data processing efficiency and to link disparate data from wearables.

PV organizations should monitor wearables data for value rather than assuming that value already exists. As technology and analysis methods are nascent in this arena, suggestions on how to capture, evaluate, and report information generated from wearable technologies will continue to evolve.

16 European Medicines Agency, London, UK. Innovative medicines initiative WEB-RADR workshop report: Mobile technologies and social media as new tools in pharmacovigilance, October 19, 2016.

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