WHITE PAPER

WEARABLES AND QUALITY ASSURANCE IN A CLINICAL TRIAL SETTING

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For sponsors and trialists alike, the idea of wearable devices that could remotely, accurately, and constantly monitor a patient's heartbeat, lung capacity, movement, and more (the list of potential targets grows longer every day) during the course of a clinical trial is breathtaking. It could change the dynamics of a trial in innumerable ways, enabling participants to travel less, while simultaneously ensuring quality and consistency of data collection, enabling real-time monitoring for adverse events even when participants are not at a trial site, streamlining incorporation of clinical data into the trial master file, and more. Additionally, wearables can lead to the creation of vast data sets that may lead to new insights about how a patient feels or functions and about the impact of innovative therapies on healthcare utilization.[1-17]

But wearable technologies — including those that might not technically be "wearable" but are intended to capture patient information remotely — pose challenges that sponsors and trialists must also factor into consideration as they plan how a trial will be conducted. Some issues are technical; others have to do with user adoption and acceptance; others have to do with the viability of wearables from a regulatory perspective. All must be considered during the trial design stage so that no surprises arise later in the study.

WEARABLES DEFINED

What are wearables? Writers on the topic have gone so far as to identify five types of personal health monitors, from countertop devices (such as blood pressure cuffs) to wearable sensors (including smartwatches and similar devices) to "intimate contact sensors" (patches and electronic tattoos), ingestible devices, and implantable devices.[7, 8, 18] More broadly defined, however, wearables have two common characteristics:

- They are digital devices that can detect and record information about the person wearing/interacting with the device. That information can range from vital signs (heart rate, breathing rate, maximum aerobic capacity, and so on) to range of motion, gait or pace, eye movement, leg movement, speech/language performance, and many other specific characteristics.
- They are autonomous, untethered devices, which is to say that they are not physically bound to a clinical trial site but capable of operating remotely and gathering the target data from the trial participant even when they are not at the trial site. Example of such an untethered devices range from a smartwatch that can perform an ECG or a set of sensors attached to a trial participant's bed that can capture leg movement and other data while the participant is sleeping at home. Even speech can be captured on a smartphone and analyzed for certain types of vocalizations or verbal expressions correlated with illness severity.

Some wearable technologies will capture data from the individual wearing the device and upload that data to an **individual's computer or smartphone**, from whence it can be uploaded to the site's clinical trial data management system (either directly or via an intermediary). Other wearable technologies may capture the data and upload it to a **data repository** maintained by the device manufacturer. Still others may capture the data and upload it directly to the **study site's data management platform** or capture the data and store it until it can be uploaded when the participant visits a trial site.

TABLE 1: EXAMPLES OF WEARABLES AND THEIR USE

Types of wearable devices	Type of activities/events that can be monitored	Representative areas of applicability

• Wrist-worn
• Skin patch/tape-based
• Arm/leg Cuff
• Finger-worn
• Clothing-embedded
• Headbands/helmets
• Other
  · Spirometers
  · Inhalers
  · Smart pill bottles/containers
  · Toothbrushes
  · Earbuds/headphones
  · Ingestibles
  · Implantables
  · Smart surfaces
	• Step count
	• Pulmonary function
	• Sleep/sleep disturbances
	• Motion/gait/falls/balance
	• Posture/pronation/supination
	• Breathing
	• Tremor
	• Dexterity
	• Cognitive performance
	• Speech analytics
	• Language analysis
	• ECG
	• Resting/sleeping pulse
	• Blood oxygen levels
	• Heart rate/rhythm
	• Elevation changes/stairs climbed
	• Duration of exercise
	• Fetal activity/pregnancy
	• Skin temperature/perspiration rate
		• Psychiatry
		• Neurology
		• Cardiopulmonary research
		• Orthopedics
		• Rehabilitative medicine
		• Public health
		• Oncology
		• Behavioral medicine
		• Biofeedback

WEARABLES IN A CLINICAL TRIAL SETTING: TECHNICAL CONSIDERATIONS

As noted, the idea that a participant can provide data on a 24x7 basis even when not on site holds attraction for all parties invested in clinical trials and drug development. As of June 2021, a search on clinicaltrials.gov using the keywords "wearable OR actigraphy OR smartwatch" identified nearly 2,250 studies (a number reflecting only a the subset of trials that have been registered in the U.S.). Add in the search term "mobile" and the total number of studies climbs to nearly 8,000 (though many of those studies involve smartphone-based applications and user-completable surveys rather than digital devices that can monitor an activity). Kaiser Associates and Intel estimate that 70% of clinical trials will incorporate some type of wearable sensors by 2025.[6]

This enthusiasm notwithstanding, whether a given wearable can deliver data in line with expectations and that will be acceptable to regulatory agencies is another question entirely. There are certain technical questions to which all prospective devices must be subjected in advance of their inclusion in a trial:

- Have they been independently **validated** and shown to capture data in a manner that is consistent with more established assessments?
- How **accurate** are the wearables compared to equipment that would otherwise be used at the trial site or in a doctor's office?
- How **consistent** are the readings from device to device if a participant must switch devices in the course of a trial?
- How **reliable** are they in terms of measurement consistency? Do they measure consistently over time?

NOT ALL WEARABLES ARE CREATED EQUAL

Many wearables fall into a class of devices that might best be called "fitness devices" or "enthusiast" devices. The most frequently used consumer wearables include ActiGraph, Apple Watch, and Fitbit.[6] Others fall into a class of devices that might be described as "medical devices." These questions of validity, accuracy, consistency, and reliability can distinguish which class a given device may fall into.[19] Depending on the monitoring and data collection features in question, some devices may fall into both categories.

> KAISER ASSOCIATES AND INTEL ESTIMATE THAT 70% OF CLINICAL TRIALS WILL INCORPORATE SOME TYPE OF WEARABLE SENSORS BY 2025.[6]

Those devices that are classified as "medical devices" by U.S., UK, and EU regulators are generally required to be manufactured, certified, validated, controlled, and distributed in accordance with a quality management system (QMS) that is approved by the respective governmental regulatory authorities. This includes any software, firmware, and data collection and transmission performed by the device.[7, 19-23]

What can further complicate this use of wearables is that the application of the device can be determinative of its classification under regulation. For example, if a device is manufactured with the intent to be a "fitness device" or for use by "enthusiasts" and a sponsor of a clinical study decides to use the device to gather and transmit data that is critical to safety, effectiveness, or other endpoints identified in the study protocol, then the wearable may be classified as a "medical device" even if it was not manufactured in accordance with regulatory standards governing and controlling medical device manufacturing.

DATA CAPTURE, STORAGE, AND TRANSMITTAL

Other technical considerations have to do with data capture, storage, and transmittal:

- **What** data are captured?
- **Where** is the data stored?
- Is the data stored in an **encrypted** or clear format?
- How does the data **move** from the device to the trial data management system?

Some devices may be purpose-built to capture only a specific type of health data (cardiovascular vital signs, for example). Other devices may capture that clinical data along with a wide range of other data points — ranging from location data to time spent on other activities such as sleeping, exercise, or various parameters associated with playing games. Much of this latter data will not be of interest in a clinical trial setting, although there are emerging trends for the use of this type of activity data to assess elements of psychomotor performance and motivation. One consideration here is this: some of the captured data may reference activities that are not germane to the trial and that the individual would not want shared.

Clarifying any patient- or caregiver-specific concerns regarding the type of data that might be shared, including possible ethics committee commentary, is an essential element before incorporating wearables into study design. Recent examples involving the use of "geolocation" devices to determine the amount of time a patient resides within the home or community offer prime examples in which confidential data may need to remain confidential rather than being incorporated into a clinical trial database.

The question of where and how data is stored is another matter to consider. Data collection and storage within the context of a clinical trial must comply with the standards for open systems and electronic records as defined in 21 CFR part 11.[24] Depending on the wearable device, there may or may not be enough onboard memory to hold all the data that trialists want to capture. If there is insufficient storage, what does the device do when capacity is reached? Some devices may offload the information to the user's smartphone, to a laptop computer, or to a proprietary base station; others may offload the information to cloud storage maintained by the device manufacturer. In a worst-case scenario, the device will simply purge the oldest record from the device to make room for new records — which, in a trial setting, could result in the loss of critical data and/or audit trail information that compromise the completeness and validity of the trial record. Different device manufacturers address these questions in different ways, but it is important to know how a device under consideration handles these matters so that the data capture and collection infrastructure supporting a trial is itself is designed with the particulars of the devices in mind.

- ☐ **What** data are captured?
- ☐ **Where** is the data stored?
- ☐ Is the data **encrypted**?
- ☐ How does the data **move**?

Other questions arise from related technical matters, such as the nature of the communications protocols used to transfer data from the wearable to the next destination (such as a smartphone or cloud-based data collection system). If a data communications channel such as Bluetooth is used, data transmission between the wearable and the collection destination will not occur unless the wearable is within a certain distance of the collection device. That prompts other questions about whether data can be cached on the wearable if the smartphone/base station is out of range.[25]

As noted, each of these challenges can be addressed, but it is important to work with trial designers who understand the scope of the questions that must be asked. In considering potential devices, for example, it is important to anticipate how much data the device will be collecting, how it will store that data, what will happen if storage hits capacity, and how it will be transferred to upstream destinations.

DATA SECURITY/DATA PRIVACY

Similarly, in considering where that data is stored, it is crucial to consider the questions of data security and data privacy. Multiple questions arise in this space. Are the data encrypted in storage? Simply put, encryption is a must-have, particularly if the site of data storage is not the device itself. As data moves further from the individual to whom it belongs, it grows more vulnerable: smartphones can be lost or stolen; cloud storage repositories that may appear to belong to a device manufacturer may in fact be operated by a third party subcontracting to the manufacturer. The repositories may or may not be in the country where the trial is running, which could create legal issues in countries covered by the EU's General Data Protection Regulations (GDPR). In the absence of a clear chain of responsibility and enforceable Business Associate Agreements (BAAs) that can ensure the security and integrity of the data, there may be unacceptable levels of exposure that could compromise data integrity and data privacy. Unless the data is protected by strong encryption algorithms, it could be misused by people who have no business accessing it.

Related to these questions about data storage and encryption are questions about how the data moves from the point of collection to the point of storage and, ultimately, to the trial data management system. This transmission process must be validated for compliance with 21CFR Part 11 as well as EU Annex 11.[26] Just as the data should be stored in an encrypted format, it should also be transmitted from the device to any data repository — whether on a patient's phone or computer, further upstream in the cloud, or on the trial data management systems itself — in a strongly encrypted format. Device manufacturers that have not built such provisions into their data management infrastructures should not be considered for use in a clinical trial setting. The lack of encryption for data in flight could be considered a failure to protect personal health information in these circumstances.

- ☐ What **volume** of data is streaming?
- ☐ How is the **trial management system** architected?
- ☐ Has data in motion been **deleted**?

Other considerations relating to the flow of data from wearables involve the architecture of the back-end systems managing the collection of trial data. Traditional trial data management systems were designed to capture data only from periodic in-clinic patient visits. A trial involving wearables may generate a stream of patient data that flows on a 24x7 basis. While this may be seen as a clear benefit of using wearables, one that lessens the possibility that important patient data might be missed, the clinical trial management systems capturing that data must be designed with that constant stream of data in mind.

A final matter related to the subject of data storage is this: Once the data captured from the wearables is securely stored in the trial data management system, what mechanisms are in place to ensure that this data has been deleted from any storage location that it might have touched while in transit? From the perspective of data privacy, it is important that this personal health information (PHI) not be left in an

intermediary cloud repository (or in a backup of that intermediary repository). It should be securely deleted from any location outside the control of the individual and the trial manager. Upon completion of the trial, steps must be taken to ensure that any residual data on the wearable itself is securely deleted.

DATA OWNERSHIP

One other important question in this area has to do with technology and the matter of data ownership. While an individual may consider his or her vital signs or ECG patterns to be protected health information — particularly if the collected data by the wearable is associated with an identifiable individual — the wearable device manufacturer may consider this to be their own proprietary research data that the device user consented to provide when they signed a user agreement the first time they powered up the device.

In a world where data is the currency of the realm, the device manufacturer may be viewing the data captured by the device as raw material from which new goods and services can be developed and marketed to the public, or the manufacturer may be looking at the raw information as the source of data that can be resold to other companies so that the other companies can promote their goods and services to given subgroups of users. Clinical trial participants may be wholly unaware of this when agreeing to participate in a trial, so it is incumbent upon the trial designer and sponsor to understand who can assert ownership of this data and to select wearables that will be appropriate to the trial and to the privacy needs of participants. Information concerning the use, storage, and protection of participant PHI must be disclosed and agreed to during the informed consent process.

- ☐ Who asserts **ownership** of the data?
- ☐ Has PHI **privacy** been addressed?
- ☐ Has **user adoption** been considered?

As with other considerations related to data security and privacy, none of these issues should discourage a sponsor from incorporating wearables in a trial. These matters simply must be taken into consideration as part of trial design, and a partner experienced in the use of wearables can help a sponsor avoid situations that could otherwise compromise the integrity of the trial. For studies in which wearables will be included, it is prudent to include quality assurance (QA) experts in the matrix team assigned to the International Classification of Functioning, Disability and Health (ICF) documentation creation and review.

USER ADOPTION CONSIDERATIONS

The one good thing about the technical considerations outlined above is that technical solutions already exist. Device manufacturers that initially built fitness trackers for enthusiasts may up their game to deliver devices that are more like medical devices, with validated levels of accuracy, reliability, security, and more. Some wearables already provide compelling answers to the questions raised above, and as time passes, the demand for devices that are viable in a clinical trial setting will only grow.

But other challenges remain. Consider user adoption. Depending on the population to be studied, there may be resistance to certain types of wearable devices. One device may seem too complex or unfriendly for older, adolescent, or chronically ill participants. Another device may be simple to wear and operate but the user may find the need for a smartphone or computer to capture data too

daunting. Is the mechanism for uploading captured data to the trial management system automated? If not, some participants may balk at the idea of using a wearable because they want neither the responsibility nor the burden of manually uploading data on a regular basis.

Some trial participants may find certain devices uncomfortable and dislike wearing them. Others will simply forget to wear them. Some participants simply will not own certain technologies that a given wearable requires (such as an Android-based smartphone or a Windows-based computer), so the trial may have to provide the supporting technology along with the wearable technology. Network access in the form of a Wi-Fi hotspot or Internet connection may also be lacking. This absence must be anticipated and contingencies prepared. These circumstances may also lead to significant increases in the cost of conducting the trial.

Any of the scenarios above may also include an education component in which the participant is instructed in the use of the device, the use of the smartphone and/or computer, the use of a Wi-Fi access point and the procedures, if any, for logging in to any back-end infrastructure to facilitate data uploads. Part of this training program may include training for caregivers and support personnel, who may help overcoming the participant's reluctance to use a wearable by ensuring that the support person can help manage the device and any related data collection system. Training may need to cover such fundamentals as the need to recharge the wearable on a regular schedule. It does no good to wear the device regularly if it is not charged and collecting data.

User adoption considerations can be addressed through a user interface testing program that includes both qualitative and quantitative information that takes into consideration the patient's perspective and the investigator's perspective.

> A USER INTERFACE TESTING PROGRAM CAN HELP IDENTIFY AND ADDRESS USER ADOPTION CONCERNS IN ADVANCE.

ON THE CHALLENGE OF SENSORS

While the issues outlined above are easy to understand where the wearable in question is a smartwatch or an unfamiliar digital pendant, other kinds of devices can present more complex adoption challenges. A wearable that involves placement of a sensor, for example, may present its own complications. The trial participant may need help attaching the sensor, for example, or may be reluctant to have the sensor(s) attached (or, removed, if removal involves repeatedly tearing sticky sensors from hair-covered or adhesive-sensitive skin). Consideration must be given to potential objections and issues so that responses and workarounds can be ready. In the case of subjects who may have reactions to the adhesives used to apply sensors, the trial sponsor would need to account for these events as potential adverse reactions and reportable safety related incidents.

Key to overcoming adoption challenges lies in the identification of the benefits of wearables to the participant. For some, the ability to avoid driving into a trial site several times each week or month is a compelling reason to overcome any reluctance that might be initially encountered. For others, though, the idea of skipping a visit to the trial site could be anathema, because they have reasons to like going to the trial site (such as the camaraderie of others who understand the experience of the illness they have) and would not want to miss a visit. For such individuals, other benefits may be paramount — such

as the ability to provide accurate data on a consistent collection basis and the importance of such data to the overall study. Successful product positioning is similar to trial positioning in that benefits and limitations can be highlighted in both circumstances using a variety of media to assure adequate patient understanding.

REGULATORY CONSIDERATIONS

Finally, how will regulators respond to the proposed use of wearable devices? The FDA has indicated a willingness to consider data captured by wearables in a clinical trial setting:

> **FDA recognizes that a wealth of RWD [real-world data] covering medical device experience exists and is routinely collected in the course of treatment and management of patients. Data collected during clinical care or in the home setting may not have the same quality controls as data collected within a clinical trial setting. Even so, under certain circumstances, RWD may be of sufficient quality to help inform or augment the FDA's understanding of the benefit-risk profile of devices at various points in their life cycle. RWD, which are typically collected for non-regulatory purposes in EHRs, registries, and administrative and claims data, may provide new insights into the performance and clinical outcomes associated with medical device use. This information can potentially be used by sponsors to demonstrate compliance with regulatory requirements and to aid the FDA in our regulatory decision-making.**[27]

At the same time, outside of the broad guidelines covering medical devices published in 21 CFR Part 11 Section H, those covering electronic records in 21 CFR Subchapter A, Part 11, and those covering privacy protections in 21 CFR Subchapter A, Part 21, the FDA has published few guidelines specifically addressing issues relating to wearables. One reason for this may be the rapid pace at which wearables have been introduced and marketed, but another may simply be that the broad guidelines in those three sections may be deemed sufficient to cover use cases involving wearables).

- ☐ What **outcomes** are you measuring?
- ☐ How **relevant** are the changes to the patient?

The FDA's willingness to consider the use of data captured by wearables, however, is not without limits. Verily, a subsidiary of Alphabet, created a wearable known as the Verily Study Watch, which was approved by the FDA in 2019 as a wearable validated for ECG data collection[28] and, in 2020, for irregular pulse monitoring.[29] A feature introduced into the device in 2020 was intended to facilitate ongoing collection of motor ability data in patients diagnosed with Parkinson's disease. Verily had developed an assessment that it called the Virtual Motor Exam for Parkinson's disease, Part III Estimator (VME Part III), an assessment intended to measure and track motor abilities as outlined in Part III of the International Parkinson and Movement Disorder Society's standardized Parkinson's disease rating scale (MDS-UPDRS). Patients would be prompted to tap the watch and move in certain ways, and the device would capture data about the motions. VME Part II was being used in observational studies taking place in the Netherlands and Japan.

In January 2021, Verily requested that the FDA approve its Virtual Motor Exam for Parkinson's disease, Part III Estimator (VME Part III) as a clinical outcome assessment that clinical investigators could use as an efficacy endpoint in drug development clinical studies.[30] In June 2021, however, the FDA refused Verily's request. The FDA did not raise any concerns about the accuracy of the data collected by the wearable. Rather, its refusal arose from a view that the data did not measure changes that are "relevant to the patients' ability to function in day-to-day life":

> **For example, a change in rigidity or finger tapping in the MDS-UPDRS Part III cannot be directly interpreted as being meaningful to patients. However, a change in speech, eating and dressing (as assessed in the MDS-UPDRS Part II) represents meaningful change in how patients function in daily life.[31]**

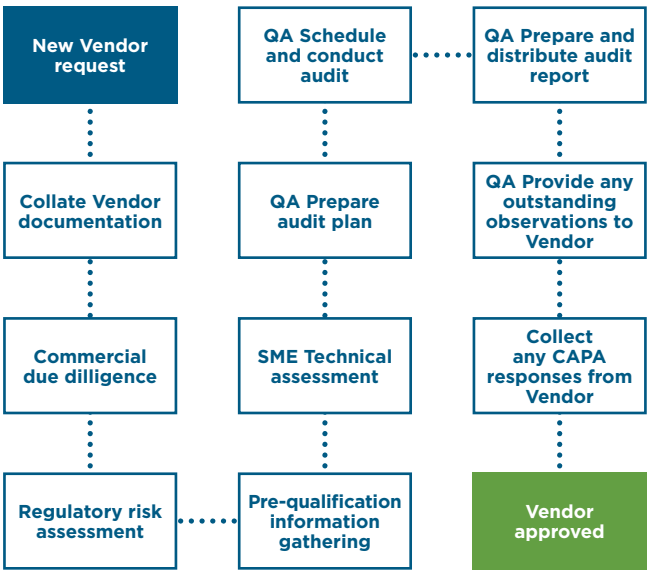
As of mid 2021, wearables continue to play a role primarily in exploratory studies. No trials yet rely on wearables as a primary measure, with the exception of one published study in pulmonary arterial hypertension.[32] While regulators are clearly interested in expanding the role of wearables in trials, they are doing so slowly, particularly given the need to establish a correspondence between the data that are gathered and a clinically relevant endpoint.

WEARABLES AND QUALITY ASSURANCE

From a practical perspective, all this means that every aspect of a clinical trial use case involving a wearable must be rigorously analyzed and validated before the wearable can be considered viable, particularly if the wearable is expected to act as a primary measure. All the questions enumerated above are essentially QA and compliance questions — regarding accuracy, consistency, endpoint specificity, data storage, data transmission, and more. The wearables must be reviewed and validated to ensure that the data they capture is accurate, consistent, and clean enough to pass regulatory scrutiny.

While it is possible to employ wearables that meet these demands, the challenge for sponsors is that many of the companies developing interesting and potentially beneficial wearables have not had their technologies validated for use in a clinical trial setting and are unfamiliar with regulatory requirements around security and privacy. Nor have they any idea how those regulations may vary between various regions where they might want to conduct clinical trials.

FIGURE 1: VALIDATING A WEARABLE VENDOR IS AN IMPORTANT PART OF THE QA PROCESS.



For sponsors, it becomes important to work with a CRO that is familiar with all the intricacies associated with the use of wearables — from the technical issues to the user acceptance issues to the regulatory issues — in the U.S., the EU, and other regions — so as to facilitate the selection and validation of technologies that will pass muster with all parties concerned. The process would include formal engagement of QA personnel at the earliest discussions of trial design, with the incorporation of a unique "wearables" workstream to be considered pending review of QA issues and remediation strategies.

SUMMARY

Wearable devices can play a valuable role in a clinical trial, capturing data about the experience of trial participants on a 24x7 basis, even when participants are nowhere near the trial site. As such, wearables extend the promise of greater data collection — potentially more accurate and more detailed data collection — at a lower cost than would be incurred if data were only collected at trial sites.

For wearables used in a trial setting to live up to that promise, though, they must provide levels of security and data privacy that not all wearables will be able to provide. They must capture, store, transfer, and protect user data — which may be considered protected health information — in a manner consistent with regulatory guidelines such as 21CFR Part 11. They must be acceptable to users and not impose undue burdens on the trial participant's quality of life. They must be shown to be capable of capturing and preserving for trial use the endpoint data relevant to the trial itself.

A CRO with experience in the use of wearables is indispensable if a sponsor is considering the use of wearables in support of a clinical trial. A knowledgeable partner in this area can advise on the viability of different wearable devices, help orchestrate a validation process if one is needed, identify areas where regulators may raise concerns, and proactively determine how best to address those concerns before they become a real stumbling block for regulators.

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