ISCTM Innovative Technologies Workgroup:
Adapting Trials (In a Hurry) for Remote Assessment Call #2

Working Group Chairs: Rich Keefe, PhD; Mike Davis, MD, PhD

FDA Panelists:

- OMP - Leonard Sacks, Beth Kunkoski, Isaac Rodriguez-Chavez, Khair ElZarrad
- DP - Mike Davis, Tiffany Farchione, Valentina Mantua, Zimri Yaseen
- COA - Elektra Pappadopoulos

Additional Panelists:

- David Walling, PhD – Licensed Clinical Psychologist; Principal Investigator for many CNS trials, Collaborative Neuroscience Research LLC
- Robert Bilder, PhD – Professor in Psychology, Psychiatry and Biobehavioral Sciences, UCLA; Chair of a COVID-19 Writing Committee that wrote recommendations/guidance for remote neuropsychological assessments on behalf of a joint organizational committee from multiple neuropsychology societies

Theme: Data Quality – How do we maximize data quality during clinical trials conducted during this pandemic period?

1. What information can sponsors collect/how can rapid adjustments to things like virtual PROs, ClinROs and PerfROs be executed to collect information related to this while remaining compliant?
2. We have a double-blind, placebo-controlled trial that is currently ongoing and have recruited about one third of our total number of subjects. Due to COVID-19 we are anticipating collecting data remotely for a number of safety (e.g. AIMS, BARS etc.) and efficacy scales (Y-GTSS, CGI etc.) as well as some PROs (Caregiver Global Impression of change etc.). the protocol is being amended and will be submitted to the agency. It is reasonable to assume that some of the data will be collected at sites (in person with face to face interviews) and some will be collected by remote means. **We would greatly appreciate your thoughts about approaches to assessing quality of data while the study is going on.**
3. What date would you use for an analysis of cohort data being impacted by COVID19?
4. For active trials, as trials go remote and shift measurements to match, how can sponsors best justify and document the changes to new measures, and compare data from the current remote assessments from previous trial data with different assessments?
5. If the subject is read the PRO and rater is completing the digital scale on subject behalf, do we need confirmation from subject that their answers were correctly marked?

Theme: Remote Assessments Method Validity

1. Ongoing studies may be at risk should stay-at-home orders become rolling over the next 18 months. This may make it necessary to conduct assessment remotely, in the context of trials not being initially set up for such assessments. Should sponsors be planning to replace such patients for which the primary endpoint is impacted, or do you see flexibility in accepting a variety of assessment collections because of COVID?
2. If a trial switches during the ongoing trial to remote assessments, why is it of benefit to switch all assessments to remote, and not on a site by site basis? The data will be "mixed" anyhow?
3. If an ongoing study is 're-tooled' from face-to-face (f2f) assessment administration to remote administration, are the FDA experts recommending or mandating that all trial centers then have to switch from f2f to remote? Meaning it would not be acceptable to switch only a certain % of sites over to using remote assessments?

Theme: Remote Assessments Content Validity

1. As those designing and implementing clinical trials adjust to the COVID situation, there is a question especially in CNS of the quarantine state and the impact of a global pandemic in general on assessment results (are people more depressed, are treatments working differently as a result of less outside time, access to clinicians or family, exercise, etc.). **How is the FDA considering these impacts?**
2. How are the psychological stressors being accounted for during analysis? This will clearly affect the data and analysis. For example, would these assessments still be valid considering a major change in the subject status?
3. Is there value in collecting data regarding whether patients in current trials are sick with COVID-19 to potentially adjust analysis plans post-hoc?
4. Could one run a sub-population analysis to investigate the impact of social stress due to COVID? Sub-Population prior and now during the crisis time?
5. The influence of social stress came up on our last call as a potentially confounding effect on measuring symptoms e.g. in a depression trial, and some other psychiatric trials. Social stress can act as a short-term but significant 'add-on' to the chronic depression severity a patient experiences. **Do the FDA experts have an expectation that a trial explicitly has to assess social stress, or is this just an 'imperfection' we currently need to live with?** Fix #1 (?): I could see for example to add a social stress outcome measurement to protocols, as attempt to quantify its impact. Fix #2 (?): Secondly, **would it be acceptable to increase the level of clinical judgement in an outcome instrument**

that measures depression (e.g. MADRS or Beck) to allow the rater for separating the disease-type depression from the 'tactical' COVID-induced depression? If yes, should such additional guidance for the administration of an outcome originate from the scale author, or test copyright owner, rather than on a trial-by-trial basis?

Theme: Remote Assessment Methodology

1. When an in person visit is not possible, patient-reported-outcomes might be collected by a clinician who would read the questions and record patient answers. Is there any guidance on this situation, particularly when the PRO is administered by an eCOA platform?
2. Related Safety Assessment Questions
    a. To what extent if any can telemedicine technologies be utilized for safety assessments such as physical examinations, electrocardiograms, clinical laboratories, etc.? (Obviously telemedicine only allows for physical inspection, not auscultation or palpation; remote ECG seems possible; remote labs probably require sending a phlebotomist to a subject's home for sample collection)
    b. How would remote video assessments assess items that require the rater to actually touch the subject, such as to evaluate cogwheeling?
    c. How are people are addressing labs and safety assessments where a drug has limited human safety data?
    d. To what extent can physician objective assessments, such as physical examination, swollen joint count, physician global assessment of condition, be made using virtual platforms such as Facetime?
3. With major recent security concerns with some of the most popular remote video tools (notably Zoom) how is the FDA considering remote video tools and are there any (or any coming) recommendations on approved technology solutions for video/video recorded visits?

Theme: Technology Access

1. In response to the question about the percentage of participants in CNS clinical trials who own devices that can be used for remote assessment, such as iPads or smart phones, the question was raised about the challenge of knowing **how to implement the platforms needed for video conferencing. CNS trial subjects more commonly have HS education or less and are not young and so may have less technological expertise.**

2. If patients do not have computers at their homes or residences, what other available options are there for remote assessments?
3. Similarly, in patients who are low functioning, what recommendations would you provide for remote assessments, for example a PANSS or EPS scales?

Theme: Ethics

1. Is there any value in trying to obtain primary efficacy assessments, through e.g. video meetings, when we upfront know that there is no validation of this? Would it be better, or more ethical to discontinue these patients from the studies?
2. To move to remote or telephonic administration of COAs instruments will require special informed consent from signed by the patient and caregivers (when applicable) either for the change on the evaluation format and also to adhere to the Data Protection regulation on each country. Since there is a clear risk to send out documentation to the patient, we should consider other options. An option could be that thorough the phone or videoconference, the patient consents before each remote evaluation. To use this method, it is also needed that IRBs are informed and approve this process. In a recent webinar organized by DIA-Direct COVID-19 on March 26, researchers from China, commented how IRBs in China evolved to meet remotely and also to speed up the process of review /approval of clinical trial documents.

Theme: Statistical Analysis – How should we analyze the data when the measurements are impacted by COVID-19 related conditions?

1. Which additional statistical analyses should be conducted after database lock to ensure that the data collected by both methods [in-person + remote assessments] can be combined and will yield valid results?
2. Many psychiatric scales were created in an era where face-to-face administration was the norm. There are some scales which have not been validated for administration by telephone or through other remote means (example: PANSS). **How should sponsors handle the analysis of assessments which had to be captured remotely during the pandemic with an instrument that has not been validated in these situations**?
3. I wonder if sponsors that will use remote versions of outcomes in ongoing trials for the evaluation of patients during COVI19, will be requested compare patients' characteristics with the aim to discard any type of difference between those patients with access to technology with those patients without. I think that patients with a lower

economical level might have less possibilities to have this type of evaluations, therefore more missing data.