Patient-Reported Outcome (PRO) Consortium's Rare Disease Subcommittee Workshop

COVID-19 Mitigation Strategies in Pediatric Rare Disease Clinical Trials Virtual Workshop

PRO CONSORTIUM
CRITICAL PATH INSTITUTE

May 7, 2021

This event will begin at 12:01 PM ET (US)

Funding Acknowledgments

- Critical Path Institute is supported by the Food and Drug Administration (FDA) of the U.S. Department of Health and Human Services (HHS) and is 55% funded by FDA/HHS, totaling $14,575,306, and 45% funded by non-government source(s), totaling $11,916,747. The contents are those of the author(s) and do not necessarily represent the official views of, nor an endorsement by, FDA/HHS or the U.S. Government. For more information, please visit FDA.gov.
- Additional support for the Patient-Reported Outcome (PRO) Consortium comes from membership fees paid by members of the PRO Consortium (https://c-path.org/programs/proc/).
- Specific funding for the establishment of the Rare Disease COA Consortium was provided by FDA grant U01FD006882.

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COVID-19 Mitigation Strategies in Pediatric Rare Disease Clinical Trials Virtual Workshop

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Critical Path Institute

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University of Minnesota

Heather Adams, PhD
Assistant Professor of Neurology and Pediatrics
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Agenda

- Introduction and overview of presentation format
- Overall issues with trial conduct
- Assessment
  - In-person assessment under pandemic conditions
  - Conducting remote assessments
- Audience discussion

About Critical Path Institute (C-Path)

- Established in 2005 by the University of Arizona and the U.S. Food and Drug Administration (FDA)
- An independent, non-profit organization
  - Dedicated to implementing FDA's Critical Path Initiative
  - Enables pre-competitive collaboration that includes regulatory input/expertise
- C-Path's aim is to accelerate the pace and reduce the costs of medical product development through the creation of new data standards, measurement standards, and methods standards that aid in the scientific evaluation of the efficacy and safety of new therapies.

PRO Consortium

- The PRO Consortium was formed in late 2008 by C-Path in cooperation with FDA's Center for Drug Evaluation and Research and the pharmaceutical industry, and formally launched in March 2009.
- The mission of the PRO Consortium is to establish and maintain a collaborative framework with appropriate stakeholders for the qualification of PRO measures and other COAs that will be publicly available for use in clinical trials where COA-based endpoints are used to support product labeling claims.

Establishment of Rare Disease COA Consortium

- The FDA's Center for Drug Evaluation and Research (CDER) funded a cooperative agreement to establish the Rare Disease COA Consortium
  - A one-year grant (U01FD006882) was awarded to Critical Path Institute (C-Path) with NORD as a sub-awardee on September 1, 2019. A no-cost extension was approved on July 17, 2019, extending funding through August 31, 2021.
- The first step taken toward the establishment of the new consortium was the creation of the Rare Disease Subcommittee within C-Path's Patient-Reported Outcome (PRO) Consortium. The PRO Consortium serves as an incubator for the maturation of a pre-competitive, multi-stakeholder consortium within C-Path's COA Program.
- Plans to launch the Rare Disease COA Consortium in Summer 2021 are underway!

Rare Disease Subcommittee Participants

PRO Consortium Members	
AbbVie	Otsuka Pharmaceutical
Amgen	Sanofi
AstraZeneca	Takeda Pharmaceuticals
Daiichi Sankyo, Inc.	UCB Pharma
Genentech/Roche	
Advisory Members	
Aeglea BioTherapeutics, Inc	Horizon Therapeutics
Agios Pharmaceuticals Inc.	Ionis Pharmaceuticals, Inc.
Akcea Therapeutics	Lysogene
Apellis Pharmaceuticals, Inc.	MeiraGTx, LLC
Applied Therapeutics	Momenta Pharma
argenx US, Inc.	Neurocrine Biosciences, Inc.
Astellas Pharma Inc.	Ovid Therapeutics, Inc.
Audentes Therapeutics	PellePharm, Inc.
BioMarin Pharmaceutical	REGENXBIO Inc.
bluebird bio, Inc.	Sangamo Therapeutics
BridgeBio	Sarepta Therapeutics
Cabaletta Bio, Inc.	Ultragenyx Pharmaceutical, Inc.
Harmony Biosciences, LLC	

Grant Sub-Awardee
National Organization for Rare Disorders (NORD)

FDA Representation
Division of Clinical Outcome Assessment
Division of Neurology Products I
Office of Biostatistics
Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine; Division of Rare Diseases and Medical Genetics
Office of Combination Products
Office of Strategic Programs
Patient-Focused Drug Development Program

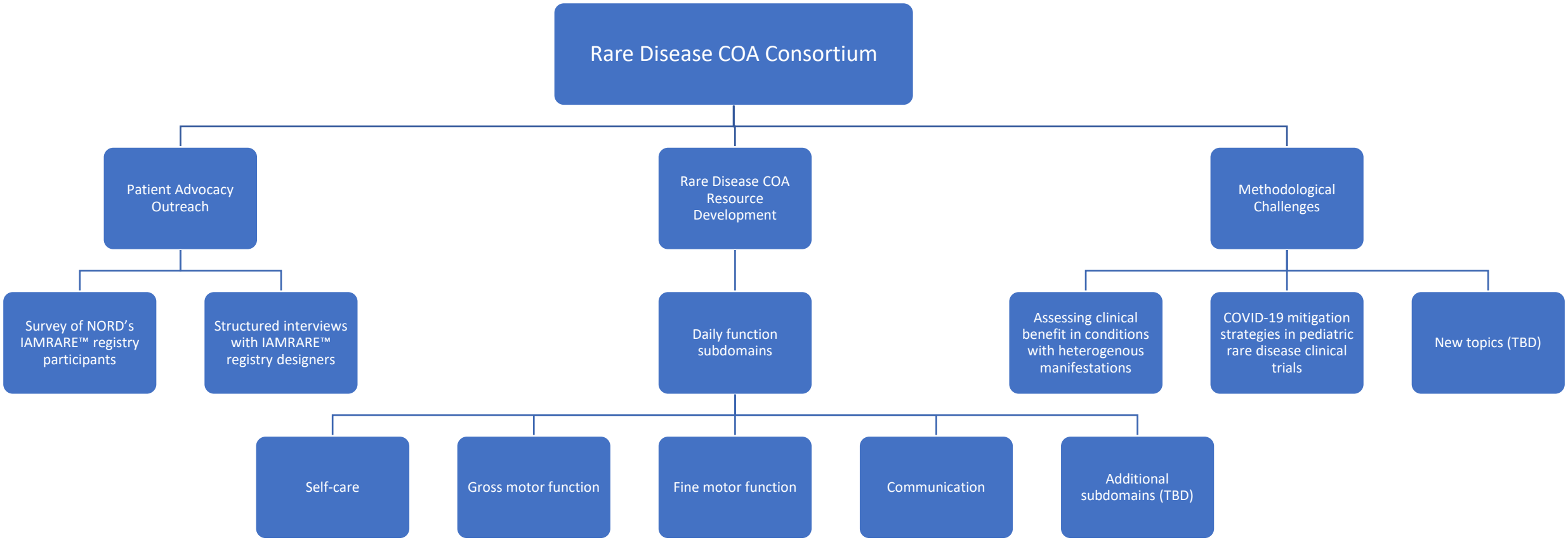
Clinical Experts
Heather Adams, PhD, University of Rochester
Kiera N. Berggren, MA/CCC-SLP, MS, Virginia Commonwealth University
Julie Eisengart, PhD, University of Minnesota

Other Representation
National Institutes of Health, National Center for Advancing Translational Sciences
Patient-Centered Outcomes Research Institute

Important Initial Decisions

- Members of the Rare Disease Subcommittee, including representatives from FDA, C-Path, National Organization for Rare Disorders (NORD), the National Center for Advancing Translational Science (NCATS), the Patient-Centered Outcomes Research Institute (PCORI), and biopharmaceutical firms determined:
- A domain approach will be used to identify COAs that might be fit-for-purpose for use as endpoint measures in treatment trials for multiple rare diseases
- Daily function was selected as the first domain
- Initial efforts will focus on pediatric populations
- Oncology will be included in subsequent efforts

Rare Disease COA Consortium Work Structure



Abbreviation: TBD = to be determined

COVID-19 Mitigation Strategies in Pediatric Rare Disease Clinical Trials

Lindsey Murray, PhD, MPH, Critical Path Institute

Overview

- The current COVID-19 pandemic have created challenges in conducting clinical trials
  - These issues are likely to persist for longer in pediatric populations where vaccination options aren't readily available
- Overarching socio-political factors that have been exacerbated by COVID-19 will not be addressed during the workshop, but are an important part of the overall conversation
  - Challenges with addressing issues related to how the demographics of populations impacted by COVID are changing racial demographics of study populations
  - Reduced enrollment for populations already understudied
- The focus of this workshop will be limited to issues specifically related to the challenges with conducting in-person and remote assessments in pediatric rare disease clinical trial settings

Learning Objectives

- Identify COVID-19 challenges to pediatric rare disease clinical trials.
- Present a range of mitigation strategies for the conduct of pediatric rare disease clinical trials under pandemic conditions.
- Present a range of mitigation strategies for conducting in-person and remote assessments under pandemic conditions.
- To provide an interactive forum for idea sharing related to COVID-19 impact and mitigation strategies across a range of stakeholders.

Resources Available

- Challenges and implementation strategies have been stratified by time period of the trial and will be presented on the C-Path PRO Consortium website.
- Overarching issues
  - Pre-trial set-up
  - Trial initiation
  - Trial implementation
  - Data Analysis
  - Regulatory

COVID-19 Impact on Study Conduct

Dawn Phillips PT, MS, PhD, REGENXBIO Inc.

Adam Shaywitz, MD, PhD, BridgeBio Gene Therapy

COVID-19 Trial Conduct Impacts

- **Site**
  - IRB reprioritizations
    - COVID vs. Non-COVID, interventional vs. natural history
  - Training
    - SIV and rater training webinars instead of in-person training
      - Reduced ability to measure comprehension or administrative competencies
  - Time constraints and competing interests
    - Site personnel time allocated to care for COVID patients
    - Site personnel away from work due to COVID exposure
  - Recruitment/enrollment
    - COVID-19 as an exclusion criteria
  - COA administration
    - Protocol deviations due to missed or off schedule visits
    - Modified administration due to use of masks/shields by raters, caregivers and patients

Mitigation Strategies

- **Site**
  - Additional training resources have been developed by many of our vendors to better meet training and real-time administrative strategies
    - Collaborative Zoom meetings where off-site clinician experts can provide support
  - Remote assessments
    - Apps developed for video assessments in the home environment
      - May need to re-evaluate endpoint positioning
  - Adapt a more flexible approach for ad-boards/focus groups with clinician experts and caregivers/patients
      - Webinar format
  - Adapt source documents
    - Include “unscheduled visits”
    - Include documentation of mask/shield use

Long-Term Benefits from Mitigation Strategies

- Remote Assessments
  - Decreased patient and caregiver burden
  - May allow for inclusion of a larger and more diverse study population
- Remote Ad-Boards
  - Promotes clinician, caregiver and patient engagement in drug developmental process with decreased burden of participation
- Efficiencies
  - Access to clinician experts via Zoom promotes greater ease and accuracy for screening in tertiary centers or home environment
  - Reduced costs for trainings, ad-boards, focus groups

Pivoting from In-Person Assessment to Remote Visit: Case Study

- Rapidly progressive neurodegenerative disease – natural history study
- Current in-person assessments consist of several neurodevelopmental scales
  - HINE-2, GMFM, TIMPSI, BSID4, CDC Milestones
- ***Challenge: which one(s) to choose for remote assessment?***

  Solution/Thought-Process:

  ➢ In depth review by outcomes specialists of in-person scales for remote applicability

  ➢ Modified training program to reflect remote assessment via video:
    - Established family kit of manipulatives (toys/other materials)
    - iPad/Tripod
    - HIPAA compliant platform

  ➢ Executed pilot study to evaluate selected scales
    - planned for parent involvement;
    - incorporated feedback from raters and parents (7 families in total participated)

  ➢ US pilot successful, remote visits now occurring; German pilot established

  ➢ All parent-facing materials were IRB / EC approved; translations included

Abbreviations: HIPAA = Health Insurance Portability and Accountability Act; IRB = institutional review board; EC = ethics committee

COVID-19 Trial Conduct Impacts

- **Impact on Caregivers and Patients**
  - Restricted or modified travel to clinical sites to participate in study
    - Reduced airline travel
    - Country- or state-mandated prohibitions for entry from other regions
  - Potential developmental impact
    - Restricted/no access to physical, occupational and speech therapy
    - Reduced educational support
  - Additional burden to families already experiencing constraints and stress
    - Regular COVID testing to enter facilities
    - Restricted number of people in attendance
    - Financial burdens

Mitigation Strategies

- **Caregiver and Patient**
  - Provide a wide range of travel options to limit exposure to COVID-19
  - Traveling earlier to quarantine
  - Develop additional caregiver questionnaires to capture the impact of reduced therapy and academic services
    - Quantify # of therapy visits pre-COVID compared to during COVID
    - Requires protocol amendment for IRB approval

Abbreviations: IRB = institutional review board

COVID-19 Trial Conduct Impacts

- **Study Data**
  - Lack of comparability data related to variability in data collected remotely or in-person
  - Lack of analysis strategies to quantify reduced therapy and academic services as a confounding variable
  - In-person data monitoring may not be possible
    - Resources may not be available off site for electronic data monitoring
  - Analysis timelines may need to be modified
    - Missing data
    - Dissemination of study results may be delayed

Mitigation Strategies

- **Study Data**
  - Video versus in-person assessment
    - Reduce potential bias through central scoring of videos with multiple raters
    - Collaborate with clinician experts over Zoom to support assessments in real time
    - Engage with vendors with extensive clinicometric experience
    - Evaluate construct validity with analysis of the relationship between parent proxy patient-reported outcomes and daily activities recorded in home
  - Define analysis strategies to deal with off schedule visits
    - May need to have a larger acceptable window for assessments

Assessments during the COVID-19 pandemic: Considerations for in-person and remote formats

Heather Adams, PhD, University of Rochester Medical Center
Kiera Berggren, MA/CCC-SLP, MS, Virginia Commonwealth University
Julie Eisengart, PhD, University of Minnesota

In-person assessments

Pre-pandemic testing

Photo courtesy of Julie Eisengart
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COVID-19 safe testing

Photo courtesy of Julie Eisengart
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Ideal versus real…

Photo (above) obtained from Google Images

Photo (above) courtesy of Julie Eisengart
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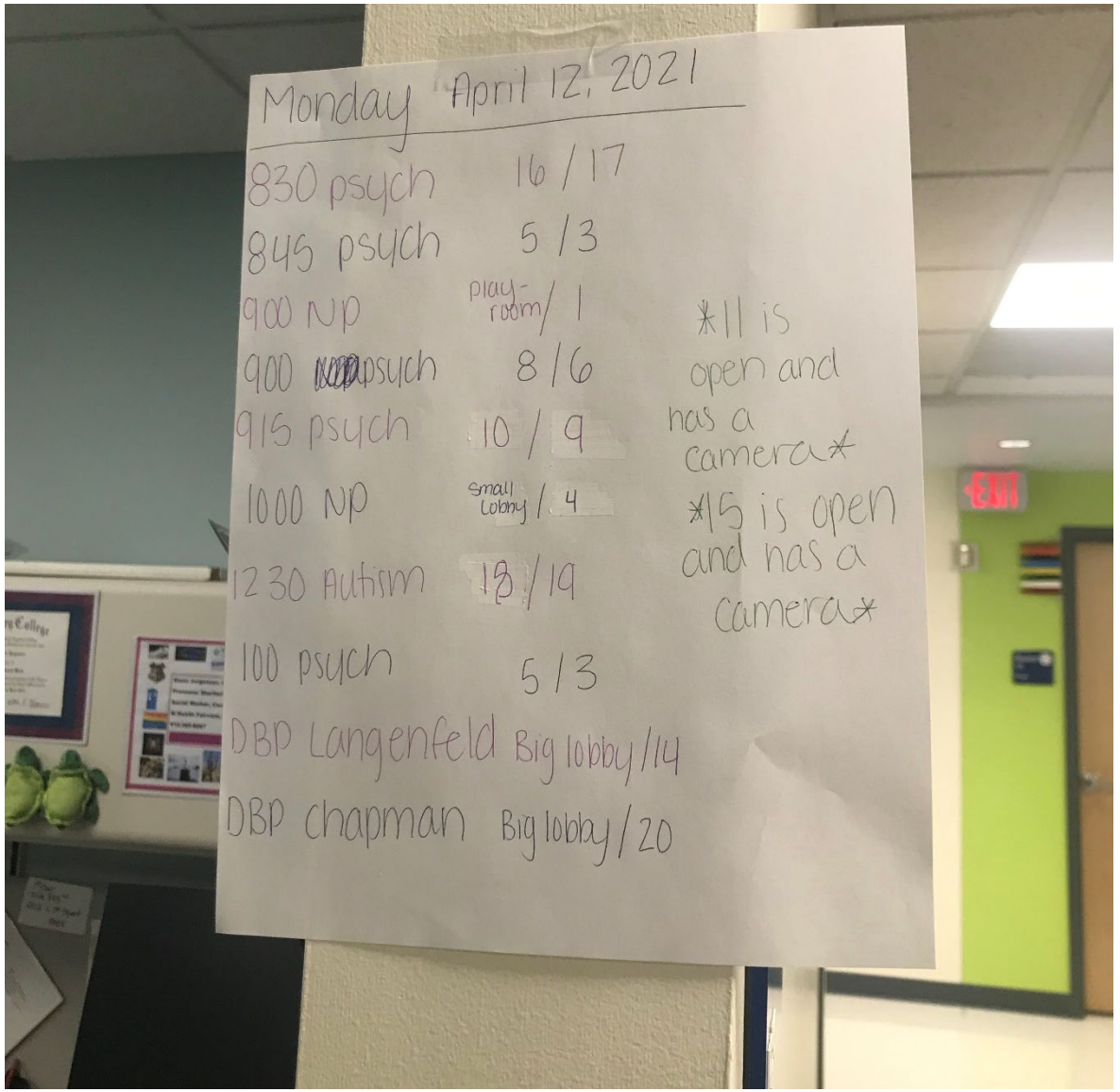
In-person assessments – study space

- Limitations in physical space
  - Clinic sites with decreased study space available
  - Access limitations
  - Regulations on face-to-face time per institution or research space
  - These limitations will likely vary across sites and in time for multi-site studies

In-person assessments – study space

- Mitigation strategies
  - Formulate plan regarding safe access to study site(s)
  - Pre-plan methods of assessment to comply with face-to-face time caps
  - Concerns around elevator usage



In-person assessments – study personnel

- Study personnel concerns
  - Increased time and training required of study personnel
  - Remote training of clinical evaluators
  - Inconsistent raters for ClinROs and PerfOs

Abbreviations: ClinRO = clinician-reported outcome; PerfO = performance outcome

In-person assessments – study personnel

- Mitigation strategies
  - Have clear training objectives
  - Use of a CRO for virtual trainings, if budget allows
  - Additional time for trainings
  - Flexibility in “test” subjects used for training/competency
  - Record initial assessments for later review by trainer
  - Ensure standardized training for all raters/evaluators

Abbreviation: CRO = contract research organization

In-person assessments – PPE and disinfecting

- PPE-related issues
  - Interference of PPE in data collection
  - Barriers to child use of PPE
  - Sites with differing regulations around use of PPE
  - Sites vary in allowed procedures
- Disinfection after use
  - The room itself
  - Items used

Photo courtesy of Julie Eisengart
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Abbreviation: PPE = personal protective equipment

In-person assessments - PPE

- Mitigation strategies
  - Develop PPE standards for the study to be applied across sites
  - Document what is being worn and by whom (participant vs study personnel)
  - Alleviate some anxiety by briefly showing a child the examiner unmasked from a distance (e.g., smiling outside the room, then masking before entry)
  - Document what activities/interactions weren't able to be conducted due to PPE
  - Additional spacing or distance during assessments
    - Use of plexiglass shield
  - Use of negative pressure room to conduct respiratory assessments
  - Additional PPE if study team is going to be assessing participant's aerodigestive system
  - Have a clear protocol for cleaning and disinfecting space and items used
    - Use of manipulatives that can be cleaned easily or disposed of

Abbreviation: PPE = personal protective equipment

In-person assessments – getting to study site

- Travel restrictions
  - Fluctuating degrees of lockdown or openness
  - COVID-19 testing requirements
    - May be local limits on testing availability
- Mitigation strategies
  - Off-peak flight times, alternative travel options
  - In-home test kits
  - Protected testing appointments at lab on-site
  - Consider use of remote assessments instead
  - Consider use of local clinical evaluator

Remote assessments

Remote Assessments

Photo courtesy of The MIND Group, led by Dr. Rene Pierpont, University of Minnesota
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Remote assessment concepts

- What is the remote site?
  - home?
  - local clinic?
  - other?

- The remote testing location, even if not an established research site, becomes a de facto study site
  - Hence, consider a 'site survey' (in concept or on paper) to assess feasibility of remote assessment

- What assessments are the most robust options (reliable, valid, feasible) for a remote context?

- Consider assessments that are already developed / normed for distance administration – *examples:*
  - Observer-reported (ObsRO) measure: Vineland Adaptive Behavior Scales
  - Patient-reported (PRO) measure: Beck Depression Inventory
  - Clinician-reported (ClinRO) measure: Unified Batten Disease Rating Scale

- Establish criteria for when some or all of a remote visit isn't feasible

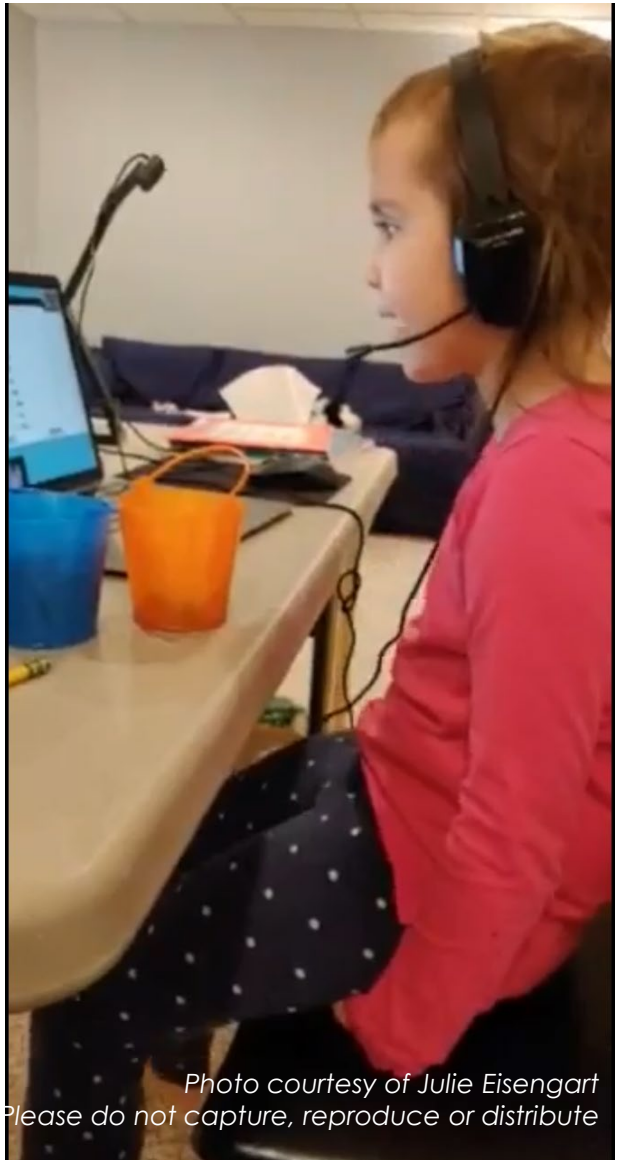
Remote assessment challenges and mitigation strategies: *site survey*

Site survey concepts for remote assessment

- Type of remote assessment
- Technology review
- Survey the environment
- Prepare study participant and caregivers for what to expect
- Establish plan for shipping and return of materials and data

Remote assessment challenges and mitigation strategies: *technology and space*

- Technology
  - Conduct a technology survey with each participant
  - Provide webcam/internet-capable device if needed
  - Conduct a technology ‘test visit’
  - Discuss back-up plan if tech problems arise
- Space
  - Assess lighting and sound
  - Safety of environment
  - Suitability of environment
  - Positioning of subject



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Remote assessment challenges and mitigation strategies: *privacy and confidentiality*

- Privacy
  - Who might be visible in the space while a visit is being conducted?
  - Is visit being recorded?
  - What features of environment are visible in the space?
  - Ask participant to dress as if they're going to an appointment (no bathrobes!)

- Confidentiality
  - Plan for secure shipment of materials to / from the participant's home
  - Plan for secure receipt by intended individual (e.g., only opened by participant?)
    - Scheduled delivery and pickup times by secure courier

- Electronic data capture (EDC)
  - For FDA-regulated studies, e-consent and other EDC must be Part 11 Compliant.

Remote assessment challenges and mitigation strategies: *pediatric assessments*

- Minimize distractions in the environment
  - Avoid testing in play-room, bedroom, etc.
  - Ensure correct positioning of child; appropriate furniture
  - Find a quiet time of day for the household
  - Choose time of day when child has energy for study tasks
  - Proactively 'secure' the environment – to prevent inadvertent interruptions or distractions

- Have a parent/caregiver on "standby" if child might need assistance during evaluation and/or to solve tech issues.

COVID-19 mitigation strategies – *why does this matter?*

- Our overarching goal is to conduct reliable, valid, safe assessments in any setting
- We must remain mindful of the modifications created in both the clinic and home. And we must remain faithful recorders of these changes.

- There are many added sources of error variance in a COVID-mitigated research approach.

- Mitigation strategies should strive to reduce and control those sources to the extent possible, while creating a positive experience for the research participant and family.

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Thank you for attending this workshop!

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