COVID-19 COMPENDIUM

WHITE PAPER

Training and Calibration is Essential for Success of COVID-19 Related Remote Monitoring

DAVID G. DANIEL, MD
SR. VICE PRESIDENT AND CHIEF MEDICAL OFFICER,
Signant Health

LEWIS M. FREDANE, MD
CLINICAL VICE PRESIDENT,
Signant Health

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This informational white paper is part of a compendium intended to share best practices and ongoing learnings related to the impact of COVID-19 on ongoing and planned clinical trials. Content is authored by a dedicated team of experienced scientists, clinicians, technologists, and data quality experts. To read other white papers in the series, please visit **www.signanthealth.com/covid**

During the COVID-19 pandemic, remote evaluations of clinical trials participants have been adapted in response to social distancing and restrictions in local travel. In such scenarios the location and manner of assessment of a participant may vary over time. For example, screening and baseline assessments may have been conducted by the primary rater, in-person, at the research site and subsequently after local stay at home orders were issued, by necessity, the participant may be evaluated remotely at their place of residence by telephone or audio-video teleconference. This presents the perilous possibility of different environmental and technical conditions of assessment and different raters for the same participant at baseline and at subsequent visits. Loss of consistency of measurement technique among raters is a well-documented source of diminished statistical power (Perkins, Wyatt and Bartko, 2000; Muller and Szegedi, 2002) and erratic ratings are associated with increased placebo response and diminished drug-placebo separation (Kott, Daniel, et al., 2017). Thus, transition from assessment of the participant at the site to remote assessment may obfuscate drug-placebo separation by introducing substantial variability and noise into measurement of symptom severity.

Pharmaceutical sponsors typically invest substantial time and energy toward calibrating investigators to interview and measure symptoms uniformly in their offices or hospitals prior to study initiation and closely monitor for loss of symptom measurement calibration thereafter. In the COVID-19 emergency, many raters will be called upon to remotely assess participants using techniques they are inexperienced with. In addition, participants and caregivers may be required to operate remote assessment technology they are unfamiliar with. Both situations may lead to marked variation in assessment technique, participant presentation and apparent symptom severity among remote visits, and certainly variation versus in-person evaluations at the site. We suggest that, to the extent feasible, raters be formally trained and calibrated in remote administration of the relevant scales prior to remotely assessing participants. We recommend that the same primary and back-up rater who evaluated the participant in person at the site evaluate the participant remotely. A sample generic remote training and calibration curriculum for the rater is shown in Table 1A and 1B.

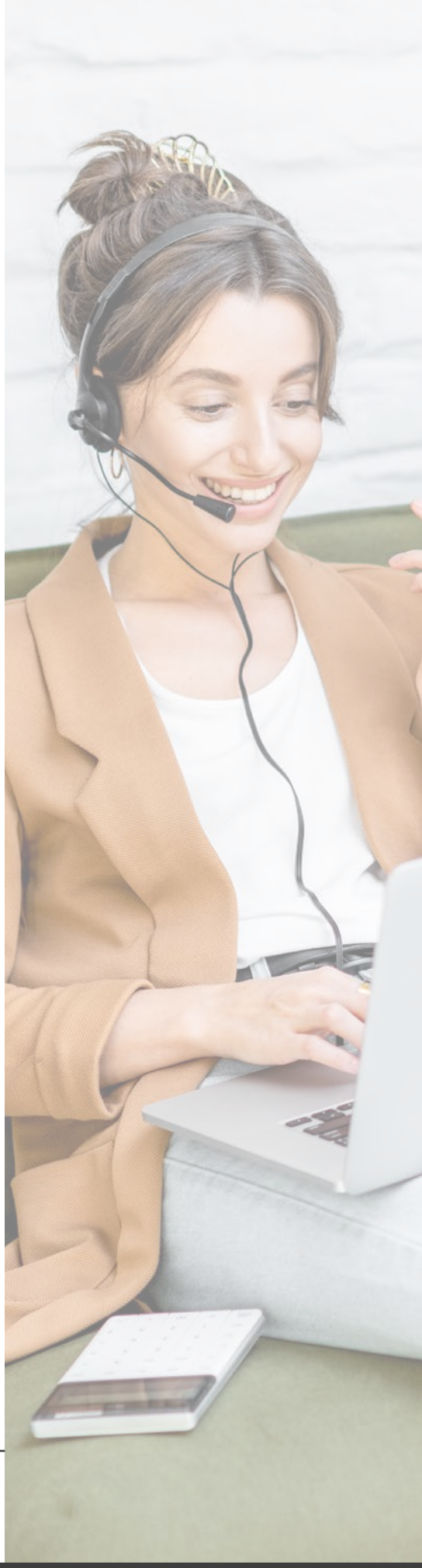

TABLE 1A. A SAMPLE GENERIC REMOTE TRAINING AND CALIBRATION CURRICULUM

Training Objectives	The purpose of this training is to provide rater with guidance on remote clinical assessments in clinical research especially during the COVID-19 crisis. The training may also be used as a guide for developing and implementing more detailed training and calibration programs tailored to specific studies and/or scales. Scale specific training should ideally include a scoring calibration exercise as well as a mock scale administration.
Training Content	**General considerations for remote clinical assessments** 1. Legal/regulatory 2. Clinical 3. Technology 4. Operational **Patient safety and well being** 1. Maintaining privacy and confidentiality during remote assessments 2. Obtaining consent 3. Responding to suicidality and other threats to safety 4. Symptom exacerbation – inadvertent collection of adverse event information 5. Considerations for vulnerable populations (e.g. adolescents, patients with cognitive impairment) **Remote scale administration** 1. Modality of the remote clinical assessments 2. When to perform remote assessments 3. Challenges and tips in assessments via telephone 4. Challenges and tips in assessments via videoconference platform 5. How to prepare participants and informants/caregivers (introducing remote assessment and instructions prior to scale administration) 6. Remote ClinRO Assessments 7. Remote PRO Assessments **Maintaining data quality** 1. Mitigating placebo response 2. Calibration and tips to maximize data quality 3. Technical considerations for videoconference assessments 4. Tips to set up videoconference equipment
Time to Complete	30 minutes
Delivery Mode	Web-based training + Brief live sessions

TABLE 1B. A SAMPLE SCALE REMOTE TRAINING AND CALIBRATION CURRICULUM

Training Objective	Ideally, all remote raters are trained and calibrated on the remote administration and scoring of the scale prior to remote assessment of participants. It is critical that the primary and back-up raters at a site align their remote interview and rating techniques. If possible, prior to remote administration with a participant, the primary and back-up raters at each site should complete a remote administration and scoring of the scale with an actor trained to portray the disorder of interest. The session should reviewed and approved by calibrated expert trainers prior to beginning remote assessments.
Scale Training Content	• Scale overview if needed. If scale training and certification has been previously completed, for example in an ongoing study, this section may be abbreviated or skipped • Overview of remote scale administration specific to telephone or video conference, best practice guidelines regarding consent, preparation of patient and environment, safety considerations, technology, scheduling, documentation • Scale and scale item specific training detailing best practice and caveats for gathering valid and reliable data, consistent with the conventions of the scale during a telephonic or video assessment • Mock administration of the scale via telephone or video conference, evluated by expert trainer either live or through review of a recording • Calibration scoring (within and across sites) of a recorded telephonic or video assessment It is highly desirable that all raters successfully complete all required components for a specific study prior to rating participants.
Time to complete	3 hours
Delivery mode*	• Online robust scale training including didactics, case examples, quizzes and practice scoring • Review of scoring results • Further training and/or individual remediation via phone, online or live training, focusing on items with poor administration and scoring calibration

**Virtual Training Challenges include time zone differences, single language presentations, connectivity challenges, especially over long periods of time. Therefore the delivery model should front load with online training. Results of that training will inform the content for following up online or live virtual training.*

The primary objectives of training are 1) to create as similar conditions to the baseline site rating as possible; 2) consistency of the interview and symptom measurement technique between the primary and back-up rater and longitudinally; 3) facilitation of a consistent comfortable setting for evaluation at the participant's residence and competent camera operation for adequate visual assessment; and 4) adequate provision of privacy for separate participant and caregiver evaluations, when indicated. Examples of training curricula for participants and caregivers are described in Tables 2 and 3.

TABLE 2. SAMPLES OF SPECIFIC INSTRUCTIONS TO RATERS

GENERAL CONSIDERATIONS FOR REMOTE CLINICAL ASSESSMENTS

- Participant safety protection is paramount
- All GCP practices should be adhered to, including good documentation practices
- Same rater who had administered the scale at a site should continue to administer the scale remotely for consistency. If this is impossible a back-up rater who has been calibrated with the primary rater should be utilized.
- Raters should continue to adhere to training conventions related to maintaining neutrality and seeking to minimize placebo response
- Raters should NOT adjust scale ratings based on a sense that reported symptoms may be situationally-based (e.g., caused by Covid-19 concerns), but rather should continue to rate symptoms as they are reported by the participant without making symptom attributions
- If adverse event-related information is reported by the participant during a remote assessment, please evaluate the participant further, suggest that the participant obtain medical attention if needed, consult with the Medical Monitor, and document accordingly
- Rater must be familiar with emergency procedures at the participant location and have a ready plan in place should emergency safety concerns arise such as imminent suicidal or violent behavior
- Follow the regulatory guidance and applicable legal requirements
- Sites are responsible for coordinating multiple scale interviews with participant in the order specified by the protocol
- In general, videoconference is preferred over telephone for clinical assessments. Telephonic rating may be acceptable for some types of scales but should be a last resort for scales that require visual assessment and used as directed by the sponsor. If specified by the sponsor telephonic interview for scales with visual components may involve asking additional probes when interviewing the participants and informants for items where visual observations are required for rating.
- Prior to rating, make sure that participant is comfortable with audio video assessment, grants consent to the mode of assessment and understands the procedures. Caregivers may be required for proper videoconference operation. Caregiver participation should be balanced against privacy concerns.
- Where possible, the informant who accompanied the participant to in-clinic visits should continue to be the informant in remote assessments. If this is not possible, make sure to note the rationale for informant change in your clinical notes and ensure the new informant is able to accurately report on the participant's symptoms
- Remote interviewer should follow all home office best practices for clinical trials and for remote assessments, e.g., video screen should not face a window
- Ensure the correct assessment is being used (some copyright holders have specifically designed scale versions and recommendation for remote assessment)

TABLE 2. SAMPLES OF SPECIFIC INSTRUCTIONS TO RATERS (CONTINUATION)

CHALLENGES FOR REMOTE ASSESSMENTS	TIPS
Lack of focus: Participant may be easily distracted during the interview	• At the beginning of each interview, remind the participant of how long the visit is likely to last and ask them to confirm they can stay on the phone/ video call for the duration and uninterrupted • Make sure both you and participant conduct the call in a room that is not located near noisy areas (e.g., kitchen) • Ensure adequate privacy--others such as family members or pets should not be around participant during the assessment • Re-direct participant attention if they appear distracted
Technology issues: Poor audio/visual quality can negatively impact the interview	• Check in with participant throughout the assessment process to make sure they can hear/see clearly • Minimize background noises if speaker phone is used • Identify alternative ways of making contact in the event of a technology failure • Make sure to note any difficulties in rating items that may be related to the administration method.
PROS	
• Consultation with scale author/holder and review of literature should guide the decision regarding mode of remote PRO completion • For eCOA studies web based ePRO completion is preferred but may not be possible in some remote situations • If the participant or caregiver is completing the PRO on paper have the participant/caregiver complete the scale during the telephonic or video visit to ensure correct day and time for PRO completion is followed • If via teleconference, participant/caregiver can show completed form to rater so it can be checked for completeness	• Return of paper form should include stamped addressed envelope. Data will need to be back entered when returned to site. Documentation must clearly detail mode of administration and data entry • There may be studies in which it is preferred for the remote rater to read the PRO to the participant/caregiver and record the scores. In this case the participant/caregiver should have the PRO available for reference during the assessment • When asked to interact vocally, participant/ caregiver might respond differently from how they responded when allowed to complete the scale alone on a tablet/paper

TABLE 3. A SAMPLE OF INSTRUCTIONS FOR PARTICIPANTS AND CAREGIVERS

PREPARATION TIPS

- Make sure your meeting room is not located in a quiet and private area
- Ensure adequate privacy—others such as family members or pets should not be around you during the assessment
- Make sure there is minimum distraction during the assessment. You may turn off your mobile phone (for teleconference assessments) or close your laptop (for telephonic assessments) during the assessment
- Select a room that is large enough to comfortably accommodate you and videoconferencing equipment
- Remember there are no right and wrong answers, please try to report your symptoms as accurately as possible
- Your rater will ask informant/caregiver to remove clocks and calendars from a room if assessments of cognition (e.g., MMSE, ADAS-Cog) are being conducted and ensure the patient is not wearing a wristwatch or has access to a mobile phone that indicates time/date

HOW TO SETUP VIDEOCONFERENCE EQUIPMENT AT HOME

- Camera should be secure and stable to prevent shaking
- Camera should be at eye-level
- Room should be evenly lit with over heading lighting or lighting behind the camera
- Reduce extraneous light from windows or other sources such as lamps

Remote administration of certain scale items may be challenging or impractical remotely. For example, telephone administration precludes evaluation of visually assessed items. Within a protocol, sites must be trained in a uniform way of handling these items. In some cases of telephone evaluation, the participant and/or caregiver may be asked to describe the visual phenomena under evaluation in lieu of direct inspection by the rater. When audio-visual assessment technology is employed the rater and participant or caregiver should have a written script describing, item by item, what parts of the body or activity (eg, walking) should be visible on the screen of the camera and at what distance. Standardization of the visual representation of the participant is critical to consistent symptom measurement. Physical and neurological examinations conducted remotely may include assessment of tactile phenomena, such as texture, turbidity and rigidity that cannot be fully evaluated by camera. Investigators must be trained with conventions to address these items given the limitations of the exam.

Ongoing data quality monitoring by blinded data analytics or external expert review of recorded remote evaluations can trigger retraining and recalibration when needed. Despite the COVID-19 emergency situation, continuity of high quality, reliable data can be achieved by careful calibration of procedures and ongoing monitoring, as described above.

Tables 1, 2 and 3 authored by Sayaka Machizawa, PsyD and Barb Enger, MSN with contributors Martina Micaletto, MSc, Danielle DiGregorio, PsyD, Juliet Brown, PhD, and Simona Iraheta, MA

REFERENCES

1. Kott, Alan; Daniel, David; Wang, Xingmei; Umbricht, Daniel (2017): The effect of accumulation of erratic changes in PANSS Negative Factor at research sites on response to placebo and drug placebo separation. Poster presentation. International Society for CNS Clinical Trials and Methodology (ISCTM). Paris, France, 9/1/2017.

2. Perkins, D. O.; Wyatt, R. J.; Bartko, J. J. (2000): Penny-wise and pound-foolish: the impact of measurement error on sample size requirements in clinical trials. In Biological Psychiatry 47 (8), pp. 762–766.

3. Müller, Matthias J.; Szegedi, Armin (2002): Effects of interrater reliability of psychopathologic assessment on power and sample size calculations in clinical trials. In Journal of Clinical Psychopharmacology 22 (3), pp. 318–325.

4. Tuerk, P. W., & Shore, P (eds) (2014). Clinical Videoconferencing in Telehealth: Program Development and Practice. New York: Springer International.

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