SIGNANTHEALTH
THE EVIDENCE GENERATION COMPANY™

WHITEPAPER

DIGITAL HEALTH TECHNOLOGIES (DHTs) IN CLINICAL TRIALS: KEY POINTS FROM THE FDA'S IMPORTANT DRAFT GUIDANCE

BILL BYROM, PHD
Vice President, Product Intelligence & Positioning
Signant Health UK

Regulatory guidance on the use of wearables and sensors to collect clinical outcomes data has been long awaited, so this draft for public consultation from FDA is enormously welcome.

The guidance defines a digital health technology (DHT) as *"a system that uses computing platforms, connectivity, software, and/or sensors, for healthcare and related uses."* This broad definition includes both sensors and wearables (and their associated software and platforms) as well as general purpose computing platforms – such as mobile devices used to collect ePRO data (e.g., using a commercial smartphone or tablet). While this broad definition is not very helpful in a single guidance – it would be timely to see guidance just specific to wearables and sensors at this point – the draft guidance does provide insights for both eCOA and data collected using wearables and sensors. I summarize some key points on each below.

ENCOURAGING INCLUSION OF THINKING AROUND BRING YOUR OWN DEVICE (BYOD) USAGE

The FDA consider BYOD in the context of sensors and wearables along with general purpose computing platforms. They state that sponsors should consider whether BYOD (e.g., the participant's own continuous glucose monitor or smartphone for using an ePRO app) may be appropriate to reliably collect data. The agency lists some of the benefits of a BYOD approach, such as familiarity and reduced participant burden (eliminating carrying multiple DHTs). In determining the suitability of BYOD, sponsors should ensure consistent precision and accuracy across all brands, models, and versions of the DHT used in the clinical trial. This is relatively straightforward for BYOD eCOA, where we have plenty of evidence supporting measurement comparability across implementations. Less straightforward is the use of BYOD when it comes to wearables and sensors. For example, we already know there can be quite large differences in outcomes data delivered by different activity monitors (Bender et al., 2017), although applying common algorithms to the raw signal data these devices provide (where it can be accessed) may reduce this variability to a satisfactory level.

As stated elsewhere, the FDA reiterated that participation should not be dependent on DHT ownership, and provisioned devices should always be available when using BYOD. When using BYOD, the minimum technical specification suitable should be defined (e.g. operating system, storage capacity, sensors etc.).

DECENTRALIZED CLINICAL TRIALS

The FDA acknowledges that remote data capture using DHTs may reduce the burden of traveling to site and encourage participation among patients who do not live near clinical trial sites. This provides an encouraging nod towards the trend of increasing decentralization.

SUPPORTIVE EVIDENCE FROM A REPRESENTATIVE POPULATION

Current recommendations for the use of DHTs include demonstration of usability and clinical validity. The FDA speaks to the importance of ensuring that supportive evidence is appropriate, providing the example that step counting using an activity monitor validated in healthy volunteers may not be considered clinically valid when used in Parkinson's disease patients, who exhibit a very different gait pattern. When we consider usability and clinical validity evidence collectively as an industry, a conservative view is often applied: evidence is often thought to be needed by studying the specific patient population. The FDA makes an encouraging argument, one in line with my own recommendations (see Muehlhausen et al, 2018 for example), stating that the appropriate population to consider for these studies may depend on whether the parameter being measured would be similarly obtained from a healthy trial participant or a similar patient population. This brings us to thinking about how to define a "representative" patient population in each use case – a helpful exercise to apply existing evidence as opposed to conducting new usability or clinical validation studies for each study or program.

EVIDENCE TO SUPPORT SELECTION OF A SENSOR OR WEARABLE FOR USE TO COLLECT CLINICAL TRIAL ENDPOINTS

The FDA states that DHTs used in clinical trials do not need to have market clearance or approval (e.g., a 510(k)). This is consistent with industry consensus group recommendations, such as those published by members of the Critical Path Institute's (C-Path) ePRO Consortium (Byrom et al, 2018) and the Drug Information Association (Walton et al., 2020). We couldn't agree more. The suitability of a DHT should be assessed based on its measurement properties in the context of use required by the clinical trial. However, in practice we know that having substantial market clearances across the globe can simplify distribution of DHTs for use in multinational trials.

The draft guidance lists several considerations related to the selection of a fit-for-purpose sensor or wearable for collection of clinical outcomes data. This includes aspects of design, usability, and safety, not to mention ensuring data security and privacy.

Data security and privacy

In addition to assuring security and privacy when storing and transmitting data from a sensor or wearable device, the FDA cites the importance of transparency over end-user license agreements and data sharing associated with some (consumer) wearables. Any third-party use of the data associated with such end-user license agreements should be explained in the informed consent document. Some consumer wearables have end-user license agreements that allow the manufacturer to use data stored in the vendor's cloud, not just to provide metrics and feedback to the user, but also for other purposes.

The Fitbit privacy statement, for example, states: *"We may share non-personal information that is aggregated or de-identified so that it cannot reasonably be used to identify an individual. For example, in public reports about exercise and activity, to partners under agreement with us, or as part of the community benchmarking information we provide to users of our subscription services."* This does not prohibit the use of these devices in clinical trials, but it should be explained to the patient as part of their decision making on whether to participate.

Measurement properties: verification and validation

The draft guidance discusses other requirements, including the verification and validation of evidence in the context of additional data to accompany a submission that uses a wearable/sensor for clinical endpoint data generation. These relate to ensuring and demonstrating suitable measurement properties sufficient for regulatory decision making.

The FDA continues by defining verification as *"confirmation by examination and provision of objective evidence that the physical parameter that the DHT measures (e.g., acceleration, temperature, pressure) is measured accurately and precisely over time"* and validation as *"confirmation by examination and provision of objective evidence that the selected DHT appropriately assesses the clinical event or characteristic in the proposed participant population."*

This seems on the surface to be reasonably aligned with the Digital Medicine Society's (DiMe) V3 framework (Goldsack et al, 2020). In verification, the agency lists elements such as confirmation that the DHT meets performance specifications, compliance with electrical safety standards, and (where appropriate) identifying conditions for reliable functioning (e.g., temperature ranges). The latter two elements should be relatively straightforward to obtain from the manufacturer. However, the FDA does not elaborate in detail regarding the expectations for verification evidence.

In their example of considerations for a hypothetical wearable, they cite understanding performance in different environmental conditions and consistency of measurement across placement location and skin colors. This does not go as far as their definition of verification, demonstrating that the physical parameter (e.g., acceleration) is measured accurately and precisely. Perhaps this is a recognition of the practical difficulties in obtaining this evidence, which if confined to assessment of the raw physical parameter measured, may not be readily available from the manufacturer. We make this observation in Walton et al. (2020), where we propose that analytical validation evidence can be sufficient where verification data is not disclosed by the manufacturer.

The draft guidance identifies the kind of validation evidence needed to support use of a wearable or sensor. A key component is demonstrating accuracy of estimates compared to a gold standard approach (where available), such as comparing a step count estimated by actigraphy against one measured by observation. This is of course a vital step, and it is encouraging to see a growing body of literature provide some of this evidence. Fitbit, for example, maintains a publication and research library that provides easy access to published studies, including validation studies (https://healthsolutions.fitbit.com/research-library/). It is also encouraging to see these libraries being maintained by some consumer device manufacturers, as we have already seen for devices marketed for research only (e.g. ActiGraph's research database: https://actigraphcorp.com/research-database/).

Other validation evidence cited by the FDA may include, as appropriate, the evaluation of precision and accuracy of the measurement based on placement location, in addition to how physical interference with the measurement is detected and dealt with (e.g., distinguishing between car travel and physical activity).

DATA INTEGRITY

Finally, the FDA speaks about data integrity in the context of minimizing missing data and device, firmware, or software updates.

Missing data

The agency states that a wearable or sensor should have suitable data storage capacity and data transmission frequency to minimize the potential of missing data. They recommend alerts, such as low battery indicators or poor mobile data signal to limit data loss or missing assessments. They also recommend procedures to identify and replace DHTs should be implemented, as needed, to limit missing data.

Software updates

Considerations around software and firmware updates affecting the measurements provided by DHTs is reiterated in the draft guidance. We also cited this as a consideration when choosing between consumer and research-grade devices in our recommendations published by the ePRO Consortium (Byrom et al, 2018). It is feasible that software and firmware updates pushed to devices by the manufacturer may affect the algorithms used to derive outcome measures, and if this is done mid-study, it could complicate interpretations of the study data. With that in mind, the FDA urges sponsors to keep a record of the timing and nature of any DHT updates.

Finally, the FDA recommends that sponsors should assess any DHT updates implemented during the study to ensure that there is no significant impact on measuring the clinical events of interest. Research-grade devices often enable sponsors to maintain the same firmware version across the study, which eliminates this potential issue. While the FDA recommends that sponsors consider locking software algorithms and firmware for the duration of the clinical investigation (unless related to important security updates), this may be more difficult to do with consumer devices. In this case, the FDA indicates that sponsors should demonstrate that the data collected before and after the update are not meaningfully different.

Overall, this is a helpful and welcomed guidance. On the surface, the guidance seems very much in line with current industry consensus group recommendations, including those published by DiMe, DIA, and the C-Path ePRO Consortium. Hopefully more detail in critical areas will be provided in the final guidance for greater clarity on evidentiary requirement expectations, but this is a very helpful starting point.

REFERENCES

01 Bender C, Hoffstot J, Combs B et al. Measuring the fitness of fitness trackers. 2017 IEEE Sensors Applications Symposium (SAS).

02 Byrom B, Watson C, Doll H et al. Selection of and Evidentiary Considerations for Wearable Devices and Their Measurements for Use in Regulatory Decision Making: Recommendations from the ePRO Consortium. Value in Health 2018; 21: 631-639.

03 Goldsack, JC, Coravos, A, Bakker, JP et al. Verification, analytical validation, and clinical validation (V3): the foundation of determining fit-for-purpose for Biometric Monitoring Technologies (BioMeTs). npj Digital Medicine 2020; 3:55. https://doi.org/10.1038/s41746-020-0260-4

04 Muehlhausen W, Byrom B, Skerrit B et al. Standards for Instrument Migration When Implementing Paper Patient-Reported Outcome Instruments Electronically: Recommendations from a Qualitative Synthesis of Cognitive Interview and Usability Studies. Value in Health 2018; 21: 41-48.

05 Walton M, Cappelleri J, Byrom B et al. Considerations for development of an evidence dossier to support the use of mobile sensor technology for clinical outcome assessments in clinical trials. Contemporary Clinical Trials 2020; 91: 105962.

WHO IS SIGNANT HEALTH?

Signant Health is the evidence generation company. We are focused on leveraging software, deep therapeutic and scientific knowledge, and operational expertise to consistently capture, aggregate, and reveal quality evidence for clinical studies across traditional, virtual, and hybrid trial models. For more than 20 years, over 400 sponsors and CROs of all sizes – including all Top 20 pharma – have trusted Signant solutions for remote and site-based eCOA, eConsent, RTSM, supply chain management, and data quality analytics. Learn more at www.signanthealth.com.

SIGNANT HEALTH
THE EVIDENCE GENERATION COMPANY™