COVID-19 COMPENDIUM

WHITE PAPER

Remote Ratings as an Adaptation to COVID-19

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COVID-19 COMPENDIUM

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**

INTRODUCTION: PURPOSE AND SCOPE

This document offers guidance implementing remote assessment as an adaptation for protocols operating during the COVID-19 crisis. This guidance focuses on obtaining data in a manner which will at least identify instances where and how remote ratings are used and offers principles to maximize the quantity and quality of data collected while working under conditions of uncertainty.

THERE ARE SEVERAL ASSUMPTIONS UNDERLYING THIS GUIDANCE:

1. Collecting some/partial information is preferable to no information, particularly for patients that are enrolled and have been randomized into a study.

2. Standardization of collection and administration are key objectives in randomized studies. Adaptive recommendations should favor administration under the best feasible methodology. There are many variables to consider with patient populations and safety situations within regions and individual sites. With regard to remote administration, this means collecting the highest quality data possible for the highest possible percentage of participants and sites. As a rule, we recommend using the approach or platform closest to that which would be used to administer the assessment at a site. Therefore, we favor methods such as video-teleconference if applicable to 90% rather than limiting all assessments to audio only telephone assessment. Even so, for the remaining 10% we note other "acceptable" methodologies (e.g. standard audio only phone interview) and recognize circumstances under which ratings are unacceptable.

3. Adaptations for remote assessments will not necessarily require validation studies to establish equivalence between modes of administration. Instead, adaptations or variations in technique must be appropriately documented to ensure the conditions of collection can be identified. IRBs should be notified when adaptations are undertaken and decisions on utilization of remotely collected data should be made by agreement between study statisticians, regulators and IRBs.

4. Study participants can meet the requirements for remote assessment. Considerations may include the participant's living situation, access to appropriate technology and basic compliance with study and assessment requirements. Sponsors may consider providing standardized, secure and compliant technology to patients to facilitate assessments.

IMPORTANT BASIC CONSIDERATIONS

LEGAL AND REGULATORY

All solutions must be safe, lawful, and implemented consistently. Obtaining and documenting informed consent has special requirements and will be dealt with separately.

OPERATIONAL

To maximize feasibility across as many circumstances as possible, the technical requirements, training requirements, and respondent burden should be minimized. However, it is not necessary to accommodate every conceivable circumstance or sacrifice what's possible for what might be perfect. For instance, we know that during typical site based operations phenomena such as rater change and inability to schedule appointments within protocol specified windows causes variance and or data loss.

LOGISTICS

An established communication plan with participant should be in place. The participant's capability to conduct a remote assessment should be evaluated through that communication channel. Their living situation, access to technology and the availability of an appropriate location to conduct the remote assessment are among the issues. Those same considerations would apply to a clinician conducting the remote assessment outside of the site. Also, the site or clinical rater's technology to conduct a remote assessment must fit the purpose of the assessment, and, when video conferencing is the appropriate solution, should be conducted on a HIPAA compliant videoconferencing platform unless reglatory exemptions have been granted.

CLINICAL

The varying level of complexity is an important consideration. Thus, it is reasonable to start with the question of when a remote visit might be permissible. From there, we can proceed with consideration of how to administer ratings in a manner that best preserves the integrity of the protocol.

SAFETY

Safety of participants and clinical staff are paramount considerations. In the context of a government declared public health emergency, clinic visits are expected to carry safety risks and will be viiewed as a violation in some areas. Ideally, under these circumstances a contingency plan for remote ratings would be activated. Such a plan would be multi-tiered, cover each type of rating in the protocol, the requirements implementing specific scales and other basic safety considerations. For example, a clinician conducting a remote assessment should know the physical location of a participant in case there is a need to contact local emergency services.

ENGAGEMENT

Scale authors and copyright holders should be consulted. Remote administration guides and equivalence studies do exist for some outcome measures. In our experience, engaged authors and copyright holders can provide practical guidance and modifications that will help standardize the administration of a given scale.

RATING SCHEMA

The recommendation is to first verify if there are equivalent or copyright holder published adaptations for remote assessments. These versions should be used and standardized across a study for remote assessments, with IRBs notified. When applicable, translations that are conducted to recognized standards should also exist for any modified versions of scales.

ASSESSMENT TYPE	PROBES	PARTICIPANT RESPONSE	INTERMEDIARY JUDGMENT	ITEM SCORED
PRO (patient reported outcome)	Direct Scale Questions →	Self Report →	None	By participant
ObsRo (observer reported outcome)	Direct Scale Questions →	Observer or caregiver report →	None	By Observer or caergiver
ClinRo (clinician reported outcome)	Interview Questions; stimulii →	Self Report, clinician observation or physical interaction →	 Clinical Rater →	By rater judgment
sClinRo (computer administered ClinRo; computerized tests)	Interview Questions →	Self report →	 Algorithm →	Computer algorithm
PerfO (Performance outcome)	Defined tasks, often over time →	Interpretation →	 Defined metric →	Scored by tester
Sensor based metrics	None →	Raw data transmission →	None	Electronic readout

PATIENT REPORTED OUTCOMES AND SIMILAR INSTRUMENTS

The defining characteristic of a PRO is the absence of any intermediary judgment between participant and score. The participant's response is the score. When collecting PRO remotely, this characteristic should be scrupulously respected. In addition, it's important to assure that the environment in which the participant completes the PRO permits the participant sufficient privacy, time, and minimizes noise and other distractors.

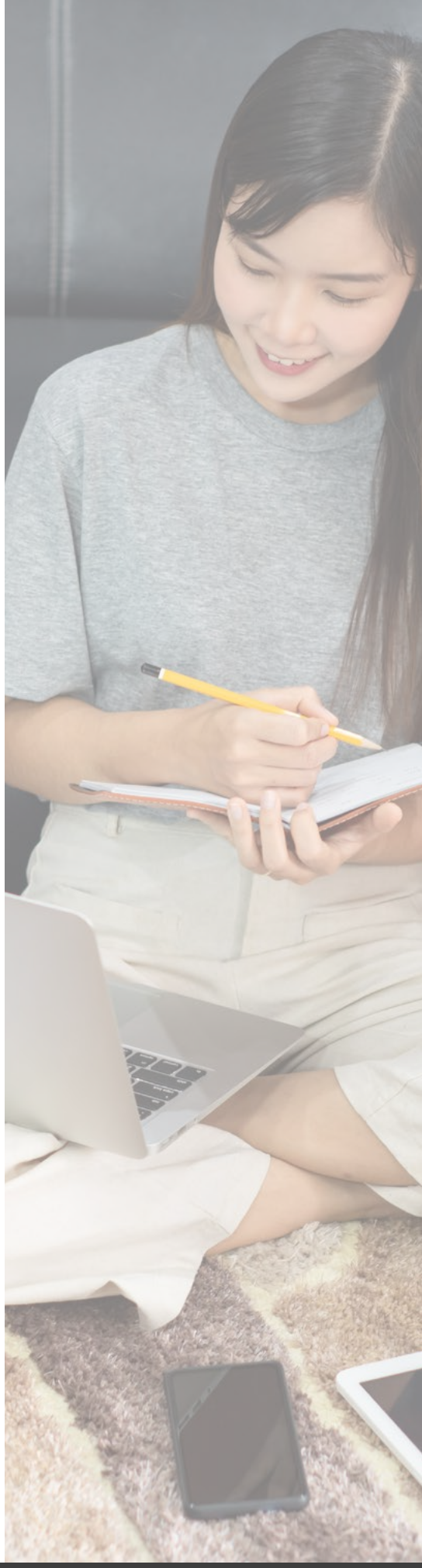
In some cases, a human rater could simply read the prompts of a PRO and record the participant's responses. If this mode of administration is undertaken, it should be continued throughout the study for consistency. In the case of PROs which collect sensitive, socially undesirable or other information considered highly private, avoiding reporting through raters or other remote study personnel is recommended. Notably it is been shown that participants report differently in regard to suicidality, sexual behavior, substance use, and items considered culturally taboo when reporting to a human as opposed to responding to papers scale or an electronic system without oversight from study personnel.

CLINICIAN REPORTED OUTCOMES (CLINROS) AND SIMILAR INSTRUMENTS

LEGACY MEASURES AS REMOTE ASSESSMENTS

Interview and clinician observation-based assessments are commonly used in clinical trials. These tend to vary in terms of complexity and administration conventions. Direct questioning, observation and, in some cases, physical interaction with the patient are used to assess different outcomes. In all cases, a trained and qualified rater, or clinician, must administer the outcome measure to patients.

For some ClinROs, there is experience and data supporting the comparability of remote ratings and in site ratings. Consideration should be given to factors which can impact data quality. For instance, there might be less concern if the same rater who had administered the scale at the site, was also the same rater responsible for administering the scale remotely.



Conversely, the concern would be much higher when the transition from a site based rater to a different rater administering the scale remotely. Furthermore, quality can suffer when a small cadre of raters might be called upon to administer a large number of ratings. Whenever possible we recommend staffing levels be maintained to minimize instances on which a rater would be called upon to administer assessment batteries to more than two participants in a given day.

Several commonly used ClinRos are listed below as examples, with high level analysis for remote assessments.

SCALE	REQUIREMENTS FOR ADMINISTRATION	CONSIDERATIONS FOR REMOTE ASSESSMENTS
MADRS (Depression)	Direct questions. No item entirely reliant on observation	Telephone administration widely accepted. Can modify questions to account for observations
PANSS (Schizophrenia)	Direct questions and observations	Telephone administration limits assessment of all items. Video is recommended for complete scale.
ADAS-Cog (Cognition; Alzheimer's)	Direct questions, observations and use of stimuli	Video is required. Provisions to administer and assess for example, written stimuli, must be taken.
Simpson Angus Scale (Movement Disorders)	Direct questions, observation and physical interaction	All items cannot be assessed; a trained assessor must physically interact with participant
CGI (multiple therapeutic areas)	Vary; can range from brief interview to analysis of other outcomes	Remote assessment should be consistent with in person requirements

COMPUTER ADMINISTERED CLINROS OR TESTS

A range of computerized assessments and tests tcan be included in study protocols. These are distinguished from PROs in that the patient's response to specific questions is interpreted to arrive at a score for each item. These can include a computer programed to simulate the judgment of a human rater. Such computer simulated ratings typically use an interactive decision tree style algorithm driven interview that is completed directly by participants. The computer uses a separate algorithm to generates the score. Another common application is computerized cognitive testing that can evaluate domains such as response speed and executive functioning.

These type of assessments can be conducted remotely if an equivalent remote version is available through a Web platform or device provided to the patient. The instructions and/or proctoring of these assessments must be included in the remote assessment procedure.

PERFORMANCE OUTCOMES

These assessments also vary widely and have a variety of considerations. Each must be evaluated for safe completion by the participant, along with the ability of the clinician to evaluate the outcome. For example, a common PerfO such as a six minute walk test raises questions on how the patient may safety and feasibility complete the test at home, along with the site's ability to accurately evaluate the test. PerfOs that are assessed by monitors or electronic devices may be more feasible.

SENSOR BASED METRICS

Much like PerfOs, any sensor based outcome that was scheduled for completion in the clinic must be evaluated for feasibility as a remote assessment. Sensors that measure actigraphy, for example, must have the capability to collect and transmit data in a patient's home, particularly if the sensor data was, for example, uploaded at site visits.

BIOMARKERS

Biomarkers for example, the use of voice analysis has become part of clinical trials and can be considered a special variant of senor based metric. Any collection of data such as voice samples that were included in site visits should be evaluated for remote assessments, with technology, validity and privacy of any PHI collected among the considerations.

WHEN TO PERFORM REMOTE ASSESSMENTS

In certain cases, remote assessments are used for trials that have patient populations that may be limited in travel, or mobility. These are typically described in protocols or other study guidance.

However, remote assessments may become necessary when a governmental authority declares a public health crisis, such as ones seen throughout COVID-19. Regardless, there are considerations to make when performing remote assessments.

Several of these considerations include scheduling of the interview, evaluation of the presence of likely confounders, including the impact of COVID-19 on the patient and assessment of potential symptoms such as a fever or current symptoms that occured during the time interval being assessed. Similar considerations may also apply to the clinician or site staff that is conducting the remote assessment.

CONSIDERATIONS FOR CLINICAL RESEARCH MOVING FORWARD

It's important to consider that COVID related public health issues are expected to continue into 2021. Clinical research studies that will be conducted during this time frame should include contingencies for remote assessments, and modifications of protocols for remote visits. The adaptations for remote assessments are also likely to become an expectation for patients, and potentially have a positive impact on enrollment in clinical research studies.

In all cases, our guidance is that each study will have unique objectives. While patient safety is an overarching issue to implement remote assessments, thoughtful approaches and engagement with experts and stakeholders in study planning can enable sponsors to conduct high quality research studies under the COVID public health crisis. The steps taken now as we as an industry transition from a response to a crisis to conducing trials in this environment will enable our industry to continue to bring beneficial treatments to patients.

Modifications allow for standardization of assessments and logistics, which in turn improve the reliability of the outcomes. These modifications do not need to correspond to what may be a conceptual view of a de-centralized trial. In CNS and Neurology, the experience and expertise of skilled, trained clinicians is critical for both patient safety and good study conduct.

Additional practical issues may include social distancing measures at site visits and the use of communal study devices for ePRO administration. A standardized, individual ePRO platform that is a 'BYOD' for use at remote and site visits is one consideration. Adequate device hardware and Internet bandwidth for participants at home are important considerations for determining feasibility of assessments that, for example, may require evaluation of movements or fine motor skills.

We have listed some strategies for modifications and contingencies below.

1 PROTOCOL MODIFICATIONS

These can include reducing the number of protocol mandated clinic visits, flexibility with remote assessments, nested validation of remote assessments, and any specific guidelines that should be followed to increase consistency and ensure regulatory compliance.

2 EQUIPMENT AND LOGISTICS

These considerations apply to both clinicians working remote from their sites and study participants at home or otherwise outside of study sites. Physical hardware and broadband requirements should be discussed and ideally standardized across the study. The participant's living situation, including a suitable location to conduct an interview, should be considered.

3 REMOTE HEALTHCARE

The requirements for study activities such as laboratory or drug delivery that may require health care professionals can create a necessity for in-home healthcare professionals. The patient population is also a consideration for these types of solutions, as is patient safety.

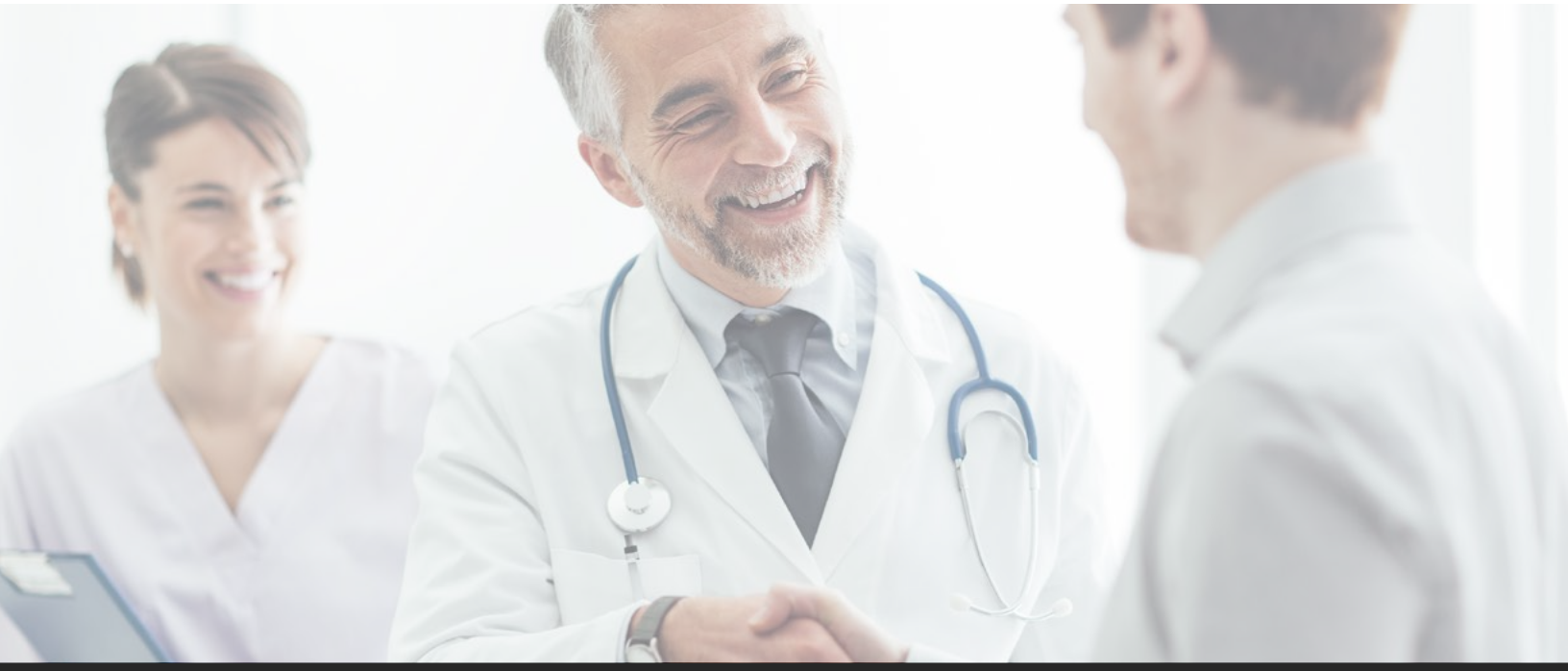
4 TRAINING

Raters may require additional training for administration of remote assessments, and safety protocols should be integrated into the study interviews. Participants may also require training or reminders.

5 ePRO STRATEGIES

Standardization of the administration of ePROs at any site visits and remote visits is an important consideration. Strategies can include device agnostic Web-based delivery, a provisioned personal device or BYOD applications for participants.

Broader strategies for remote assessments can include the creation of meta-sites, and allowances for raters at unaffected sites to conduct remote assessments with participants at affected sites. These considerations should be discussed with regulators and other stakeholders. Regulatory guidance issued during the course of the COVID crisis has been supportive of remote assessment strategies that are pragmatic. Additionally, remote assessments may consider addressing COVID related impacts to a participants



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