Original Article

Impact of coronavirus disease-19 pandemic on pediatric vaccine clinical trials

Neeta Hanumante[1], Dipali Desale[2]

From [1]Associate Professor, Department of Pediatrics, [2]Clinical Research Co-ordinator, Clinical Research Unit, Bharati Vidyapeeth (Deemed to be University) Medical College and Hospital, Pune, Maharashtra, India

ABSTRACT

Introduction: The coronavirus disease (COVID)-19 pandemic has affected nearly every facet of life, including clinical research, and has had an adverse and extensive impact on clinical trials including pediatric vaccine trials. Across the globe, countries implemented a variety of restrictions to people's everyday lives, which have substantially impacted the ability to conduct pediatric vaccine trials. **Objectives:** The objectives of the study were to assess the impact of the COVID-19 pandemic on enrollment and follow-up of clinical trial participants in pediatric vaccine clinical trials and simultaneously to explore various strategies used for overcoming these challenges during the COVID-19 pandemic period. **Materials and Methods:** Data of 10 pediatric vaccine clinical trials were obtained from the clinical trial records of the Clinical Research Unit. The number of subjects enrolled, number of study dropouts, protocol deviations, and reasons for participant dropout/deviations were recorded from these pediatric vaccine clinical trials carried out before and during the COVID-19 pandemic period from March to December 2020. These metrics were then compared with their counterparts recorded during our study to statistically assess the impact of the COVID-19 pandemic. Various factors which have affected the recruitment and follow-up in pediatric vaccine clinical trials and various strategies used to curtail subject dropout and protocol deviations during COVID-19 pandemic were studied in detail. **Results:** The primary and most visible impact of the COVID-19 pandemic was that protocol deviations and study dropouts were significantly higher for the trials conducted during COVID-19 pandemic period. The difference between proportion of protocol deviations and study dropouts in the pediatric vaccine clinical trials conducted during pandemic and trials conducted before pandemic was statistically significant (<0.05). The recruitment for ongoing trials was also adversely affected**.** **Conclusion:** At our site, the COVID-19 pandemic has affected the conduct and recruitment of pediatric vaccine trials markedly in an adverse manner. The protocol deviations and study dropout were significantly higher during the COVID-19 pandemic period. To counter these effects and still have the trials retain their effectiveness, we found that it is essential to implement measures and strategies for maintaining compliance and safe conduct of clinical trials. Adoption of telemedicine may offer promise in terms of a way forward for conducting clinical trials.

Key words: Coronavirus disease-19 pandemic, Protocol deviation, Subject dropout, Telemedicine, Vaccine trials

The World Health Organization declared coronavirus disease (COVID)-19 a public health emergency of international concern on January 30, 2020, and later declared a pandemic on March 11, 2020 [1]. The first confirmed case of coronavirus in Maharashtra was reported on March 9, 2020, in our city of Pune. Gradually, the pandemic spreads to all parts of the country, and eventually, the tally of COVID-19 cases by December 2020 touched 10 million.

The COVID-19 pandemic has affected nearly every facet of life, including clinical research and has had an adverse and extensive impact on clinical trials including pediatric vaccine trials. Across the globe, countries implemented a variety of restrictions to people's everyday lives which included, country-wide lockdowns, and social distancing, which have been major detrimental factors for the conduct of pediatric vaccine trials [2]. The present study was proposed to assess the impact of the COVID-19 pandemic on enrollment and follow-up of clinical trial participants in pediatric vaccine clinical trials and simultaneously to explore various strategies used for overcoming these challenges during the COVID-19 pandemic.

Access this article online	
Received - 21 April 2021 Initial Review - 09 May 2021 Accepted - 14 June 2021	Quick Response code
DOI: 10.32677/IJCH.2021.v08.i06.001	

MATERIALS AND METHODS

This observational, cross-sectional study was conducted in the Clinical Research Unit of a tertiary care multispecialty hospital in Pune, where pediatric vaccine clinical trials are routinely

Correspondence to: Dr. Neeta Hanumante, Associate Professor, Department of Pediatrics, Bharati Vidyapeeth (Deemed to be University) Medical College and Hospital, Pune, Maharashtra, India. E-mail: neeta.hanumante@gmail.com

conducted. The required approval was obtained from the Institutional Ethics Committee before the study being conducted. Pediatric vaccine clinical trials carried out during COVID-19 pandemic period from March to December 2020 were included in the study and pediatric vaccine clinical trials conducted from March to December 2019 as a comparison group.

Data of pediatric vaccine clinical trials were obtained from the clinical trial records of the Clinical Research Unit, while strictly maintaining confidentiality. The data, that is, number of subjects enrolled, number of study dropouts, protocol deviations, and reasons for participant dropout/deviations were collected from each of the five pediatric vaccine clinical trials that were ongoing during the COVID-19 pandemic period from March to December 2020. Similar data from five vaccine clinical trials conducted during March to December 2019 were used for comparison. From a qualitative standpoint, the site had employed various strategies with an aim to lessen the adverse impact of the COVID-19 pandemic on the above metrics, which were also studied in detail.

The details of amendments done in the clinical trial protocols to salvage the integrity of ongoing trials during COVID-19 pandemic were recorded. Various factors during COVID-19 pandemic which have adversely affected the recruitment and follow-up in pediatric vaccine clinical trials were also studied in detail. Strategies used by the site for clinical trial-related activities, where in-person interface was needed as per protocol, were also documented as part of this study.

Statistical results concerning categorical variables were shown as frequency and percentages. Z-test for difference between two proportions was used, to test the highest proportion of dropouts and deviations between the studies carried out before and during the COVID-19 pandemic. $p<0.05$ was considered to be statistically significant.

RESULTS

Table 1 shows that before COVID-19 pandemic, there were no protocol deviations reported in studies except in study IV, which had only 2/97 (2.06%) protocol deviations. Furthermore, the study participant dropout rate was less before COVID-19 pandemic period, maximum (6.19%) being in study IV.

As shown in Table 2, during the COVID-19 pandemic period, except for study V, protocol deviations were reported in all the other studies; the highest of them being in study IV (21.43%).

The above table shows that during COVID-19 pandemic period, all the studies have reported study participant dropout and the highest being in study I, 18.18%.

Table 3 shows that the "Z-test result for difference between two proportions of protocol deviations" before and during COVID-19 pandemic is statistically significant ($p<0.001$).

Table 4 reveals that the "Z-test result for difference between two proportions of subject dropout" before and during COVID-19 pandemic period is 0.04, which is statistically significant (<0.05).

DISCUSSION

The current COVID-19 pandemic has created unforeseen challenges in conducting clinical trials due to mandated lockdowns and implemented travel restrictions. The pandemic has impacted innumerable patients, sponsors, research monitoring entities, trial staff, and investigators [3]. In India, nationwide lockdowns were declared by the government in four phases as – Phase 1: March 25, 2020–April 14, 2020 (21 days), Phase 2: April 15, 2020–May 3, 2020 (19 days), Phase 3: May 4, 2020–May 17, 2020 (14 days), and Phase 4: May 18, 2020–May 31, 2020 (14 days). After this period, reopening was planned gradually; offering relaxation in the restrictions in a phased manner.

We studied data of five ongoing pediatric vaccine trials over a period of 9 months during the COVID-19 pandemic, that is, from March to December 2020. For comparison, we extracted data from five pediatric vaccine trials which were conducted during March–December 2019 before the pandemic onset. In each of these trials, metrics such as total enrollment, protocol deviations, subject dropout, and possible reasons behind these deviations were studied thoroughly. From a qualitative standpoint, the site

Table 1: Study details before COVID-19 pandemic

Study number	Enrolled cases	Dropout number	Dropout percentage	Deviation number	Deviation percentage
I	38	2	5.26	0	0.00
II	65	1	1.54	0	0.00
III	94	5	5.32	0	0.00
IV	97	6	6.19	2	2.06
V	63	0	0.00	0	0.00

COVID: Coronavirus disease

Table 2: Details of studies during COVID-19 pandemic

Study number	Enrolled cases	Dropout number	Dropout percentage	Deviation number	Deviation percentage
I	33	6	18.18	6	18.18
II	107	19	17.76	13	12.15
III	38	2	5.26	4	10.53
IV	42	3	7.14	9	21.43
V	51	1	1.96	0	0

COVID: Coronavirus disease

Table 3: Z-test for difference between two proportions of protocol deviations

Group	Samples	Deviation	Proportion	p-value
Before COVID-19 pandemic	97	2	2.06	<0.001
During COVID-19 pandemic	42	9	21.43	

COVID: Coronavirus disease

Table 4: Z-test for difference between two proportions of subject dropout

Group	Samples	Dropouts	Proportion	p-value
Before COVID-19 pandemic	97	6	6.19	0.04
During COVID-19 pandemic	33	6	18.18	

COVID: Coronavirus disease

had employed various strategies with an aim to lessen the adverse impact of the COVID-19 pandemic on the above metrics, which were also studied in detail.

As shown in Table 1, before the COVID-19 pandemic, clinical trials have had very few protocol deviations, that is, only in study IV, 2/97 (2.06%) children visited the site later than the window period. In contrast to this, during the COVID-19 pandemic period, except for study V, protocol deviations were reported in all the other studies; the highest of them being in study IV (21.43%). The difference between the proportion of deviations before and during the pandemic was statistically significant with $p<0.001$.

A majority of protocol deviations at our site could be attributed to the fact that the parents along with their children traveled to their native places and returned only when the phased reopening began. As a result, they visited the site later than their allowed window period. Few of the parents were scared to bring their children to the hospital site for study visits, as our hospital was functioning as a COVID hospital. Some parents could not visit the site due to difficulty in arranging transport for their children. Unavoidable missed visits and study visit deviations during the COVID-19 pandemic have also been reported in various other studies [4-7]. Padala *et al*. [8] have mentioned that out-of-window period visits because of COVID-19 pandemic have led to minor protocol deviations but may not lead to discontinuations from the study. Panda *et al*. [5] have stated that protocol deviations are likely to occur more frequently during the COVID-19 pandemic, whereas Byrd *et al*. [6] have stated that study participants might avoid academic medical centers and other clinical research institutions during the pandemic, causing protocol deviations.

Similar to our experience, Hasford [9] has reported that a major factor affecting clinical trials during COVID-19 pandemic was the lockdown with its travel restrictions and physical distancing requirements. These measures were adopted with an aim to protect patients and health care workers from getting infected, but created considerable problems for conduct of clinical trials. Patients became reluctant to visit physicians and hospitals, since they felt anxious about getting infected. Kunz *et al*. [10] have mentioned that various lockdown and quarantine measures may disrupt the trial conduct and patients may be unable to attend their scheduled visits.

During the COVID-19 pandemic, the participants of study IV could not come to our site for study visits and hence telephonic safety follow-up was carried out after discussion with the sponsor, in lieu of in-person visits. Later, the study IV protocol was amended, to allow telephonic safety follow-up when in-person visit was not possible and the visit-window period was also extended.

The protocols for study I and II were also amended. In study I, concomitant vaccinations were allowed along with the study vaccine, as it was not possible for subjects to visit the site multiple times for receipt of other scheduled vaccines. An option for telephonic visits was provided for safety follow-up of study visits and to also serve as a source for identification of unsolicited adverse events. The amended protocol also allowed replacement of subjects to maintain the power of the study to 90%. In study II, the window period for visit was extended to an additional 90 days, so the subjects who visited the site late could be included in per-protocol analysis.

Beane *et al*. [11] have stated that the protocol amendments should be used primarily to protect patients and research staff, but can also be used strategically to adapt protocols and avoid trial suspension. Thus, investigators may be able to maintain accrual of new patients or continue to collect important data from currently enrolled patients. Fleming *et al*. [12] have reported that a protocol amendment or revised statistical analysis plan could specify additional modifications to planned study procedures, patient populations, and statistical methods made in response to the pandemic.

As expected, subject dropout in the clinical trials increased markedly during the pandemic period as compared to pre-COVID clinical trials (Table 2), ($p<0.05$). The primary reason for subject dropout was their inability to be present on-site for study visits. The dropout rate was highest in study II, as a majority of study follow-up visits coincided with the early lockdown period. The site tried to reduce study dropout by telephonically following up with the subjects and requested parents to bring their children whenever possible, even if it was later than the allowed window period.

It has been reported that the pandemic has mainly affected the conduct of clinical trials unrelated to the COVID-19 disease [2,5,12,13]. Earlier studies have documented a slowdown in completing trials [9,14] and even suspension of non-COVID-19 clinical trials [15,16], during this pandemic period. Mitchell *et al*. have reported that some studies which have continued have seen a significant reduction in their recruitment numbers [2].

At our site, the COVID-19 pandemic did affect subject recruitment for studies I, IV, and V. For studies II and III, recruitment was completed before the onset of lockdown and hence was not affected. For studies I and IV, the enrollment commenced a month before the lockdown, so targeted recruitment could not be achieved. The enrollment in study V was markedly affected, which was a booster study of previously enrolled infants,

in which only 51 out of 96 subjects could be enrolled. Similar to our experience, Poongothai *et al*. [7] have reported that enrolling trial participants in an ongoing trial remain a great challenge during the COVID-19 pandemic period.

Different strategies were used at our site to optimize in-person study visits during the COVID-19 pandemic. The site maintained good rapport with study participants throughout the study period. Subjects were scheduled for on-site visits by spaced out appointments, so as to maintain social distancing norms. All safety measures were strictly followed and study procedures were completed in the shortest time possible. It has been reported that for randomized trials, communication from research staff and good rapport with patients is likely to help protect against dropout or non-adherence [7,12,17]. The Central Drugs Standard Control Organization, European Medicines Agency, and Food and Drug Administration have come out with the guidelines on the management of clinical trials during the COVID-19 [7]. Indian Council for Medical Research released guidelines in April 2020, for review of clinical trials during COVID-19 pandemic.

A positive outcome of the COVID-19 pandemic has been the shift in the attitude of the regulatory bodies toward the use of telemedicine [8]. In many EU member states, telemedical physician-patient interactions are permitted, thus the frequency of personal follow-up visits can be reduced if not completely avoided [9]. Many studies during the COVID-19 pandemic have recommended the option of using telemedicine, as trial participants may not be able to visit the site for protocol-specific visits [11,13,14,18-20]. Telemedicine has been used effectively during the COVID-19 pandemic, at our site as well. Remote study monitoring of ongoing clinical trials was done by sponsors/ Clinical Research Organizations during this pandemic, which has also been reported by many other researchers [5,15,19,21,22]. As is the case with all the above findings, small sample size was the limitation of our study.

CONCLUSION

At our site, the COVID-19 pandemic has affected the conduct and recruitment of pediatric vaccine trials markedly in an adverse manner. We noted that protocol deviations and study dropout were significantly higher during the COVID-19 pandemic period. To counter these effects and still have the trials retain their effectiveness, we found that it is essential to implement measures and strategies for maintaining compliance and safe conduct of clinical trials. In the likelihood of study participants being unable to attend the study site for follow-up or adverse events, we believe that telephonic contact would be a safe yet effective replacement. Remote data collection was limited before the COVID-19 pandemic; however, adoption of telemedicine may be a promising way forward in clinical trials.

REFERENCES

1. Mahajan P, Kaushal J. Epidemic trend of COVID-19 transmission in India during lockdown-1 phase. J Community Health 2020;45:1291-300.
2. Mitchell EJ, Ahmed K, Breeman S, Cotton S, Constable L, Ferry G, *et al*. It is unprecedented: Trial management during the COVID-19 pandemic and beyond. Trials 2020;21:784.
3. Collier EK, Hsiao JL, Shi VY. Conducting clinical trials during the COVID-19 pandemic. J Dermatolog Treat 2020;31:330-2.
4. Akacha M, Branson J, Bretz F, Dharan B, Gallo P, Gathmann I, *et al*. Challenges in assessing the impact of the COVID-19 pandemic on the integrity and interpretability of clinical trials. Stat Biopharm Res 2020;12:419-26.
5. Panda PK, Stockler MR, Gulia A. Clinical research during coronavirus disease pandemic: Challenges and way forward. Indian J Med Sci 2020;72:101.
6. Byrd JB, Bello N, Meyer MN. Pandemic pandemonium: Pausing clinical research during the COVID-19 outbreak. Circulation 2020;141:2045-7.
7. Poongothai S, Anjana RM, Aarthy R, Kasthuri S, Begum MA, Karkuzhali K, *et al*. Strategies adopted in conduct of clinical trials amidst Coronavirus disease-2019 (COVID-19). J Diabetol 2020;11:81-5.
8. Padala PR, Jendro AM, Padala KP. Conducting clinical research during the COVID-19 pandemic: Investigator and participant perspectives. JMIR Public Health Surveill 2020;6:e18887.
9. Hasford J. Impact of the COVID-19 pandemic on clinical trials with drugs. Expert Opin Drug Saf 2020;19:1373-5.
10. Kunz CU, Jörgens S, Bretz F, Stallard N, van Lancker K, Xi D, *et al*. Clinical trials impacted by the COVID-19 pandemic: Adaptive designs to the rescue? Stat Biopharm Res 2020;12:461-77.
11. Beane JD, Dedhia PH, Ejaz A, Contreras CM, Cloyd JM, Tsung A, *et al*. Conducting clinical trials in the time of a pandemic. Ann Surg 2020;272:e219.
12. Fleming TR, Labriola D, Wittes J. Conducting clinical research during the COVID-19 pandemic: Protecting scientific integrity. JAMA 2020;324:33-4.
13. Psotka MA, Abraham WT, Fiuzat M, Filippatos G, Lindenfeld J, Ahmad T, *et al*. Conduct of clinical trials in the era of COVID-19: JACC scientific expert panel. J Am Coll Cardiol 2020;76:2368-78.
14. Nabhan C, Choueiri TK, Mato AR. Rethinking clinical trials reform during the COVID-19 pandemic. JAMA Oncol 2020;6:1327-9.
15. Asaad M, Habibullah NK, Butler CE. The impact of COVID-19 on clinical trials. Ann Surg 2020;272:e222.
16. Desai S, Manjaly P, Lee K, Li SJ, Manjaly C, Mostaghimi A. The impact of COVID-19 on dermatology clinical trials. J Invest Dermatol 2020;141:676-8.
17. McDermott MM, Newman AB. Preserving clinical trial integrity during the coronavirus pandemic. JAMA 2020;323:2135-6.
18. Singh AG, Chaturvedi P. Clinical trials during COVID-19. Head Neck 2020;42:1516-8.
19. Davis S, Pai S. Challenges and opportunities for sponsors in conducting clinical trials during a pandemic. Perspect Clin Res 2020;11:115-20.
20. Guo T, Chen C, Chiang C, Chen CT, Hsiao CF. Operational experiences in China and statistical issues on the conduct of clinical trials during the COVID-19 pandemic. Stat Biopharm Res 2020;12:438-42.
21. Izmailova ES, Ellis R, Benko C. Remote monitoring in clinical trials during the COVID-19 pandemic. Clin Transl Sci 2020;13:838-41.
22. Gaba P, Bhatt DL. The COVID-19 pandemic: A catalyst to improve clinical trials. Nat Rev Cardiol 2020;17:673-5.

Funding: None; Conflicts of Interest: None Stated.

How to cite this article: Hanumante N, Desale D. Impact of coronavirus disease-19 pandemic on pediatric vaccine clinical trials. Indian J Child Health. 2021; 8(6):202-205.