

Clinical Trials Facing “Serious Adverse Events” during the Ongoing COVID-19 Pandemic

Abstract

Aims and Objectives: The ongoing COVID-19 pandemic is having a profound impact on the current clinical trials. We wanted to document the extent of the disruption amongst Indian clinical trial sites. **Materials and Methods:** We conducted an online survey among oncologists in India with active trials to document their experience with challenges and novel solutions. **Results:** A total of 60 oncologists replied of which 40 had ongoing trials with open recruitment. Majority of them had stopped screening (55%) and recruitment (62.5%). Almost half of the sites did not have adequate infrastructure (47.5%). Almost all the sites had enrolled patients worried about the impact of COVID-19 on their health outcome (up to 87.5%). The majority of sites had problems with adherence to study schedule of events (87.5%) and administration of study medication (42.5%). A total of 55% of the sites had provided the option of virtual visits. Both investigators (75%) and sponsors/contract research organizations (67.5%) had reached out to each other to maintain study integrity. More than half the centers had difficulty related to adverse events and serious adverse events (documentation and reporting; up to 75%). **Discussion:** Regulatory authorities in several countries have announced guidelines on the conduct of clinical trials during the COVID-19 pandemic. Whether the disruption lasts for a short or long time, its impact on clinical trials is going to be irreparable.

Keywords: Compliance, lockdown, recruitment, research, standard operating procedures

Introduction

With the global COVID-19 severe acute respiratory syndrome coronavirus 2 pandemic having infected almost 1.5 million patients across more than 200 nations, we are faced with unique challenges changing how we live in a little over 4 months.^[1] This has put at risk the future of almost all the ongoing clinical trials (262,366 registered on clinicaltrial.gov).^[2] Unprecedented circumstances not envisaged in “business continuity disaster preparedness” have brought to reality our worst nightmare. All aspects of clinical trials are under threat – be it recruitment, immediate care of ongoing patients, adhering to study schedule of events, monitoring or compliance with reporting to drug authorities, and/or ethics committees/institutional review boards (ECs/IRBs). This will also affect the robustness of the data generated as well as its analysis to follow in the medium and long term.

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We anticipate that most stakeholders would be “learning on the job” on how to deal with challenges thrown up by the COVID-19 pandemic. Doctors are currently between a hard place and the rock, having to juggle two competing responsibilities. As a medical professional, our first priority will remain to help tackle the ongoing pandemic and save the lives of as many patients as possible. At the same time, we feel ethically obliged to fulfill our obligations as principal/co-investigators for ongoing clinical trials. This means that we have to triage our professional time allotment during these trying times.^[3]

Hence, we decided to conduct a survey among oncology principal investigators (PIs) from India, the results of which are being reported here.

Methods

We initially participated in online discussions and agreed to the format of the final 19 questions and their respective answer options. The multiple-choice

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questions were then converted into an online Google form. The link to this Google form was then forwarded through WhatsApp discussion groups involving oncologists. The online survey was open for 24h on March 27, 2020. The replies received were downloaded as an Excel sheet. Unique E-mail addresses of responders were used to confirm that there were no duplicate entries. Thereafter, we tabulated and analyzed the results limited to those responders who had at least one ongoing clinical trial.

Results

Over a 24-h period, a total of 60 oncologists responded to the survey. This was on the day that the global COVID-19-positive cases were just under 600,000.^[1] Of these, 20 did not have an open ongoing clinical trial [Table 1, Q1]. Hence, the results represent the 40 responders who had active ongoing clinical trials and met this sole inclusion criterion. Incidentally, all of them were involved in trials whose objective(s) were unrelated to COVID-19 [Table 1, Q2].

Screening and recruitment [Table 1, Q3 and Q4]: The majority of sites had stopped screening (22/40, 55%) and recruitment (25/40, 62.5%). About one-third (15/40, 37.5%) were still screening and recruiting. Three centers were not sure.

Staffing and space [Table 1, Q5]: The sites were almost equally divided among those who still had adequate staff and space to look after trial patients (18/40, 45%) and those who did not (19/40, 47.5%). Once more, three sites were not sure.

Patient concerns about COVID-19 pandemic [Table 1, Q6–8]: The majority of sites (33/40, 82.5%) made it a point to discuss additional risk related to COVID-19, even though it was not part of the approved informed consent. On their own, patients asked questions regarding their concerns about the COVID-19 pandemic in 35/40 (87.5%) centers. A total of 3 (7.5%) centers had patients who withdrew consent/discontinue on the trial due to COVID-19 fears. Another 8 (20%) centers had documented withdrawal of consent by their patients, where the reason was not disclosed. This gives a total of 11/40 (27.5%) sites who had one or more patients withdrawing consent.

Protocol compliance and deviations [Table 1, Q9–12]: Difficulties in adherence to scheduling and compliance were faced by 35/40 (87.5%) sites. So also, challenges in performing timely trial-related investigation were reported by 31/40 (77.5%) sites. Problems with providing investigational product (IP) were faced by 17/40 (42.5%) centers. A total of 22/40 (55%) centers had already incorporated the option of virtual visits in place of in-person visits.

Sponsor/contract research organization (CRO)/EC/IRB communication [Table 1, Q13–16]: PI/co-PI from 30/40

(75%) had already reached out to their respective sponsors or CROs for clarity regarding their trial during the COVID-19 pandemic. Similarly, 27/40 (67.5%) centers had received communication from their sponsors or CROs. A total of 15/40 (37.5%) sites reported difficulty in reporting serious adverse events (SAEs)/protocol deviations/protocol violations as required by the protocol. While EC/IRB remained functional in 15/40 (37.5%) sites, it was not operational in an equal number (14/40, 35%). At 11/40 (27.5) sites, it was not clear whether the EC/IRB was able to do its activity or not.

Safety data-related adverse events and SAE [Table 1, Q17–19]: A total of 23/40 (57.5%) sites had developed new standard operating procedures (SOPs) to facilitate adverse event reporting and 26/40 (65%) had done the same for SAE reporting. Admission of patients due to SAE while the COVID-19 pandemic was ongoing was reported by 7/40 (17.5%) sites.

Discussion

A PubMed search using “COVID-19” done on March 28, 2020, revealed 1795 references, which became 3075 references by April 8, 2020, an increase of 71% in the short span of 12 days.^[4,5] This is a reflection of the health-care professionals’ commitment and focus on tackling the COVID-19 pandemic. With the number of deaths crossing an astounding figure of more than 80,000, the current unprecedented disaster has impacted all walks of our lives, including ongoing clinical trials. In our study, the first proof was the fact that only about one-third (37.5%) of responding oncology centers continued to screen and recruit new patients [Table 1].

While research priorities should be and remain focused on prevention, mitigation, or treatment of COVID-19, our responsibility toward other ongoing clinical trials should not be forgotten.^[6] One of the challenges that we could identify was regarding the adequacy of sufficient space and staff for trial-related activities. It was a stumbling block in 47.5% of the sites included in this study. Redeployment of medical staff for COVID-19 duties coupled with the inability of the nonmedical staff to reach their place of work due to travel restrictions (e.g., lockdown) results in only a skeletal staff available for clinical trials. In addition, some hospitals may have to redeploy clinical trial space to expand inpatients’ capacity. Images of hoards of COVID-19 patients lying in hospital corridors (especially from the USA, Spain, and Italy) confirm this to be a reality.^[7–9]

The majority of sites (33/40, 82.5%) made it a point to discuss additional risk related to COVID-19, even though it was not part of the trial requirement. We believe that this is a very important initiative by the investigators, since evidence was quickly emerging from China (confirmed later from Italy) that cancer patients did poorly if infected with COVID-19.^[10] On their own, patients asked questions

Table 1: Replies to the 19 multiple-choice question online survey among oncologists

Question number	Question	Replies		
		Yes	No	Not sure/not applicable
1	Are you involved as PI/co-PI for any ongoing clinical trial at present?	40	20	00
Further evaluation is limited to the 40 responders who had ongoing clinical trials				
2	Is the primary objective of your ongoing clinical trial related to COVID-19 pandemic?	0	40	0
3	Is screening, to identify new patient for enrolment into clinical trials, currently open at your center?	15	22	3
4	Is recruitment for eligible new patient into clinical trials, currently open at your center?	15	25	0
5	Do you currently have sufficient dedicated space and/ or staff to look after your clinical trial patients?	19	18	3
6	In addition to the sponsor and EC approved consent form, do you also discuss COVID-19 pandemic-related risks with your clinical trial patients (new or old)?	33	7	0
7	For patients already recruited and ongoing, are your patients concerned/ asking questions about how the COVID-19 pandemic will affect them?	35	5	0
8	For patients already recruited and ongoing, have you instance of any patient withdrawing consent due to ongoing COVID-19 pandemic?	03	29	8
9	For patients already recruited and ongoing, are you having difficulty with scheduling and complying with follow-up visits as per clinical trial schedule?	35	5	0
10	For patients already recruited and ongoing, are you having difficulty with investigations as per trial schedule of events?	31	9	0
11	For patients already recruited and ongoing, are you facing difficulty in providing IP (study medication) to patients?	23	17	0
12	For patients already recruited and ongoing, have you provided alternate to hospital visits replacement with virtual visit/consultation?	22	18	0
13	Have you contacted the CRO or sponsor for any clarification or advice regarding ongoing clinical trials?	30	10	0
14	Has your trial CRO or sponsor contacted you with any clarification or advice regarding ongoing clinical trials?	27	13	0
15	For your ongoing clinical trials, have you faced any difficulty in reporting SAEs/protocol deviations/protocol violations to EC or CRO or sponsor?	15	25	0
16	For your ongoing clinical trials, during the current COVID-19 pandemic is your EC/IRB functioning?	14	15	11
17	For your ongoing clinical trial patients, have you devised/are following new SOP to document adverse reactions (e.g., telephonic/virtual follow-up)?	23	17	0
18	For your ongoing clinical trial patients, have you devised/are following new SOP for identifying SAEs (e.g., telephonic/virtual follow-up)?	26	14	0
19	For your ongoing clinical trials, during the current COVID-19 pandemic have you had to admit and treat any of your patients for SAEs?	7	33	0

COVID – Coronavirus disease; CRO – Contract research organization; SOP – Standard operating procedure; IRB – Institutional review board; SAEs – Serious adverse events; EC – Ethics committee; IP – Investigational product

regarding their COVID-19 pandemic concern in 35/40 (87.5%) centers. A total of 27.5% of centers experience patients withdrawing consent, which is exceedingly high and has not been reported earlier from India.^[11] We can only assume that the COVID-19 pandemic was the reason, even if that has not been disclosed formally. These data were generated when the global burden of COVID-19-positive cases was just under 600,000. It has now almost tripled and its impact on withdrawal from trials is also likely to be significant.

It was not surprising that almost all the sites faced difficulties in adherence to trial schedule of events (such as

hospital visits, investigations, and administration of IP). In order to reduce deviations, just over half the centers had commenced virtual visits. Now that the Medical Council of India has notified telemedicine guidelines (March 25, 2020), all health-care facilities will be able to connect with their patients remotely and effectively.^[12]

Effective lines of communication are key to the success of any project. In this instance, the investigators were more proactive in communicating with the other party (75%) as compared to the trial sponsors/CROs (67.5%). This is to be lauded. In spite of such efforts, some difficulty still existed in complying with mandatory reporting specified in

trial protocols. The importance of using alternate pathways and backup options in disasters and emergencies needs further emphasis. Our survey showed that ECs were either nonoperational (35%) or their status not communicated to the investigators (another 27.5%). State- and country-wide lockdowns to tackle the COVID-19 pandemic did test disaster preparedness plans quite severely and showed us that that real-world situations are sometimes quite different from what we have anticipated in the past.

With the COVID-19 pandemic taking the lives of more than 89,000 humans, emphasis is back on safety. We have previously reported on how efforts are ongoing to protect frontline health-care workers in this war.^[13] Protecting trial patients also requires timely recognition of and prompt management of adverse events and SAEs. To address this, majority of sites had actually developed new SOPs to identify and report them among their trial patients. It is interesting to note that SAE admissions were required in a significant fraction of trial sites. Segregated access to health-care facilities, identification of COVID-19 status, and admission in appropriate wards are key to the safety of such trial patients. To reduce their risk of contacting COVID-19 infection while in hospital, additional prophylaxis and/or mitigation methods may be required to accelerate recovery and timely discharge from the hospital.

This survey results will help us better understand the challenges faced by clinical trials while fighting the COVID-19 pandemic. Corrective measures will prevent irreparable consequences to the integrity of trial data. Authorities stepping in to help provide guidelines include examples from India, the UK, and the USA.^[14-17]

Conclusion

We are assuming that ongoing clinical trials (as well as normal life) shall remain disrupted for at least 3 months from now. Will it influence the evaluation of their data by regulatory authorities? Where trial subjects had been impacted by COVID-19 infections, it certainly will. This might also be the case where data to evaluate the primary objective have significant gaps or deviations. However, the darkest of clouds will have a silver lining. We are hoping that the resilience of fellow investigators will lead to innovative solutions, trial rules might be rewritten, and protocols may have a new section of alternative options in case of disasters.^[18] We hope all of us can come together to bring the clinical trials out of the SAE that they are suffering from right now.

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Conflicts of interest

There are no conflicts of interest.

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