# Wearable Devices in Clinical Trials: Hype and Hypothesis

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**The development of innovative wearable technologies has raised great interest in new means of data collection in healthcare and biopharmaceutical research and development. Multiple applications for wearables have been identified in a number of therapeutic areas; however, researchers face many challenges in the clinic, including scientific methodology as well as regulatory, legal, and operational hurdles. To facilitate further evaluation and adoption of these technologies, we highlight methodological and logistical considerations for implementation in clinical trials, including key elements of analytical and clinical validation in the specific context of use (COU). Additionally, we provide an assessment of the maturity of the field and successful examples of recent clinical experiments.**

## WHY CONSIDER USING DIGITAL DEVICES IN CLINICAL TRIALS?

Use of (and hype surrounding) wearable technologies has skyrocketed in recent years. We define here wearable technologies as sensors and/or software applications (apps) on smartphones and tablets that can collect health-related data remotely, i.e., outside of the healthcare provider's office. The data can be collected passively or may require a user's input. An accelerometer embedded in a wristband or a cell phone is an example of a sensor passively collecting data about a person's physical activity and movement. Software (e.g., ePRO (electronic Patient Reported Outcome)) can output a patient's report capturing health-related information, collected by means of a cell phone app or a web-based interface. Additionally, some technologies, such as smart-cap bottles designed to monitor medication adherence, can use a combination of a sensor and app-based data collection. The event recording is triggered by a user action (opening the bottle), but the data are transmitted from a sensor to a server passively via Bluetooth. The transmission is mediated by a cell phone app.

Ten years on since the introduction of the iPhone, we have witnessed an almost complete change in how people communicate with each other, access media/content, and interact with that content. Most noticeably, in healthcare and beyond, this shift has led to a complete change in the expectations surrounding reporting of events. Digital disease detection has shifted outbreak-detection timeframes from months to hours with social media.[1] The US Food and Drug Administration (FDA) now encourages safety adverse event reporting via mobile apps. Hospitals are using Fitbits on inpatients to monitor recovery and mobility. Patients interact regularly online with healthcare facilities. Twitter and other social media can report and post opinions on products and services far faster and more broadly than almost any business.[2,3]

At the same time, rising costs of healthcare are of immense concern and the possibility of healthcare virtualization via digital devices has been heralded by relentless hype. For remote monitoring of cardiovascular parameters, activity (including gait, balance, and many other forms of motion measurement), body temperature, galvanic skin response, blood oxygen saturation, and multisensor/multisystem monitoring,[4] advanced wearable device research and development is continuously improving. Common form factors include wearable watches/bracelets, patches, textiles, and garments (**Table 1**). All of these sensor devices are being built with the ability to monitor continuously and communicate data in real time or intermittently. While maturity, promise, and quality all vary greatly at the moment, clearly these sensors and devices have the potential to become an integral part of the future of healthcare and biopharmaceutical development.

## PROMISES AND CHALLENGES OF USING WEARABLES IN CLINICAL TRIALS

### Promises in healthcare

Wearable devices can collect data on a 24/7 basis in natural settings as people go through their daily routines at home and work. The data collection can be enhanced by digital diaries depicting key features of personal health and lifestyle. The best-known wearable devices are commercial fitness trackers that collect mobility and some vital sign data.[5] Similar wearables cannot be

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Received 10 October 2017; accepted 29 November 2017; advance online publication 2 April 2018. doi:10.1002/cpt.966

**Table 1 Examples of wearable sensors**

| Device type | Data collected | Examples |
|---|---|---|
| Wrist worn | Actigraphy, HR (Heart Rate), BP (Blood Pressure), EDA (Electrodermal activity) | Actiwatch Spectrum by Phillips, ActiGraph Link by ActiGraph, E4 by Empatica, ViSi Mobile by Sotera Wireless |
| Skin patch | ECG (Electrocardiography), actigraphy, skin temperature | BioStampRC by MC10, HealthPatch by Vital Connect, BodyGuardian by Preventice |
| Cuffs | BP, HR | Intellisense Digital BP Monitor by Omron Healthcare |
| Finger worn | HR, SpO2 | iSpO2 Pulse Oximeter by Massimo |
| Clothing embedded sensors | HR, HRV (Heart Rate Variability), ECG, Breathing Rate, actigraphy | Smart shirts by Hexoskin |
| Headbands | EEG (Electroencephalogram), EMG (Electromyography) | EMOTIV EPOC by Emotiv, 4D FORCE by 4D FORCE |

marketed as medical devices unless the device performance has been established prior to release to the market. This is a big step forward compared to the traditional means of health-related data collection. For example, basic physiological data, e.g., vital signs and telemetry, are traditionally collected only during doctor's office visits or as a part of medical product clinical trial procedures. These data represent a very limited snapshot of a person's phenotype and physiology. Inferences about a person's health are made based on the extrapolation of such a snapshot to extended periods of time, potentially weeks and months. This extrapolation is also based on patients' memory recall of incidents preceding the office visit. Decisions about the patient's health, disease status, and treatments are made comparing data collected in doctor's offices to population averages, which may or may not be relevant to a particular individual. Additionally, there are well-known issues related to in-clinic measurement of vital signs, including white-coat hypertension.[6] There is a growing recognition that population-based values need to be adjusted for factors such as age, gender, medication status, demographics, and other factors.[7,8] These adjustments can be made if there are data available for specific subpopulations of interest. This may also be done using the individual's own baseline data collected over extended periods of time, which would enable a precision medicine approach. Data frequently collected over extended periods of time can provide deeper understanding of disease variability, which is likely to be an important contributor to treatment response variability. Having larger and denser datasets will help to characterize intra- and interpatient variability. Additionally, there is growing evidence that replacing paper diaries with electronic versions can greatly improve the quality of subjectively reported outcome data,[9–11] such as pain and functional status, by ensuring compliance, timely collection of the data, avoidance of secondary data entry errors, and reduced administrative burden.[11] Replacing paper diaries and patient memory recall with electronic means of data collection is likely to continue and expand with technological advances in the future. Moreover, wearable device data combined with other data such as genomics or other high-throughput technologies have the potential to create a comprehensive multilayer picture of a person's health and can deepen our understanding of how to combine genotyping with deep phenotyping.

## Promises in drug development

The applications mentioned above are also attractive for drug development in both early- and late-stage clinical trials. Collecting dense data from trial participants using wearables in natural settings—often not collectible otherwise—may fundamentally change how clinical trials are designed and conducted. In early clinical drug development, collection of dense physiological data may identify early safety issues and inform dose adjustments and dosing frequencies, or lead to discontinuation of development of certain drug candidates. The study subjects would not have to be confined to the pharmacology units all the time to have the data collected. In the late stages of clinical development, creating novel endpoints by means of wearable technologies has applications in multiple disease areas (**Table 2**). These novel endpoints may provide more sensitive measures of disease activity compared to traditional scales, enabling faster and more objective readouts in clinical trials. Additionally, sensors can provide objective measures of traditionally subjectively reported outcomes, such as pain and fatigue, complementing or even completely replacing self-reports. Another attractive feature includes portability to home settings and simplification of measures traditionally done in hospitals. Sleep data collection by means of actigraphy can serve as an example.[12] Important parameters of sleep, such as sleep duration and number and duration of awakenings, can be collected by wrist-worn actigraphy devices. This could replace sleep studies that are not practical for long-duration monitoring and provide data collected in natural home settings, which are more likely to represent a person's regular sleep patterns. Although actigraphy data do not provide details on a deeper level, e.g., sleep phases, the procedure is very noninvasive and easy to implement. Actigraphy-based sleep data also highlights the need for clinical validation of new wearable-based endpoints.

Other promising wearable technology can be seen in phone/tablet apps. The best-known examples include medication adherence monitoring, medication reminders, and patient engagement. Medication adherence is a big area of concern in multiple therapeutic areas.[13] The reasons behind nonadherence are multifaceted and include socioeconomic factors, access to health care, communication means with healthcare professionals, patients' education, and understanding of the impact of nonadherence to the treatment outcome.[14] Moreover, cell phone apps can provide data to monitor medication adherence and help with timely

**Table 2 Novel endpoints: application, benefits, and examples**

| Application | Benefit | Examples and references |
|---|---|---|
| Safety monitoring/patient phenotyping | • Early safety signal, dose and frequency adjustments, discontinuation of certain drug candidates<br>• Better understanding of mechanistic and pharmacological drug profile if combined with PK and wet lab test data | Vital sign, e.g. HR, RR, skin temperature, BP, and actigraphy[37,39] |
| Novel endpoints | • Mobility as a measure of quality of life<br>• Sleep studies in the home settings for extended periods of time<br>• More sensitive measures than traditional clinical scales in movement disorders | • Actigraphy in Oncology[53]<br>• Actigraphy as a measure sleep in a home settings[54–56]<br>• Gait and tremor in Parkinson's disease[57,58] |
| Medication adherence monitoring and intervention | • Improved adherence<br>• Informed decisions about dose adjustments<br>• Increased efficiency in postmarket data collection | • Adherence surveys<br>• Drug intake reminder apps<br>• Objective data on drug intake - smart cap bottles |
| Patient enrollment and retention in clinical trials | • Fewer obstacles to enroll in clinical trials<br>• Reduced burdens for patients to participate<br>• Increased patient outreach | • Remote enrollment and consent apps<br>• Reminder apps about study procedures and clinical trial progress |

intervention by medical personnel and caregivers.[15] Medication reminder apps, enhanced by alert personalization and available to both patients and caregivers, were found to improve medication adherence.[16] Additionally, a number of digital technologies were developed to collect objective adherence data with smart-cap bottle and blister pack technologies. However, the effectiveness of these technologies in improving patient adherence has yet to be confirmed in well-powered, controlled studies.[17]

Cell phone apps and web-based interfaces are increasingly used for remote patient enrollment, patient consent, and retention in clinical trials, making the process more convenient and enabling better outreach to remote patients. Clinical trial patient retention may be enhanced by delivering app-mediated reminders, providing information about upcoming visits and operational updates about clinical trial conduct, encouraging compliance, facilitating communication with medical personnel, and making the logistics of participation easier.

The totality and combination of applications can provide a basis for telemedicine and enable partially or completely remote clinical trials, bringing drug development to difficult-to-reach populations. Time and cost could be reduced by decreasing the number of clinic visits and potentially by avoiding use of other expensive medical devices such as telemetry. Time, convenience, and cost savings are big potential benefits of wearable devices, although currently development and adoption costs are militating against such savings. Nonetheless, data delivered by wearable technologies have the potential to improve detection of treatment effects and demonstrate how these effects relate to underlying disease characteristics, improving our understanding of the treatment–response relationship and enhancing personalized medicine.

## CHALLENGES

The promising potential of wearable devices has attracted enormous attention, including the start of experiments,[18] and a number of deals between biopharmaceutical, contract research organization (CRO), and device companies have been announced.[19,20] Nevertheless, the major impact expected from digital technologies on biopharmaceutical R&D has not yet materialized.[21] The reasons behind the lack of major transformation include scientific, regulatory, ethical, legal, data management, infrastructure, analysis, and security challenges.

### Scientific

Many devices, particularly consumer-grade, are marketed with promises to improve health and wellness with no scientific evidence behind this claim.[5] Properly designed, well-powered studies with a clear statement of a medical problem are required, rather than technology choice-seeking applications.[22] Moreover, drug development and device engineering are historically separate scientific fields. On the one hand, biopharmaceutical R&D scientists are generally not familiar with devices, which creates a barrier for adoption of wearable technologies in drug development clinical trials. On the other hand, device engineers are not conversant with the drug development process and regulatory requirements for drug approvals. The solution would be to bring device engineers into drug development to educate biopharmaceutical R&D and enable adoption of device technologies.

### Regulatory

In the US, the drug and device marketing approval paths are separate and the oversight is done by different divisions of the FDA. The majority of wearable devices are classified as Class II devices cleared as 510(k), which requires establishing technical performance in comparison to a predicate (i.e., legally marketed) device that uses a similar engineering solution. The requirement doesn't include establishing an association with a clinical outcome such as a disease condition. This requirement exists only for 510(k) *de novo* devices when there is no predicate device available. Therefore, a device under consideration needs to be tested in a specific population relevant to the device label claims in order to establish an association with a disease condition. If such a 510(k)-cleared device is intended to support an efficacy claim on a drug label, a link between the device readout and an efficacy parameter of

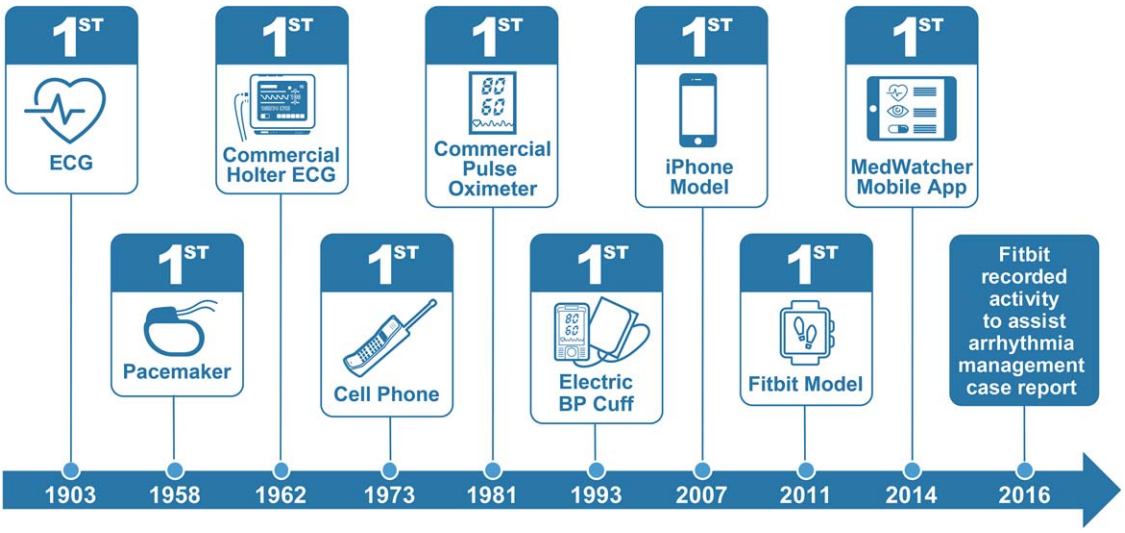


**Figure 1** The timeline for market release of technologies enabling wearable device use in healthcare.

interest needs to be established in the context of drug development. It also has to be supplemented by the device analytical performance data indicating that the device is appropriate for an intended use. Additionally, the field is plagued by a lack of shared understanding of methodologies and terminology. A similar issue was successfully overcome in the field of laboratory biomarkers with the widely accepted concept of "fit-for-purpose validation" and well-developed and shared terminology.[23–25] The same approach can be adopted by the wearable device field and several precompetitive initiatives have made significant progress towards achieving this goal.[26,27]

### Data infrastructure, processing, analysis, and interpretation

The infrastructure challenges are multifaceted. Drug development clinical teams are not familiar with the massive amounts of 24/7 data to be processed and integrated with the rest of study data. The sensor data structure is very different compared to traditional data collected at predefined timepoints by clinical sites and consists of multiple layers: raw unfiltered data, raw filtered data to eliminate invalid data in accordance with the scoring algorithms, data consisting of the secondary derivatives, and data derived from the secondary derivatives for interpretation. The outstanding questions include: who is the data originator, what constitutes source data, which datasets are required to maintain an audit trail, and what should be reported as a final result. These are the topics of debate by the industry and the regulators, but the recommendations that would help to harmonize the field have not been established. Moreover, the processing and analysis of massive data, as well as result visualization and interpretation, presents a formidable challenge. Machine-learning methods enabling automated data processing and an improved signal recognition were demonstrated to be useful in solving this issue.[11] Additionally, there are no well-developed standards that would help to organize, annotate, and standardize the data and provide data mapping tools to electronic data capture (EDC) databases. The lack of mobile technology data standards is exacerbated by the fact that wearable devices sometimes report variables pertinent to the same phenomenon (e.g., mobility) but use different terminology, and data processing algorithms are not disclosed. The solution should include industry-wide standards for data and terminology, processing principles for similar sets of data, and transparency requirements around data processing algorithms.

### Ethical and legal

This category of challenges includes data ownership and sharing, consent requirements, privacy, security, and substantial geographical differences in approaches to addressing these challenges. US and European legislation seems headed in different directions concerning scope, consent, data sharing, and processing.[28] In the US, consumer-grade and medical devices are regulated differently. The data obtained via medical devices are covered by HIPAA and require patient consent for data collection and sharing. On the other hand, the data obtained by consumer-grade devices, although it may contain legitimate health information such as disease condition, lifestyle, biometric, mobility, and behavioral patterns, can be shared in a deidentified, aggregate manner without explicit stipulation concerning who will have access to the data. In the EU, new General Data Protection Regulation (GDPR) regulations do not draw distinctions pertaining to a device type and cover all data generated by wearable devices or apps in the medical context.[29] Additionally, the EU requires clearly defined purposes for data use, consent for data reuse and sharing, and allows patients to withdraw their consent at any time.

### Data security

In the practical consideration of privacy, security, and compliance, it can be helpful to separate compliance from privacy and security, as compliance tends to be retrospective in nature, but ensuring privacy and security must be proactive and forward-looking.[30] Much has been written about general and advanced privacy and security with respect to medical data and devices.[31,32]

**Table 3 New families of privacy and security controls**

| Control family | Key example controls |
|---|---|
| Access Control | Account Management, Access Enforcement, Information Flow Enforcement |
| Awareness & Training | General Awareness Training, Role-based Training |
| Audit & Accountability | Audit Event Management, Audit Review Analysis & Reporting |
| Assessment, Authorization & Monitoring | Annual Assessments, Assessment Guidelines, Independent Assessment |
| Configuration Management | Baseline Configuration, Configuration Change Control |
| Contingency Planning | Contingency Plan, Contingency Training, Contingency Plan Testing |
| Identification and Authentication | User Management, Device Management, Management of Unique Identifiers |
| Individual Participation | Individual Consent, Redress, Access, Privacy Notices and ACT Statements |
| Incident Response | Incident Response Policies & Procedures, Training, Testing, Handling, Monitoring |
| Maintenance | Controlled Maintenance, Maintenance Tools, Personnel, Local & Non-local |
| Media Protection | Media Access, Media Marking, Storage & Transport, Sanitization and Use |
| Privacy Authorization | Authority to Collect, Purpose and Sharing |
| Physical and Environmental Protection | Physical Access Authorization & Control, Monitoring |
| Planning | Security & Privacy Plans, Updates, Rules of Behavior, Impact Assessments |
| Program Management | Program Plan, Roles, Resources, Inventory, Architecture and Performance |
| Personnel Security | Personnel Screening, Risk Designation, Transfer and Termination |
| Risk Assessment | Security Categorization, Assessment and Vulnerability Scanning |
| System and Services Acquisition | Resource Allocation, Systems Lifecycle, Acquisition and Documentation |
| System and Communications Protection | Application Partitioning, Security Function Isolation, Boundary Protection |
| System and Information Integrity | Flaw Remediation, Malicious Code Protection, Monitoring, Alerts & Advisories |

Fortunately, guidance recently released by the US National Institute of Standards and Technology (NIST) details new families of privacy and security controls that can be used as the basis of design and audit, as shown in **Table 3**.[33] Focusing specifically on wearable sensors and devices, the guidance deems it essential that all personally identifiable information (PII) and all personal health information (PHI) must be protected, and that the devices themselves be protected from any form of outside interference, whether accidental or malicious. The predominant generic issues include: the device security of any mobile devices, tablets, and cell phones that are used to collect, store, or transmit information; the potential complications of commingling study sponsor-collected PHI on the personally owned device of a research study participant; secure data transmission and receipt; secure account management; data encryption; data blinding; and data backup and device fidelity. It is essential to understand that these concepts are generic by necessity. Specific solutions will always be required depending on the exact device model, the specific device operating system, the intended method of network connectivity, the intended data capture and processing strategy, and many other variables that will be study-specific. Using several potential methods of network connectivity as examples, **Figure 2** illustrates just some of the most common and potential cyber threat vectors that exist for the three primary types of device connection: Bluetooth, WiFi, and cellular as described by the NIST. The take-home message here is simply that cyber security is increasingly complex, but also well understood and manageable. Success requires a thorough benefit–risk assessment by experts just like any other medical intervention.

## SPECIAL CONSIDERATIONS FOR CLINICAL TRIALS

The application of wearable devices to clinical trials and drug development is in a similar state to that of biomarkers in the early 2000s. At that time, considerable confusion abounded regarding the appropriate use and validation of biomarkers. Tremendous efforts were applied to biomarker activities resulting in refined approaches, particularly the definition and framework for analytical validation, clinical validation, and qualification.[24,25,34] Considerations for the use of wearable devices in a clinical trial should include primarily scientific aspects with a patient-centric approach in mind (**Figure 3**). However, operational aspects, such as patient and site personnel training, device acceptability to patients and patient compliance, data reporting, and transfer and management are critical for obtaining valid and interpretable data. In addition, there is a critical role for validation, both analytical and clinical, in the utility of wearable devices (**Figure 3**).

### Scientific considerations

The scientific approach should start with a health condition or an aspect of health important to patients that has not been addressed to a satisfactory level by current standards of disease management care. Once it is defined, a scientific hypothesis

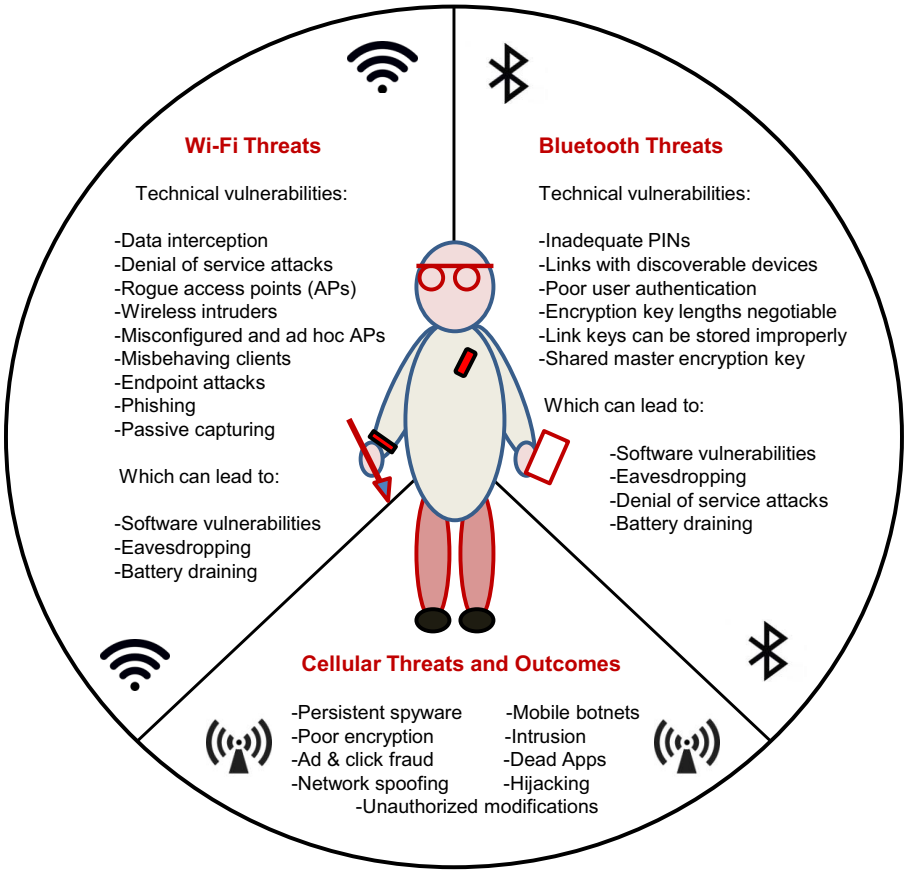


**Figure 2** Most common and potential cyber threat vectors.

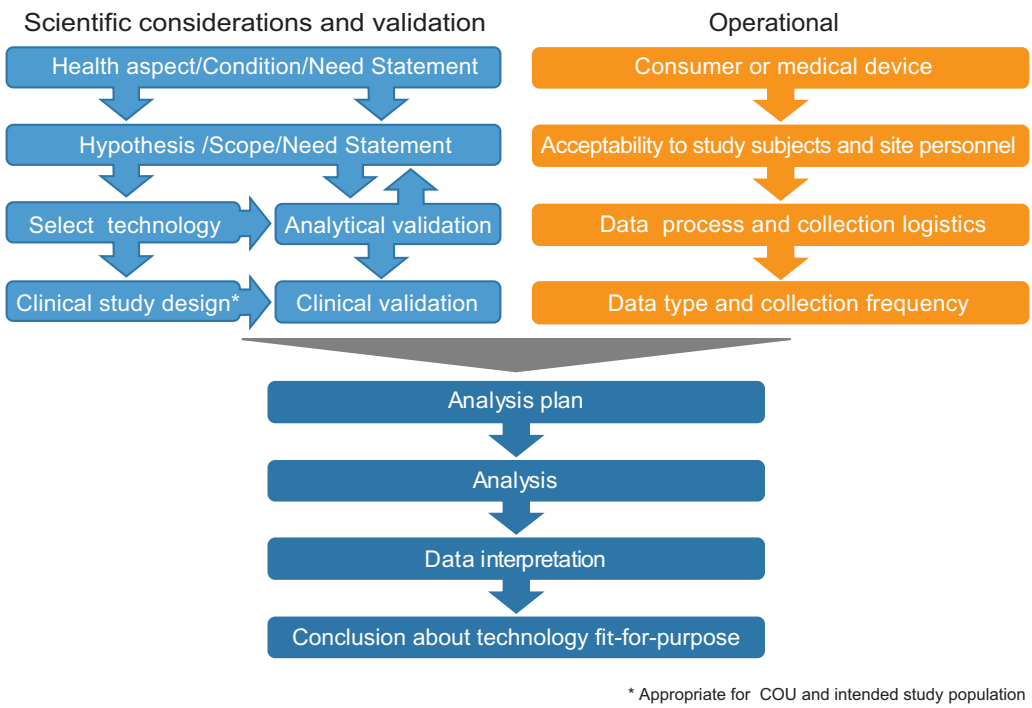


**Figure 3** Scientific, validation, and operational considerations for wearable device implementation in clinical trials.

should be formulated to define the scope of an experiment to be conducted. For example, current assessment of morning stiffness and sleep in rheumatoid arthritis (RA) patients is based on self-reports. The standard tools of data collection include patient self-reports during the doctor's office visits based on memory recalls and patient diaries. Having objective data reflective of these health parameters can be very informative for patient care management including management of adverse events, medications, and dose adjustments. Once the scope is defined, the next step would entail finding a suitable technology to capture the data of interest. In the case of RA, study results indicate that wrist-worn actigraphy devices can differentiate RA patients from healthy controls and can provide useful information about mobility in the context of drug treatment.[35,36] The hypothesis should be tested as one of the objectives in a clinical study. The hierarchical order of an objective of interest, e.g., primary, secondary, or exploratory, will depend on the strength of evidence supporting the hypothesis. The testing can be achieved in an observational or an interventional study. An observational study would be appropriate when no data or limited data about the link between a disease/health aspect and device-derived readouts exist. An interventional study is more appropriate if the goal is to establish a process for wearable data collection in the context of drug treatment and to support efficacy claims or guide treatment decisions. Additionally, a device under consideration should be appropriate for a given study population.

The general validation framework includes a need statement, context of use (COU), analytical validation, clinical validation, and qualification, if necessary for a regulatory purpose (**Figure 3**). A need statement is a concise and coherent description of the knowledge gap or drug development need (e.g., improved safety monitoring) and interfaces with the scientific aspect of the wearable. The COU, which also interfaces with the scientific aspects of a wearable, is a concise description of how a wearable is intended to be used in drug development. With a particular COU, analytical validation establishes if the device performance characteristics are acceptable. Analytical validation or technical performance established for purposes of 510(k) clearance would entail establishing device performance parameters under conditions as close as possible to real-life use. This goal can be achieved by comparing device performance to a traditional tool for collecting the data if available,[37] or another device with well-established performance.[7] Some of the analytical validation parameters may be already established during device calibration done by the device manufacturer and may include important information such as conformity to a gold standard and sensor precision under various testing conditions, but may require an independent validation in the COU. Understanding performance characteristics is necessary for deciding if a device can measure what is needed in a particular COU. If a medical device is under consideration, device performance is established for the purposes of device clearance. However, it may not be appropriate in an intended study population or COU. For instance, if a device has been tested in normal healthy volunteers but is intended for future use in a particular disease, both the hardware and the software performance need to be established in the context of disease to render the device use as "fit-for-purpose." The lack of testing in the intended study population may result in inappropriate data processing and even loss of the data.[38] Also, with a particular COU, clinical validation establishes that the wearable device acceptably identifies, measures, or predicts the concept of interest. Clinical validation includes establishing an association with a specific disease condition to make sure that the data are interpretable and provide useful information for patient care management.[37,39] Both analytical and clinical validation can be done in dedicated device evaluation studies or can be incorporated as one of the endpoints in drug development clinical trials. In the first scenario, multiple devices may be evaluated with appropriate controls embedded in the study, e.g., drugs modulating blood pressure for blood pressure monitoring devices. The disadvantage of this study type is the lack of assessment of device impact on other study procedures routinely performed in drug development, such as frequent blood draws for pharmacokinetics (PK) or imaging procedures. In the second scenario, adding devices to drug development clinical studies as exploratory endpoints provides an opportunity to establish tolerability and acceptability of the device by the study participants and sites in the context of other study procedures. These considerations are a starting place, but require input from stakeholders and a further discussion between the biopharmaceutical industry, device manufacturers, and regulators. It is conceivable that qualification will ultimately be necessary for wearables, similar to surrogate endpoints. Based on a formal regulatory process, it is a conclusion within the stated COU that a drug development tool can be relied upon to have a specific interpretation and application in medical product development and regulatory review. We are not aware of any instances of wearable use requiring this level of scrutiny.

### Device choice and logistical considerations

Both consumer and medical-grade devices can be considered for drug development clinical trials. Medical-grade devices require less work prior to inclusion in clinical trials, as their performance may be established for the purpose of a clearance or approval process and the information is available on the device label. That said, consideration of the intended COU is necessary prior to application. However, consumer-grade devices may not yet have established performance, and device analytical and clinical validation studies are needed to ascertain that a device of interest is fit-for-purpose. The raw and derivative data availability from the device should be considered carefully, as often only secondary derivatives and summary data are available; this may provide an incomplete audit trail. Device acceptability by study subjects is critical to successful implementation. Device technical characteristics such as size, convenience to wear, battery life, and impact on daily life activities should be considered carefully. These characteristics may require patients' input prior to study initiation to ensure successful adoption of a technology. If technology acceptance by users is not known before the study start, a small pilot study may be warranted to obtain these data, as acceptance will have a major impact on patients' compliance. We found that having hands-on experience by clinical scientists directly involved in clinical study design and conduct is highly beneficial. It accelerates

device implementation by clinical teams and allows scientists to rule out early devices that are unlikely to be easily accepted by study participants and may not provide interpretable data. Devices are usually administered by clinical site personnel, trained to pass information to the subjects and be available to help if study subjects are experiencing difficulties. In addition to subject and site personnel training, the data process flow should be mapped before the study start to evaluate the impact of data flow on study participants and other clinical trial procedures. Examples include requiring a cell phone for data synchronization, specific phone models compatible with apps, translations if needed, frequency of data synchronization, and specific computer models for device docking. Compliance of study subjects contributing data should be monitored. Interventions such as reminders to the subjects should be implemented to improve compliance if it falls below a certain threshold.

Decisions need to be made up front about the timing of data processing into secondary derivatives and data review. If data need to be reviewed in near real-time, the data processing, analysis, and visualization need to be established and tested before the study start. Follow-up procedures, if warranted, need to be determined as a part of a clinical study protocol. Retrospective data processing and analysis are more suitable for exploratory endpoints, as they provide more room for experimentation with raw data processing and visualization options, and can be done in an iterative manner. Data use should be clearly defined in the study protocol and it should be stipulated whether such use has any impact on patient care or any other study procedures. In addition, decisions would have to be made on how to handle subjects who may have an allergic or any other adverse reaction to the components of wearable devices. Depending on the intended use of the data, subjects with known adverse reactions to the components of a device may be excluded from the study or allowed to participate in other study procedures; this is appropriate if consent to the wearable device portion of the study is optional and the lack of participation does not have a major impact on overall study data integrity.

Considerations for including devices in the clinical studies are multidimensional (**Figure 3**). R&D and healthcare organizations have a number of hurdles to overcome to make wearable technology implementation a routine procedure. Further development of analytical and clinical validation methodologies and the wide adoption of devices according to the fit-for-purpose principle will remain critical for future success.

## WHAT THERAPEUTIC AREAS ARE MOST APPROPRIATE AND WHY?

In theory, wearables can be used broadly across therapeutic areas for deep phenotyping, detection and interpretation of adverse events, assessment of quality of life, and measurement of efficacy. Wearable and digital approaches could provide signal detection for conditions such as depression by measuring increases in sleep or decrease in activity, signs associated with depression. For example, wearables were recently suggested to be helpful in the detection of early signs of Lyme disease.[7] Any therapeutic intervention that may impact quality of life could benefit from measurement of movement or in some cases where a patient diary is required. One example is a collaboration between PatientsLikeMe and Biogen to better characterize multiple sclerosis patients,[40] where activity and mobility are clearly tied to quality of life. Some therapeutic areas may not require use of a wearable, but rather simple mobile phone applications such as Apple's ResearchKit.

Since many wearable devices can readily measure heart rate as well as blood pressure, the cardiovascular therapeutic area is a major focus for use of wearable devices. Cardiac monitoring in both healthy individuals and specific disease populations allows monitoring for cardiac events 24/7 and enables better-informed care. Cardiovascular disease areas in which wearable devices have been or could be used include congestive heart failure, hypertension, and dysrhythmias. For example, The Zio Patch (iRhythm Technologies, San Francisco, CA) is a single-lead electrocardiographic, continuously recording ambulatory adhesive patch, recently approved by the FDA. In a recent study, the device's 14-day monitoring of beat-to-beat cardiac rhythm had a 57% greater diagnostic yield than the standard 24-h Holter monitoring.[41]

Neuroscience uses of wearable devices are manifold, including the monitoring of sleep, cognition, and movement disorders. Wearable devices commonly measure selected sleep parameters and activity. To assess patients for obstructive sleep apnea outside the laboratory setting, use of medical devices has been steadily increasing.[42] IBM Watson Health and the American Sleep Apnea Association have launched the SleepHealth app to conduct a study identifying connections between sleep habits and health outcomes. This app will record movement and heart rate during sleep and track connection between sleep quality and daytime activities, alertness, productivity, general health, and medical conditions. It will amass the largest collection of sleep data to date. Parkinson's disease is another area that has shown promising results and insight via wearables and machine-learning techniques. The sensors in wearable devices can be paired with mobile phone apps to measure symptoms such as tremor, balance, gait, memory, and some vocal characteristics.

There are examples of wearable use in respiratory diseases, immunology, and rheumatology. For example, GlaxoSmithKline (GSK Philadelphia, PA) (in collaboration with Medidata and POSSIBLE Mobile) are starting an RA trial called PARADE8.[43] It is expected to evaluate 300 patients through a mobile application that tracks common RA symptoms such as joint pain and fatigue, and gathers these data through a mix of surveys and sensor-enabled tests (e.g., recording motion through wrist exercises). This trial is gathering data on the everyday lives of people with RA to gain insight and learn more about the condition. WristOx2 by Nonin Medical (Plymouth, MN) is a pulse oximeter that monitors and measures heart rate and blood oxygen levels, and is targeted towards people who have asthma and are at risk of chronic pulmonary obstruction disease. In 2014, Novartis (Hanover, NJ) launched an observational trial with Qualcomm Life (San Diego, CA) collecting biometric data from chronic lung disease patients in their homes using smartphones connected to Qualcomm's cloud-based 2net Platform.[19]

Another therapeutic area addressed by wearable devices is metabolic disorders, including diabetes and obesity. A recent

systematic review of mHealth (Mobile Health)-related studies on diabetes and obesity treatment and management found that over half of the reported positive effects of interventions based on primary outcomes.[44] Accurate glucose monitoring is something currently in development, as it is not readily available in smartwatches, but several companies are developing prototypes. For example, Dexcom (San Diego, CA) have developed a continuous glucose monitoring application that uses a dermal implant with a probe capable of monitoring blood glucose every 5 min, eliminating the need for finger sticks. The Freestyle Libre Flash Glucose Monitoring System by Abbott (Abbott Park, IL) is a wearable skin sensor that has received regulatory approval. Recently, a pilot study of a patient-centered, smartphone-based, diabetes care system found that a 12-week application of the system to patients with inadequately controlled type 2 diabetes resulted in a significant HbA1c reduction.[44]

## PROGRESS IN CLINICAL TRIALS TO DATE

Recent reviews of wearable monitoring systems have shown that the key implementation challenges are patient and provider engagement, connectivity and device communication, and clinical validation.[45] Per earlier discussion, we have emphasized the importance of rigorous clinical investigation in a stepwise manner where devices are tested in successively less controlled circumstances prior to full investigation in patients' homes. Several wearable devices (ViSi Mobile and HealthPatch) designed for continuous vital signs monitoring were studied in a general hospital ward and compared with vital signs measurements by nurses.[37] The study showed generally promising results, including patient and clinician experiences, but the number and types of artifacts/errors demonstrated the need for significant improvement before equivalence with traditionally used measures can be achieved.

We conducted similar experiments in interventional clinical studies. Our goal was to evaluate 510(k)-cleared wearable devices in the context of drug development clinical trials and ascertain whether devices of interest are fit-for-purpose for vital sign and cardiac rhythm monitoring; this was done in normal healthy volunteers for the purposes of deep phenotyping and expanded safety monitoring. Our experimental design included establishing both analytical and clinical validation by comparing device performance with conventional measures done at the sites, and testing devices in experiments with certain clinical positive controls such as an increased heart rate after certain drug administration. Additionally, we queried important operational parameters such as acceptability by the study subjects and site personnel, and we collected data on subjects' compliance and gained institutional experience with logistics of implementation of wearable technologies. Our data indicate that the technologies are acceptable to the study subjects; however, compliance may decrease when subjects use the devices at home. The feedback from the site personnel indicated high rates of adoption and eagerness of use with a clear need for dedicated technical training and hands-on experience before the launch. Analytical validation experiments demonstrated variable concordance with traditional measures, depending on the variable of interest. Higher concordance was observed with the data collected by another device vs. data collected manually. Consistent with the findings reported by other groups,[37,39] these devices have a propensity to generate a number of artifacts that should be reduced before further broad implementation of technology for safety monitoring. Additionally, we found that a combination of vital sign monitoring with actigraphy readouts, such as mobility counts, facilitates interpretation of vital sign values not collected at the resting state. Overall, our results demonstrated feasibility of collection of vital sign data using wearable devices; however, implementation of such devices for safety monitoring should proceed with caution and should include mandatory verification that a technology of interest is fit-for-purpose.

Looking at ours and others' studies, we see a common theme of great progress and promise but also of technologies that are not quite ready for prime time. Looking at other sensor/device domains, we see similar themes. For example, in a recent in-clinic validation study of a cuffless device for measuring blood pressure, the device demonstrated less than a 5-mmHg variance from conventional measurement in 46% of the study population, but 23% of the originally recruited subjects had to be excluded upfront due to device calibration error.[39]

As previously discussed, there is a sharp difference in measurement accuracy and data/device fidelity between clinical and consumer-grade motion detecting devices but we are hopeful that this gap will eventually disappear. Within the clinical setting, motion detection sensors are being successfully used in increasingly complex observation and analysis scenarios. In one recent motion measurement study of early Parkinson's disease patients, timed "Up and Go" tasks were measured with far greater than 90% sensitivity, but this level of clinical-grade motion measurement required the wearing of special suits that had 17 sensors per body segment.[46]

## CONCLUSION

Wearable technologies are promising and have the potential to fundamentally change healthcare and drug development by changing the means of collecting, processing, and visualizing health data. Potential applications are diverse, have utility in multiple therapeutic areas, and are likely to evolve rapidly. The ultimate goal should be a better understanding of disease variability, responses to treatment along with a reduction of healthcare costs, and increasing efficiency in conducting clinical trials. Additionally, adopting new ways of remote data collection can bring new treatments and care management to all patients in need. Challenges presented by adoption of wearable technologies are not insignificant. The scientific community would benefit from frequent information exchange to share the results and learning experiences; this would facilitate the development and adoption of best practices for technology implementation, data collection, analysis, and interpretation. Currently, the field is full of enthusiasm, but more data are needed from rigorously designed studies to displace the hype and adopt scientific methodologies to generate and test scientific hypotheses. Further dialog between the biopharmaceutical industry and device manufacturers to develop methodological approaches and shared understanding of the experiments is required to fulfill the requirements of analytical

and clinical validation. This conversation would constitute a major step forward facilitating the adoption of wearable technologies in clinical trials.

### Definitions

**Analytical validation.** Establishing that the performance characteristics of a test, tool, or instrument are acceptable in terms of its sensitivity, specificity, accuracy, precision, and other relevant performance characteristics using a specified technical protocol (which may include specimen collection, handling and storage procedures). This is validation of the test's, tool's, or instrument's technical performance, but is not validation of the item's usefulness.[24]

**Clinical validation.** Establishing that the test, tool, or instrument acceptably identifies, measures, or predicts the concept of interest.[24]

**Consumer devices** are devices marketed directly to individuals. An example would be a Fitbit wrist-worn device or an iPhone. The individuals are responsible for managing their devices, including data backup and the decisions around software upgrades. Some of these devices fall under the FDA definition of general wellness products and are considered low-risk devices.[47] There is no requirement to establish device performance before the release to the market.

**Context of use (COU).** A statement that fully and clearly describes the way the medical product development tool is to be used and the medical product development-related purpose of the use.[21]

**Medical devices** are defined by the FDA as is "an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is . . . intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals."[48]

Medical devices have to be approved/cleared by the FDA before they can be released to the market. The approval/clearance path depends on the intended use of the device and also upon indications for use. Devices are classified into Class I, II, and III devices based on the risk the device poses to the patient and/or the user.[49] Depending on the device classification, a Premarket Approval (PMA) or 510(k) clearance is required before release to the market.[50] The FDA stipulates 510(k) as: "a premarket submission made to FDA to demonstrate that the device to be marketed is at least as safe and effective, that is, substantially equivalent, to a legally marketed device. Submitters must compare their device to one or more similar legally marketed devices and make and support their substantial equivalency claims."[51] Medical devices are also a subject to HIPAA security and privacy rules.

**Medical need/necessity.** The AMA defines medical necessity as: "Health care services or products that a prudent physician would provide to a patient for the purpose of preventing, diagnosing or treating an illness, injury, disease or its symptoms in a manner that is: (a) in accordance with generally accepted standards of medical practice; (b) clinically appropriate in terms of type, frequency, extent, site, and duration; and (c) not primarily for the economic benefit of the health plans and purchasers or for the convenience of the patient, treating physician, or other health care provider."[52]

**Wearable technologies** are sensors and/or software applications on smartphones and tablets that can collect health-related data remotely.


## ACKNOWLEDGMENTS

The authors thank Mike Mangiapane for help with editing the article, and Justo Torres for help with Figures 1 and 3 graphical designs.


## CONFLICT OF INTEREST

Elena Izmailova, Eric Perakslis, and John Wagner are employed by Takeda Pharmaceuticals International Co.

## AUTHOR CONTRIBUTIONS

Concept and design: Izmailova, Perakslis, Wagner. Drafting of the article: Izmailova, Perakslis, Wagner. Editing and final revision of the article; Izmailova, Perakslis, Wagner.




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