

SHORT REPORT

The impact of COVID-19 on autism research: A cross-sectional analysis of discontinued or suspended clinical trials

Monika Neale¹  | Elizabeth Landers² | Nicholas B. Sajjadi²  |
Anya Mazur-Mosiewicz³ | Micah Hartwell^{2,3}

¹College of Osteopathic Medicine, Kansas City University, Joplin, Missouri, USA

²Office of Medical Student Research, Oklahoma State University Center for Health Sciences, Tulsa, Oklahoma, USA

³Department of Psychiatry and Behavioral Sciences, Oklahoma State University Center for Health Sciences, Tulsa, Oklahoma, USA

Correspondence

Monika Neale, College of Osteopathic Medicine, Kansas City University, Joplin, MO, USA.

Email: mneale@kansascity.edu

Abstract

Due to uncertainties associated with the COVID-19 public health crisis, several clinical trials had to be withdrawn or postponed. Our investigation aimed to assess the rate of discontinuation of clinical trials focusing on Autism Spectrum Disorder. Of the 197 registered trials included in our systematic review, 15 (7.6%) were discontinued, with nearly half of these explicitly citing COVID-19 as their reason for discontinuation. Pharmacological trials were six times more likely to be discontinued during the pandemic than non-pharmacological studies. The difference between the likelihood of discontinuation was statistically significant (OR: 6.13; 95% CI: 1.22–30.71). There was no evidence of association between funding source and reasons for discontinuation. Limitations, along with implications for future trials are discussed.

Lay Summary

We investigated the impact of the COVID-19 pandemic on the discontinuation rate of autism clinical trials. We found that drug trials were six times more likely to be discontinued during the pandemic compared to behavioral, diagnostic, and nutritional trials. The overall discontinuation rate was notably lower in autism clinical trials than in other areas of medical research. We recommend an examination of the methodology of the continued autism trials to assess their applicability in other fields.

KEYWORDS

autism, clinical trials, COVID-19, discontinuation, pandemic

INTRODUCTION

The COVID-19 pandemic has interrupted access to routine medical services (Czeisler et al., 2020) and impeded medical research in multiple ways, including reductions in participant recruitment for clinical trials (Sathian et al., 2020). Physicians are typically the primary source of referrals for research participation (Clark et al., 2019), and limited access to healthcare during the pandemic was bound to reduce outpatient referrals for clinical trials. Moreover, the United States Food and Drug Administration (FDA) guidelines for the *Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency* urged clinical trial sponsors to carefully consider the additional potential risks to participants during

the pandemic and either modify or discontinue studies (FDA, 2020).

The FDA guidance combined with social distancing recommendations from the Center for Disease Control (CDC) presented new ethical dilemmas (Bierer et al., 2020) and made it challenging to continue ongoing trials that were not considered “life-saving” and recruit for upcoming studies (Ledford, 2021). These challenges were compounded by reallocating medical research staff to aid hospital efforts, the startup of massive COVID-19 research efforts, inadequate supply of protective personal equipment, interruptions in medical/drug supplies, and uncertainty of continued financial support (Asaad et al., 2020).

Timeliness and consistency are critical for all clinical trials. The time-sensitive nature of autism research lies

with efforts to find ways to reliably diagnose autism as early as possible (Shirley, 2005) and deliver early interventions. Additionally, research evidence can help inform clinical practice (Thurm & Swedo, 2012), and make new diagnostics and treatments available to the growing number of autism referrals (CDC, 2020b), which further underlines the importance of continuity of clinical trials.

Consequently, suspending or discontinuing autism research may negatively impact patients, their family members, and medical practitioners because despite decades of research, we still lack preventative measures, and no universally efficacious interventions for the core symptomatology of autism exist (CDC, 2020a). Considering the possible negative consequences of slowing autism research during the pandemic, our objective was to examine publicly available data to assess the frequency of discontinuation of autism clinical trials during the COVID-19 public health crisis.

METHODS

On August 13, 2021, we performed a systematic search of [ClinicalTrials.gov](https://clinicaltrials.gov), an international registry of both privately and publicly funded interventional studies (NIH: U.S. National Library of Medicine, 2021), for trials related to autism. Our search included the following terms: “Autism,” “Autism Spectrum Disorder,” “Child Development Disorders,” and “Neurodevelopmental Disorders.” The expert search string is presented in Supplement S1. We included interventional trials in any phase and in any country. Studies must have been listed as “recruiting,” “active, not recruiting,” “enrolling by invitation,” “suspended,” “terminated,” or “withdrawn.” We excluded studies that were completed before 02/2020—prior to the COVID-19 pandemic. The “last update posted” date was used as a proxy for trial status change. We used the date range 01/01/2020–07/31/2021 to identify all trials potentially affected by the COVID-19 pandemic up to the time of our search. The identified trials were subsequently extracted for trial status, conditions treated, interventions implemented, outcome measures, sponsors/collaborators, phases, enrollment, funding, study type, study design, start date, primary completion date, completion date, first posted date, results first posted, last update, and trial locations.

In a blinded, duplicate manner, two of us (MN and EL) screened the trials for relevance to autism and only studies involving participants with autism were retained. Studies including participants with other neurodevelopmental disorders, such as ADHD or intellectual disability only, have been excluded. The same two authors, also in a blinded, duplicate fashion, manually extracted reasons for discontinuation provided on the [ClinicalTrials.gov](https://clinicaltrials.gov) website. Disagreements were discussed and decided by revisiting the text, and, if extractors were

unable to reach agreement, a third author (MH) acted as arbiter. Trials that explicitly mentioned COVID-19 as a reason for discontinuation were coded as such. For other trials, we coded the provided explanation or “reason not provided.”

A Mann–Whitney U test was used to determine if there was a significant difference in enrollment between trials discontinued due to COVID-19 compared to other discontinued trials. Fisher Exact tests were used to determine if there was an association between trials that were canceled due to COVID-19 and funding source and trial location (US and non-US-based). Funding sources were coded into *Industry* (if any industry involvement was reported), *US Government* (if any US Federal agency, Veterans Affairs, Department of Defense was reported), and *Other* for registered CTs receiving funding from sources not falling into previously mentioned categories. *Other* is a “funded by” category that investigators can select on [ClinicalTrials.gov](https://clinicaltrials.gov), and we used it as defined therein. Further, if a study was coded as multiple funding sources (e.g., a study was reported to have both *Government* and *Industry* funding), it was re-coded as *Government* as the study would report to governmental guidelines. As a post-hoc analysis, we performed a logistic regression analysis to determine the association between types of intervention (drug vs. behavioral) and discontinuation during the COVID-19 pandemic.

Statistical analyses were performed using Stata 16.1 (StataCorp, College Station, TX). An Institutional Review Board determined that this project did not qualify as human subject research and, therefore, it was not subject to further oversight.

RESULTS

Search return and study characteristics

The search of [ClinicalTrials.gov](https://clinicaltrials.gov) returned 494 studies. We excluded 297 studies, 274 of which were not related to autism and 23 that were completed prior to the pandemic. Thus, our sample consisted of 197 trials. Among these studies, there were a total of 54,594 participants, with a median of 86 participants (IQR: 42–180) per trial. There were 137 (of 197, 69.5%) US-based trials and 60 (30.5%) international trials. Of the 197 trials, 16 (8.1%) were funded through industry, 38 by the US Government, and 143 were categorized as *Other*. Interventions among these 197 trials varied—with 51 (25.9%) being behavioral or psychotherapy, 40 (20.3%) drug trials, 39 (19.8%) diagnostics, 25 (12.7%) care-provider training or case management, with the remaining consisting of 12 (6%) device, 8 (4%) diet/supplements, 11 (5.6%) physical activity, 1 electro-convulsive therapy, 1 surgery (0.5%), and 9 (4.6%) trials that were classified as *other*.

TABLE 1 Rates of discontinuation of trials during COVID-19 pandemic and stated reasons

Type of intervention	Total <i>n</i>	Discontinued <i>n</i> (%)	Reason for discontinuation				
			COVID-19 <i>n</i> (%)	Feasibility <i>n</i> (%)	Funding <i>n</i> (%)	Recruitment <i>n</i> (%)	Did not meet endpoint <i>n</i> (%)
Drug	40	8 (20)	4 (50)	0 (0)	0 (0)	2 (25)	2 (25)
Behavioral or psychotherapy	51	2 (3.92)	2 (100)	0 (0)	0 (0)	0 (0)	0 (0)
Physical activity	11	1 (9.09)	0	0 (0)	1 (100)	0 (0)	0 (0)
Device	12	1 (8.33)	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)
Parent/provider training	25	1 (4)	0 (0)	0 (0)	1 (100)	0 (0)	0 (0)
Diagnostics	39	1 (2.56)	0 (0)	1 (100)	0 (0)	0 (0)	0 (0)
Electroconvulsive therapy	1	1 (100)	0 (0)	0 (0)	0 (0)	1 (100)	0 (0)
Diet or supplements	8	0 (0)	–	–	–	–	–
Surgery	1	0 (0)	–	–	–	–	–
Other	9	0 (0)	–	–	–	–	–

TABLE 2 Associations of reasons for discontinuation by trial characteristics

Characteristic	Reason for discontinuation		<i>p</i>
	COVID-19 <i>n</i> (%)	Non-COVID-19 <i>n</i> (%)	
Number of CTs	7 (46.67)	8 (53.33)	
Location of CTs			Fishers exact
Non-US	1 (6.67)	1 (6.67)	1.0
US	6 (40.00)	7 (46.67)	
Funding source			Fishers exact
Industry	1 (6.67)	2 (13.33)	1.0
US Government	1 (6.67)	0	
Other	5 (33.33)	6 (40.00)	
Enrollment			Mann–Whitney <i>U</i>
Median (IQR)	30 (15–80)	3 (1–11)	$z = -1.91, p = 0.056$

Discontinuation

As shown in Table 1, among the 197 studies, 15 (7.6%) were suspended, withdrawn, or terminated between January 1, 2020, and July 31, 2021, with a total of 735 participants enrolled. The median enrollment of discontinued trials was 12 (IQR: 1–52). Of these 15 studies, seven (46.7%) explicitly reported discontinuation due to COVID-19.

The trials that were discontinued due to COVID-19 had a median enrollment of 30 (IQR: 15–80) and a total of 368 participants. Of the seven trials that were discontinued due to COVID-19, two (28.6%) were behavioral/psychotherapy, four (57.1%) were drug trials, and one (14.3%) was a device trial. Among the eight trials that did not explicitly state the pandemic as a reason for discontinuation, three (37.5%) reported recruitment, two (25%) indicated not meeting endpoints, two (25%) listed

funding, and one (12.5%) reported feasibility as reasons for discontinuation.

Associations of discontinuation reasons and trial characteristics

The Mann–Whitney *U* test did not show a statistically significant difference in trial sample size and discontinuation for COVID-19 compared to other reasons ($z = -1.91, p = 0.056$; Table 2). We also found no statistically significant association between funding source and termination reason (COVID vs. non-COVID; $p = 1.0$), nor among trial locations (US vs. non-US; $p = 1.0$).

Our post hoc analysis showed that there was a statistically significant association between types of intervention (drug vs. behavioral) and discontinuation, with odds showing drug trials were more likely to be discontinued than behavioral trials (OR: 6.13; 95% CI: 1.22–30.71).

DISCUSSION

The overall discontinuation rate of registered autism trials between January 1, 2020 and July 31, 2021 was 7.6%, impacting 735 participants, which is a lower overall rate compared to other areas of clinical research (Desai et al., 2021). Nearly half of the autism trials that were discontinued explicitly cited COVID-19 as the primary reason for discontinuation.

Overall, 368 participants were enrolled in the trials impacted by COVID-19. Over 200 of these participants were children between the ages of 2–8 years old. Given the increasing number of children hospitalized with COVID-19 between May 2020 and May 2021 (Delahoy et al., 2021), the decision to halt autism trials involving children was likely necessary when switching to teleconsultation or other non-face-to-face methodology would compromise the integrity of the trial.

Drug trials were the most vulnerable to terminations and suspensions during COVID-19 with a discontinuation rate of 20%, impacting 574 participants, which indicates a sixfold likelihood of discontinuation when compared to non-pharmacological interventions. Half of the discontinued drug trials cited COVID-19 as the reason for discontinuation, likely reflecting interruptions in drug and medical supplies (Asaad et al., 2020). Two more studies indicated recruitment issues, which may be attributable to the pandemic and changes in FDA guidelines.

Diagnostic testing, behavioral approaches, and parent-mediated interventions appeared to be flexible study designs with discontinuation rates of under 4% affecting a total of 102 participants. These trials may have had an online component or were easily converted to telehealth, as suggested by the FDA (U.S. Department of Health and Human Services, Food and Drug Administration, 2020). Lindgren et al. (2016), showed similar efficacy between telehealth and traditional clinic-based Applied Behavior Analysis (ABA) treatment for autism, which further supports a decision to adapt protocols to online participation without compromising internal validity while incorporating an extra safety measure.

Of the 11 trials investigating “physical activity” to manage symptoms of autism, only one trial was discontinued, and it was due to funding. This is a noteworthy finding indicating that demonstrations accompanying physical activity interventions could also easily be adapted to a web-based experience, as described in the PLANE project by Ketcheson and Pitchford (2021). Although the full effect of telehealth physical activity interventions is not widely studied, a systematic review by Seron et al. (2021) demonstrated its efficacy.

None of the eight “dietary or supplements” trials were discontinued. This is most likely attributable to the fact that dietary interventions tend to be home-based and therefore sheltered from the risks associated with office visits. Further, dietary supplements are not regulated by

the FDA (Center for Food Safety & Applied Nutrition, 2020), which may have allowed for additional flexibility.

One of the short-term implications of clinical trial discontinuation is that individuals whose only access to treatment was through participation in these trials missed an opportunity for services. Long term, however, having to adjust study designs due to the pandemic allows researchers to evaluate the adaptability of their methods. Given the overall successful continuation of the majority of clinical trials of autism research, methods from these clinical trials should be assessed for adaptability in other fields of medicine and behavioral therapies where applicable.

LIMITATIONS

Given the ambiguity surrounding the reasons for discontinuation, it is highly probable that some of the studies that were postponed or discontinued due to “recruitment” or “reason not provided” between March 2020 and August 2021 were influenced by some aspects of the pandemic, even though COVID-19 was not explicitly mentioned. Therefore, our current survey is likely to be an underestimate of the increase in autism trial discontinuation due to COVID-19.

Unfortunately, while lessons learned from trials that continued during the pandemic would be very informative in aiding future study designs, the modifications to clinical trial protocols were not publicly available, further contributing to the limitation of the current study.

Additionally, due to the limited nature of publicly available data, we were unable to determine whether the trials that did continue would be free from selection bias, or even adequately powered at their conclusion. It is likely that the continued trials were impacted by participant attrition similar to hundreds of other trials, just not to the degree that would warrant discontinuation. Therefore, selection bias and power should be carefully considered when interpreting or evaluating generalizability of studies that continued despite the COVID-19 pandemic.

CONCLUSION

Clinical trials are vital to the progression of autism treatments and our understanding of symptomatology. Our study found that while only 7.6% of clinical trials focused on autism were discontinued during the COVID-19 pandemic; pharmacological trials were most affected. As other studies focusing on the disruption of clinical trials and other autism research are currently underway, we have yet to discover the full scope of COVID-19’s impact not only on autism research, but the degree to which a public health emergency can cause lasting effects on the entire research community.

CONFLICT OF INTEREST

The authors have no conflicts of interests to disclose.

ETHICS STATEMENT

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial or non-financial interest in the subject matter. Further, the authors have no financial or proprietary interest in any materials discussed. The current study does not meet the conditions for human participants and/or animal research, therefore was not subject to IRB review, nor did it require informed consent.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Monika Neale  <https://orcid.org/0000-0002-0603-3271>
Nicholas B. Sajjadi  <https://orcid.org/0000-0003-1716-2404>

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SUPPORTING INFORMATION

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