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22 March 2022

To: Food and Drug Administration, HHS

Re: Docket No. FDA-2021-D-1128

The International Society for CNS Clinical Trials and Methodology (ISCTM) welcomes this opportunity to respond to the FDA request for comment regarding the guidance document: *Digital Health Technologies for Remote Data Acquisition in Clinical Investigations Guidance for Industry, Investigators, and Other Stakeholders.*

The ISCTM offers these comments for consideration based on our experience and expertise in human CNS research. The ISCTM is an independent organization focused on advancing the development of improved treatments for CNS disorders. No member of this Working Group, comprised of scientists, clinicians, trialists, statisticians, former regulators and drug developers from both industry and academia, received compensation for comments provided. Comments represent individual opinions and not that of the institution, agency, or company affiliation of group members.

The ISCTM formed a group, led by Richard Keefe, Michael Sand and Debra Hoffmeyer, to review and provide comments on behalf of the Society. The authors (in alphabetical order) of the comments provided below are:

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COMMENTS ON THE DIGITAL HEALTH TECHNOLOGIES FOR REMOTE DATA ACQUISITION IN CLINICAL INVESTIGATIONS GUIDANCE FOR INDUSTRY, INVESTIGATORS, AND OTHER STAKEHOLDERS:

General Comments

ISCTM welcomes this guidance and is encouraged that the FDA has provided recommendations to sponsors, investigators, and other stakeholders on the use of digital health technologies (DHTs) to acquire data remotely from participants in clinical investigations evaluating medical products.

It is understood that these recommendations address some information that should be contained in an investigational new drug application (IND) or investigational device exemption (IDE) application for a clinical investigation in which the sponsor plans to use one or more DHTs or in a marketing application that includes such a clinical investigation. It is clear this draft guidance will represent the current thinking of the Food and Drug Administration and it does not establish any rights for any person and is not binding on FDA or the public. However, without providing additional clarifications the present guidance may make drawing clear conclusions surrounding DHT's and their use in investigations difficult. Providing more introductory information and precise definition of DHTs and what this guidance covers with additional clarifications in processes for use of endpoints, i.e., primary, secondary and/or exploratory, and relevance to label claims could help clarify this process to assist investigations and sponsors.

ISCTM looks forward to the ultimate adoption of guidance that clearly advances the methodology and outlines recommendations that address selection of DHT's, use of DHT's for trial endpoints, identification of potential risks and management of risks of DHT's in clinical investigations and to facilitate the use of DHTs in clinical investigations which may provide us with a broader picture of how participants feel or function in their daily lives. ISCTM is prepared to and would readily participate in further public debate to achieve this goal.

I. INTRODUCTION

The document states in line 15-16 *"(DHT) is a system that uses computing platforms, connectivity, software, and/or sensors, for healthcare and related uses."* ISCTM suggests a better definition of the term "system". As even an entire series of Deep Machine Learning algorithms and/or programs could be classified as a DHT making the development and regulation of such complexities exceedingly difficult to achieve. Additionally, to consider adding "general purpose" to line 16 before computing platforms to be consistent with line 24 and Glossary definition line 813 and 826.

Line 21 states, "*... DHT's available for potential use in a clinical investigation, some of ...*" ISCTM suggest clarifying if this guidance applies to common tools already in use.

ISCTM agrees with line 26 - 27. Additionally, we encourage the FDA to consider updating lines to state, "*A clinical investigation can use multiple DHTs to collect a range of information that may include clinical, physiological, psychological, behavioral, or functional data,* environmental, location, sensory, social interactions and any other yet undetermined data that could be collected for completeness.

ISCTM agrees with lines 48–50 "*Some of the considerations in this guidance may also be helpful for uses of DHTs other than remote collection of data to evaluate endpoints in a clinical investigation (e.g., enrichment strategies).*" Reference to Note 10 is made here. However, the use of DHT for enrichment should be clarified. i.e., will this be reflected in label.

II. BACKGROUND

Line 70 – 72 "*Some DHTs also may facilitate the direct collection of information from participants who are unable to report their experiences (e.g., infants, cognitively impaired individuals)."* ISCTM respectfully recommends FDA to consider adding infants, individuals with cognitive, motor, or speech impairments).

III. REGULATORY CONSIDERATIONS AND ENGAGEMENT WITH THE AGENCY

Line 110 – 111 "*Devices intended 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.*" Reference to Note 14 is made here.

ISCTM respectfully requests FDA to consider that using "exemption" on line 111 could be problematic in relation to what is stated on lines 127 and 128 in the draft guidance.

Line 126 – 127 "*Developers of DHTs may choose to pursue qualification of DHTs as a Drug Development Tool (DDT) or a Medical Device Development Tool (MDDT) for a specific* ***context of use.****"*

Please consider consistency regarding statements of qualification of a DHT and what DHTs are exempt. This statement contradicts with line 111.

IV. CONSIDERATIONS WHEN USING DIGITAL HEALTH TECHNOLOGIES IN CLINICAL INVESTIGATIONS

No recommendations.

A. Selection of a Digital Health Technology and Rationale for Use in a Clinical Investigation

As pertaining to lines 158-170, please consider adding examples of clinical events or characteristics of disease or condition to be measured under the numerical listings under the introductory paragraph, such as "the clinical event or characteristic of the disease or condition of interest that is to be measured, the proposed trial population, the design of the clinical investigation, and the characteristics of the DHT that may influence trial participant use."

1. Clinical Investigation Population

No recommendations.

2. Design and Operation of DHTs

ISCTM suggests line 203 to read, *"Trial participants should be informed about how to respond to those alerts,* and expectations for frequency and timeliness of responding to alerts."

Line 214. ISCTM respectfully requests the FDA to add another bullet. If the algorithm has been validated in a different patient population, not in your disease under study, you might want to look at which data and test. Additionally, it should be recommended that raw data should be available if a DHT is fit for purpose.

3. Use of a Participant's Own DHT or General-Purpose Computing Platform and Telecommunications

No recommendations

B. Digital Health Technology Description in a Submission

No recommendations

C. Verification, Validation, and Usability of Digital Health Technologies

Line 276- 277 "*provision of objective evidence that the physical parameter that the DHT measures*"
ISCTM suggests for the purposes of this guidance, verification is confirmation by examination and provision of objective evidence of the parameter that the DHT measures (e.g., acceleration, temperature, or pressure as examples of physical parameters, or affect, cognition or symptoms as examples of psychosocial parameters) is measured accurately and precisely over time.

1. Sensor-Based DHT

Line 308 – 310 states, "When *the protocol permits use of more than one brand or model of DHT to collect the same data in a clinical investigation, sponsors should verify that measurements across protocol specified DHTs are consistent*." ISCTM suggests this could be problematic because the measurements across different devices may require a non-inferiority verification and validation trial to be run before (or in parallel?) to the one in object.

2. DHT Software

No recommendations

3. General-Purpose Computing Platforms

No recommendations

4. Interoperability

Line 363 – 364 *"Sponsors should ensure the ability of connected systems in the clinical investigation to effectively and securely exchange information."*
ISCTM agrees this is an especially important topic in the field of digital data exchange. However, this language could have monitoring / inspection lability. Additionally, please provide clarification of what this means, and if it does imply that each step of a data transfer must have interoperability.

5. Usability Studies

No recommendations

D. Evaluation of Clinical Endpoints From Data Collected Using Digital Health Technologies

No recommendations

1. Defining the Clinical Endpoint

No recommendations

2.Establish Clinical Endpoints

No recommendations

3. Novel Clinical Endpoints

Line 441 – 445 states, *"How the endpoint relates to other endpoints of effectiveness that have been used to support a marketing authorization for a similar indication (e.g., clinical scales, patient reported outcomes, hospitalization, mortality). In the absence of related endpoints evidence from other sources of information (e.g., literature or input from stakeholders and experts) may support use of the endpoint."* ISCTM respectfully requests clarification if

convergence with established endpoints is required to be cross-sectional, longitudinal, and defined in terms of treatment response. Does treatment sensitivity on the part of previously used endpoints need to be demonstrated empirically alongside a new endpoint or can it be assumed?

E. Statistical Analysis

No recommendations

F. Risk Considerations When Using Digital Health Technologies

No recommendations

1. Clinical Risks

No recommendations

2. Privacy-Related Risks

No recommendations

3. Informed Consent

Line 561 – 562 states, "*The informed consent process should explain the type of information that will be collected by the DHT and how that information will be used and monitored."* ISCTM respectfully requests FDA to consider if the use of Machine Learning and Artificial Intelligence may preclude the ability to state precisely what the subject is giving consent to and whether the consent should be focused on the data collected and its level of de-identification.

G. Record Protection and Retention

On lines 624-625 FDA states, *"Review of these data may be necessary to reconstruct and evaluate the clinical investigation, and the data should be available for inspection."* ISCTM respectfully recommends FDA to delete or clarify this sentence as it pertains to the DHT device or to the durable electrotonic data repository.

ISCTM respectfully requests FDA to consider adding, "collected by the DHT", to line 627. It would read, *"When the protocol specifies review of the source data, collected by the DHT, by the clinical investigator…"* Additionally, please clarify review of source device itself or the data repository where the data is sent.

H. Other Considerations When Using Digital Health Technologies During a Clinical Investigation

1.Sponsor's Role

ISCTM respectfully requests FDA to consider adding "and communicating their contact information to trial participants or study personnel," after, "*Develop a plan for technical assistance,"* on line 649.

Lines 671 – 673 states, *"Develop a safety monitoring plan that addresses how abnormal measurements related to participants' safety (e.g., hypoglycemia, arrhythmia, apnea) measured by DHTs will be reviewed and managed."* ISCTM respectfully requests FDA to consider clearly specifying what the expectations are for the safety management plan, particularly considering the role of the Sponsor versus the responsibilities of the local site investigators for safety.

2.Investigator's Role

No recommendations

3.Training

ISCTM respectfully requests FDA consider amending line 694 to read," *Training trial participants and trial personnel* and caregivers *on the appropriate use of DHTs and, as applicable*,"

ISCTM suggests adding, cellular network, to line 732. *"Connecting to wireless or cellular networks"*

ISCTM suggests adding "not related to patient safety" on line 737 *"Responding to DHT signals…"*

4.DHT Updates and Other Changes

FDA states on lines 762-764, "When feasible, sponsors should consider locking software algorithms for the duration of the clinical investigation to avoid variability that can make results difficult to interpret. When software algorithms are not locked, sponsors should make plans to demonstrate that the data are not meaningfully different." ISCTM respectfully requests the FDA to clarify the relationship between locking software algorithms and variability. If possible, please provide examples.

5.DHT Error or Loss

No recommendations

GLOSSARY

Recommended update to line 873 and 874. **Remote data collection -** Collection of data from locations that are distant from the investigator or trial personnel. Data can be collected independent of clinical evaluation or other formal assessment by the investigator and can include data collected passively or actively by the patient and independent of the investigator.

APPENDIX A: EXAMPLES OF POTENTIAL DIGITAL HEALTH TECHNOLOGY (DHT) USE IN CLINICAL INVESTIGATIONS

No recommendations

Table 1: Sensor-based hardware example

No recommendations

Table 2: Software example

No recommendations

Table 3: Sensor-based hardware and software example

No recommendations

Table 4: Multiple DHTs example

No recommendations

APPENDIX B: EXAMPLE OF SELECTING A DIGITAL HEALTH TECHNOLOGY (DHT) FOR A CLINICAL INVESTIGATION

No recommendations

Table 1: DHT Summary

No recommendations

DHT Selection, Verification and Validation

No recommendations

Usability Testing

No recommendations

Endpoint Justification

No recommendations