TITLE: A Hybrid Clinical Trial Delivery Model in the COVID-19 Era

RUNNING HEAD: A Hybrid Clinical Trial Delivery Model

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[H1] Impact of the COVID-19 pandemic on pediatric rehabilitation and clinical research

Apart from the devastating fatal, economic, and societal consequences, the COVID-19 pandemic has resulted in unprecedented challenges to healthcare access for children with developmental disabilities.[1] At the same time, the pandemic has also led to major healthcare innovations that deserve further reflection and ongoing research.[2] In fact, some of these innovations may find their way into routine clinical practice even beyond the pandemic. Everyday citizens have been

innovative to help solve urgent healthcare needs, for example, creating aerosol boxes to prevent infectious spread among clinicians, 3D-printed ear guards to reduce pain from prolonged mask wearing, or 3D-printed ventilator valves to reduce their shortage.[2] In the face of shelter-in-place and social distancing guidelines, clinicians and caregivers of children with disabilities have also shown extraordinary resilience in finding alternative ways to continue offering therapeutic services using telehealth/videoconferencing platforms as well as face-to-face (F2F) visits with appropriate precautions. Prior to the pandemic, F2F interaction (and not telehealth) was the mainstay of pediatric clinical practice. However, the social restrictions during the pandemic, the advances in videoconferencing technologies, transition to online schooling, and the openness to remote videoconferencing within the clinical community as well as amongst children and families have clearly propelled the use of telehealth for pediatric rehabilitation.

In the Spring of 2020, pediatric research was also hindered due to the early lockdowns and a more guarded approach to resuming research with children with disabilities due to their greater vulnerability to infections.[3] Many clinical trials testing effects of pediatric therapeutic interventions have been halted or will have a delayed start as researchers eagerly await the post-pandemic period. With the ongoing surges in infection rates and the possibility of more infectious COVID-19 variants with greater risk to children,[4] it will be a while before we enter the post-pandemic period. The pandemic has catastrophically affected children with disabilities and specifically, those affected by Autism Spectrum Disorder (ASD) due to loss of services, alterations in methods of offering services (telehealth vs. F2F), parents having to play an active role in their child's virtual therapy/schooling, family stressors of working from home, job loss, or caring for multiple children, loss of access to peer/expert interactions, and the loss of the daily structure of a school day.[5-6] Therefore, it behooves us as clinicians and clinical researchers to be

more pragmatic and adapt our interactions to meet the needs of children and families by continuing clinical practice/research safely in spite of the pandemic-related social restrictions. For example, a more pragmatic approach that embraces fewer restrictions in participant recruitment and offers more flexibility in intervention context and providers could be implemented in clinical research.[7]

In Fall 2019, this research team had started a randomized controlled trial (RCT) comparing the effects of creative movement and standard of care, seated play interventions on the motor and social abilities of children with Autism Spectrum Disorder (ASD), which came to a sudden halt with the onset of the pandemic. In this point of view article, we justify our approach to modifying our ongoing clinical trial design to accommodate telehealth and implement a hybrid clinical trial delivery model. Our current study design is much more pragmatic and feasible for families and we plan to continue using this approach in future intervention studies even after the pandemic is over.

[H1] Evolution of clinical practices for children with disabilities

Early on in the pandemic, pediatric family support services such as schools and childcare centers were closed resulting in greater caregiving burden on parents. However, these services have since evolved and now offer a hybrid learning model with a combination of online synchronous and asynchronous learning as well as F2F interactions with appropriate precautions.[8] Similarly, for children with disabilities, there was a substantial lack of access to basic educational and therapeutic services with reports of 43-60% of children losing educational access, 63-70% losing access to therapeutic services (ie, Physical Therapy, Occupational Therapy (OT), and Speech therapy), 53-73% losing access to behavioral/psychiatric services (ie, Applied Behavioral

Analysis (ABA) therapy, social skills, counseling, psychiatry), and 87%-89% losing access to recreational services that promote physical activity and social connections.[9] Over the last few months, clinical practices have evolved and now incorporate hybrid therapy models, with both early intervention and school-based services being offered via telehealth using HIPAA-compliant and secure videoconferencing platforms. For example, there is new evidence to support the efficacy of early screening and diagnostic evaluations for ASD using the TELE-ASD-PEDS model, a parent-mediated, telehealth-based early screening method.[10] School-based therapies such as ABA, OT, physical therapy, and Speech therapies are also being offered virtually or F2F based on state-mandated guidelines and family preferences.[8,11,12]

Diversifying a creative movement intervention trial

Consistent with these trends in pediatric clinical practice, our research team also made swift accommodations to our ongoing clinical trial protocol: a) early on, we adopted a virtual telehealth format, and b) presently, we offer families the options of "virtual telehealth using Zoom" or "F2F with precautions". Precautions for F2F study delivery include use of 6-feet social distancing, facial barriers worn by all, hand sanitization before and after participation, pre-visit checks for COVID-19 exposure or symptoms, behavioral agreement to leave masks on throughout the session, and post-visit cleaning of surfaces and touchpoints.

Previously, all study-related interactions were F2F with expert clinicians using standardized testing or training supplies (ie, different testers and trainers per child). Upon rethinking our approach, we have modified our study format to provide flexibility to families by offering a choice of a parent-mediated, expert-facilitated (via Zoom telehealth) intervention or a completely expert-provided (F2F) intervention. Figure 1 shows telehealth intervention delivery for the

creative movement and standard of care, comparison groups. In the parent-mediated approach, we still use standard supplies for testing but deliver the tests with parental assistance. For training sessions, we try our best to incorporate household supplies to make it easier for caregivers to participate. We collaborate with the parent (and the child, when appropriate) by setting up parent-child meetings before the test/training sessions to explain the test/training instructional materials, receive feedback on how the sessions need to be modified to suit the child's needs, and how best to engage the child with ASD using the most effective interaction/reinforcement strategies. We also receive feedback on their study/intervention experiences from the parent and the child. This family-centered approach helps us tailor the intervention to the parent's comfort level as well as the child's likes/dislikes.

Using the PRECIS tool,[13] we evaluated our RCT design before and after the outbreak of the COVID-19 pandemic and see a clear shift towards more pragmatism or real-world immersion. The PRECIS tool classifies RCTs on a multidimensional continuum of explanatory (i.e., lab-based under ideal conditions with most explanatory scored as 1) to pragmatic trials (i.e., real-world or within usual conditions with most pragmatic scored as 5). Each author scored our pre- and post-COVID RCT design for each of the 10 PRECIS tool domains (Fig. 2). A higher total score on the PRECIS tool indicates a more pragmatic approach. We used the majority rule to obtain a final PRECIS score for each domain (pre-COVID total: 27 points, post-COVID total: 33 points). Figure 2 shows how our previous RCT design became more pragmatic from accepting telehealth and parent-mediated interventions.

Our RCT design has undergone two clear pivots over the last one year. The first pivot was in the early part of the pandemic when we adopted a fully telehealth-based approach to testing and training. The second pivot occurred recently when F2F research with precautions was reinstated

and with that we are able to offer families both telehealth and F2F options based on their preference and this approach will continue for the remainder of the study. We acknowledge that these adaptations may have certain negative methodological consequences.

More specifically, a pragmatic approach may lead to more variability in study delivery because researchers have less control over the delivery process leading to less standardization of testing and variations in test and intervention delivery for multiple reasons. Parents may utilize different child interaction strategies while prompting, reinforcing, and shaping their child's behaviors. The home environment and context during telehealth will differ compared to expert interactions in the home/lab setting. Children's oppositional tendencies could make them more non-compliant with a parent and perhaps more compliant with an unfamiliar expert or vice-versa. Parent-child dynamics will play an important role when using the telehealth format. Another issue is the structural set up of the testing area. Each house is configured differently and while we have standardized our walking and running distances to the structural limitations of homes by marking out standard distances and increasing the number of movement cycles; it is still a test variation that may affect our study results. For example, the shuttle run test requires the child to run a 50-foot distance back and forth to bring back a small object (ie, 100 feet in total). Instead, we use a 10-feet distance and ask the child to bring 5 small objects to complete the 100-feet shuttle run. Overall, methodological variations are bound to happen when the study becomes more pragmatic and is in the hands of caregivers in relatively uncontrolled environments and will ultimately increase variability of the data collected.

[H1] Lessons Learned: Pros and Cons of Telehealth Intervention Research

The aforementioned pragmatic, ecologically-valid, and family-centered approach of providing movement interventions to children with ASD comes with multiple pros and cons.[5,6-16] Pros of

using a hybrid clinical trial delivery model are: a) increased geographical access to study participants across the country, b) reduced travel time from lab to intervention site, c) increased ecological/external validity through parent-mediated interventions that are no more limited to expert providers only, d) greater real-world carryover reported by parents through improved child interactions and interest in physical activity or creative movement (eg, singing, moving, dancing, etc.) outside of the training context, e) increased tailoring of the intervention to meet family needs and preferences, and f) preferred method of study delivery for certain subgroups with greater health risks. On the other hand, the cons of such a model are: a) remoteness between the clinician and child during the virtual sessions making it harder to build relationships and requiring greater effort and enthusiasm from the clinician, b) inability to offer hand on hand prompting in the moment, with movement feedback being limited to verbal and visual inputs, c) increased caregiver burden to keep the child focused and engaged during the tasks and to model/demonstrate training activities for the child, d) technical issues related to audio and video transmission during internet calls, e) additional time taken to pre-plan kit drop-offs and parent training meetings and to explain tasks within sessions, and f) difficulty in applying the approach for children with greater cognitive and behavioral impairments because they have a difficult time attending to the laptop screen and present with a lot of negative behaviors, which in turn increases the parent's intervention burden and stress.

[H1] Lessons Learned: Impact on Methodological Rigor of the RCT

While pragmatic modifications to clinical trial formats are justified to make progress during the pandemic; many research studies including ours could be negatively impacted in their methodological rigor. Modifications to study protocols and procedures in light of the pandemic call for the research community to show more candor by systematically reporting on changes to

study designs during the dissemination phase and for reviewers to show greater flexibility during the review process.[14]

Next, we discuss the different considerations that could affect the methodological rigor of studies conducted during the pandemic. First, studies that started before the pandemic and continued during the pandemic have an inherent source of variability due to the change in the natural experiences of children and families. For example, loss of services, shift to online/telehealth platforms, increase in family stressors, loss of daily structure associated with school-based and after school programming, greater developmental decline, and increase in negative behaviors/non-compliance in children are all factors that are likely to impact outcomes of interventions provided during the pandemic. How much a child is affected by these factors and their ultimate group assignment, will create natural confounds for group differences. We plan to compare the baseline social, motor, and behavioral skills of children with ASD using the Social Motor Function Classification System to assess and control for children's baseline performance[15] which to some extent will control for COVID-related experiential differences across groups. Secondly, if a portion of the study sample received F2F interactions (before or during the pandemic) and others received telehealth interactions then that is a major confound that should be controlled across groups. We plan to recruit a similar number of participants seen F2F and via telehealth across all groups. Moreover, adding a new factor to our study may require a larger study sample to uncover significant between-group differences.

Third, researchers should document the major pivots in their study and account for these changes in their study design and data analysis. Fourth, the increased pragmatism of the RCT may also lead to greater amount of missing data as the study is less controlled by experts and more in the hands of parents and caregivers within uncontrolled environments. Overall, researchers may

need to recruit larger samples, adopt statistical approaches that allow for the use of baseline characteristics and methodological differences as covariates in the analyses, and conduct subgroup analyses to better explain their results. The aforementioned considerations will increase the sources of variability in the studies, thereby increasing the possibility of obtaining non-significant results and should not be used to penalize research groups when evaluating/reviewing studies from the pandemic era for publications and grants.

[H1] Future Recommendations

If clinical researchers continue to use a hybrid clinical trial delivery model in future studies, they must ensure that testing/training clinicians are fully trained to understand the nuances of the videoconferencing tool used. Along the same lines, a lot of pre-planning will go into developing parent-friendly instructional materials with appropriate visuals or short videos to explain the technical nuances of the hardware and software used for study delivery. When possible, it might be easier to request the parent for brief access (< 15 minutes) to the test or training area in their home to set up the space with the laptop and webcam and show them the technical nuances. A laptop/iPad can be provided to families who do not have the ideal recording device. Advanced planning will be needed to drop-off or mail the appropriate test/training supplies or to gather a list of household supplies for the training sessions.

We acknowledge that many questions still remain unanswered about the hybrid clinical trial delivery model. Telehealth versus F2F methods of test/training delivery need to be validated by comparing primary outcomes across the two methods. Various factors causing variations in natural experiences during the pandemic could affect a child's performance when participating in intervention studies. Studies must acknowledge and address the different study confounds that may occur by implementing changes to study design as well as corrective statistical approaches.

In the long-term, diversifying intervention study designs to be inclusive of different clinicians, participants with wide-ranging abilities, tailored interventions, and a range of clinical settings will make clinical trials more pragmatic and externally valid. We hope that such hybrid clinical trial delivery models will continue to thrive in the long-term even beyond the duration of the pandemic.

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Clerical/ secretarial support: A. Bhat, C. Cleffi, S.Srinivasan

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Disclosure

The authors completed the ICMJE Form for Disclosure of Potential Conflicts of Interest and reported no conflicts of interest.

Ethics

Written consent was obtained for the photos.

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Figure Legends

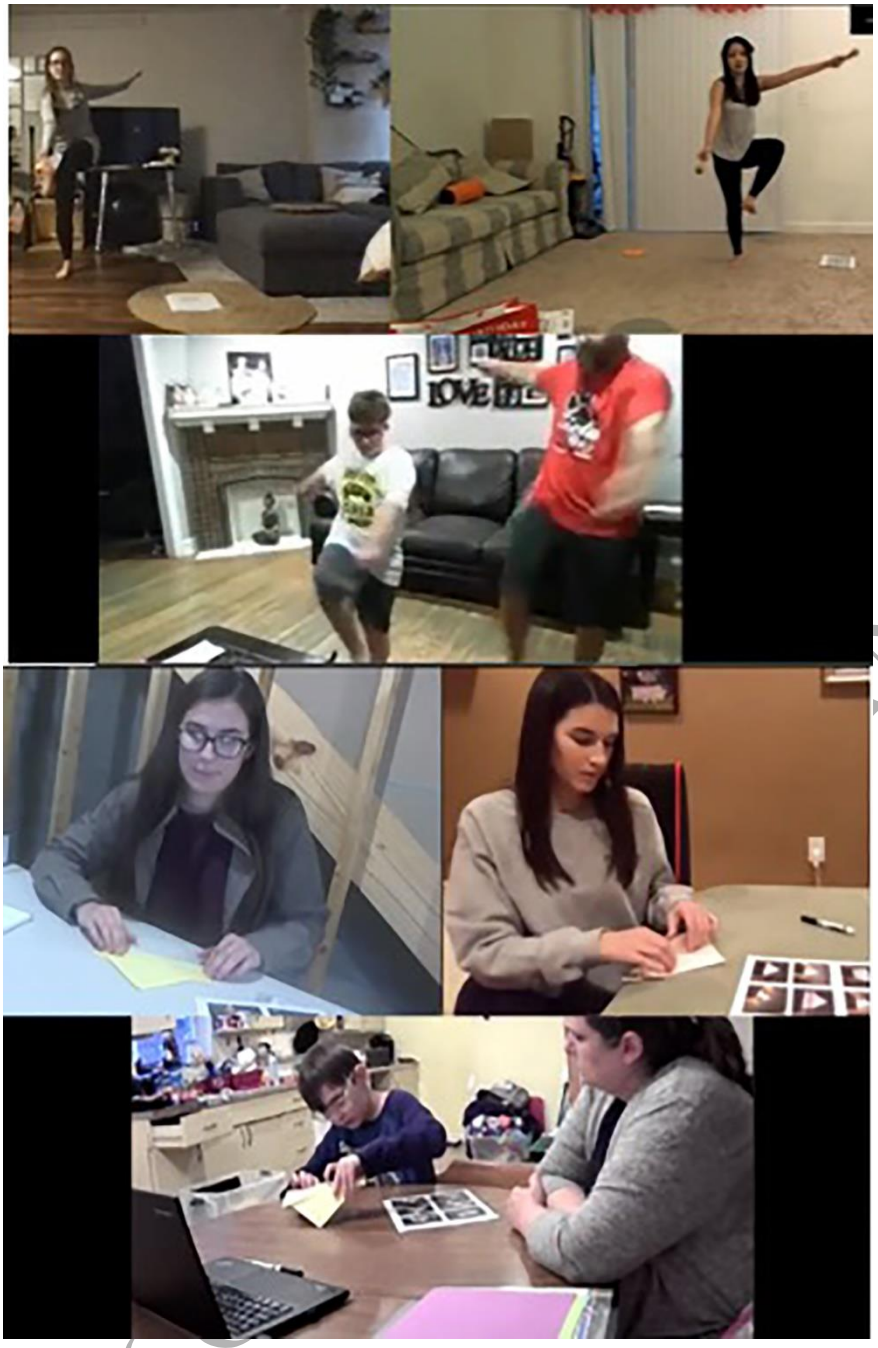

Figure 1. Telehealth intervention delivery for the creative movement group (top 3 photographs) and the standard-of-care seated play groups (bottom 3 photographs).

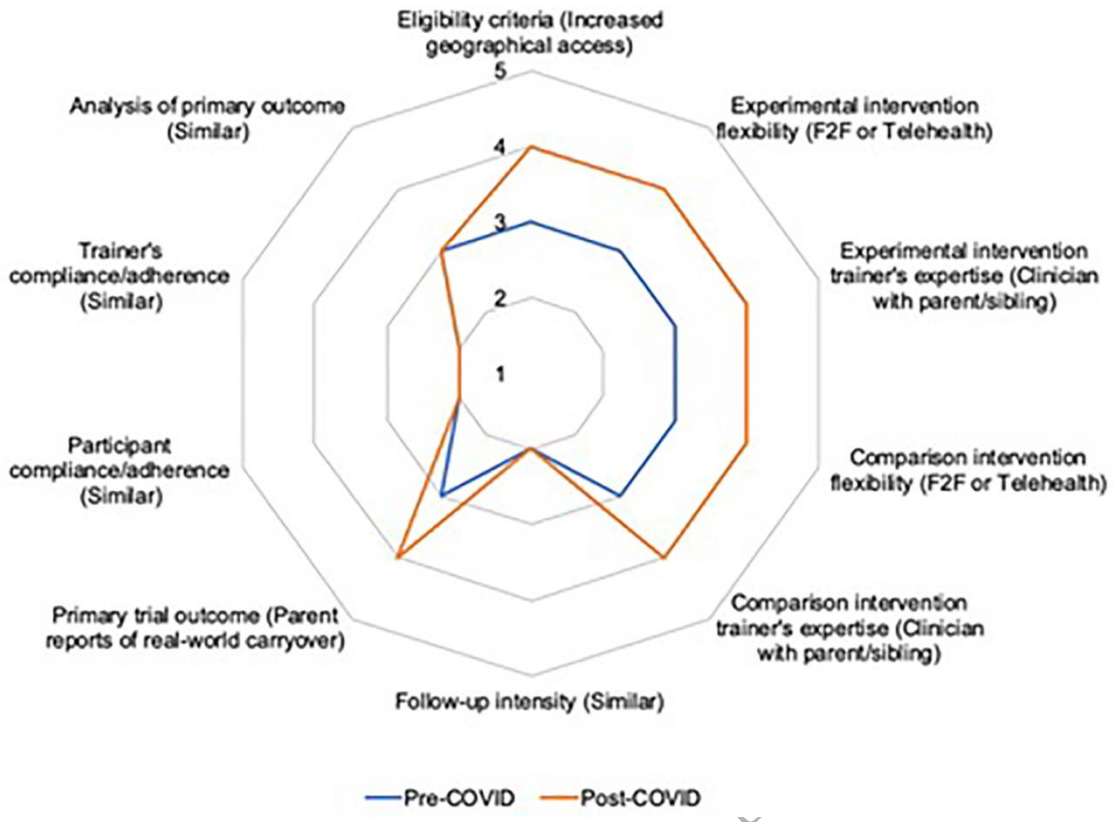

Figure 2: PRECIS scoring summary for pre-COVID and post-COVID RCT study design