



March 23, 2022

Lauren K. Roth  
Associate Commissioner for Policy  
Food and Drug Administration, Dockets Management Staff  
5630 Fishers Lane, Rm. 1061  
Rockville, MD 20852

RE: ACRO comment submission on Food and Drug Administration [Docket No. FDA–2021–D–1128]  
*Digital Health Technologies for Remote Data Acquisition in Clinical Investigations*

Dear Ms. Roth,

The Association of Clinical Research Organizations (ACRO) represents the world's leading clinical research and technology organizations. Our member companies provide a wide range of specialized services across the entire spectrum of development for new drugs, biologics and medical devices, from pre-clinical, proof of concept and first-in-man studies through post-approval and pharmacovigilance research. ACRO member companies manage or otherwise support a majority of all FDA-regulated clinical investigations worldwide. The member companies of ACRO advance clinical outsourcing to improve the quality, efficiency, and safety of biomedical research.

ACRO thanks the Agency for releasing this draft guidance on *Digital Health Technologies for Remote Data Acquisition in Clinical Investigations*. ACRO is pleased to provide the following comments.

**I. General comments:**

ACRO is pleased to see that a specific guidance has been developed that covers the elements to be considered for the use of a digital health technology in clinical trials. The considerations for device selection and risk -- in particular in relation to how these affect the patient -- are clear and sensible. We welcome, in particular, that the FDA is willing to consider the value of the data collected by DHTs as part of the investigation into an endpoint.

We are happy to see that sponsors can and should leverage verification/validation performed by the manufacturer to support their own validation/submission. We are also pleased to see the guidance specify source data as the data in the durable electronic data repository, rather than the data collected on the DHT devices themselves. We thank the Agency for additional clarity around use of DHTs in relation to sensors and the additional considerations given to the data.

The guidance indicates that the use of participants' own DHTs or General Purpose Computing Platforms is acceptable and viable. While the recommendations around use of participants' own DHTs are sensible, we ask that the final guidance discuss challenges in implementing this in the context of a clinical investigation (e.g., participants updating their own devices during the course of the investigation, and the new device not being suitable). Sponsors/CROs/Sites need to be made aware of vendor system updates and the potential impact. There should be a process to communicate these changes to the clinical study teams who can then assess if the updates are applicable to their studies/sites/patients and how this should be communicated.

We recommend that the introduction to the guidance document notes the need to ensure that the use of computerized technology in clinical trials does not disadvantage or reduce access to clinical trials for those participants who are unable or unaccustomed to use the technology. The use of electronic methods may unintentionally discriminate against people who are not comfortable with, or who cannot use, such technology, and this could introduce bias into the clinical trial. We recommend that the final guidance should make clear that alternative methods should be available for trial participants unable or unwilling to use electronic methods.

The draft guidance does not address offboarding procedures as participants leave the clinical trial. We recommend adding text to the guidance to confirm that offboarding procedures should exist to ensure that access to systems specific to the clinical trial is no longer possible when an individual leaves.

## II. Line-Specific Comments

### **Lines 197-198:**

The current text states: *“Operational specifications (e.g., data storage capacity, frequency of data transmission) should be adequate to minimize missing data.”*

ACRO recommends adding the text highlighted in bold in order to emphasize the use of secure systems and the maintenance of data integrity.

*“Operational specifications (e.g., data storage capacity, frequency of data transmission) should be adequate to minimize missing data. **The computer system used to access trial data should be designed in such a way that retrieved data regarding each individual subject in a study is attributable to that subject.**”*

### **Line 214:**

This line is currently blank. We recommend the addition of the following text.

*The training needs of participants in order to ensure appropriate use of the DHT should not be excessive.*

### **Lines 231-233:**

The current text reads: *“The sponsor should identify specific DHTs or general-purpose computing platforms (brand, model, and/or version) that meet the minimum technical and performance specifications.”*

As above, we recommend adding the text highlighted in bold in order to emphasize the use of secure systems and the maintenance of data integrity:

*“The sponsor should identify specific DHTs or general-purpose computing platforms (brand, model, and/or version) that meet the minimum technical and performance specifications **while ensuring data integrity and security.**”*

## **Lines 257-258:**

The current text reads: *“For many commercially available DHTs, the technical specifications and descriptions provided by the DHT manufacturer may be sufficient.”*

The text in this sentence could be interpreted that commercially available devices can be used as part of clinical investigation by using documentation provided by the manufacturer, with no mention of them having been validated with the intended use being for a clinical investigation.

We recommend that this statement be updated to clarify that where the commercially available DHT has been investigated in the context of a clinical trial by the manufacturer their documentation may be sufficient.

## **Lines 309-310:**

The current text reads that: *“sponsors should verify that measurements across protocol-specified DHTs are consistent. (See section IV.A.3.)”*

Some apps record only to the primary server’s time zone. We therefore recommend adding the text highlighted in bold to ensure that dates and times are recorded using a single consistent time zone for each computerized system:

*“sponsors should verify that measurements across protocol-specified DHTs are consistent. (See section IV.A.3.). **Sponsors should give consideration to how the time of data capture will be captured in a standardized manner utilizing a single consistent time zone across protocol-specified DHTs.**”*

## **Lines 372-373:**

The current text reads: *“Usability studies are a critical component in confirming the suitability of the DHT and/or general-purpose computing platform for the proposed clinical investigation.”*

Clarification is needed. We interpret this as follows: For a DHT to be used in the clinical investigation, it is mandatory that usability studies have already been performed.

Yet, this seems to contradict the sentence described in the previous concern (Line 257-258) where the guidance suggests using manufacturers documentation could be sufficient for the submission. Lines 372-373 are asking for usability studies which may not have been conducted by commercial DHT manufacturers.

ACRO recommends that this statement be updated to clarify that where the commercially available DHT has been investigated in the context of a clinical trial by the manufacturer their documentation may be sufficient.

## **Lines 404-407:**

The current text reads: *“A precise definition of an endpoint typically specifies the type of assessments made (e.g., activity level, average heart rate, sleep quantity and quality), the timing of those assessments, the tools used for the assessments, and other details, as applicable, such as if (and if so, how) multiple assessments for a trial participant will be combined.”*

Use of a DHT may allow continuous capture of data that, in a clinical trial that does not use a DHT, would be captured only at specified timepoints. Consequently, DHT use could result in a significant increase in data points requiring analysis. We therefore recommend that the final guidance should explain that the clinical trial protocol should specify exactly which data points will be used for efficacy analysis and explain how DHT-captured data will be monitored for safety signals, as indicated in the text highlighted in bold:

*“A precise definition of an endpoint typically specifies the type of assessments made (e.g., activity level, average heart rate, sleep quantity and quality), the timing of those assessments, the tools used for the assessments, and other details, as applicable, such as if (and if so, how) multiple assessments for a trial participant will be combined. **The clinical trial protocol should specify exactly which data points captured by a DHT will be used for the efficacy analysis and explain how DHT-captured data will be monitored for safety signals.**”*

**Lines 567-569:**

The current text reads: *“The informed consent process should specify who may have access to data collected through the DHT during or after the clinical investigation (e.g., sponsor, investigator, subject, DHT manufacturer, other third parties) and during what time frame.”*

For clarity, we recommend that the guidance should make clear that relevant “other third parties” should be named in the informed consent information by adding the following in bold:

*“The informed consent process should specify who may have access to data collected through the DHT during or after the clinical investigation (e.g., sponsor, investigator, subject, DHT manufacturer, other **named** third parties) and during what time frame.”*

**Lines 587-589:**

The current text reads: *“Sponsors and investigators proposing use of DHTs for data collection should understand how such agreements or terms of service may affect trial participants and consider this information when developing informed consent documents.”*

We recommend that the final guideline should make clear that sponsors and investigators should explain how such agreements or terms of service may affect trial participants by including language such as:

*“Sponsors and investigators proposing use of DHTs for data collection should explain in the informed consent information how such agreements or terms of service may affect trial participants.”*

**Lines 622 & 623:**

The current text reads: *“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.”*

The assumption from this statement is that the raw data collected by the DHT are not considered to be source data. Also, if the data pass from a DHT device to an initial data platform (for example a DHT manufacturers cloud platform) and then on to its final destination (for example the Sponsor or CROs data store), that the data are only considered source data at the final data storage location.

ACRO recommends that this statement, or an additional statement, is added to this section to clearly outline that the data from the collection device, and any data locations that are “transitory” are not considered source data, until they reach the final location.

**Lines 622-625:**

The current text reads: *“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.”*

Use of the term “generally” may confuse the message that FDA is trying to convey here, and we recommend its deletion. As data in the durable electronic repository are considered to constitute the source data, it follows that the DHT provides only temporary storage and therefore that retention of DHT devices is not required after the relevant data have been uploaded to the durable electronic repository. This is an important point for sponsors, investigators and CROs and therefore we recommend that it is clearly stated, as indicated in the text highlighted in bold:

*“For data collected directly from study participants through DHTs, FDA would 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. **Retention of the DHT devices through which the data were captured will not be necessary after the data have been uploaded to the durable electronic repository.**”*

**Lines 682-683:**

The current text reads: *“Ensure that participants understand what information will be collected by the DHT and how the security and privacy of data collected by the DHT will be maintained.”*

For consistency with lines 567-569, we recommend the text should also make clear that investigators should ensure that participants understand who will have access to their data, as proposed in the text highlighted in bold:

*“Ensure that participants understand what information will be collected by the DHT, **the parties that will have access to their data**, and how the security and privacy of data collected by the DHT will be maintained.”*

**Line 989:**

The current text reads: *“Because an endpoint might involve high-volume, high-frequency data . . . ”*

This is one (of only two) mentions that data collected via DHT can, in many cases, be very high volume, which presents challenges of transfer, storage, analysis et cetera. The guidance does not give clear guidance or considerations for managing such high volumes of data.

ACRO recommends that a section of the guidance focus on the challenges of collecting, managing and analyzing such large volumes of data collected via DHTs during a clinical investigation. For example, effective data governance to ensure clean, precise, correctly formatted data is required. Data storage costs, security, and performance issues need to be considered. Geographical data restrictions, in particular where cloud solutions may result in patient data being transferred across regions, should be considered. Finally, reporting and visualization of data into a meaningful context should also be considered.



ASSOCIATION OF CLINICAL RESEARCH ORGANIZATIONS

Thank you for this opportunity to provide feedback. Please do not hesitate to contact ACRO ([knoonan@acrohealth.org](mailto:knoonan@acrohealth.org)) if we can provide additional details or answer any questions.

Respectfully submitted,

A handwritten signature in cursive script that reads "Karen A. Noonan".

Karen Noonan, Senior Vice President, Global Regulatory Policy