COVID-19 Mitigation Strategies in Pediatric Rare Disease Clinical Trials

Introduction

This document was created by the COVID-19 Mitigation Strategies in Pediatric Rare Disease Clinical Trials Team within the Patient-Reported Outcome (PRO) Consortium's Rare Disease Subcommittee. The team was comprised of representatives from Critical Path Institute (C-Path), Food and Drug Administration (FDA), biopharmaceutical firms, the National Organization for Rare Disorders (NORD), and academic institutions.

The objectives of the team were the following:

- To identify challenges and mitigation strategies associated with pediatric rare disease clinical trials under COVID-19 pandemic conditions, including:
  - Socio-economic/demographic/societal concerns
  - Trial-specific concerns
    - Pre-trial set-up
    - Trial initiation
    - Trial conduct, including in-person and remote assessment
    - Data analysis
    - Regulatory interactions

The team met weekly over a 4-month period, and these efforts culminated with a virtual workshop on COVID-19 Mitigation Strategies in Pediatric Rare Disease Clinical Trials held on May 7, 2021. The workshop is available to view on the PRO Consortium website (https://c-path.org/view-now-covid-19-mitigation-strategies-in-pediatric-rare-disease-clinical-trials-virtual-workshop/).

For additional information about this document or our organization, please email Lindsey Murray at lmurray@c-path.org.

The following provides a summary of high-level considerations for clinical trials that were underway when the COVID-19 pandemic started vs. issues specific to trials that were initiated under COVID-19 pandemic conditions.

Issues specific to clinical trials that were underway when the pandemic started

- Need to pivot from in-person assessment to remote assessment
  - Potential need to abandon COAs that could not be assessed remotely
- Need to retrain sites and raters
- Unanticipated missing data
- Unanticipated study visit variability
- Increased withdrawal rate from studies
- Comparability of data collected pre- and post-pandemic within the study
- Need to document protocol deviations due to COVID-19 pandemic conditions
- Potential need to re-evaluate endpoint hierarchy
- Need to retroactively assess impacts of COVID-19 on participant readiness to participate in clinical trials

Issues specific to clinical trials that were being initiated during the pandemic

- Study launch in a virtual environment
- Comparability of data collected pre- and post-pandemic across studies
- Ability to pre-select COAs that can be assessed remotely
- Ability to build in additional time for recruitment and study conduct
- Ability to systematically document protocol deviations due to COVID-19 pandemic conditions

Overall factors

- Children won't be vaccinated as soon as adult populations, so the challenges identified will persist for longer in pediatric populations.

Silver linings

- Push to expand virtual assessment options likely to help enrollment in future studies
- Decreased cost for studies related to decreased travel reimbursements for participants
- Decreased patient and caregiver burden associated with travel for local assessments

The table on the following pages summarizes the collective challenges and mitigation strategies compiled across the lifecycle of clinical trials by the COVID-19 Mitigation Strategies in Pediatric Rare Disease Clinical Trials Team and is organized into the following sections:

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Stage	Challenge	Mitigation Strategies
Pre-trial set-up	• Economic and logistical impacts to families in terms of trial and research participation (initial enrollment and/or completion)	• Utilize different transportation methods to reduce COVID-19 risk ○ Not regular commercial flights • Address travel limitations or COVID-19 testing prior to taking flights • Limit family member involvement • Identify hotel accommodations ahead of time • Increase reimbursement for participation and travel due to unemployment • Extend site visits necessitating hotel stays to avoid travel back-and-forth from the site between study visits
	• Vulnerable, immune-compromised populations avoiding interaction with health care system/clinics unless there is a serious emergency	• Televisits • Local laboratory use vs. study clinical sites to reduce travel requirements
	• Required COVID-19 testing • Testing may not be available locally or in a timely fashion	• Pay/reimburse for COVID-19 testing (when available) • Is COVID-19 testing required by the institution or for the study protocol as an exclusion criterion? • At home COVID-19 testing (often similar pricing to drug store testing, can be mailed directly to/returned from the home, can be done with just a saliva sample - less invasive, often with a faster turnaround than state-sponsored testing)

COVID-19 pandemic challenges and mitigation strategies in pediatric rare disease clinical studies

Stage	Challenge	Mitigation Strategies

Pre-trial set-up (continued)	• Impact on participant readiness to participate in a clinical trial due to COVID-19	• Capture impacts of COVID-19 on the family and patient ahead of trial participation or retrospectively
		  ○ Educational/Academic impacts
		  ○ Clinical care impacts
		  ○ Support treatment impacts (missing physical therapy (PT) or occupational therapy (OT) or speech therapy)
		  ○ Caregiver work status

	• Impacts on natural history studies ○ These studies have been de-prioritized with no clear immediate benefit, but the data are essential to provide comparator data for future clinical trials	• Consider remote assessment – treat home environments as study sites • Select assessment tools that have already been validated and/or commonly used in an electronic, online, or virtual format (e.g., Vineland Adaptive Behavior Scales can be sent as a link to participants) • Consider how necessary and/or valid the assessments are, particularly if pivoting to in-home assessment
	• Lack of research funds	• Partnerships with patient advocacy groups may offer some bridge funding, as these groups often express a concern that their communities are being left behind in the COVID-19 pandemic. However, many patient advocacy groups have seen their philanthropy efforts significantly reduced in 2020.
	• Challenges with how COVID-19 disproportionately impacted some populations leading to changes in racial demographics of study populations Reduced enrollment for populations already understudied	• Need to make sure that clinical trial participants are representative of the target population in terms of demographic and clinical characteristics • Focus on clinical training for disease identification in under-served populations

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Stage	Challenge	Mitigation Strategies

Trial Initiation	• Impacts on study personnel available/required to conduct research
	  ○ Hospitals/medical centers may not have enough beds/space/use of clinics to bring trial participants in for procedures because of the number of COVID-19 patients – this is an unpredictable factor
	  ○ Significant additional work to participate in training remotely, remote assessment visit conduct, tech support for participants
		• Delay study visits
		• Require study principal investigators (PIs) to ensure that hospital resources are available to complete study visits successfully or proactively plan for how to enroll and initiate patients
		• Plan for slower recruitment to avoid overwhelming clinical staff
		• Educate patients on COVID-19 related risks post-trial

	• Challenges with clinical site training and start-up activities in a virtual environment
	  ○ Test subjects may not be available, or may be adults/convenience samples vs. target
	  ○ Trainers need additional training on teaching in a virtual environment
	  ○ Trainees must show mastery of training in settings that don't represent their usual clinical interactions
	  ○ Uncertainty around mastery of competencies in trainee, unable to see "real world" examples vs. following the rules of implementation in a structured environment
		• If there are funds, use a clinical research organization (CRO). CROs are typically secured by the sponsor/pharmaceutical company of the trial where funds are more plentiful. Utilization of a CRO is often helpful, as they have experience conducting virtual trainings
		• Allow additional time to train trainers to conduct virtual training sessions
		• Flexibility in who a trainee uses as a "test" subject to show competency without compromising training objectives
		• Ensure clear training objectives are established *a priori*
		• Have video assessments recorded of the initial "live" assessments for review by trainer to ensure trainee competency or have the trainer participate in the first few assessments to ensure trainee competency

	• Impact of existing institutional budgets on ability to adapt to added staff/logistical needs	• Ensure good communication between sponsors and sites • Set expectations on budget and timelines • Have individual meetings between study staff and sponsors to address issues

Stage	Challenge	Mitigation Strategies
Trial Initiation (continued)	• Challenges related to training study personnel for multi-site studies or for those that use a central rater for training	• Develop trial networks for sites participating in a trial to promote connection and support amongst investigators, particularly for investigators new to rare disease ○ Individual site trainings vs. central training
	• Impact of study start up, especially for researchers new to rare diseases	• Promote access to rare disease resources to learn about the rare disease they'll be working in ○ Rather than conferences or in-person meetings, what online resources are available? ○ Example: MPS MasterClass provided virtually https://www.mpsmasterclass.com ○ Patient Advocacy Group websites usually have rich information on their populations and communities; this information can be critical to understanding the condition at a level deeper than what is available in the scientific descriptions or journal articles – for example, disease-related limitations that could affect testing and/or the patient and family experience during the trial; even glimpses into the community's disease-specific culture
	• Institutional Review Boards (IRBs) prioritizing some studies over others due to COVID-19 can impair ability to get IRB approval	• Build more time into timelines; anticipate delays • Site-by-site assessments of how resources will be used at each site to provide to the IRB describing how sponsors will handle need for flexibility • eConsent on REDCap for non-FDA-regulated clinical studies; if system is Part 11 compliant there is the possibility to complete eConsent for clinical trials
	• Reposition endpoint model and assess if the planned endpoints are reasonable and required	• Exploratory endpoints might be elevated (e.g., remote assessments become even more important and support caregiver report)

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Stage	Challenge	Mitigation Strategies
Trial Conduct	• No/little comparability data on clinical outcome assessment (COA) administration via telehealth environments available	• Select COAs that have already been validated and/or commonly used in an electronic, online, or virtual format (e.g., Vineland Adaptive Behavior Scales can be sent as a link to participants) • Equivalence studies between data gathered pre- and post-pandemic conditions within trial
	• Physical space limitations with availability to conduct in-person evaluations	• Elevator accessibility; limitations on the number of people in an elevator at one time • Safety protocols at the site for getting to the clinic office (e.g., temperature checks at the entrance, companion restrictions)
	• Interference of personal protective equipment (PPE) and related precautions with conduct of in-person clinical assessments	• Document what PPE is being used and by whom (study team and participant) • Document what activities/interactions weren't able to be conducted due to PPE • Additional spacing or distance • Use of negative pressure room to conduct respiratory assessments • Additional PPE if study team is going to be touching the participants' mouthes/respiration • Additional cleaning requirements of space and manipulatives or use of alternative manipulatives that can be sterilized or disposed of
	• Out of window COA data collection due to COVID-19 exposures/closures	• Consult with biostatistician on options/feasibility of controlling for timing variation, in collaboration with disease experts to advise on anticipated disease processes and/or treatment processes during the extended window

COVID-19 pandemic challenges and mitigation strategies in pediatric rare disease clinical studies

Stage	Challenge	Mitigation Strategies
Trial Conduct (continued)	• Inconsistent raters/evaluators for ClinRO assessments and PerfO assessments	• Use different raters • Conduct testing locally for neurodevelopment testing • Remote assessment for physical therapists/raters rather than in-person • Plan additional testing to assess for inter-rater reliability
	• Content applicability of COAs (e.g., evaluation of in-school activities that aren't occurring)	• Skip a particular COA if it's no longer relevant • Document learning environment for school-related activities • Try to ensure that monitoring of school-related activities is consistent across non-pandemic vs. pandemic environment

	• Challenges with documenting mitigation strategies on existing study documents
	• Challenges with balancing site accommodations due to COVID-19 pandemic conditions and maintaining study protocol procedures
	• Unscheduled visits
		• Call all visits "unscheduled" and have a central rater map the visits to the relevant planned study visits
		• Document
		  ○ Date of visits
		  ○ COVID-19 pandemic precautions used
		  ○ If assessments that are high-risk (respiratory assessments) are skipped
		  ○ Environment – in-home or hotel vs. clinic
		  ○ Document missed visits and reasons for missing the visit

	• Impact of COVID-19 pandemic on target outcome measures • COVID-19 infection as an exclusion criterion	• Sensitivity analyses of participants with and without COVID-19 on outcomes ○ Document as adverse event (AE) vs. exclusion criteria, record symptom severity, hospitalization • Determine a timeframe post-COVID-19 infection/symptoms within which a participant could enroll

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Stage	Challenge	Mitigation Strategies
Trial Conduct (continued)	• Interrupted care and treatment of investigational drugs	• Document missed visits or visits outside study window • Home-health service to obtain data or use clinical staff to conduct in-home assessments (need to balance variability in raters vs. missed data)

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Stage	Challenge	Mitigation Strategies
Data Analysis	• Developmental/educational impacts on children due to pandemic impacting interpretation of COA efficacy results	• Quantify the extent of the impact ○ Therapy services pre-COVID pandemic vs. since pandemic ○ Ways to describe current academic setting, school resources ○ IRB amendment required to add this mid-trial that can delay enrollment and data collection ○ Possibility to compare with natural history data, if available, to see if there are unanticipated changes
	• No/little evidence available on pooling data collected via different administration modes (e.g., web and in-person)	• Conduct small comparability test between scores for in-person vs. remote assessment • Sensitivity analysis may not be possible; may have to anticipate greater amounts of variability
	• Missing data • Inability to compare data collected during pandemic with data collected outside of pandemic conditions • Impact of changes to studies for statistical analyses ○ What is an acceptable range of variability?	• Meyer RD. et al (2020): Statistical Issues and Recommendations for Clinical Trials Conducted During the COVID-19 Pandemic, *Statistics in Biopharmaceutical Research*. https://doi.org/10.1080/19466315.2020.1779122 Bacchieri A. et al. (2020): Risk and mitigation actions for clinical trials during COVID-19 pandemic (RiMiCOPa). *Contemporary Clinical Trials Communications* 20 (2020). https://doi.org/10.1016/j.conctc.2020.100682 • [Internet], Implications of Coronavirus Disease (COVID-19) on Methodological Aspects of Ongoing Clinical Trials, European Medicines Agency, 2020 Apr 25. https://www.ema.europa.eu/en/implications-coronavirus-disease-covid-19-methodological-aspects-ongoing-clinical-trials • FDA Guidance for Industry, Statistical considerations for clinical trials during the COVID-19 public health emergency. https://www.fda.gov/media/139145/download

Stage	Challenge	Mitigation Strategies
Regulatory Interactions	• Uncertainty around regulatory acceptance of mitigation strategies	• European Medicines Agency, International regulators provide guiding principles for COVID-19 clinical trials [Internet], Available from: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/guidanceclinicaltrials_covid19_en.pdf • FDA Drug and Device Resources, ClinicalTrials.gov - clinical trial conduct during the COVID-19 pandemic [Internet], Available from: https://www.fda.gov/drugs/coronavirus-covid-19-drugs/clinical-trial-conduct-during-covid-19-pandemic
	• Considerations for handling anticipated increase in protocol deviations	• IRB frequently will dictate how many protocol deviations/types of protocol deviations are permissible
	• Starting a trial pre-pandemic vs. during the pandemic (mid-trial pivot challenge vs. initiating a trial during the pandemic).	• Switching to electronic mode of data collection (paper vs. electronic)

The PRO Consortium's Rare Disease Subcommittee COVID-19 Mitigation in Pediatric Rare Disease Clinical Trial Team and Affiliations

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