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Special Considerations for Child Psychiatric Trials During a Global Pandemic

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As the COVID-19 pandemic continues, many sponsors, CROs, investigators and IRBs have modified clinical trials, moving visits from clinics to living rooms worldwide. When trial participants are children, a more complex decision process must govern when and for whom a move to virtual visits is possible. Simply by virtue of their age, children are defined by law as a vulnerable population whose safety in research receives special protection. Additional protection is needed when children have psychiatric illnesses that put them at risk of harm to themselves or others. As outlined below, decisions to move child psychiatric trial visits from face-to-face in-clinic to virtual and remote require careful deliberation and multiple special considerations.

Regulatory Considerations

IRBs should be consulted before any formal plan to alter the trial is enacted. During the COVID-19 pandemic, IRBs have been especially responsive. The risks/benefits of retaining the child in the trial versus discontinuing the child must be weighed, suitable plans for assessing and ensuring the child's safety must be identified and means for collecting valid study data must be provided.

Safety Considerations

Safety considerations are key in any decision to move from face-to-face to virtual visits. Is the study medication one that can be safely administered at home? How will medical emergencies be handled? How will psychiatric emergencies such as psychotic exacerbations and increased suicidality be handled? What are the specific measures in place to ensure the child is treated? Will the parent/caregiver agree to all supervision requirements imposed, including providing the address and phone number of the virtual visit site so that police or EMS can be summoned if needed? Is there a plan if the child has been exposed to COVID-19? Is there a plan if the child develops other illnesses or adverse events potentially related to the study medication? All of these questions, and more, depending on the nature of the trial, must be thought through and addressed with the overseeing IRB, participants, and parents/caregivers.

Sponsors, CROs, and investigators must evaluate closely the ability of the parent/caregiver to adhere to all protocol requirements. This is even more critical when visits move from in-clinic to virtual. In addition to supervising medication administration and accountability, the parent/caregiver must be willing and able to be present in the home throughout the virtual visit to answer questions about the child and to assist in securing emergency services if needed.

Virtual visits should not take place without a parent/caregiver present.

Practical Considerations

In addition to safety considerations, practical considerations must be considered in any decision to move from live to virtual visits.

Telephone and internet access are required for both investigator and participants. If using video, laptops, tablets or other devices with video capabilities may be required. If investigators and participants do not have access to equipment, sponsors and CROs may be able to supply them instead. However, all of this must be determined prior to going remote.

Assessment tools such as rating scales and diaries may be accessible to investigators and participants. Thus, the mechanics of providing these will need to be considered.

With respect to data entry, investigators and investigative staff will need a means of entering visit data into the study database. They will also need ready access to all collected data – including data from other raters at the visit, if applicable, and including past data – to make dosing and other medical decisions and to ensure the child's continued safety in the trial. A means for ensuring such data access will need to be established.

Validity and Data Integrity Considerations

The Pandemic's Effect on Children

The overall effect of the current pandemic on children is unknown. Physical effects of exposure on the brain and body systems, compounded with psychological effects of social isolation, grief, and fear of disease may exert unique effects that differ by age, study drug, psychiatric illness under study, and region of the world. For this reason, regulators have requested that data be flagged as having been collected pre or post the COVID-19 pandemic, even if there is no change in administration method.

Some investigators, in what they believe are good-faith attempts to preserve data integrity, may try to "undo" pandemic effects by adjusting their symptom ratings to try to approximate what the symptom might have been had the pandemic not occurred. This should be strongly discouraged. When it comes to psychiatric symptom assessments, investigators should "rate the symptoms as they see them" without adjusting or attempting to parse out pandemic effects. Effects of the pandemic will be examined statistically for all trials with pre and post pandemic data.

The Effect on Data of Switching to Remote Administration Mid-study

The effect of switching to remote administrations mid-study is unclear, although one would expect to find increased variability. Attempts to maintain as much consistency as possible with in-clinic assessments should be made. For example, whenever possible the same rater should interview the child, the same assessment order should be maintained, and the same parent/caregiver should provide information. For some assessment measures there may be existing literature supporting equivalence between remote and in-person modalities. If these are available, sponsors and CROs may wish to include such citations in their regulatory submissions. In all cases, when moving from live to remote we recommend flagging the administration modality in the database. This will allow for subsequent analysis of administration type and possible effects on data.

General Tips for Remote Assessment with Children During a Pandemic

Video conferencing is preferred over telephonic visits when moving

from in-person to remote visits in that these allow for an "eyes on" assessment of the child's physical and mental status and serve as a better approximation of the "in-clinic experience".

That said, cameras, phones, laptops, and other means of video conferencing all differ, and attention and some modifications, or even equipment provisioning, may be required to make protocol-mandated assessments. For example, close-up views may be needed to measure rashes or orofacial movements, while widescreen views may be needed to assess full-body views for some of the dyskinesia scales. The parent/caregiver may need to hold the camera during an assessment of the child to ensure correct camera positioning and image capture.

Specific Tips for Virtual Visits in Child Psychiatric Trials

The visit should begin with both the child and the parent/caregiver in the room together. The investigator should explain that while the child and parent/caregiver interviews can be separate, it is mandatory for the parent/caregiver to be nearby to help with technical aspects and to answer questions about the child.

Before beginning any protocol assessments, it is helpful to spend a bit of time helping the child become familiar with the new setup and the fact that the visit will now be remote. Investigators should engage the child in neutral "small talk" about the child's day as needed to promote the child's comfort, while also introducing the trial and the technology.

Investigators should explain what will happen using simple terms and concepts. Asking the child to explain back the activities of the day and why they are being done virtually will help ensure that the child understands. Investigators should also allow the child the opportunity to express any concerns or worries about the technology or the virtual visit itself.

As noted previously, it is important that the investigator work with the parent/caregiver to ensure that the camera is positioned appropriately to capture the body parts required. This is true of scales that require visualisation of the full body to assess symptoms such as fidgetiness, tics, and hyperactivity/hypoactivity.

Finally, it's important to remember that at some point during the remote assessment (often the end), a medically responsible investigator must separately interview the child and the parent/caregiver to determine:

- Adverse events
- Dosing or discontinuation considerations
- Compliance with study medication, and
- Any known or suspected exposure to COVID-19

Specific Guidance for Remote Administration of Commonly Used Scales in Child Psychiatric Trials

K-SADS-PL
This scale requires separate interviews with the parent/caregiver and the child. Although the copyright holder has indicated that a phone interview is acceptable, we recommend videoconferencing of, at minimum, the child portion. This is because some disorders (e.g., ADHD, tics, and psychosis, for some typical examples) benefit greatly from visualising the child during the interview (motor activity, motor tics, and responding to internal stimuli, respectively, using the above example disorders).

C-YBOCS
In non-remote settings, this scale is typically done with the parent/caregiver and child together in the room. Typically, the opportunity is given for either party to then speak alone with the interviewer. This approach should be maintained. Although videoconferencing is preferred, it is possible to administer the scale by phone because it is based on verbal report alone.

CY-BOCS-ASD
In non-remote settings, the scale is often administered solely to the parent or caregiver. If this is what has occurred in the trial previously, this should be continued. As the scale does not rely on visualisation, it is possible to administer this by phone.

YGTSS
In non-remote settings, the scale is typically administered with the parent/caregiver and the child together in the room. As noted above, if this is what occurred in the trial prior to the remote assessment, this method should be continued. Videoconferencing is required to visualise any expressed tics (or demonstrated examples of tics).

CDRS-R
This interview requires separate interviews with the parent/caregiver and the child, while also requiring visualisation of the child for some of the items. Videoconferencing is required.

ADHD-RS
In most trials, the interview is done solely with the caregiver. Thus, telephone administration is possible.

CGI-S/I
Regardless of the indication, the CGI-S and CGI-I requires the investigator's overall consideration of all relevant information about the illness under study. The assessment must include, in addition to a review of collected relevant data, a clinical interview with the child and a separate interview with the parent/caregiver. To best capture the full clinical picture, videoconferencing is clearly preferable to phone; for some conditions (e.g., ADHD, motor tics, among others) videoconferencing may not only be preferred but required.

PANSS
The scale requires separate interviews with the parent/caregiver and the child. As many of the items require visualisation of the child, we strongly recommend videoconferencing for the child interview.

In Summary
While child psychiatric trials present specific considerations and challenges during a global pandemic, they are still possible. With thought, planning, and careful oversight, many trials can be modified to successfully continue remotely.

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Dr. Busner is Clinical Vice President of Signant Health, with specific scientific and clinical oversight responsibility for child psychiatric and pediatric orphan disease services including protocol consultation, rater training, endpoint quality and eCOA. Dr. Busner has over 35 years of experience as an academic clinical psychiatric researcher. She has served as Principal Investigator of 49 industry sponsored clinical trials and Sub-Investigator of an additional 35, and has directed the psychiatric clinical trials units of two major medical schools. She served continuously on University Institutional Review Boards (IRBs)for the 20 years that preceded her move to Signant Health. Dr. Busner is an active contributor to the psychopharmacology literature and has authored or co-authored over 130 peer-reviewed articles and national or international scientific presentations. Dr. Busner has trained thousands of psychiatric clinical trial investigators across the globe and lectures frequently on the application of objective rating scales in the assessment of diagnosis and efficacy in psychopharmacology, ethics in psychiatric research, the placebo effect in psychiatric research and techniques for its minimization, the role of IRBs and clinical trial methodology. Dr. Busner received her PhD in Experimental Social Psychology and her MA in General Psychology from Adelphi University. She is licensed to practice psychology in Pennsylvania, Missouri and New York.