March 22, 2022

Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA-2021-D-1128: Digital Health Technologies for Remote Data Acquisition in Clinical Investigations; Draft Guidance for Industry, Investigators, and Other Stakeholders

Dear Recipient:

The Biotechnology Innovation Organization (BIO) thanks the Food and Drug Administration (FDA or Agency) for the opportunity to submit comments regarding the Draft Guidance *Digital Health Technologies for Remote Data Acquisition in Clinical Investigations*.

BIO is the world's largest trade association representing biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO's members develop medical products and technologies to treat patients afflicted with serious diseases, to delay the onset of these diseases, or to prevent them in the first place.

BIO believes that the Draft Guidance generally provides greater clarity around FDA's approach to regulate remote data acquisition, which will encourage the use of digital tools and methods in product development. We also appreciate that the Draft Guidance encourages leveraging of prior work in the verification and validation of DHTs, which will be critical as the field advances. To further enhance the Guidance, we believe that a number of areas would benefit from more explanation, examples, and references. We have identified through our comments areas where these additions would be beneficial.

I. Benefits of DHTs

BIO believes that it could be valuable to note in the background that DHTs may facilitate better oversight of patients participating in remote studies and allows sponsors to collect data that is more relevant to patients' needs. More robust engagement and communication may ensure data quality, data integrity, patient safety, and help investigators to monitor patient compliance with the protocol by allowing for real-time data availability. This may also help the sponsor to understand data collection is occurring reliably and allows Clinical Research Associates to ensure oversight of their trial sites. Notably, any such monitoring can be performed without unblinding data through restrictions on the extent and form of access provided by the platform.

Biotechnology Innovation Organization
1201 Maryland Avenue, SW, Suite 900
Washington, DC 20024
202-962-9200

II. *Engagement Across FDA*

We appreciate that the Agency has included a section on "regulatory considerations and engagement with the Agency". While this section is helpful, we request further clarification. As the use of DHTs for remote data acquisition touches on the work of many Centers at FDA, BIO greatly appreciates that the guidance was developed as part of a cross-center effort that included, CDER, CBER, CDRH and the OCE. With respect to the fact that multiple Centers could be involved in DHT review and oversight, it would be helpful if the agency could provide further clarity on how and when to engage OCE, CDRH, CBER and CDER throughout the development of a DHT for remote data acquisition in clinical trials. Additionally, it would be helpful if the Agency could provide information regarding the involvement of the Digital Health Center of Excellence when developing a DHT, including a strategy for engagement, if relevant for the development of certain types of DHTs.

BIO also asks that the FDA provide more information on how Sponsors or DHT developers can engage with the Agency outside of the IND or IDE pathway on the verification and validation of DHTs for use as data collection tools in drug or device development. While we appreciate the section on regulatory engagement, we note that it seems to confound qualification of DHTs with qualification of DHT-derived measures (e.g., biomarkers and clinical outcome assessments (COAs)). BIO acknowledges that there are existing pathways, such as the CDRH's pre-submission program and CDER's ISTAND pilot, but we note that the former is specific to medical devices while the latter is currently unfunded and limited to a small number of submissions. Equally, BIO supports the Agency's use of the "least burdensome[1]" approach when communicating with multiple Centers for the development of DHTs which may fall within device classification.

III. *Submissions*

BIO recognizes the Agency's outline of relevant DHT design and operational submission elements, as well as the need to establish that the DHT is fit-for-purpose. We further request that FDA provides additional guidance regarding when such information is required throughout clinical development. For example, the Agency should clarify if the intention for the level of detail outlined in section IV-B, is to be submitted in pivotal study protocols only, where the DHT is used to support primary or secondary endpoints for safety or efficacy. It is recommended that this information would not be included for early clinical studies where the Sponsor is still generating evidence to establish the DHT is fit for purpose or is using the DHT for exploratory endpoints.

Throughout this draft guidance FDA provides information regarding content that should be included in the submission supporting the use of a DHT in a clinical investigation. However, it is unclear where in the submission this information should be provided. We suggest that the

[1] FDA Guidance, The Least Burdensome Provisions: Concept and Principles, 2019

information should be included in Module 5. This clarity will drive consistency in submissions and reduce inefficiency resulting from improper placement of information which can lead to delays in review timelines.

IV. Global Harmonization

BIO recommends that FDA consider how the standards it adopts may be harmonized globally to support adoption of these methods. Harmonization considerations in this space may include privacy , data confidentiality, and evidentiary considerations for demonstrating clinical relevance of DHT-derived measures.

V. Leveraging Prior Data

BIO appreciates that FDA encourages Sponsors to leverage any existing information from a DHT manufacturer where applicable and appropriate, to support the DHT's suitability in a clinical study. However, there remains ambiguity regarding the situations in which a Sponsor can leverage such existing data versus being required to generate new data supporting the DHT in question.

Although the guidance gives considerations for verification and validation, the guidance lacks specific considerations of when the context of use will be considered sufficiently similar to solely rely on the DHT manufacturer's data. Further, when the use is considered a new use, the guidance lacks both a framework for determining the appropriate evidentiary requirements for verification and validation as well as a practical example for these evidentiary requirements. Multiple sources currently give examples such as Digital Medicine Society's Measurement Dossier and an article titled "*Considerations for development of an evidence dossier to support the use of mobile sensor technology for clinical outcome assessments in clinical trials*".[2] We recommend the FDA to provide similar recommendations for digital health technology evidentiary requirements for verification and validation or reference an available source as guidance.

VI. DHT Usability

In addition to Human Factors studies, BIO requests that FDA considers other ways to show that a DHT is usable by its intended use population such as cognitive debriefing studies, usability or satisfaction surveys evaluation of usability assessing as needed. This is particularly important for non-device-DHTs.

VII. Device Specifications

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[2] Walton, MK, Cappelleri, JC, 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. Contemp Clin Trials 2020; 91: 105962.

We were pleased to see the discussion of bring-your-own devices in the Draft Guidance. Further clarification about the minimum specifications and expectations for the use of such devices would greatly support development programs. For example, discussion around the minimum specifications for how minor variations in display of information across device types can be addressed with streamlined assessment would be valuable. We believe flexibility in the use of such products would benefit trial conduct and support trial participation.

VIII. Data Management

BIO generally supports the Agency's Draft Guidance language regarding data collection, storage, and protection. We acknowledge that 21 CFR Part 11 and the current Draft Guidance *Use of Electronic Records and Electronic Signatures in Clinical Investigations Under 21 CFR Part 11 – Questions and Answers* also addresses data integrity when utilizing electronic services in clinical investigations. However, BIO requests that for the FDA consider the following additional points of concern:

- Please provide more clarity on source data management in the DHT guidance. Currently, there is no substantiative guidance on source data management. We understand that the agency considers source data to be the data once entered into the study database, however, we recommend that the agency make this clearer in the final guidance.
- The agency should elucidate what safeguards may need to be in place to ensure the integrity of source data.
- The agency should add clarification around the types of raw data that will need to be submitted to support a regulatory decision.
- We also recommend the agency discuss analytical considerations specific to hybrid designs, particularly regarding data source heterogeneity (clinic and remote measurements).
- We note that the guidance represents concerns over data loss associated with loss of connectivity. It would be helpful for FDA to note that this may be mitigated through off-line mode functionality (i.e., the ability of the device to continue to collect data without connectivity, and subsequent uploading when connectivity is achieved).
- Data Archiving:
    - Please clarify if the durable electronic data repository can be managed by the sponsor, and, if so, what needs to be demonstrated to ensure that it meets the applicable requirements (e.g., 21 CFR Part 11 requirements).
    - It would be helpful if the Agency can clarify further whether raw data need to be retained and transferred to the EDR. This is relevant in determining what data the

clinical investigator must retain and what data must be made available to FDA. We note that the raw data files could also consume significant computing resources to maintain as they can be very large in size and may pose challenges. Additionally, in some cases, the raw data may not be transmitted from the device and available to the Sponsor.

IX. *Future Guidance Considerations*

While outside the scope of this Guidance, BIO believes there are a few related topics that should be considered for future guidances. These include:

- Updating the current FDA information sheet, Recruiting Study Subjects | FDA, which currently does not address more modern tools of participant recruitment.
- Addressing the use of DHTs to measure biomarkers and clinical outcome assessments (COAs). We recognize that this topic introduces unique considerations beyond those currently outlined in FDA's Biomarker Qualification Guidance and the Patient-Focused Drug Development (PFDD) Methodological Guidance Series. For example, DHTs enable quantification of functionally relevant characteristics of behavior such as gait parameters and the acoustic features of speech. In the guidance, it is unclear how FDA will determine categorization of such measures and what evidence can be provided to establish their clinical relevance. BIO believes that quantification of a function should be considered a COA and available for use as the basis for traditional approval.

X. *Conclusion*

BIO appreciates this opportunity to submit comments regarding the Draft Guidance *Digital Health Technologies for Remote Data Acquisition in Clinical Investigations*. Specific, detailed comments are included in the following chart. We would be pleased to provide further input or clarification of our comments, as needed and we look forward to future opportunities to collaborate with the Agency on this critical topic.

Sincerely,

Leslie Harden, Pharm.D.
Director, Science and Regulatory Affairs
Biotechnology Innovation Organization

SPECIFIC COMMENTS:

LINE/ SECTION	ISSUE	PROPOSED CHANGES Added text is noted with underlined font
I. INTRODUCTION		
42 (289, 306, Section F)	The management of risks identified during the study is not adequately discussed within this guidance; for example, if new risks are identified during the clinical study, how they will be addressed and reported? How will new mitigations addressing the risks be considered in the study? There are many places in this guidance where risk mitigation efforts should be included.	BIO recommends that the Agency clarifies the scope and intent of the guidance and why remote acquisition is being treated differently, if that is the case.
32-33	While we agree with the spirit of the guidance to use best practices for development of DHTs, the scope of "clinical investigation in which the sponsor plans to use one or more DHT in a marketing application" seems to be broad and may stifle the use of these DHT-derived measures as exploratory endpoints, to collect information on validation and sensitivity to change, before potentially considering their use more formally for a labeling claim.	BIO recommends that the Agency clarify that while the recommendations of the guidance apply broadly to all endpoints, they may also be relevant for endpoints supporting a labelling claim.
48-50	While the focus of the guidance is on using DHTs for remote collection of data to evaluate endpoints in clinical investigation, which we understand and support, DHTs may also be used to evaluate biomarkers. Biomarkers may be used as an endpoint (a surrogate endpoint) or used in a clinical trial in other ways, such as to define treatment allocation arms or to enrich a clinical trial.	BIO recommends that the FDA clearly states that DHTs could be used to evaluate biomarkers, clinical outcome assessment, endpoints & surrogate endpoint. Additionally, it would be helpful if the guidance states that DHTs can be used to evaluate safety, as well as efficacy. Additionally, acknowledging that the risk assessment, and consequently different level of verification and validation, may be different if the data from a DHT is being used to evaluate

	Data from DHTs might also be used to evaluate safety, as well as efficacy	say a prognostic biomarker versus a safety parameter versus an endpoint of interest.
II. BACKGROUND		
68-70	This draft guidance should be consistent with FDA's Patient-Focused Drug Development (PFDD) framework.	BIO recommends that FDA clearly indicate in this draft guidance that DHTs can collect data through passive monitoring or through active test, and that the measures assessed by DHTs can be COAs or biomarkers. Providing examples of each type here or in Appendix A would be helpful.
75	We note that "behavioral" data is not defined in FDA's BEST glossary or in FDA's PFDD glossary.	BIO recommends that FDA clearly indicate how measures of behavioral data will be categorized (e.g., as biomarkers or clinical outcome assessments).
74-95	When describing the DHT's initially (lines 74-95) would suggest that this be in a table format for simplicity -such as using a table that lists DHT component (eg, software), outcomes measured (eg, continuous/intermittent recording of physiological/behavioral data), examples (eg, blood pressure, glucose levels), link to tables in appendix A with examples of the technology	BIO recommends the addition of a link to tables in appendix A with examples of the technology
Line 83	The guidance states, "These DHTs may be used to administer electronic clinical outcome assessments (eCOAs) including electronic patient-reported outcome (ePRO) instruments and electronic performance outcome (ePerfO) instruments."	BIO recommends that FDA update these glossaries to include definitions for ePRO, ePerfO, and eCOA. The eCOA definition should be clear if it includes only those COAs that are administered electronically, or if it also includes sensor-derived clinical outcome assessments such as those that are captured through continuous or

	We note that while eCOAs, ePROs, and ePerfOs are recognized in the literature, they are not defined in FDA's BEST glossary or in FDA's PFDD glossary and there may be different interpretations of what these terms refer to.	intermittent measurement (e.g., passive monitoring of physical function).
97-98	This section of the draft guidance discusses transfer of data captured by DHT, but no requirements are provided.	BIO requests that the agency clarify Good Clinical Practices (GCP) expectations and requirements.
III. REGULATORY CONSIDERATIONS AND ENGAGEMENT WITH THE AGENCY		
Footnote 14	"It is possible that a DHT, as proposed for use in a clinical investigation of a drug or biological product under an IND, may meet the definition of a significant risk device under 21 CFR 812.3(m) and require submission of an IDE application to FDA under part 812 for the same clinical investigation. In these cases, when information required under 21 CFR 812.20 is also contained in the IND, sponsors should consult with CDRH regarding ways to streamline the IDE application submission process for the particular clinical investigation. See, e.g., 21 CFR 812.20(d)."	In situations where sponsors have to submit an IND and an IDE in parallel, BIO asks that CDER/CBER and CDRH collaborate in order to streamline both reviews to ensure the tool development and/or the trial is not delayed. We also ask that CDRH applies its "The Least Burdensome Provisions: Concept and Principles" guidance1 to the IDE application submission process and ensure a collaborative review with CDER/CBER.
109-115	Even when a DHT meets the definition of a medical device under the FDC Act, we do not believe that every use in a clinical trial renders the device an investigational device subject to 21 CFR Part 812. Rather, in most instances the device will not be the object of the investigation and the Investigation will not be a clinical investigation to determine safety and effectiveness of the device. As such, it is unclear how these would meet the definition of an investigational device and why 21 CFR	BIO recommends the following language: "Devices intended **only** for use in clinical investigations are exempt from most requirements applicable to devices, including premarket clearance or approval, as long as the investigation complies with applicable requirements under 21 CFR part 812.14. Therefore, DHTs that meet the definition of an investigational device and are used in clinical investigations of medical products typically would be exempt from applicable requirements to obtain

	Part 812 would automatically apply. Additionally, in some cases, the device will be used consistent with its cleared or approved intended use and in the same population.	marketing authorization and other device requirements, as long as the clinical investigation is compliant with part 812."
121-122	We suggest using "lead center" language in this section for clarity and to make clear that sponsors should consult with the center with primary jurisdiction over the clinical trial (which could be a trial of a combination product). We suggest also clarifying that sponsors do not need to directly engage with the center that has jurisdiction over the tool (e.g., CDRH, or Digital Health Center of Excellence) separately. Rather, we understand the lead center will consult appropriately with the other center as needed.	BIO recommends the following language: "Sponsors should engage early with the ~~appropriate~~ lead Center responsible for the medical product under investigation to discuss use of DHTs in a specific clinical investigation.[17] The lead Center will consult other centers as appropriate regarding the use of the DHT in the trial."
124- 144	The draft guidance states "FDA also has qualification programs that are intended to support the development of tools for use in assessing medical products and that provide another avenue for sponsors and other stakeholders to engage with the Agency…."	In certain cases, a concept of interest may measure disease impacts that are relevant to patients' experience across a range of disease areas. In these cases, it would be useful for the Agency to describe how a single DHT can be qualified to measure the same concept of interest across multiple diseases with overlapping signs and symptoms, and what evidence should be submitted to support this.
133-134	"Developers of DHTs may choose to submit qualification proposals to the appropriate CDER/CBER DDT Qualification Programs."	Clarification would be helpful as to whether verification (of hardware/ firmware) and analytic validation of DHTs will become part of the CDER COA and Biomarker Qualification Programs (i.e., for digital measures that are COAs or biomarkers, respectively). Alternatively, FDA should specify if these qualification programs will continue to be specific for review of COA or biomarker

	We note that FDA has previously deemed review of the DHT to be out of scope in COA qualification submissions.	measures, with verification and validation of the DHT reviewed separately (e.g., through the ISTAND pilot or another pathway).
IV. CONSIDERATIONS WHEN USING DIGITAL HEALTH TECHNOLOGIES IN CLINCAL INVESTIGATIONS		
208-209	"Operational specifications (e.g., data storage capacity, frequency of data transmission) should be adequate to minimize missing data." We appreciate FDA's outlining considerations that should be evaluated in selecting a suitable DHT. We agree with the assertion that a sponsor's network systems should be adequate to handle the voluminous data that may be generated. Clarity would be helpful, however, in outlining a sponsor's obligations with respect to methods of analyzing these data for adverse events. Gathering data continuously, as opposed to single point in time measurements at a clinical study visit, could seem to result in a higher number of adverse events – some of which may be spurious or non-events. We do not believe it is useful or consistent with the approach to clinical trials generally for sponsors to prospectively mine these data for adverse events. Rather, we suggest that sponsors should develop reasonable approaches to capture adverse events, and we encourage the Agency to articulate if there are methodologies or approaches FDA believes are appropriate. We suggest adding a footnote that sponsors can propose and justify their approach. We further suggest that FDA consider directing sponsors to resources such as the "CTTI Framework of Approaches	We suggest that FDA edit this bullet as follows: "Availability of operational specifications (e.g., data storage capacity, frequency of participant data capture/sampling and sponsor network systems transmission) should be adequate to handle the volume of data obtained from frequent or continuous recordings. [1] [1] [Footnote text] Sponsors may develop and justify reasonable approaches to analyzing continuous data for adverse events, consulting available resources as appropriate."

Biotechnology Innovation Organization
1201 Maryland Avenue, SW, Suite 900
Washington, DC 20024
202-962-9200

	for Safety Monitoring and Managing Safety Signals when using Mobile Technologies for Data Capture."	
222-226	The guidance states, "When allowing participants to use their own DHTs or general-purpose computing platforms, sponsors should ensure that the measurements are consistent across all protocol-specified DHTs. This approach may not be appropriate for clinical investigations that require highly specialized or customized 226 measurements."	BIO requests that the Agency provide examples of the type of "highly specialized or customized measurements" that are not appropriate for bring your own device (BYOD).
237	The sponsor is required to ensure consistent and accuracy across all brands, models, and/or versions of DHTs.	BIO recommends that the Agency provide examples of acceptable evidence to be provided by sponsors to demonstrate this. BIO also recommends that the Agency emphasize the need to consider the participants disease state and any associated physical, psychological or mental disability when selecting a DHT.
237-239	Original guidance text: "The sponsor should ensure consistent precision and accuracy across all brands, models, and/or versions of DHTs or general-purpose computing platforms specified for use in a clinical investigation protocol. See section IV.C of this guidance."	BIO recommends the following edit, "The sponsor should endeavor to ensure consistent precision and accuracy across all brands, models, and/or versions of DHTs or general-purpose computing platforms specified for use in a clinical investigation protocol. If technology progresses during the trial, additional versions and models could be added by the sponsor, so long as the performance of the DHTs are comparable."

	This can be difficult for sponsors, when participants are using their own DHT/general computing platforms (i.e., cell phones). In many cases the vendor may be able to provide this assurance and the sponsor can certainly audit for that, but as noted above the lifecycle of these brands/models is short and will change over time, and so sponsors cannot always ensure a participant will use the same "bring your own" device over the course of the trial.	
257 - 258	For many commercially available DHTs, the technical specifications and descriptions provided by the DHT manufacturer may be sufficient.	Since this requirement is too general, it is suggested to provide an example or template of what this specification and description should contain at the minimum. For example, for a consumer grade device/computing platform (e.g. accelerometer running on iOS or Android platform), the complete specifications of validation and verification documents would be difficult to receive from the manufacturer due to their intellectual property. Hence, based on the expectations, the manufacturer could include all the required information in their product documents for sharing with their customers.
263	The draft guidance states, "...ensure privacy and security"	BIO recommends that the Agency reference current best practices or guidances associated with this topic.
268-270	Current text: To help show how integrity of the data collected with DHTs will be or is maintained, sponsors 269 should include information about data management, including collection, storage, transmission, 270 and archiving in the submission.	BIO recommends that the Agency provide further explanation to how and how much data will be transmitted to investigators would be helpful to stay in compliance. We recommend allowing sponsors to share information

	The guidance did not include clear retention and archival expectations for investigators.	with investigators either by sharing a copy with site OR investigators accessing electronically as needed.
General Comment	BIO acknowledges and appreciates flexibility outlined in the guidance; however, more examples would be helpful.	BIO suggest that more clarification is needed on what data FDA would need that would be enough to support validity of a tool. The guidance should provide more information as to what verification, validation is needed for target populations. DHT has a very objective validation process. The guidance should describe how sponsors can leverage data that already exists. Additionally, guidance should describe whether a DHT measuring the same endpoint (i.e. movement) can it be used across disease areas. More flexibility and considerations for rare disease drug development should be added to this guidance, especially with regard to verification and validation.
272-299	Sponsors may need to perform positive control studies if using an existing DHT	BIO recommends that the Agency add clarification associated with positive control studies
274-289	The guidance notes the definitions of Verification and Validation as footnotes.	BIO recommends that the Agency convert the footers 27, 28 and 29 to the body of the guidance due to its importance and do not want readers to ignore/omit due to its placement in the footer. BIO also recommends that the Agency incorporate in the final guidance the verification of the metadata including

		the audit trail if applicable, to enable ease of audits and inspections to demonstrate the reconstruction of trial sequence of events.
283 - 284	The guidance states, "Verification and validation may begin with benchtop studies, progress to testing in healthy volunteers, and continue in individuals representing the population to be studied in the clinical investigation."	We request that FDA consider including recommendations that validation of software components, especially in the event of an upgrade, could be carried out on retrospective data sets when appropriate. For example, if an algorithm is used to detect cough, it may be appropriate to validate newer versions of the algorithm on previously captured audio files rather than in a prospective new study.
343-352	It may be the case that in any one clinical program or trial, that data may be collected in multiple ways. For example, some patients may use paper COAs, and other patients may use eCOAs. When using DHT software to gather data, one important aspect of validation is pulling data from paper COA and an eCOA.	BIO believes that pulling of data is appropriate, when addressed with the appropriate validation. In order to add clarity, we request FDA to add language to the guidance that acknowledges one clinical program or trial may have data collected in multiple ways and that it may be pulled together, as scientifically appropriate.
349-350	The draft guidance states "Among others, content validation, construct validation, and normative testing may be appropriate…" We note that this statement may lead to confusion. For a COA, measurement properties such as content validity and construct validity apply to the measure (e.g., the questions and responses), rather than the software (e.g., the app used to collect the measure).	BIO recommends deleting this statement or, at a minimum, clarifying that it only applies only to a novel COA captured with DHT software, not to the DHT software itself, and not to an existing COA captured with new DHT software.

372	The guidance states, "...confirming the suitability of the DHT…"	BIO's suggested revision: "...confirming the suitability and scalability of the DHT…"
372-376	Regarding usability studies in human subjects, we appreciate FDA's flexibility in the guidance that allows sponsors to take various approaches to analyzing the usability of a DHT for a specific trial population. BIO recognizes that not every method for assessing usability involves or requires a separate human factors study. However, to avoid confusion, we suggest referring to "usability evaluations" in the guidance and the glossary, instead of "usability studies," which may be confused with human factors studies because the two terms are often used interchangeably. Usability evaluations could include assessments of usability in early-phase trials, assessments of whether a usability or human factors study is needed (use-related risk analysis), usability studies, or actual human factors studies. As noted in footnote 35, industry may refer to existing FDA guidance regarding Human Factors studies of medical devices, to determine whether a usability study or evaluation is needed and how it should be designed. These guidance documents recommend a cohort size of at least 15 subjects, which may be challenging to achieve in oncology indications that tend to move quickly from first in human to registrational trials. It would be helpful to know what cohort size the FDA believes is appropriate for assessing usability of a DHT for use in a clinical trial.	BIO recommends the following text: "Usability ~~studies~~ evaluations are a critical component in confirming the suitability of the DHT and/or general-purpose computing platform for the proposed clinical investigation.[35] These ~~studies~~ evaluations are considered part of the validation process and should enroll a cohort that is similar to intended trial participants. Sponsors should discuss the appropriate cohort size with FDA in the context of DHT and endpoint selection and the analysis plan. Usability ~~studies~~ evaluations should test the ability of future participants to use the DHT as directed in the trial protocol."

	We recommend that the Agency and sponsors discuss the appropriate cohort size in the context of DHT and endpoint selection and analysis plans.	
412-416	DHTs at times provide a continuous stream of data, not a specific data point or endpoint. A data transformation is then needed to extract the specific data points/endpoints needed from the data stream. If the endpoint were derived by the supplier of the DHT/a third party, we would expect a sponsor would/should be responsible for ensuring the algorithm applied is appropriate and its application has been validated. If a sponsor derived the endpoint themselves, we would expect they would document and validate the algorithm applied in a manner that is similar to other derived endpoints (e.g., quantitative measurements of tumor burden for the evaluation of tumor response).	BIO recommends the following language: "When DHT measurements replicate existing measurements (e.g., weight measurements at home versus in the clinic) for the same clinical endpoint, FDA generally would not expect sponsors to provide a new justification for the endpoint. However, validation of the new way to measure the endpoint should be provided to support its reliability. Such validation would include validation of the technology used to process the data stream and the algorithm/method used to derive the measure/endpoint."
411-417	The guidance recommends verification and validation of a DHT that measures the same construct as an existing on-site endpoint. Can you clarify whether a hybrid design including both measures, e.g., an at-home DHT measuring an endpoint between two on-site visits, can both use and validate the DHT.	In addition to existing endpoint and novel endpoint, BIO recommends that FDA discuss "mixed" measure endpoints resulting from hybrid designs

426	The guidance states, "However, this may also lead to challenges in establishing an optimal and clinically relevant endpoint."	BIO suggests that it would be helpful if this point could be elaborated on by describing what challenges are being referred to (e.g., DHTs are able to detect more aspects but some of these may not be relevant to the individual, etc).
428-432	Original guidance text: "The principles that should guide development of novel endpoints based on data captured by DHTs are the same as the principles for developing novel endpoints captured by other means. Sponsors should obtain input from stakeholders (such as patients, disease experts, caregivers, clinicians, engineers, and regulators) to ensure that the novel endpoint is both clinically relevant and the data is adequately captured by the DHT. Discussions with the relevant review division are also important in these situations." We agree that the principles governing development of novel endpoints based on DHTs and novel endpoints generally should be the same and that relevant stakeholders should be consulted as part of this process. However, we believe the guidance could benefit from a clearer articulation that the determination of clinical relevance is based on judgment (as signified by the need to discuss with the relevant FDA review division) and is	BIO recommends that FDA expand on the sequencing of a determination that an endpoint is clinically relevant versus the verification, analytical validation, and clinical validation of a DHT. We believe it would be helpful to explicitly state that clinical relevance of the endpoint is a determination based on judgment that is followed by verification and validation (including clinical validation) to determine whether the DHT is adequate for its proposed use.

	a prerequisite to verification, analytical validation, and clinical validation of the DHT.	
456	The example provided for justifying a novel endpoint using a DHT is around the use of a portable device which provides similar data as lab-based PSG for at-home sleep monitoring. The DHT measurement in this case replicates existing measurements (PSG), and the endpoints (e.g., sleep parameters) likely does not need new justification (according to lines 413-414). We think that this is not a very good case to demonstrate "justification of a novel endpoint"; it does not address cases where the clinical concept of the endpoint is entirely novel and where no existing traditional measure is available.	BIO requests that FDA provide another example around novel clinical endpoints, for example, physical activity measurements in free-living conditions.
General comment	The terms "reliable" is used in these two sections whereas we think that it would add clarity if the terms "precision" and/or "accuracy" would be used at these places to not mix with the reliability assessments (a measure can be reliable but not accurate).	
435-456	Use of digital tools in clinical trials brings forth the opportunity to combine measures that are COAs and biomarkers for new insights on patients using large amounts of passively collected data. Some novel endpoints may be composite endpoints that evaluate both a biomarker (e.g., how a patient responds to an intervention or therapeutic intervention) and how a	BIO recommends the following language: "When justifying a novel endpoint using data captured by the DHT, sponsors should address the following: • Whether the endpoint is a clinically meaningful reflection of how a participant feels, functions, or survives; or whether it measures a valid biomarker; or whether it combines both a biomarker and a

	patient feels, functions, or survives. For example, developing a risk calculator with sensor-based EKG data from a biometric sensor (biomarker) + patient reported outcome on how a patient feels daily (COA) to predict risk of a heart attack. We understand that FDA suggests using DHTs in tandem with other methods of measuring patient outcomes, such as PROs and other COA tools, however, it is not clear how to validate technology measuring a novel endpoint that is a composite of these two things, which have historically been treated differently from a regulatory validation perspective. We understand that FDA would expect the sponsor to justify the novel endpoint. We suggest adding more clarity as to whether the sponsor must justify all elements of a composite endpoint or whether it is sufficient for the sponsor to provide a justification for the endpoint as a whole. Are there statistical models to validate measurement of composite endpoints that can be used? We acknowledge and reference both the FDA Draft Guidance: *Multiple Endpoints in Clinical Trials Guidance for Industry* and ICH E9, respectively.	clinical outcome assessment; • […] • Whether the novel endpoint (or composite novel endpoint) is a sufficiently reliable measure of disease severity or health status (e.g., mild, moderate, or severe) to allow assessment of disease modification or progression."
460-464	In addition to non-inferiority, when the control is not a concurrent placebo (e.g., Real World Data external control) or an active control (even for superiority), using a DHT could have additional challenges/limitations.	"Analyses of data collected from DHTs should be discussed in a statistical analysis plan. • Non-inferiority trial designs may not be appropriate where there is a lack of historical evidence of effectiveness of the control treatment when measured

	We suggest adding an additional bullet point to elaborate further on statistical and design considerations regarding possible DHT limitations when the control group is not a typical placebo group, especially in an external Real World Data control setting.	using DHTs, making it difficult or impossible to define the non-inferiority margin. • When DHT clinical studies are considering use of an external historical control, attention should be paid if the control uses different DHTs or different practice with the same DHT and consider impact of those differences.”
466-468	The guidance should further discuss if there are special considerations about the heterogeneity of data sources for those clinical constructs that are measured both on-site and also with a DHT (e.g., hybrid design)	BIO recommends that the agency discuss analytical considerations specific to hybrid designs
466-474	We applaud the agency for the reference to the ICH E9 addendum on estimand in the Statistical Analysis section. We believe the section can further emphasize that that use of DHTs can have an impact on the target estimand as well as the analytical methods and the estimate, beyond intercurrent events. We also believe that carefully considering whether and how use of DHTs impact the main questions of interest or each of the estimand attribute (i.e., population, treatment, variable, intercurrent event, and summary measure) can help guide and justify design and analytical choices.	BIO recommends the agency add considerations related to all five attributes of the estimand framework to guide the thinking about the impact, if any, of using a DHT on analytical methods
470-475	We request FDA clarify this statement by providing additional guidance or examples on censoring rules or missing data imputation for DHT as intercurrent events.	Also, since intercurrent events are needed for the primary and key secondary endpoints, BIO recommends adding the following underlined text:

		"Statistical analysis plans should prespecify intercurrent events that may be related to the primary and key secondary endpoints derived from the DHT and, as applicable, the general-purpose computing platform and how these events will be accounted for in the analyses to address the scientific questions of interest."
473-474	The list of examples of intercurrent events provided are typical intercurrent events specific to DHTs; however, all the classical intercurrent events affecting non DHTs endpoints could also apply. The current wording may suggest the DHTs-specific ones may be the only example of events that apply.	BIO recommends the following change: In a clinical investigation using DHTs, missing or erroneous data may occur as a result of intercurrent events similar to the ones applicable to non-DHTs endpoints, as well as some more specific to DHTs, such as:
473 - 486	The guidance states, "In a clinical investigation using DHTs, missing or erroneous data may occur as a result of intercurrent events, such as: …" It is unclear under what evidence Sponsors should provide to account for missing data.	BIO suggests that FDA provide considerations for reporting and addressing missing data, including what evidence is sufficient to support a conclusion that data are intermittently missing at random.
481 - 482	"Trial participant error or non-compliance with study procedures using the DHT or general-purpose computing platform" When participants do not complete a task according to instructions, it is unclear if and when it would be	BIO requests that FDA describe considerations for how sponsors can minimize the need to exclude data from analysis (e.g., through training), and expectations for documentation of any excluded data.

	appropriate to exclude the data from analysis and what evidence should be provided to support doing so.	
551-555	The draft guidance states that, "The informed consent process must describe any reasonably foreseeable risks or discomforts to the subject (see sections IV.F.1 and IV.F.2 of this guidance), including reasonably foreseeable risks or discomforts related to the use of the DHT in the clinical investigation. Information regarding what may be done to mitigate the risks most likely to occur should also be considered for inclusion."	In case of potential discomforts or other incidents related to a DHT that is being used as a drug development tool, BIO requests that the Agency clarifies the expectations regarding incident reporting. Other potentially related guidances: • Reporting Medical Device Adverse Events for Manufacturers, Importers and Device User Facilities • Instructions on Voluntary Malfunction Summary Reporting Program • Instructions for Completing Form FDA 3500A • eMDR - Electronic Medical Device Reporting • Medical Device Reporting for Manufacturers - Guidance for Industry and Food and Drug Administration Staff FDA Guidance: Medical Device Reporting for User Facilities (PDF Only) (PDF - 313KB)
520-542	The draft guidance is missing additional privacy risks associated with certain DHT solutions.	BIO recommends that the FDA consider adding additional language or bullet points. Additional risks to consider are configuration and agreement by the end-user (e.g., sharing locations).
591-631	We appreciate that the draft guidance includes a section covering Record Protection and Retention. It is noted that relevant data captured from the DHT along with metadata should be transferred to the durable electronic	It would be helpful if the Agency can clarify further whether raw data need to be retained and transferred to the EDR. For example, for at-home sleep measurement, it is not clear whether the "source data" refer to the raw EEG data, the epoch-level sleep staging data, or the summary

	data repository (EDR) and that data in the durable EDR generally constitute the source data for a DHT.	endpoint data. This is relevant in determining what data the clinical investigator must retain and what data must be made available to FDA. We note that the raw data files could also consume significant computing resources to maintain as they can be very large in size and may pose challenges. Additionally, in some cases, the raw data may not be transmitted from the device and available to the Sponsor.
597	This section could benefit from definition and clarity of "source data" for DHT and what constitutes "complete data" (line 612). Is unstructured raw data prior to signal processing "inspectable" and will be required for submission?	In the last portion of section G there is a paragraph regarding site review of source data by a study investigator per protocol. It would be good to understand retention/access to source data when those source data are not called out for investigator review in the protocol and may otherwise be uninterpretable (e.g., raw sensor data)
611-612	The draft guidance states that, "Sponsors should discuss with review divisions the type of DHT data recorded from each Participant and data format to be submitted for FDA review." It is important to understand the format in which the required data is to be submitted for FDA review. Although data will be submitted in CDISC standards,	BIO recommends that the Agency notes in the guidance that multiple data formats may be required based on the DHT used in a given study.

	these additional data likely will have to be submitted in another format.	
622- 625	The draft guidance states, "For data collected directly from study participants through DHTs, FDA would generally consider the data in the durable electronic data repository to constitute the source data. Review of these data may be necessary to reconstruct and evaluate the clinical investigation, and the data should be available for inspection."	We would appreciate clarification in the draft guidance what level of data is in scope for inspection and should be retained. For example, should raw (unprocessed data) directly from the sensor be retained or is FDA referring to feature (processed) time series data, or aggregate feature (further processed). It would also be helpful to understand if FDA requires data described above to be retained in any particular format to allow it to be inspection ready.
627-630	In the context of source data retention by the site, it may not be possible to provide to the site all individual data points collected through continuous sensor monitoring.	BIO recommends that the Agency consider provisions based on the nature of the DHT and the volume of data being collected. It may be easier for the site and on the context of data investigation to have direct access to events of interest and/or summary of data characteristics.
641-690	FDA regulatory and ICH guidelines that cover good clinical practices are overarching and cover all clinical trials, whether they employ a DHT or not. And sponsors and investigators follow GCP. We feel having a section in this guidance that has "cherry picked" a few aspects of GCP could be taken out of context and lead to confusion	In order to not inadvertently cause confusion, BIO recommends that FDA add a clear note of the existing Good Clinical Practice guidances and that they should be followed, in addition to the recommendations specific to DHTs provided in this guidance.
671-672	The draft guidance is rightly suggesting the need to establish a safety monitoring plan to address how	BIO recommends that the final guidance to also address the accountability of the investigator regarding the oversight of patient's safety beyond periodic review of DHT data as safety events will likely be generated real

	abnormal measurement related to patient's safety will be reviewed and managed.	time in the context of continuous data collection through DHT.
716	The draft guidance states, "Setting up, activating, and operating DHTs and, as applicable, general- purpose computing platforms"	BIO suggests expanding this bullet to include considerations for software updates and/or procedures for malfunctions/deficiencies and hardware upgrades
732	The draft guidance states, "Connecting to wireless networks"	BIO suggests revising as follows: "Connecting to wireless networks as well as how the data is handled in cases of intermittent connectivity."
734	The draft guidance states, "Handling known adverse events associated with the DHT (e.g., rash from actigraphy bands)"	BIO suggests revising as follows: "Handling known adverse events associated with the DHT (e.g., rash from actigraphy bands) and clearly delineating the adverse events associated with the DHT vs the study drug, when possible."
760, 768	It is unclear how the Agency defines "meaningfully different".	BIO recommends that the Agency provide more detail on how "meaningfully different" is defined.
	The guidance indicates that clinical risks associated with any "reasonably foreseeable risks or discomforts" should be declared within the form.	BIO recommends that the Agency only include foreseeable risks that could pose moderate injury to the patients and any associated mitigation within the ICF
GLOSSARY		
880-881	As noted previously, to avoid confusion, we suggest referring to "usability evaluations" in the guidance and the glossary, instead of "usability studies," which may be confused with human factors studies because the two terms are sometimes used interchangeably. Usability	BIO recommends the following edit: "Usability evaluations: Evaluations conducted to demonstrate that the DHT can be used as intended by the intended trial population, without serious errors or

	evaluations could include assessments of usability in early-phase trials, assessments of whether a usability or human factors study is needed (use-related risk analysis), usability studies, or actual human factors studies.	problems. These could include assessments of usability in a trial setting, use-related risk-analysis to determine whether usability studies are needed, or actual usability or human factors studies."
APPENDIX		
Table 1	The examples included in Table 1 and Appendix B could be more realistic and detailed. Table 1: it would almost never be the case that a consumer activity tracker would be useful without paired software, or a general-purpose computing platform e.g., where does the data go/how do you get the data off the device? Appendix B provides an important example yet could be improved with more context. FDA marketing authorization is presumably for the device, yet there is no mention of authorization in a particular target population of intended use. It is unclear if the Sponsor is using prior marketing authorization with the same intended use, and same intended measurement. Currently points 1, 2, 3, would be expected to have been included in validation/verification steps in lines 935-948 for the intended population in which the device received marketing authorization. As for the same intended measurement, the example refers to a device with approval for use 'in the home setting.' Would that not have included prior validation/verification of nightly monitoring of sleep? Additional details on the	BIO recommends the following: The examples included in Table 1 and Appendix B could be more realistic and detailed. Additional details on the hypothetical example of the DHT that received marketing authorization (e.g., sponsor measuring sleep in a different way/different time than marketing authorization supports) would be helpful.

	hypothetical example of the DHT that received marketing authorization (e.g., sponsor measuring sleep in a different way/different time than marketing authorization supports) would be helpful.	
894	We suggest that this table be revised to also include the digital measure (e.g., sleep latency, sleep efficiency, sleep awakening) and proposed endpoint.	