



Wearable Devices and Mobile Technology in Clinical Trials

Kirsten Messmer, PhD, RAC
Principal Regulatory Affairs Specialist, PPD

David Blackman
Senior Director Business Innovation, PPD

Robert Cumming
Regulatory Affairs Manager, PPD

Karin Coyne, PhD, MPH
Vice President, Outcomes Research, Patient-Centered Research Evidera

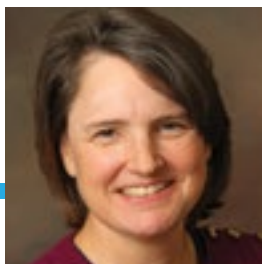
Wearable device technology has seen a rapid increase in market size over the last decade. The use of wearable device and mobile health (mHealth) technology in clinical trials has also increased considerably in recent years. The rapid evolution of this technology combined with patient-centric data generation provides cost-effective options for drug development. On the other hand, reliability and validation of devices and data, privacy concerns, and regulatory acceptance are slowing the integration of

these valuable tools as novel endpoints into clinical trials. Despite that, wearable devices and smart technology are transforming the drug development process.

Wearable Technology – Not a New Concept

Analysts at Gartner predict that 310.4 million wearable devices will be sold in 2017, an increase of 16.7% from units sold in 2016. \$9.3 billion of the \$30.5 billion revenue in the U.S. from wearable technology predicted for 2017 will be generated from smartwatches alone. By 2021, 504.65 million wearable devices are predicted to be sold.¹

This is not surprising since the fascination with and the history of wearable technology may reach back as far as the 17th century when Cheng Dawei created the abacus ring. A small abacus was embedded into a silver ring and may have been used by traders.^{2,3} Although Leonardo da Vinci sketched a mechanical device that could be used to measure strides to aid road mapping, it was Abraham-Louis Perrelet in 1780 who invented the first pedometer to measure steps and distance walked. The pedometer was based on the automatic pocket watch mechanism that



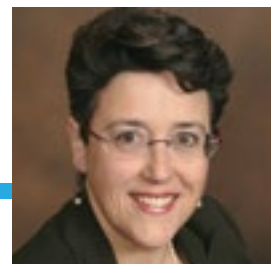
Kirsten Messmer



David Blackman



Robert Cumming



Karin Coyne

winds itself up while the wearer is walking.⁴ Large-scale use of pedometers is credited to the Japanese walking clubs of the 1960s. At the time, a company produced the Manpo-kei – the 10,000 steps meter – laying the basis for the currently proposed health goal of 10,000 steps per day.⁵ The Fitbit, announced in 2008 and finally released in 2009,⁴ incorporated additional measurements such as heart rate, and estimates of calories burned and floors climbed. Wearables have evolved from the pedometer to a variety of devices such as watches, wristbands, chest bands, patches, headsets, and contact lenses that can measure a range of physiological parameters including steps taken, heart rate, electrocardiograms, glucose levels, and brainwaves, to name just a few.

The use of wearable devices in the clinic originated in the 1980s with the introduction of the Motionlogger®, a device the size and weight of a deck of cards strapped around the wrist to detect motion. These actigraphs were in regular use in clinical sleep research by the late 1990s.^{6,7} In August 2017, the National Institutes of Health clinical trials database returned over 170 results for the search term ‘fitbit’, over 300 for ‘wearable’ and over 440 studies for ‘mobile app.’ There is an exponential proliferation of collaborations between pharmaceutical companies and technology giants such as Apple, Google, and Microsoft, as well as start-ups, focused on the development of and applications for wearables and bio-sensing technology to support drug development in clinical trials and mHealth in general.

Today’s ‘wearables’ also called ‘wearable devices’ or ‘wearable technology’ encompass electronic technologies or computers integrated into clothing or accessories that can easily be worn. They generally combine sensors for biometrics and a communication capability that allows for data monitoring in real time and remote access to the data. mHealth or ‘mobile Health’ implements the use of mobile computing, monitoring devices, and communication technologies to monitor patient biometric parameters, as well as collect/maintain medical data and records by healthcare providers.⁸ Wearables and mHealth provide the advantage of direct ‘shareability’ of the data with relatives, friends, and, if the patient consents, the physician or healthcare provider. The data generated are specific to the patient and allow for personalized treatment decisions by a healthcare provider, or in some cases motivational support. The advantages for clinical drug development and healthcare in general are palpable. While this article looks at the advantages, uptake, and challenges for using wearables/mHealth in clinical trials, many of these apply seamlessly to the general healthcare of a patient particularly for chronic diseases.

Implementing wearable devices and mHealth into clinical drug development has many advantages, including reducing the burden on patients by decreasing or even eliminating follow-up visits to research centers, and allowing data collection over a wider window of time to

provide complete tracking of physiologic parameters, medication administration, and adherence to clinical study activities. The true benefit of wearable devices and the implementation of digital/mHealth lies in the advantages afforded to patients, investigators/trial sites, and sponsors.

What Does the Implementation of Wearables/ mHealth in Clinical Trials Offer?

Over the last few decades, access to quality medical care has improved and contributed to increased longevity. However, with longer lives, the incidence of chronic diseases increases, thereby further burdening healthcare professionals. Avenues to more efficiently manage patient care and data collection in clinical trials are required. The implementation of wearable devices and mHealth may alleviate some of the pressure on healthcare professionals by empowering patients to self-monitor, reducing the necessity for frequent visits to healthcare facilities and providing more data and behavioral insight for the drug development process.

Reducing the burden of healthcare-related tasks may be the largest benefit for patients. The broad familiarity of consumers with devices like the Fitbit, Jawbone, smartwatches, and smartphones facilitates the integration of similar devices specific for healthcare applications. The ability of a device to deliver prompts for various tasks, encourage medication dosing compliance, and to share physiologic data adds convenience to any treatment program.

Implementing wearable devices and mHealth into clinical drug development has many advantages, including reducing the burden on patients by decreasing or even eliminating follow-up visits to research centers, and allowing data collection over a wider window of time ...

A PPD study employing two devices, a blood pressure cuff and an activity monitor connected to the patient’s smartphone, showed that patients were more comfortable using the consumer device that they are already familiar with rather than a device provided by a clinic or sponsor. Generally, patients are more comfortable using a device they already own versus using a study-specific device provided by the investigative team.⁹ Additionally, devices/ apps that provide good documentation, quality of care options, and enhanced communication with a provider increased patient confidence and compliance with their treatment and care.¹⁰

Wearable devices continuously record the data in real-time and enable investigators and healthcare providers to track clinical trial participant status between site visits. Instead of using data gathered during a brief office visit

with various short tests such as a six-minute walk test for mobility, wearable devices allow for collection of movement data continuously over the entire observation period of the trial. This process contrasts significantly with the prior traditional method that required office visits for testing or the review of diary entries. Using wearable devices, available biometric and activity measures can be collected automatically, adding consistency and accuracy with time-marked data. Since most wearable devices are paired with a mobile app for data logging, care providers or investigators can remotely access the data collected by the device to efficiently reduce the number of office visits or even eliminate the need for office visits.

The use of wearable devices and access to the stored information allows healthcare providers and clinical researchers to gain additional insight into a disease process and participants' response to treatment.

The use of wearable devices and access to the stored information allows healthcare providers and clinical researchers to gain additional insight into a disease process and participants' response to treatment. Subjective participant data that might be influenced by a participants' status will be replaced with the objective data collected by the device. Real-time data access may aid signal detection and early detection of adverse events and facilitate decision making by a care provider or researcher on treatment adjustments based on the data collected.

Similarly, sponsors developing drugs also benefit from the implementation of wearables/mHealth into clinical trials by taking advantage of device capabilities to provide patient data that may be helpful in the development of new treatment options. Wearables today are more sophisticated and accurate, and measure a wider range of biometric and physiologic data, which can effectively characterize disease severity and progression.

Collected individualized data and the identification of population subsets responding more favorably to a medication (i.e., precision medicine) can contribute further to the understanding of the disease and targeted treatment development for the above or below average responders. Additional insight into various disorders may provide the opportunity to establish more sensitive measures of disease assessment through the better understanding of symptoms provided by the digital data.

Partnerships between the Pharmaceutical and Technology Industry

Companies outside the healthcare sector appreciate the utility of wearables and are increasingly getting involved

by providing tools to harness the possibilities wearables and mHealth provide for clinical trials. Apple developed ResearchKit, open-source software that allows researchers to create mobile apps supporting efficient data collection specialized to therapeutic area. CareKit, another open source framework provided by Apple, allows for the development of apps to assist patients to manage their own healthcare more efficiently.¹¹

Qualcomm, perhaps best known for the Qualcomm Snapdragon in smartphones, offers the medical grade, FDA quality 2net™ Connectivity Platform that enables healthcare connectivity and integration for hospitals, at home, and on-the-go care. Medical device data management is secure, rapid, and compliant to HIPAA privacy standards.¹²

Although the two technologies are very different, both play an important role in the overall wearable device integration into healthcare and clinical trials. Apple provides platforms for the development of customized apps for data collection and Qualcomm's 2net™ platform ensures secure storage, connectivity of devices, and accessibility to data.

Collaborations between pharmaceutical and technology companies have also sprung up recently. In 2016 Novartis teamed with Qualcomm to develop internet connectivity to deliver data directly to the cloud for its inhaler to monitor the use of the drug Onbrez® in patients who have COPD. A launch of the device is planned for 2019. In 2017, Novartis signed a deal with EU-based Propeller Health to use Propeller's digital platform with its inhaler.^{13,14}

Blood sugar level monitoring in insulin-dependent diabetes patients is another area where pharmaceutical and technology companies interface. A collaboration between Google and Novartis to develop smart contact lenses that can autofocus to correct vision issues and monitor blood glucose levels for diabetic patients was announced in 2014. It was initially expected to yield a commercial product as early as 2016. However, Novartis recently declared the project as high-risk and long-term.¹⁵

In 2016, Sanofi and Alphabet's (owner of Google) Verily Life Sciences company formed the joint venture Onduo to collect and analyze information from patients to improve diabetes care.¹⁶ Similarly, Abbott received European approval for its Freestyle Libre Pro™ continuous glucose monitoring system in 2015 and FDA approval in 2016. The sensor worn on the back of the upper arm eliminates the need for finger pricks and records data for up to 14 days.¹⁷

The opportunity for partnership is largest for chronic diseases that benefit from daily monitoring. Wearable devices are already available for monitoring patients with congestive heart failure, hypertension, sleep apnea, diabetes, and chronic obstructive pulmonary disease (COPD).¹⁸

Regulatory Oversight in the U.S. and Europe

In the U.S., the Federal Trade Commission (FTC) developed an interactive tool to guide sponsors developing mobile health apps to determine which federal laws may apply.¹⁹ Depending on the functionality, intended user, intended use, and risk, various laws overseen by the Office for Civil Rights (Health Insurance Portability and Accountability Act), Food and Drug Administration (Food, Drug and Cosmetics Act) and/or the FTC (Federal Trade Commission Act) may apply. For this article, we will only address the oversight provided by the FDA and the guidance issued.

In February 2015, the FDA issued an updated guidance for “Mobile Medical Applications” which supersedes guidance by the same name issued in 2013.²⁰ The guidance makes a distinction between mobile apps that will not fall under FDA oversight and FDA regulated mobile medical apps that meet the statutory definition of a medical device with the app intended to be used as a medical device or to “transform a mobile platform into a regulated medical device.” The FDA intends to exercise “enforcement discretion” for many of today’s wearable technology for health tracking by patients and/or healthcare providers. In July 2016, the FDA released guidance “General Wellness: Policy for Low Risk Devices” clarifying that the FDA does not intend to regulate ‘general wellness products’ defined as products that “are intended for only general wellness use” and present a low risk even if they meet the definition of medical device.²¹ However, wearable devices intended to diagnose or treat a medical condition would still fall under FDA regulation and would need to conform with HIPAA as a medical device. Even though a device may fall under the general wellness use and be outside of FDA’s regulation, if data from the device are used to inform clinical trial results, the data needs to be validated to ensure reliability and validity. The FDA is currently revising guidance to implement the clarification of the regulation of medical software provided by the 21ST Century Cures Act.²²

The FDA intends to exercise “enforcement discretion” for many of today’s wearable technology for health tracking by patients and/or healthcare providers.

Meanwhile, the European Medicines Agency (EMA) has not released any specific guidance addressing wearables or mHealth but has recognized the importance of their use for drug development. Opportunities for valuable data generation through wearable devices were discussed at a workshop to identify the opportunities of Big Data.²³ The new Medical Device Regulation clarifies that “software in its own right, when specifically intended by the manufacturer to be used for one or more of the medical purposes set out in the definition of a medical device, qualifies as a medical device, while software for general

purposes, even when used in a healthcare setting, or software intended for life-style and well-being purposes is not a medical device.”²⁴

The Clinical Trials Transformation Initiative (CTTI) released guidance on endpoint recommendations in June 2017. This public-private partnership of pharmaceutical companies, academics, and regulators such as the FDA are tasked with developing standards for the implementation of mobile technology in clinical trials. The CTTI established four project areas to identify challenges related to clinical trials using mHealth: legal and regulatory, stakeholder perceptions, mobile devices, and novel endpoints. The just released guideline advises that selection of novel endpoints should be guided by outcome measures that are meaningful to patients, the device should be selected based on the outcome measure determined, and endpoints should be selected using a systemic approach.²⁵

The above messaging regarding novel endpoints is key for wearable devices and mHealth. While the allure of the devices is certainly apparent, the matching of “fit for purpose” and endpoints that are clinically meaningful to patients is essential. As recommended by CTTI, select the endpoint first, then select a device. After selecting the device, additional validation work may be needed to demonstrate that the device indeed does measure the endpoint it was designed to measure in the target patient population. Such efforts are similar to the validation efforts of developing other clinical outcome assessments (e.g., FDA PRO guidance, 2009²⁶). Regulatory authorities are willing to consider wearable or mHealth novel endpoints, but will need to see the strength of evidence to support the endpoints.

In September 2017, the FDA announced the new Entrepreneur-in-Residence (EIR) program seeking entrepreneurs to work from the White Oak Campus at least three days a week to develop the Software Precertification Pilot. The Precertification Program, a mandatory part of the Digital Health Innovation Act,²⁷ will support the development of a tailored approach to software regulation. The software design and business metrics experts selected as EIR will analyze software business processes, model data collection, and determine regulatory requirements for the implementation of digital technology in clinical trials.²⁸

Challenges and Implementation

Reading the literature on wearable and mHealth implementation in general healthcare and its utility in clinical trials identified concerns on data standardization, analysis, and integration of data into existing information management systems; ownership and data privacy; and device-related technical limitations such as battery life, operational consistency, and accuracy. Additionally, there are also the human factors related to device usability such as consistency in wearing the device, following all prompts provided, and the general familiarity and uniform handling of the device and the included functions. However,

technology is evolving at an ever-faster pace and the challenges from yesterday are diminishing for today and tomorrow.

The implementation of wearable devices and mHealth could potentially bring economic advantages in the form of cost and time savings for patients as well as sponsors. Since potentially almost all monitoring and data collection can be done remotely through the connectivity of the device, the number of clinic visits can, at the least, be reduced significantly. In the best case, office visits could be eliminated completely. For the patient, this means less time to travel, less time spent at an office, and less time lost for daily activities. For the sponsor, it means less cost to cover physician time and travel cost reimbursement.

The sophistication and reliability of the devices has consistently and exponentially improved while the functionality with respect to the range of measurable parameters and the accuracy of the recorded data support the implementation of this technology in the clinical development process. The means for storing and analyzing the data are also being adapted to further support the implementation of this technology as a valuable research tool.

Conclusion

The use of wearable devices, smartphones, and mHealth provides an opportunity for real-time data generation and analysis to monitor a health-related condition, reduce the need for frequent physician office visits, and allow the collection of data required in the research and development of new medicinal products or medical devices. Although the integration of these applications is still challenged by regulatory uncertainty, data handling and analytic capabilities, as well as the complete integration into the research processes, these perceived hurdles are diminishing as the technology continues to improve. The full implementation of mobile trials soon will bring about the cost and time savings and return on investment sought by all stakeholders. ■

For more information, please contact Kirsten.Messmer@ppdi.com, David.Blackman@ppdi.com, Robert.Cumming@ppdi.com, or Karin.Coyne@evidera.com.

REFERENCES

1. Gartner.com. Gartner Says Worldwide Wearable Device Sales to Grow 17 Percent in 2017. Gartner Press Release. August 24, 2017. Available at: <http://www.gartner.com/newsroom/id/3790965>. Accessed October 6, 2017.
2. China Culture.org. The Story of the Chinese Abacus. Available at: http://en.chinaculture.org/classics/2010-04/20/content_383263_4.htm. Accessed October 6, 2017.
3. Interesting Engineering.com. Berman T. The Smart Ring: From the 17th Century Wearable Abacus to Today. March 4, 2017. Available at: <https://interestingengineering.com/smart-ring-17th-century-wearable-abacus-today/>. Accessed October 6, 2017.
4. Richard MacMagnus. *Trackers – How Technology is Helping Us Monitor & Improve Our Health*. Chapter 2: The Pedometer on Steroids: Tracking Activity with Fitbit. <https://books.google.co.uk/books?id=0AihBwAAQBAJ&pg=PT60&lpg=PT60&dq=Perrelet+pedometer&source=bl&ots=e30qOGQKUq&sig=hobfIEGrYMISEzWM-CPC5Qimqrc&hl=en&sa=X&ei=wBuQVdSIE4qu7ga6s6vIBA&ved=0CEYQ6AEwBg#v=onepage&q=Perrelet%20pedometer&f=false>
5. Harvard Health Publishing. Counting Every Step You Take. *Harvard Health Letter*. September 2009. Available at: https://www.health.harvard.edu/newsletter_article/counting-every-step-you-take. Accessed October 6, 2017.
6. Ilancheran M, Zammit GK. Impact of Actigraphy in Clinical Research. *Applied Clinical Trials*. February 5, 2016. Available at: <http://www.appliedclinicaltrials.com/impact-actigraphy-clinical-research>. Accessed October 6, 2017.
7. Kellner O, Bastuji H, Adeleine P. Actimetry in Sleep Medicine. *Sleep Breath*. 1997;2(1):33-39. Available at: <https://link.springer.com/article/10.1007/BF03038855>. Accessed October 6, 2017.
8. Park, YT. Emerging New Era of Mobile Health Technology. *Healthc Inform Res*. 2016 Oct;22(4):253-254. doi:10.4258/hir.2016.22.4.253.
9. Morton N, Blackman D. The Growing Availability of Wearable Devices: A Perspective on Current Applications in Clinical Trials. *Applied Clinical Trials*. May 27, 2016. Available at: <http://www.appliedclinicaltrials.com/growing-availability-wearable-devices-perspective-current-applications-clinical-trials>. Accessed October 6, 2017.
10. Pennel NA, Dicker AP, Tran C, et al. mHealth: Mobile Technologies to Virtually Bring the Patient into an Oncology Practice. *Am Soc Clin Oncol Educ Book*. 2017;37:144-154. doi: 10.14694/EDBK_176093.
11. Apple.com. ResearchKit and CareKit. Available at: <https://www.apple.com/researchkit/>. Accessed October 6, 2017.
12. Qualcomm.com. Qualcomm HealthCare. Available at: <https://www.qualcomm.com/solutions/health-care>. Accessed October 6, 2017.
13. Tyer D. Novartis Sets Sight on Connected Inhaler. *PMLive Digital Intelligence Blog*. January 14, 2016. Available at: http://www.pmlive.com/blogs/digital_intelligence/archive/2016/january/novartis_sets_sights_on_connected_inhaler_905496. Accessed October 6, 2017.

14. Tyler D. Novartis Signs 'Connected Inhaler' Deal with Propeller Health. *PMLive Digital Intelligence Blog*. February 13, 2017. Available at: http://www.pmlive.com/blogs/digital_intelligence/archive/2017/february/novartis_signs_connected_inhaler_deal_with_propeller_health_1186549. Accessed October 6, 2017.
15. Taylor NP. Novartis Chairman: Google Smart Lens is a High-Risk Project. *FierceBiotech*. March 2, 2017. Available at: <http://www.fiercebiotech.com/r-d/novartis-chairman-google-smart-lens-a-high-risk-project>. Accessed October 6, 2017.
16. Reuters. Sanofi, Google Parent Form \$500 million Diabetes Joint Venture. September 12, 2016. Available at: <http://www.reuters.com/article/us-sanofi-alphabet-diabetes/sanofi-google-parent-form-500-million-diabetes-joint-venture-idUSKCN1110AM>. Accessed October 6, 2017.
17. Abbott.com. Abbott Receives FDA Approval for the Freestyle Libre Pro™ System, a Revolutionary Diabetes Sensing Technology for Healthcare Professionals to Use with their Patients. Abbott Press Release. September 28, 2016. Available at: <http://abbott.mediaroom.com/2016-09-28-Abbott-Receives-FDA-Approval-for-the-FreeStyle-Libre-Pro-System-a-Revolutionary-Diabetes-Sensing-Technology-for-Healthcare-Professionals-to-Use-with-Their-Patients>. Accessed October 6, 2017.
18. Vegesna A, Tran M, Angelaccio M, et al. Remote Patient Monitoring via Non-Invasive Digital Technologies: A Systematic Review. *Telemed J E Health*. 2017 Jan;23(1):3-17. doi: 10.1089/tmj.2016.0051.
19. Federal Trade Commission.com. Mobile Health Apps Interactive Tool. Available at: <https://www.ftc.gov/tips-advice/business-center/guidance/mobile-health-apps-interactive-tool>. Accessed October 6, 2017.
20. U.S. Food and Drug Administration. Guidance for Industry and Food and Drug Administration Staff: Mobile Medical Applications. February 9, 2015. Available at: <https://www.fda.gov/downloads/medicaldevices/.../ucm263366.pdf>. Accessed October 6, 2017.
21. U.S. Food and Drug Administration. Guidance for Industry and Food and Drug Administration Staff: General Wellness: Policy for Low Risk Devices. July 29, 2016. Available at: <https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm429674.pdf>. Accessed October 6, 2017.
22. 21ST Century Cures Act. Public Law 114-255, 114TH Congress. December 13, 2016. Section 3060. Clarifying Medical Software Regulation. Available at: <https://www.congress.gov/114/plaws/publ255/PLAW-114publ255.pdf>. Accessed October 6, 2017.
23. European Medicines Agency. Identifying Opportunities for 'Big Data' in Medicines Development and Regulatory Science. Report from a Workshop Held by EMA on 14-15 November 2016. 22 February 2017. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Report/2017/02/WC500221938.pdf. Accessed October 6, 2017.
24. Regulation (EU) 2017/745 of the European Parliament and of the Council, 5 April 2017. EUR-Lex. Official Journal of the European Union. Available at: <http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=OJ:L:2017:117:TOC>. Accessed October 6, 2017.
25. Clinical Trials Transformation Initiative. CTTI Recommendations: Developing Novel Endpoints Generated by Mobile Technology for Use in Clinical Trials. June 2017. Available at: <https://www.ctti-clinicaltrials.org/files/novelendpoints-recs.pdf>. Accessed October 6, 2017.
26. U.S. Food and Drug Administration. Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. December 2009. Available at: <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf>. Accessed October 6, 2017.
27. U.S. Food and Drug Administration. Digital Health Innovation Action Plan. June 2017. Available at: <https://www.fda.gov/downloads/MedicalDevices/DigitalHealth/UCM568735.pdf>. Accessed October 6, 2017.
28. U.S. Food and Drug Administration. Digital Health Entrepreneur-in-Residence Program. September 11, 2017. Available at: <https://www.fda.gov/MedicalDevices/DigitalHealth/DigitalHealthPreCertProgram/ucm574784.htm>. Accessed October 6, 2017.