# Comments on Using Technologies and Innovative Methods to Conduct Food and Drug Administration-Regulated Clinical Investigations of Investigational Drugs

## Docket No. FDA-2015-N-3579

**December 28, 2015**

**Submitted by:**

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**Introduction and Background**

On behalf of Critical Path Institute (C-Path), we are submitting the following comments to the Federal Register Docket No. FDA-2015-N-3579 on "Using Technologies and Innovative Methods to Conduct Food and Drug Administration-Regulated Clinical Investigations of Investigational Drugs."

There is growing interest and activity in identifying, evaluating and qualifying innovative technologies for use in drug development. While regulatory pathways and FDA guidance documents exist for pursuing the qualification of novel Drug Development Tools (DDTs) and Medical Devices Development Tools (MDDTs) for Qualification, this Federal Register request for comments provides an additional avenue for FDA to obtain information on promising technology platforms that could accelerate the assessment of innovative drug treatments. C-Path commends the FDA for putting forth this initiative as a visible and meaningful step towards advancing the regulatory science of these rapidly evolving assessment tools.

Critical Path Institute (C-Path) was founded in 2005 as a 501(c)(3) corporation based in Arizona with the support of a planning grant from the State of Arizona. C-Path's mission is to be a catalyst in the development of tools to advance medical innovation and regulatory science. We achieve this by leading teams that share data, knowledge and expertise resulting in sound, consensus based regulatory science.

Since 2005, C-Path has created 12 consortia that include over 1,300 scientists, from 61 global bio-pharmaceutical companies, academia, the FDA, the European Medicines Agency (EMA), patient advocacy organizations, and the National Institutes of Health (NIH). C-Path's consortia are partially funded by the FDA as part of the Critical Path Public-Private Partnerships (http://www.fda.gov/AboutFDA/PartnershipsCollaborations/PublicPrivatePartnershipProgram/ucm166082.htm).

The comments contained herein represent those of two C-Path consortia: Coalition Against Major Diseases (CAMD - see Appendix 1), and Electronic Patient-Reported Outcomes Consortium (ePRO- see Appendix 2).

**Appendix 1**

# Comments on Using Technologies and Innovative Methods to Conduct Food and Drug Administration-Regulated Clinical Investigations of Investigational Drugs

**Docket No. FDA-2015-N-3579**

**December 28, 2015**

**Submitted by:**

**Coalition Against Major Diseases**

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**Introduction**

On behalf of the Coalition Against Major Diseases (CAMD) at the Critical Path Institute (C-Path), we are submitting the following comments to the Federal Register (FR) Docket No. FDA-2015-N-3579 on "Using Technologies and Innovative Methods to Conduct Food and Drug Administration-Regulated Clinical Investigations of Investigational Drugs."

CAMD consists of more than 20 member organizations from industry, government agencies, patient advocacy organizations, key opinion leaders and regulatory authorities. The focus of our consortium is to accelerate the development of Drug Development Tools that increase the efficiency of delivering innovative treatments for devastating diseases such as Alzheimer Disease and other related dementias. Our comments are based upon the experience of our member organizations' use of biosensors, wearable devices and other digital biomarkers, and the data generated by these devices in clinical trials, as well as some of the challenges faced. CAMD is responding to four of the "Issues for Comment" listed in Section III of the FR notice: Questions 1, 2, 3 (a) and 4 (a, b, d-i), that we think would be most impactful to the Drug Development and Medical Device community implementing these clinical tools.

Digital data collection technologies are rapidly evolving on four major fronts: 1) Electronic Health Records that store a diverse set of information related to an individual's health; 2) Electronic capturing of clinical data for Patient-Reported Outcome (PRO) Instruments and other Clinical Outcome Assessments (COAs); 3) Improved data collection and reporting technology platforms for clinical trials; and 4) Digital biomarkers (i.e., devices that objectively measure biological events or patient function). These technologies would provide a means to continuously and reliably measure a variety of responses that could be used to correlate/corroborate information gathered by other means, such as statements made by the patient or the caregiver (if concurrently assessed) regarding their perception of signs and symptoms, as well as their functional capabilities. The major focus of the feedback that CAMD is providing will be on use of digital biomarkers in clinical trials and their potential qualification as Drug Development Tools. CAMD's members view this as a key opportunity to expand the drug development community's armamentarium of tools to assess clinically meaningful functional outcomes with greater sensitivity, frequency, and objectivity. The commentary is framed around the following three themes related to Drug Development Tools (DDTs) and Medical Device Development Tools (MDDT) Qualification:

- **Data Standards:** Scientifically-based consensus on the standardized way to record, structure and report data generated by digital biomarkers, via the development and adoption of CDISC standards is a gap that must be addressed. Doing so will: 1) enable the integration of various data sources to quantify the predictive accuracy, utility and reliability of digital biomarkers in clinical trials; 2) enable the prospective collection of data in standardized format in both clinical trials and observational studies; and 3) expedite regulatory submissions to FDA, EMA and other regulatory authorities.
- **Digital Biomarkers as Drug Development Tools:** The development and adoption of CDISC standards for digital biomarkers will also provide the basis to increase the level of understanding of the role that digital biomarkers could play as potential drug

development tools, to, for example, enrich populations selected for clinical trials, track and quantify disease progression, or identify and quantify treatment effects in clinical trials. Understanding such roles could also lead to the formal regulatory endorsement of digital biomarkers as drug development tools, either through formal qualification processes at FDA and EMA, or through other mechanisms such as "fit-for-purpose" decisions by FDA.

- **Defining Clear Context of Use (COU) Statements:** In order to lead to meaningful regulatory endorsement processes for digital biomarkers as drug development tools, it is imperative that clear COU statements be developed, based on the current state-of-evidence and a clear rationale for the application of digital biomarkers in the drug development process.

**Section III Issues for Comment addressed by CAMD:**

**<u>Section III, Question 1:</u> What technologies, communication infrastructure, or innovative methods are being used to conduct clinical investigations? FDA is aware of several groups conducting and interested in conducting clinical investigations using mobile technology and remote methods for data collection. FDA requests feedback on experiences with implementing such methods or models (for example, lessons learned), as well as information supporting the use of any suggested technologies, methods, or models, including any characteristics that would make the technology more or less desirable for use in clinical trials.**

**CAMD Response:** CAMD's perspective is that applications of digital biomarkers in clinical trials are useful to cover the following scope:

- **Function**: Electronic monitoring of activities in and outside of home (patterns of sleep, eating, drug adherence, walking, social interactions via phone and computer, cognitive task assessments, etc.), fine motor skills (e.g., typing or keystroking on computer or smartphone, regarding motor speed and accuracy in symptomatic trials of PD patients).
- **Physiological measures:** Pulmonary function tests (peak flow meter), ECG, EEG, blood pressure, heart rate, movement (accelerometer), speech/voice analysis, blood glucose monitoring (e.g., Continuous Glucose Monitoring (CGM) devices), blood ketone monitoring, oxygenation ($pO_2$ saturations).
- **Symptoms**: Electronically reported diary of symptoms by patients and caregivers, patient-reported outcomes, adverse events, and reporting of mood.

CAMD would like to highlight the following considerations that may eventually translate into documented superiority over human observer assessments. These potential attributes include:

- Minimizing observer rater training required, leading to more uniform data collection.
- Minimizing observer bias influenced by prior personal experiences or cultural norms.
- Reducing cross-site variability when conducting large multi-site trials.

- Assuming reduced variability of measures across sites, together with the potential for calculating daily within subject means and variabilities, the numbers needed to detect effects (i.e., disease progression or treatment effect), as well as the numbers of individuals exposed to potential treatment harm, would be significantly reduced. This may be especially significant in two key challenge areas for drug development: a) reducing sample sizes and study durations (Dodge, Zhu et al., 2015), thereby increasing probability of success, in early-phase clinical trials; and 2) conduct of studies in orphan populations where the size of the patient population may be limiting.
- Reduced costs related to less frequent clinician engagement.
- Home-based measurements with digital biomarkers could provide real-world data with reduced errors compared to assessments performed at clinic visits (e.g., a person with poor memory may incorrectly report on their activity; someone disorientated during a hospital visit may give inaccurate answers to functional questionnaires).
- Ability to conduct longitudinal trials over years without the concern about changing clinical staff and corresponding rater reliability and related reduction in the amount of missing data.
- Enhanced safety monitoring by allowing real-time capture of biometric information and adverse event reporting by study subjects.
- Collection of digital biomarker data in an anonymized manner, and then structuring and reporting those data using CDISC standards would build the necessary foundational information required to advance two of the FDA's Scientific Priorities:
    - #2. Stimulate Innovation in Clinical Evaluations and Precision Medicine to Improve Product Development and Patient Outcomes;
    - #4. Ensure FDA Readiness to Evaluate Innovative Emerging Technologies.

While there are publications that suggest "…biomarkers can only indirectly measure the meaningful aspect of health." (Walton et al., 2015), CAMD considers that this view is influenced by historical publications that have characterized biochemical biomarkers as more static and infrequent assessments. Some experts in the field may view any biosensor measurement as being "indirect", however, both EEG (electroencephalograms) and ECG (electrocardiograms) are early examples of digital biomarkers that directly reflect clinically meaningful indices of brain and cardiac function, respectively, as measured by biosensors (Oweis and Hijazi, 2006; Quiroz et al., 2011; Martis et al., 2014; Lee et al., 2014;Cecchi et al., 2015).

CAMD's viewpoint is to include digital biomarkers that can assess dimensions of sleep quality (Dodge et al., 2012), physical activity (Campbell et al., 2011; Austin et al., 2014; Hayes et al., 2014), speech (Dodge, Mattek et al., 2015), social networking (Dodge et al., 2014) and drug adherence (Hayes et al., 2009), as clinically meaningful indices foundational to health maintenance that are also related to or impact cognitive performance (Kaye et al., 2015; Dodge, Zhu et al., 2015). While CAMD's focus is on neurodegenerative diseases with memory impairment, this type of information would likely be a valuable assessment across many major disorders. Moreover, CAMD suggests that, following the collection of an appropriate data set, it will become clear that digital biomarkers, as measured by a biosensor, are analogous to the COA categories of Observer-Reported Outcomes (ObsROs) and Performance Outcomes (PerfO).

## Digital Biomarkers: Biosensor Observed Measures

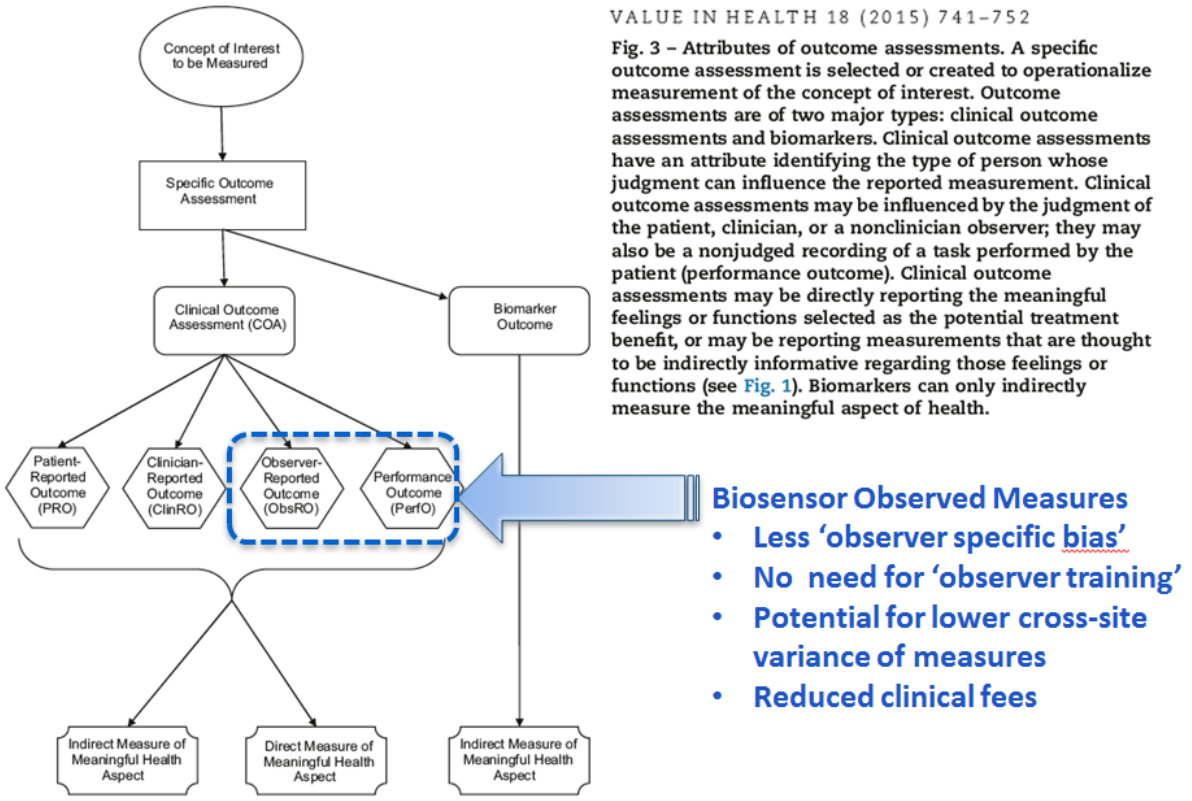


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**Fig. 3 – Attributes of outcome assessments. A specific outcome assessment is selected or created to operationalize measurement of the concept of interest. Outcome assessments are of two major types: clinical outcome assessments and biomarkers. Clinical outcome assessments have an attribute identifying the type of person whose judgment can influence the reported measurement. Clinical outcome assessments may be influenced by the judgment of the patient, clinician, or a nonclinician observer; they may also be a nonjudged recording of a task performed by the patient (performance outcome). Clinical outcome assessments may be directly reporting the meaningful feelings or functions selected as the potential treatment benefit, or may be reporting measurements that are thought to be indirectly informative regarding those feelings or functions (see Fig. 1). Biomarkers can only indirectly measure the meaningful aspect of health.**

In summary:

1. Digital technologies are being used in multiple ways (e.g., safety, clinical efficacy, diagnostic, enrichment biomarker, etc.).
2. As such, different evidentiary standards need to be met dependent on context of use.
3. These technologies open new horizons for data collection (e.g., continuous monitoring, greater ecological validity, etc.).
4. We need to be able to maintain an open dialogue the regulators with regards to shaping the development, validation, clinical relevance research, etc. as new approaches may be needed that do not fit established categorizations.

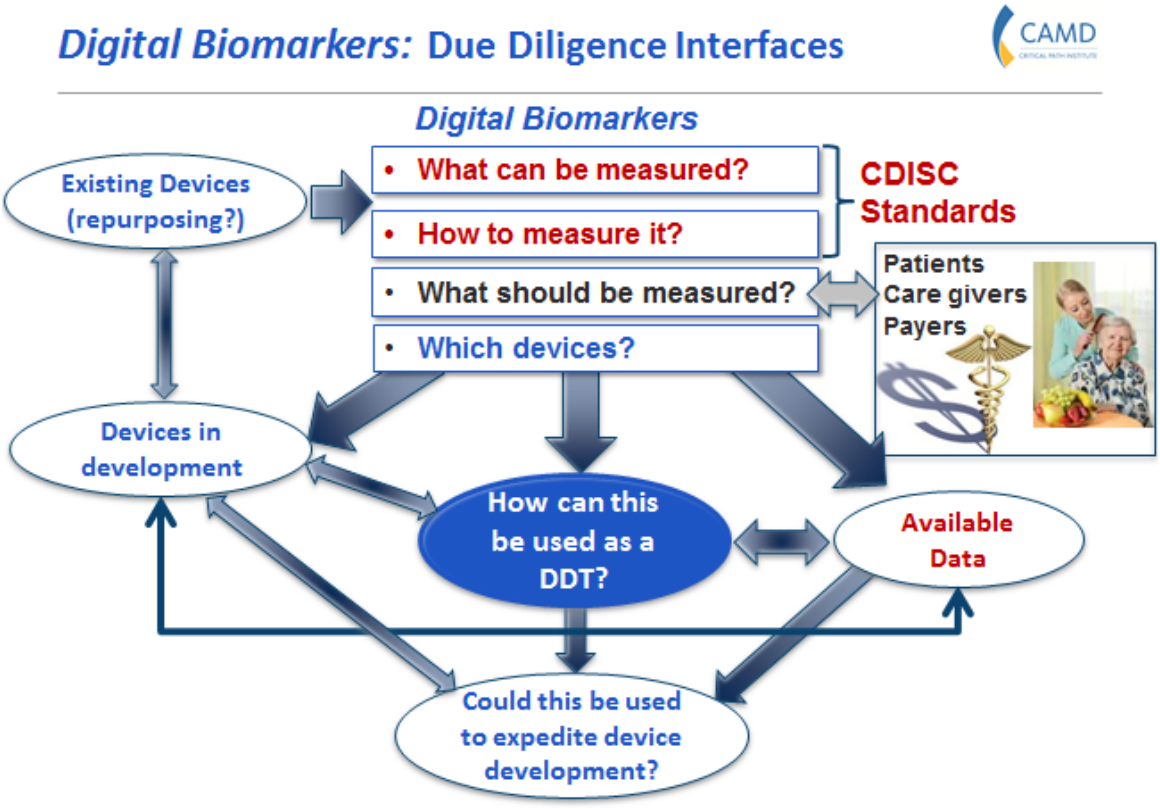
**Section III, Question 2: What are ways FDA could encourage adoption of these technologies and innovative methods in the conduct of clinical investigations?**

**CAMD Response:** CAMD recommends convening a 'Digital Biomarkers' workshop in the second quarter of 2016 that engages the industry (Pharma companies and Medical Technology/Device

companies) and both regulatory and academic thought leaders to identify current knowledge and gaps regarding the applicability of digital biomarkers as drug development tools, which will lead to a collaborative environment between the FDA and the industry in identifying the potential pathways for regulatory endorsement of digital biomarkers as Drug Development Tools. To garner a broad perspective within the neurodegenerative diseases space, we suggest this workshop leverage learnings across three major diseases (Alzheimer Disease, Parkinson Disease, and multiple sclerosis) using CAMD, the Critical Path for Parkinson's (CPP) and Multiple Sclerosis Outcomes Assessments Consortium (MSOAC) at Critical Path Institute to serve as a nexus of coordinating a due diligence meeting. The workshop outcomet would result in a journal publication that details current gaps and challenges, as well as best practices and industry guidelines as they exist. In addition, members of FDA, representing both CDRH and CEDR, as well as industry representatives, would be presenters to inform the participants of examples where digital technologies have been integrated into novel clinical trial design, and what level of data was necessary to achieve their specific "context-of-use".

Inclusion of digital biomarkers under the biomarker qualification pathway would enable letters of support for incentivizing use in clinical trials.

Eventually, issuance of FDA guidance would provide a more concrete framework which will facilitate consistent acceptance across FDA review teams and Divisions.



**Section III, Question 3: Identify any clinical, cultural, business, regulatory, or other barriers perceived by stakeholders that serve as a disincentive to the use of technology to facilitate the conduct of clinical investigations.**

**a. What challenges do stakeholders anticipate in adoption of these technologies or methods? Are there challenges in complying with regulatory requirements surrounding the conduct of clinical investigations that use such technologies or methods?**

**CAMD Response:** A perceived regulatory barrier is that CDISC standards for collecting, organizing and analyzing data collected by digital biomarker technologies (wearables and remote monitoring) have not been established. Consequently, biomarker qualification by regulatory agencies will be difficult to achieve until standards are in place. CAMD is interested in working with the FDA to find ways to support the development of these standards. CAMD has had a track record of contributing to the development of such standards, and is interested in working with the FDA to bridge the necessary regulatory science gaps that exist.

While initiating this process could be less onerous for therapeutic areas (TAs) where CDISC standards exist (Alzheimer Disease, Parkinson Disease, multiple sclerosis, etc.), an assessment is needed to determine how to deal with data from diseases where clinical similarities in manifestations exist, but TA CDISC standards do not.

Another challenge the field is facing is the fast pace that technologies are evolving. Providing guidance on how bridging studies should be conducted to migrate from one technology (biosensor) platform to another is required. Defining the considerations to establish how many cohorts must be studied before a new platform is considered replicable and "validated" is essential.

The quality control aspect is vitally important as we need to ensure that the patient data are correct and valid. There is an error rate allowed for all devices. Collecting data to define the acceptable variance for these measures is critical. Defining evidentiary expectations for establishing reliability and, as well as assessment relative to gold standards would be informative.

Finally, specific to utilizing devices in clinical trials, the sponsor must consider the investigators' and patients' access to a wireless network (i.e. WiFi) or provide an alternative means to support the site's access to the Internet. Some sites have firewalls and/or policies that might present challenges with implementing technology, so these would need to be well-explored prior to deploying.

**Section III, Question 4: FDA is interested in obtaining information on potential trial participant acceptance, privacy, and human subject protection issues that may occur as a result of the use of technologies and innovative methods for the conduct of clinical investigations. In particular, FDA is interested in assessing potential trial participants' interest, tolerance, concerns, and willingness to participate in clinical investigations that**

**involve nontraditional settings or utilize new technologies. FDA is also interested in identifying the factors that affect trial participant awareness, acceptance, enrollment, and retention for these investigations.**

**a. Are there specific patient groups or therapeutic areas that could particularly benefit from these types of technologies or methods?**

**CAMD Response*:*** Historically most clinical trials have collected information used to derive inclusion/exclusion criterion in clinical trials as well as use in determining treatment impact (i.e., efficacy) with Patient-Report Outcomes (PROs). Patients, caregivers and regulators have consistently acknowledged the importance of the "voice of the patient".

While ethically this perspective should never be revoked, there are examples of patient groups where the objectivity, reliability and face-validity of the information gathered can, and should be, called into question. In particular, individuals who are cognitively impaired or demented, by definition, will not be able to recall information with the veracity that is required for a properly conducted trial with PROs (Mak et al., 2015).

Use of digital biomarkers can provide a means to continuously, and reliably measure a variety of responses that could be used to correlate/corroborate statements made by a patient. For example, if a patient states that…" they have felt lethargic and haven't gone out to do anything outside the home"…., yet, objective data from home monitors indicate their gait speed is above average, their total room transitions are above their average, and their time spent outside of the home environment is above average, this clearly indicates that the individual is losing perspective with what is actually happening. Of course the converse could be true as well. They …"feel energetic and have had a productive day"…, yet the objective data indicate otherwise. In other disease states, for example Parkinson's disease, it is not readily obvious how the physical signs of the disorder correlate with impairment in activities of daily living. The ability to access patient performance data could potentially enhance our understanding of disease biology and enable design of PROs with greater relevance to how the patient feels or functions.

Many clinical trials have tried to adjust for this dilemma by having family caregivers "corroborate" the performance of their loved one. However, especially in the aged Alzheimer's population, a spouse/close relative or friend may be somewhat impaired themselves, or given the stress of continual care, may experience a compromise of their own health, as well as the veracity of their account (Razani et al., 2007; Varela et al., 2011). An added benefit of digital technologies platforms would be the ability to extend the assessments to the caregivers themselves. Treatments that exert a positive effect on the patient conceivably would indirectly benefit the health of the caregiver. Monitoring these types of dual benefits should be of great interest in helping to prioritize access and relative value of treatments for Payers within the Health Care Community.

Lastly, digital biomarkers could be more broadly applied to rare diseases where patient populations are small and established clinical outcomes scales are not yet well established, or

no reliable biochemical biomarker exists for the evaluation of the disease and impact of treatment.

**b. What new opportunities for the conduct of clinical investigations are created through the use of continuous or intermittent remote monitoring and data collection?**

**CAMD Response:** "In reviewing New Drug Applications for the treatment of Alzheimer Disease, the FDA has maintained that claims of improved cognition should be accompanied by evidence of improvement in function. However, the premise that effective cognitive improvement will be manifested in the functional assessment of patients is untenable in the case of early-stage Alzheimer's disease, which is increasingly the target of drug development efforts. We simply do not yet have drug-development tools that are validated to provide measures of function in patients with Alzheimer's disease before the onset of overt dementia." (Kozauer and Katz, 2013). Unfortunately, while it is possible to measure changes in cognitive performance with treatment, with currently used clinical instruments for Activities of Daily Living (ADLs), detecting treatment changes in ADLs is particularly difficult without prolonged exposure to a treatment, i.e., greater than three months(Rogers et al., 1998; Mohs et al., 2001). In contrast to ADLs, which consist of activities such as dressing, grooming, bathing, toileting, and feeding oneself, instrumental ADLs (IADLs) consist of activities such as preparing meals, performing household chores, running errands, traveling outside of one's neighborhood, keeping track of one's schedule and appointments, managing the finances, and doing the taxes. While impaired ADLs are a manifestation of Alzheimer Disease, only IADLs have been shown to be measurable during MCI (Marshall et al., 2015). More sensitive and robust measures of function that are related to IADLs, and could be monitored with digital biomarkers, will be required to achieve this to monitor function earlier in the pre-symptomatic stages of dementia.

One hallmark of "impaired" physiological (or even mechanical/electrical) feedback circuits is an increased incidence of variability in response (Gouillard, 2006). Gaining an understanding of the when and how these variances occur would give us greater insights into pathophysiological diseases (Marder, 2011). Given the limited/poor sensitivity of current instruments in early disease, collecting this type of information with digital biomarkers, and corroborating with longitudinal studies that these "events of variability" are prognostic of transition to MCI and eventually dementia, could be transformational for the field of neurodegenerative disorders. As it has been shown that sleep time, physical activity, and drug adherence are already changed at the time of MCI (Dodge, Zhu, 2015), determining when in the progression to MCI the variance of these types of 'functional ADLs' increase, may become a valuable way to detect those at risk to worsen, prior to a measurable change in memory function.

A final consideration is that one of the attributes of continuously collecting digital biomarker measures is that it would enable the generation of mean responses and the associated variance for a given individual. In doing so, it becomes possible to determine within individual statistics

that could be used to define that treatment is required or that a given treatment was effective (Dodge, Zhu et al., 2015). This approach is consistent both with the notion of enabling a 'Personalized Medicine' approach, and integrating 'Real World Data' into a treatment plan.

**d. What are some of the anticipated benefits to trial participants that may occur as a result of the use of these technologies or off-site methods in clinical investigations?**

**CAMD Response**: The use of technology in clinical trials can benefit trial participants through:

- Enhanced patient comprehension (e.g., educational videos), engagement, recruitment, retention, compliance (e.g., visit reminders).
- More rapid assessment of drug effect (Adverse Effects and Efficacy).
- Better access to treatment for those in more remote areas of countries.
- Decreased frequency and length of study visits in office.
- Diminished travel burden and costs.

**e. Are there perceived challenges to participation in clinical investigations utilizing these types of technologies or methods because of concerns regarding inadvertent disclosure of trial participants' information or breach of privacy? Are there concerns relating to the integrity of data collection or encryption or the secure transmission of information?**

**CAMD Response**: The rapid adoption of wearable devices threatens to repeat the experience of electronic health records (EHRs), in which a lack of standards for vendor-specific EHR databases was a major contributing factor to the current lack of interoperability in EHRs. Of the user requirements developed by CDISC in 2009 for electronic source data (eSource) collection instruments (http:www.cdisc.org/esdi-document), wearable devices presently have no accepted standards or standard practices available for ten of the twelve eSource requirements (eSR), namely:

eSR1: An instrument used to capture source data shall ensure that the data are captured as specified within the protocol.
eSR2: Source data shall be accurate, legible, contemporaneous, original, attributable, complete and consistent.
eSR3: An audit trail shall be maintained as part of the source documents for the original creation and subsequent modification of all source data.
eSR6: The sponsor shall not have exclusive control of a source document.
eSR7: Source data shall only be modified with the knowledge or approval of the investigator.
eSR8: Source documents and data shall be protected from destruction.
eSR9: The source document shall allow for accurate copies to be made

eSR10: Source documents shall be protected against unauthorized access.
eSR11: The location of source documents and the associated source data shall be clearly identified at all points within the capture process.
eSR12: When source data are copied, the process shall ensure that the copy is an exact copy preserving all of the data and metadata of the original.

Creation of a funding mechanism to support the enhancement of CDISC standards to handle data from Digital Biomarkers should be a high priority for the FDA. Not doing so quickly will result in an incredibly large backlog of data that has questionable regulatory science utility. The cost and time required for remapping it to CDISC standards would be daunting.

**f. Are there unique considerations for ensuring integrity of the source data, for example, authenticity and reliability?**

**CAMD Response:**

- Patients with dementia cannot be asked to declare their collected data as authentic. Reliability may have to be matched with some unique biometric identifier.
- Ascertainment that it is the actual clinical trial subject who entered the data, rather than some other person may be helped by identification mechanisms such as fingerprint identification, iris scan, keystroke analysis, etc.
- Data encryption and password protection of devices are required.
- The platform for each device should allow for subject training on-demand, as well as evaluation of patient use of the platform.
- Standard operating procedures (SOPs) are needed for all electronic or mobile devices, and these SOPs should have validated processes to ensure that the collected data are saved with a date and time stamp of collection, uploaded, and transfered from one device to another and to the database.
- Simulations of the data collection, transfer, integration, analysis, and security must be performed and accuracy demonstrated prior to the actual clinical trial.

**h. What are the challenges presented when data are collected using the Bring Your Own Device (BYOD) model? What are the perceived barriers to pooling data collected from different devices provided by individual trial participants, as well as pooling data from the BYOD model with data collected at the investigational site or on paper forms? How should situations such as mid-study user device switches be handled?**

**CAMD Response:** The incorporation of BYOD capabilities in clinical trials will be useful, but it poses additional challenges due to:

- The lack of uniformity in technical platforms.
- The rapidly changing platforms /software (e.g., devices are changed about every two years at contract renewal or earlier, some patients will have "dinosaur" devices that are too old to be compatible with the system requirements).
- The ultimate need to merge the data onto a single platform.
- Data protection and security.
- Technical connectivity (WiFi, Bluetooth, etc.).

Some suggestions to address these challenges:

- Sponsors should collaborate to streamline the development and delivery of some uniform and shared technologies and methods without compromising the individual sponsor's investigation. Sponsors must foster excellent internal communications and alignment of various stakeholders, such as medical, legal, quality, compliance, informatics, etc. Sponsors should seek external collaboration and advice on these matters as needed.
- For data identification and collection, the variable names with the portal or website must be standardized between devices and remain similar over time.
- MiFi (mobile WiFi) devices can be used to assist with WiFi connections.
- Patients with more chronic and/or mild illnesses might be more receptive to using technology than those with other more acute/rapidly changing/severe diseases, such as advanced cancer.

**i. What are the challenges or special considerations with recruiting and/or retaining potential trial participants with low levels of computer literacy or individuals who may have limited or no access to mobile technologies, computer devices, or the Internet? How can these challenges or special considerations best be addressed?**

**CAMD Response:** Over the next decade, trial participants with low technological literacy or individuals with limited or no access to technology will diminish, making this group a minority that may merit consideration in tailored studies.

- People with certain challenges may need special accommodations to participate in clinical trials.
- The elderly: there is a bias at sites that elderly have relatively more difficulties using the electronic devices. They may need more training, time to complete tasks, or other accommodations.
- Visually impaired: technology to enlarge text or provide audio should be tapped.

- Poor literacy or inability to sign name: alternate identification measures should be considered, e.g., fingerprint signatures.

**References:**

Austin, D., Cross, R.M., Hayes, T., Kaye, J. (2014) Regularity and predictability of human mobility in personal space. PLoS One. 2014; 9(2): e90256

Campbell, I., et al. (2011) Measuring changes in activity patterns during a norovirus epidemic at a retirement community. Conf Proc IEEE Eng Med Biol Soc. 6793-6.

Cecchi, M., Moore, D.K., Sadowsky, C.H., Solomon, P.R., Doraiswamy, P.M., Smith, C.D., Jicha, G.A., Budson, A.E., Arnold, S.E., Fadem, K.C. (2015) A clinical trial to validate event-related potential markers of Alzheimer's disease in outpatient settings. Alzheimers Dement. Dec; 1(4):387-94.

Dodge, H.H., Mattek, N.C., Austin, D., Hayes, T.L., Kaye, J.A. (2012) In-home walking speeds and variability trajectories associated with Mild Cognitive Impairment. Neurology 78:1946-1952.

Dodge, H.H., Ybarra, O., Kaye, J.A. (2014) Tools for advancing research into social networks and cognitive functions in older adults. International Psychogeriatrics. April; 26(4): 533–539. (PMC3943694) http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3943694/11.

Dodge, H.H., Zhu, J., Lee, C.-W., Chang, C.-C.H., Ganguli, M. (2014) Cohort Effects in Age-Associated Cognitive Trajectories. J Gerontol A Biol Sci Med Sci. Jun; 69(6):687-94. (PMC4022091) http://www.ncbi.nlm.nih.gov/pubmed/2427006212.

Dodge, H.H., Zhu, J., Mattek, N., Austin, D., Kornfeld, J., Kaye, J. (2015) Use of high-frequency in-home monitoring data may reduce sample sizes needed in clinical trials. PLoS One 2015:17;10(9):e0138095. doi: 10.1371/journal.pone.0138095 (PMC4574479) http://journals.plos.org/plosone/article?id=10.1371/journal.pone.013809513.

Dodge, H.H., Zhu, J., Mattek, N., Bowman, B.A., Gregor, B.A, et al. (2014) Characteristics associated with willingness to participate in a randomized controlled behavioral clinical trial using home-based personal computers and a webcam. Trials;15:508. http://www.ncbi.nlm.nih.gov/pubmed/2553963714.

Dodge, H.H., Mattek, N., Gregor, M., Bowman, M., Seelye, A., Ybarra, O., Asgari, M., Kaye, J.A. (2015) Social Markers of Mild Cognitive Impairment: Proportion of Word Counts in Free Conversational Speech. Current Alzheimer Research, 12(6):513-9. http://www.ncbi.nlm.nih.gov/pubmed/2602781415.

Goaillard, J.M. (2006) Variability, compensation and homeostasis in neuron and network function. Nat Rev Neurosci 7:563–574.

Hayes, T.L., Cobbinah, K., Dishongh, T., Kaye, J.A., Kimel, J., Labhard, M., Leen, T., Lundell, J., Ozertem, U, Pavel, M., Philipose, M., Rhodes, K., Vurgun, S. (2009) A study of medication-taking and unobtrusive, intelligent reminding. Telemedicine and e-Health; 15(8).

Hayes, T.L., Riley, T., Mattek, N., Pavel, M., Kaye, J.A. (2014) Sleep Habits in Mild Cognitive Impairment. Alzheimer Disease & Associated Disorders. Jun; 28(2):145-50.

Kaye, J., ,Mattek, N., Dodge, H.H., Campbell, I., Hayes, T., Austin, D., Hatt, W., Wild, K., Jimison, H., Pavel, M. (2014) Unobtrusive measurement of daily computer use to detect mild cognitive impairment. Alzheimer's & Dementia, 10(1): 10-7.

Kozauer, N., and Katz, R., (2013) Regulatory Innovation and Drug Development for Early-Stage Alzheimer's Disease. NEJM., 368: 13.

Lee, H., Brekelmans, G.J., Roks, G. (2015) The EEG as a diagnostic tool in distinguishing between dementia with Lewy bodies and Alzheimer's disease. Clin Neurophysiol. 2015 Sep; 126(9):1735-9.

Mak, E., Chin, R., Ng, L.T., Yeo, D., Hameed, S. (2015) Clinical associations of anosognosia in mild cognitive impairment and Alzheimer's disease. Int J Geriatr Psychiatry. Dec; 30(12):1207-14. doi: 10.1002/gps.4275. Epub 2015 Mar 9.

Marder, E., (2011) Variability, compensation, and modulation in neurons and circuits. PNAS, September 13, vol. 108 (suppl. 3): 15542–15548.

Marshall, G.A., Zoller, A.S., Lorius, N., Amariglio, R.E., Locascio, J.J., Johnson, K.A., Sperling, R.A., Rentz, D.M., and for the Alzheimer's Disease Neuroimaging Initiative (2015) Functional Activities Questionnaire items that best discriminate and predict progression from clinically normal to mild cognitive impairment. Curr Alzheimer Res. 12(5): 493–502.

Martis, R.J., Acharya, U.R., Adeli, H. (2014) Current methods in electrocardiogram characterization. Comput Biol Med. May; 48:133-49.

Mohs, R.C., et al. (2001) A one year, placebo-controlled preservation of function survival study of donepezil in patients with Alzheimer's disease. Neurology, 57(3): 481-488.

Oweis, R. and Hijazi, L. (2006) A computer-aided ECG diagnostic tool. Comput Methods Programs Biomed. Mar; 81(3):279-84.

Quiroz, Y.T., Ally, B.A., Celone, K., McKeever, J., Ruiz-Rizzo, A.L., Lopera, F., Stern, C.E., Budson, A.E. (2011) Event-related potential markers of brain changes in preclinical familial Alzheimer disease. Neurology. Aug 2; 77(5):469-75.

Razani, J., Kakos, B., Orieta-Barbalace, C., Wong, J.T., Casas, R., Lu, P., Alessi, C., Josephson, K. (2007) Predicting caregiver burden from daily functional abilities of patients with mild dementia. J Am Geriatr Soc., 55:1415–1420.

Rogers, S.L. (1998) Donepezil improves cognition and global function in Alzheimer's disease. Arch. Intern. Med., 158: 1021-31.

Varela, G., Varona, L., Anderson, K., Sansoni, J. (2011) Alzheimer's care at home: a focus on caregivers strain. Prof Inferm., 64:113–117.

Walton, M.K., Powers III, J.H., Hobart, J., Patrick, D., Marquis, P., Vamvakas, S., Isaac, M., Molsen, E., Cano, S., Burke, L.B. (2015) Clinical Outcome Assessments: Conceptual Foundation—Report of the ISPOR Clinical Outcomes Assessment – Emerging Good Practices for Outcomes Research Task Force, Value in Health, Volume 18, Issue 6, p739-940.

**Appendix 2**

# Comments on Using Technologies and Innovative Methods to Conduct Food and Drug Administration-Regulated Clinical Investigations of Investigational Drugs

**Docket No. FDA-2015-N-3579**

**December 28, 2015**

**Submitted by:**

**Electronic Patient-Reported Outcome Consortium**

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**Introduction**

On behalf of the Electronic Patient-Reported Outcome (ePRO) Consortium at the Critical Path Institute (C-Path), we are submitting the following comments to the Federal Register Docket No. FDA-2015-N-3579 on "Using Technologies and Innovative Methods to Conduct Food and Drug Administration-Regulated Clinical Investigations of Investigational Drugs."

In an effort to assist FDA in gathering evidence surrounding some of the key questions posed to stakeholders, the ePRO Consortium believes it will be beneficial to provide comments representing the perspective of ePRO vendors. Our comments are based upon the experience of our member firms in collecting data electronically in clinical investigations.

The ePRO Consortium was established on April 1st, 2011**.** The ePRO Consortium's member firms provide electronic data collection technologies and services to the medical products industry for capturing patient-reported outcome (PRO) endpoints in clinical trials. The mission of the ePRO Consortium is to advance the science of clinical trial endpoint assessment by collaboratively supporting and conducting research, designing and delivering educational opportunities, and developing and disseminating best practice recommendations for electronic collection of clinical outcome data.

Our comments are organized around the Issues for Comment listed in Section III of the FR notice: Questions 1, 2, 3 (b) and 4 (a-i). The names and affiliation of the ePRO Consortium members who contributed to this response are listed at the end of our comments.

**Section III "Issues for Comment":**

**Section III, Question 1. What technologies, communication infrastructure, or innovative methods are being used to conduct clinical investigations? FDA is aware of several groups conducting and interested in conducting clinical investigations using mobile technology and remote methods for data collection. FDA requests feedback on experiences with implementing such methods or models (for example, lessons learned), as well as information supporting the use of any suggested technologies, methods, or models, including any characteristics that would make the technology more or less desirable for use in clinical trials.**

PRO instruments measuring patients' symptoms or functioning are direct measures of treatment benefit and can provide the basis for marketing approval decisions and labeling claims. The electronic modes used to collect PRO data in clinical trials include:

- Desktop computers
- Laptop computers
- Tablets
- Interactive Voice Response (IVR) systems, where patients use a telephone to listen to questions presented audibly and then respond to the questions by pressing a key on the telephone keypad or saying a number

- Handheld devices, where patients either use a dedicated device provided by the investigator site or use their own handheld device (typically a smartphone; this is the "Bring Your Own Device" or BYOD approach)

For all platforms other than IVR, assessments may be accessed through software that is available locally on the device or through a Web connection.

The ePRO Consortium has generated a variety of presentations and publications that provide the collective "lessons learned" from the Consortium members – these lessons include best practices for collecting ePRO data in clinical trials and descriptions of the strengths, weaknesses, and open questions surrounding new technologies and approaches. Publications authored by the Consortium include:

- Best practices for migrating paper instruments to electronic platforms (Coons et al., 2009)
- Overview on ePRO data collection and the use of ePRO data collection technologies in clinical trials (Coons et al., 2014)
- Best practices for including mixed modes of administration (e.g., paper and electronic modes) in clinical trials (Eremenco et al., 2014)
- Considerations regarding the use of BYOD approaches in clinical trials (Gwaltney et al., 2015)
- Recommendations for optimizing the collection of ePRO data in clinical trials (Fleming et al., 2015)
- Considerations regarding whether or not to require patients to respond to all items in an electronic assessment (O'Donohoe et al., 2015)

Although there are too many key messages in these publications to be listed here, we do wish to comment specifically on the use of mobile technologies to collect PRO data electronically in clinical trials.

- Even though mobile devices could be used to collect data at clinical sites, the primary value of using mobile technology in clinical trials is to collect data in the subject's natural environment, not in the clinic. This 'field-based' approach is discussed below.
- There are two primary approaches to collecting PRO data through mobile technologies: (a) a dedicated device approach, where devices are purchased by sponsors and are provided to research subjects by clinical sites to exclusively run software related to collecting PRO data, and (b) a BYOD approach, where subjects use their own handheld device – typically a smartphone – to enter PRO data electronically.
- The use of dedicated handheld devices in clinical trials is well established. For example, subjects are highly compliant with daily electronic diary assessment schedules implemented through dedicated handheld devices (Stone et al., 2002). Numerous products have been approved based on primary and/or secondary endpoints that were supported by PRO data collected through dedicated electronic devices.
- BYOD approaches are emerging and potentially offer several advantages over dedicated devices. Specific considerations regarding BYOD are presented below and in one of the ePRO Consortium publications (Gwaltney et al., 2015). There are several open questions about the use of BYOD –

including operational, privacy and security, and scientific questions – that should be addressed before BYOD is widely used in pre-approval clinical trials where internal validity is paramount. We look to the FDA to collaborate with industry and the ePRO Consortium to collect the evidence needed to quickly answer these open questions and generate general best practice guidelines for BYOD that can be applied across therapeutic areas.

One key question that is often raised about BYOD is the equivalence of PRO data collected across different electronic devices. The use of different devices across subjects, or even within a single subject over time, is an inherent feature of BYOD trials. However, these devices may have different screen sizes, use different fonts, or present text in different ways. Major differences in how subjects see items on screen can be controlled. For example, the software program can ensure that patients are presented with a single item at a time and that subjects do not need to scroll to view response options. Nevertheless, the presentation will differ in some way across devices. This raises the concern that subjects' responses may be biased in some way by how the items look on screen. This concern was initially voiced in discussions regarding the equivalence of paper and electronic modes of administration, where the 'look and feel' of the presentations varied widely. Even in that relatively extreme comparison, scores were generally equivalent (Gwaltney et al., 2008; Muehlhausen et al., 2015). This suggests that the relatively minor differences seen across different electronic platforms should not bias responses. Indeed, the available evidence comparing different electronic modes (e.g., IVR, handheld, desktop) suggests that the mode exerts very little influence on responding (Bjorner et al., 2014). Therefore, although additional data are needed, we do not believe that cross-mode equivalence is a significant barrier to the uptake of BYOD in clinical trials.

Another interesting area where lessons have been learned about the electronic capture of PRO-based endpoint data is through the experience the ePRO Consortium has had with the Irritable Bowel Syndrome (IBS) Working Group within C-Path's PRO Consortium. In this particular therapeutic area, electronic capture of PRO-based endpoint data is preferred over paper-based data collection in clinical trials due to the frequency in which data collection might be necessary and the need for the subject to be able to enter data remotely (e.g., home, work, school). However, there were a number of operational and measurement issues that need to be considered when implementing PRO measures on ePRO data capture platforms.

In collaboration with the IBS Working Group, the ePRO Consortium conducted an electronic implementation assessment and performed the initial electronic implementation on a handheld ePRO device (e.g., smartphone). Although designed to be implemented electronically, the implementation process had its challenges in regard to operational and measurement-related decisions. The experience gained and lessons learned through the implementation process and the best practice recommendations for electronic implementation of new and existing PRO instruments are knowledge and expertise that the ePRO Consortium has and is in the process of publishing.

**Section III, Question 2: What are ways FDA could encourage adoption of these technologies and innovative methods in the conduct of clinical investigations?**

The benefits of electronic capture of clinical outcome assessment (COA) data are widely known. Some of the specific benefits derived by clinical trial sponsors include: improved subject compliance, improved protocol compliance, elimination of secondary data entry errors, reduced administrative burden, reduced sample size requirements, remote monitoring of data and real time access for data review (Fleming et al., 2015), among others. Advances in technology and the adoption/acceptance of the technology by sponsors and the general public have increased the capabilities and made electronic COA data capture in clinical trials a viable option for sponsors.

Regulators have encouraged the electronic capture of COA data (FDA PRO Guidance; FDA Guidance on Electronic Source Data) and should continue to do so. This support from the FDA has motivated clinical trial sponsors to transition from the well-established tradition of paper-based data collection to electronic modes of data capture. In order to increase the confidence of those using electronic capture of COA data in clinical trials, the ePRO Consortium is developing a set of recommendations on how to mitigate the risk of study sites and/or subjects deviating from planned electronic data capture protocols. Continued support for the electronic capture of COA data is an essential step in continuing to increase adoption of these modes and moving away from paper-based data collection.

Aside from using the various electronic modes listed in our response to the first question, the ePRO Consortium has also begun examining the adoption of wearable devices in clinical trials. These devices are able to gather a wealth of health information from subjects and would allow us to develop new correlations in clinical trials that were not previously possible. Yet their adoption has been slow due to lack of clarity as to whether the data they generate would be acceptable in a clinical trial. Use of wearable medical devices to measure activity and exercise, posture, heartrate and a wide range of other physiological measurements present an opportunity to plan for the incorporation of such data into clinical trials (and direct feeds into technology supporting clinical trials). Standardized methods and data standards must first be developed to streamline the integration of “wearable data” such that it can be aggregated and analyzed accurately. Standards for data transfer and formatting in a manner that ensures quality and integrity of results are also necessary.

The ePRO Consortium recommends convening the electronic patient-reported outcome industry, stakeholders and thought leaders to identify knowledge gaps regarding electronic data capture in clinical trials, define technologies accepted for use in clinical trials, and identify specific needs and best practices around use and data formats for “wearable data” to ultimately create a more collaborative environment between FDA, patients and industry. We recommend convening a consensus development meeting using the ePRO Consortium to serve as a driver of best practices and industry guidelines. The desired outcome of the workshop is the formulation of a position paper co-authored by meeting participants that outlines common goals and a framework for accomplishing these goals through the collaboration of the ePRO Consortium, FDA, patients and industry.

Stakeholders who can contribute experience, clinical evidence, or expertise in the field of clinical trials, particularly in the field of electronic patient-reported outcome assessment, would be invited to participate at this workshop.

Stakeholders invited to participate would include:

- FDA
- ePRO companies: leaders from the technology and innovation teams with expertise on use and implementation of technology in clinical trials
- Pharmaceutical industry: leaders from health outcomes units and ePRO teams
- Patients

**Section III, Question 3: Identify any clinical, cultural, business, regulatory, or other barriers perceived by stakeholders that serve as a disincentive to the use of technology to facilitate the conduct of clinical investigations.**

**a. What challenges do stakeholders anticipate in adoption of these technologies or methods? Are there challenges in complying with regulatory requirements surrounding the conduct of clinical investigations that use such technologies or methods?**

Key stakeholders in the adoption of technology include patients, clinicians, caregivers, investigators and other clinical research staff. As previously described, most people understand the advantages of electronic data capture instead of paper-based data collection; however, the use of new technologies make it a difficult decision for clinical teams especially moving from paper to electronic capture of PRO data for the first time. Even though mobile ePRO, including BYOD is becoming more common place, there are perceived barriers that need to be considered and mitigated.

- Lack of knowledge and awareness – Many stakeholders do not have the expertise or basic knowledge of the new technologies which may result in the clinicians, investigators and other study team members not wanting to risk using technology for electronically capturing clinical data points. ePRO companies providing electronic data capture services must have plans in place to educate the clinical teams and other stakeholders, if necessary.

- Fear of change – Generally, people are afraid of change and the unknown. Stakeholders may have a fear of complicated technology which can be a factor in the acceptance of new technologies like apps, wearables, and sensors.

- Privacy and security of data – Concerns over privacy and data security arise when study subjects are allowed to use their own smartphones or tablets (BYOD) for electronic collection of data supporting clinical trial endpoints. ePRO service providers have developed solutions that protect the subject's privacy, ensure secure and encrypted data transfer, and reduce the risk of deleting the app.

- Who pays for the data with BYOD – Traditionally, in ePRO studies, patients are provided a smartphone by the sponsor company. The cost for sending data entered by the subject is automatically covered by the sponsor. With BYOD, the patients are expected to use their own device and data plan and, therefore, are burdened with the cost of sending/transmitting data. Reimbursement for an appropriate proportion of the data plan costs should be considered.

**b. What are the perceived barriers or challenges to obtaining and documenting informed consent or obtaining institutional review board review, approval, and oversight for clinical investigations utilizing these technologies or methods?**

*The ePRO Consortium is not providing comments in response to this question.*

**Section III, Question 4: FDA is interested in obtaining information on potential trial participant acceptance, privacy, and human subject protection issues that may occur as a result of the use of technologies and innovative methods for the conduct of clinical investigations. In particular, FDA is interested in assessing potential trial participants' interest, tolerance, concerns, and willingness to participate in clinical investigations that involve nontraditional settings or utilize new technologies. FDA is also interested in identifying the factors that affect trial participant awareness, acceptance, enrollment, and retention for these investigations.**

**a. Are there specific patient groups or therapeutic areas that could particularly benefit from these types of technologies or methods?**

Our experience indicates that all patient groups and/or therapeutic areas benefit from the inclusion and use of technology. With the abundance of technology and, in particular, smart devices in daily life, previous concerns in regard to technology literacy, end-user confidence, access to technology, and/or connectivity are no longer barriers. Technology increases the flow and timeliness of data to the study team from participants, allowing stakeholders to make time-sensitive, study-related decisions based on the feedback. All therapeutic areas are benefited, particularly those where patient function is limited. The introduction of interactive devices allows users with limited mobility, often times bed-ridden, to provide clinical feedback by touch or voice, with minimal effort and high accuracy.

**b. What new opportunities for the conduct of clinical investigations are created through the use of continuous or intermittent remote monitoring and data collection?**

Continuous or intermittent remote monitoring allows study teams to remain agile through the duration of the study (Fleming et al., 2015). This flexibility benefits the safety of its participants as well as the quality and quantity of the data being collected.

**c. What are some of the anticipated risks to trial participants that may occur as a result of the use of these technologies or off-site methods in clinical investigations?**

One of the biggest concerns expressed by clinical trial sponsors is data backup in instances where the technology function fails or when devices are lost or stolen. Today's risks are highly mitigated through the careful monitoring of activity that can be achieved through the use of technology by way of alarms and notifications. Additionally, improvements in software allow us to remotely disable and reset devices in the field in cases where devices become lost or stolen, allowing for maximum data integrity and confidentiality.

**d. What are some of the anticipated benefits to trial participants that may occur as a result of the use of these technologies or off-site methods in clinical investigations?**

There are many benefits for trial participants. For instance, technology allows ease of use, increases compliance through alarms and reminders (Fleming et al., 2015), clarifies programming that can lead to more and better data, and allows mobility for users to collect and transfer time-sensitive information.

**e. Are there perceived challenges to participation in clinical investigations utilizing these types of technologies or methods because of concerns regarding inadvertent disclosure of trial participants' information or breach of privacy? Are there concerns relating to the integrity of data collection or encryption or the secure transmission of information?**

Perceived challenges are oftentimes due to miscommunication or misinformation. Traditionally, subject responses and subject identifying information are safeguarded separately to maintain integrity and security. Furthermore, extensive security protocols are followed to provide up-to-date encryption during collection and transmission, and as mentioned before, today's technology allows for remote management, thus adding another layer of security for users.

**f. Are there unique considerations for ensuring integrity of the source data, for example, authenticity and reliability?**

Procedures are put in place on the front-end (study subject facing) and the back-end (internal programming) to ensure data integrity. Front-end procedures would include the use of pin/passwords for proper authentication and the assurance that the end-user has been properly trained in the usage of the technology. Back-end procedures would include current encryption protocols and data backup procedures. Whether or not the source records are adequate to inspire confidence in the study depends on the quality, integrity and validation of the processes used for capture as well as the storage and protection of the records. Given role-based procedural controls and authentication that ePRO systems provide, these eSource records are not subject to tampering or modification by the sponsor—only the investigator or authorized designee can make edits and all edits are in the audit trail for each item, form and subject.

**g. How should validation of participant-operated mobile devices be addressed?**

The sponsor needs to clearly provide criteria on minimum requirements for participant-operated mobile devices prior to allowing a particular device in the study (e.g., operating system, device screen size, screen resolution, memory/storage capacity). The sponsor should also consider and disclose the potential cost to the end-user for transmitting data from their personal devices; data cost may include the study application's initial download, scheduled assessments, and software upgrades.

**h. What are the challenges presented when data are collected using the Bring Your Own Device (BYOD) model? What are the perceived barriers to pooling data collected from different devices provided by individual trial participants, as well as pooling data from the BYOD model with data collected at the investigational site or on paper forms? How should situations such as mid-study user device switches be handled?**

Field-based PRO assessments, administered outside of a clinic, can be critical to evaluating the efficacy and safety of new medical treatments. Subjects are typically provided electronic devices, such as smartphones, to respond to assessments in their preferred environment (e.g., home, work, school). Conducting ePRO methods using provisioned devices can be costly and requires subjects to carry a dedicated device. The BYOD approach addresses many of these concerns. As mentioned earlier, the ePRO Consortium has identified operational, privacy/security, and scientific/regulatory considerations regarding BYOD (Gwaltney et al., 2015).

The BYOD model provides many benefits to the end-user, which includes the ability to use one device for all their activities and the assumption that their comfort level is at its maximum with their own device. If participant devices meet previously established functional parameters, it mitigates concerns on the ability to pool data from such devices. Mid-study device changes should be seamless as long as the new device falls within the established parameters for the device criteria set for the study.

**i. What are the challenges or special considerations with recruiting and/or retaining potential trial participants with low levels of computer literacy or individuals who may have limited or no access to mobile technologies, computer devices, or the Internet? How can these challenges or special considerations best be addressed?**

Proper site and end-user training and the site's attitude towards technology are crucial to the success of low computer literacy end-users for any study participant. Training is paramount in assuring that the participant is knowledgeable and comfortable using new technologies. Access to a knowledgeable and patient-sensitive support team throughout the study helps the user with technology concerns. In order to include all potential users, even in instances where the study team wants to follow a BYOD model, the study team must consider and be prepared to provide limited amounts of hardware to those with limited resources or access.

Best practices documents for maximizing electronic data capture options during the development of new PRO instruments, migrating new PRO instruments to a new data collection mode and implementing PRO response scale options are available at http://c-path.org/programs/epro/. These documents have been developed by the ePRO Consortium to set industry standards for electronic implementation of PRO measures.

***Name and affiliation of ePRO consortium members contributing to these comments:***

- Cindy Howry, YPrime and Vice Director, ePRO Consortium
- Tim Davis, ExcoInTouch
- Paul O'Donohoe, CRF Health
- Mario Donoso, Bracket
- Chad Gwaltney, ERT

**References:**

Bjorner JB, Rose M, Gandek B, Stone AA, Junghaenel DU, Ware JE. Method of administration of PROMIS scales did not significantly impact score level, reliability, or validity. Journal of Clinical Epidemiology 2014;67(1):108-113.

Coons SJ, Gwaltney CJ, Hays RD, Lundy JJ, Sloan JA, Revicki DA, Lenderking WR, Cella D, Basch E. Recommendations on Evidence Needed to Support Measurement Equivalence between Electronic and Paper-Based Patient-Reported Outcome (PRO) Measures: ISPOR ePRO Good Research Practices Task Force Report. Value in Health 2009;12(4):419-429.

Coons SJ, Eremenco S, Lundy JJ, O'Donohoe P, O'Gorman H, Malizia W. Capturing Patient-Reported Outcome (PRO) Data Electronically: The Past, Present, and Promise of ePRO Measurement in Clinical Trials. The Patient-Patient-Centered Outcomes Research 2014;8(4)301-309.

Eremenco S, Coons SJ, Paty J, Coyne K, Bennett AV, McEntegart D. PRO data collection in clinical trials using mixed modes: report of the ISPOR PRO mixed modes good research practices task force. Value in Health 2014;17(5):501-516.

Fleming S, Barsdorf AI, Howry C, O'Gorman H, Coons SJ. Optimizing electronic capture of clinical outcome assessment data in clinical trials: the case of patient reported endpoints. Therapeutic Innovation & Regulatory Science 2015;49(6):797-804.

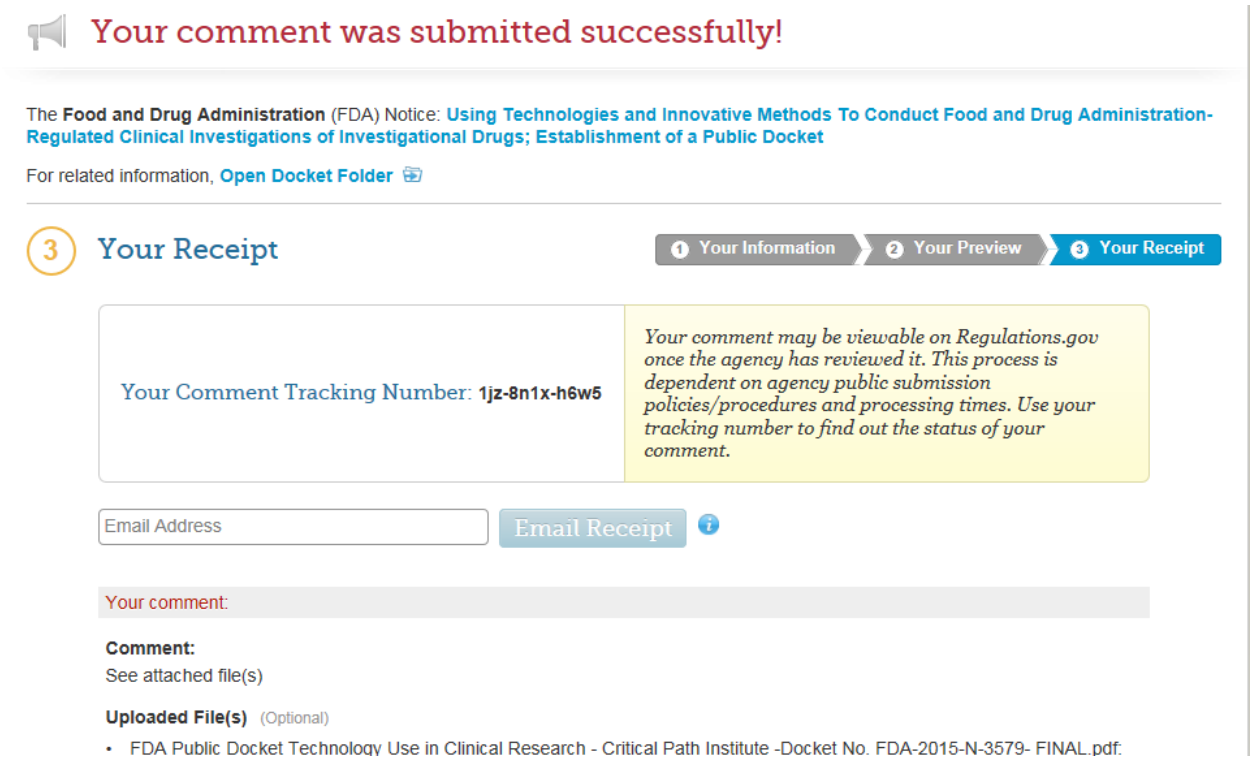
Gwaltney CJ, Shields AL, Shiffman S. Equivalence of electronic and paper-and-pencil administration of patient-reported outcome measures: a meta-analytic review. Value in Health 2008;11(2):322-333.

Gwaltney C, Coons SJ, O'Donohoe P, O'Gorman H, Denomey M, Howry C, Ross J. "Bring Your Own Device" (BYOD): The Future of Field-Based Patient-Reported Outcome Data Collection in Clinical Trials? Therapeutic Innovation & Regulatory Science 2015;49(6):783-791.

Muehlhausen W, Doll H, Quadri N, Fordham B, O'Donohoe P, Dogar N, Wild DJ. Equivalence of electronic and paper administration of patient-reported outcome measures: a systematic review and meta-analysis of studies conducted between 2007 and 2013. Health and quality of life outcomes. Published online on October 7, 2015.

O'Donohoe P, Lundy JJ, Gnansakthy A, Greene A. Considerations for requiring subjects to provide a response to electronic patient-reported outcome instruments. Therapeutic Innovation & Regulatory Science 2015;49(6):792-796.

Stone AA, Shiffman, S. Capturing momentary, self-report data: A proposal for reporting guidelines. Annals of Behavioral Medicine 2002;24(3):236–243.



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