



COVID-19 and Clinical Trials: An Aftermath

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Abstract

In the recent times of the COVID-19 Pandemic crisis, the clinical trial has caught a lot of interest. The whole world is waiting anxiously for a medication or a cure that can cure this dreaded disease or a vaccine that can prevent it. The COVID-19 pandemic has put a huge strain on supporting the clinical trial endeavour and will moreover likely impact key trial results; these impacts should be considered during each and every phase of conducting the trials like the data analysis, investigation and interpretation. All things considered, the reactions to the pandemic have additionally presented innovations and developments that will help the conduct of clinical studies. Our article aims to give an overview of how this dreaded pandemic has had an impact on clinical trials. Trials have confronted numerous vulnerabilities and tremendous challenges including focusing on patient safety in the midst of the pandemic, consenting and selecting participants into trials, data collection and management. Innovation has given numerous answers for these difficulties, and trial managers have adjusted to better approaches for working while proceeding to conduct their clinical trials.

Introduction

The COVID-19 pandemic has set down our lives, with millions of people infected and thousands of deaths around the whole world^[1]. Social distancing, masks and hand sanitization have emerged as the recommended strategy to reduce

the spread of the virus. This has caused challenges in daily human life, burdened health care systems with an increasing need for adequate staff, hospital resources, personal protective equipment, and also presented a challenge for the conduct of clinical trials^[2]. Also shortages of medical/support

staff, inadequate monitoring, travel issues due to restrictions, interruptions of supply chains for investigated products, uncertainty over continued funding, and restrictions imposed by sponsors are some of the many issues facing clinical trials during the pandemic.

The pandemic has significantly altered the delivery of medical services and clinical research around the world. 90% of clinical trial sites shut down enrolment around the world. The quick initiation of more than 1,000 COVID clinical trials contrasts with the decline in non-COVID-19 research. Due to these issues, regulators, sponsors, and professional organizations including the U.S.FDA and other related authorities have released guidance on how to conduct clinical trials in the era of COVID-19^[3-6]. These assertions promote the standards of security for patients and research team members while endeavouring to safeguard preliminary uprightness^[7]. Some strategies in order to limit in-person data collection and to maintain social distancing are put forward. New administrative and regulatory reports facilitate remote and electronic/digital collection of the trial data, some specific methodologies and standardized practices have not been established^[6,7].

The pandemic has made huge interruptions to clinical trial research across the world. As in different aspects of life, the infection has seriously influenced the ability to conduct trials in protected and effective manners. This is especially true when considering that trials often deal with vulnerable participants who are at risk of exposure to COVID-19. A large number of trials have been suspended or halted on account of the troubles in proceeding under lockdown conditions. Simultaneously, the pandemic has seen a phenomenal reorientation in clinical trial research towards COVID-19. Both of those aspects—the disturbance and the quick, effective readjustment to address a new challenge guarantee that the impacts of the COVID-19 pandemic will be felt in clinical research long after the underlying impacts have faded^[8].

Clinical Trials during COVID-19

Clinical trials have for quite some time been a chief strategy for testing and approving new medications and treatments. New medication endorsement is predicated on fruitful trials into the safety and efficacy of new treatments. Trials can include many various sites throughout the world, all with various effects and government regulations on what is permissible. When we start taking into account, the total manpower and other requirements associated with a clinical trial, the extent of the issue starts to appear terrifying. In addition to researchers who formulate the protocol for the trial and who work to secure the funding (either from governments, foundations, pharmaceutical or device manufacturers), clinical trials include caregivers and nurses who work with patients at clinical trial sites, resident doctors, postdoctoral fellows, scientists, and others who work on the analysis of data generated by the trial, some of whom might connect with patients, yet everyone is crucial for the final-research.

Fig 1: According to the US Public Library of Medication's website ClinicalTrials.gov it was found that among a total of 1052 suspended clinical trials during the predetermined period, 905 revealed the reason for the suspension of trials was the pandemic^[9]

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clinical trials**



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Trials that were halted, by and large, were halted from enrolling new patients. Patients who were at that point enlisted generally continued to receive treatment as institutions and researchers attempted to make changes to how care was provisioned to deal with the reality of COVID-19. Fergus Sweeney, head of clinical studies and manufacturing at the European Medicines Agency, told The Lancet that one of the vital parts

has been social distancing to secure patients and staff, however guaranteeing the wellbeing of patients in testing and treatment is also important. *“If people can't visit a hospital at usual intervals, it may be that they need to be provided with a medication for longer period, or indeed that medication is distributed to their home by a distributor”*, Sweeney said^[8].

Fig 2: New Challenges for clinical trial includes:

Varying lockdown period	This across the geography makes it challenging for conducting clinical trials
Increasing enrolment of COVID-19 patients	If the patient gets infected with COVID-19, it may alter the result
Risk for trial participants	Most of the trial sites are hospitals which are converted to dedicated COVID care
Patient unavailability	Lack of availability of patients due to the pandemic crisis

In light of that, various trials have moved from the distribution of medications at the trial site to direct to patients, whereby trial drugs are circulated and given to patients in their homes. Numerous in-person visits for check-ups and other aspects of trials were shifted to the teleconferencing Administration (FDA) issued guidance on securing patient safety during the pandemic. The FDA guidelines advised researchers and trial sponsors to *“determine that protection of a subject’s safety, and rights is best served by continuing a study participant in trial as per*

protocol or by discontinuing the administration or use of investigational product or even participation in trial”.^[8]

Who is at loss due to the impact of COVID-19 on trials?

- Patients with end-stage diseases (E.g.: stage IV cancer) who have not responded to traditional treatments;
- Patients who are live with debilitating conditions which are chronic;

The pandemic has created break in the flow of clinical trials across the world and has affected the ability to conduct research in safe and effective ways. This is especially true when considering that these researches are often dealt with vulnerable subjects those who are at risk from exposure to this deadly virus.

Around 80% of non-COVID-19 trials are either stopped or being interrupted, according to Michael Lauer, deputy director at the US National Institutes of Health^[9]. But these effects are beyond just trials. Labs closed, conferences cancelled, supply chains for equipment lost, resources lost, financial losses within academic centres affecting their research operations. Researchers have been deployed to working in emergency medical care away from the clinical trials. The cancellation of trials will have a major impact early career researchers^[8].

Table 1: How to manage clinical trials during a pandemic? Here are some recommendations:^[10]

Ethics	The Foundation of expedited ethics approval locally is principal as a modification in the protocol is needed to guarantee studies can continue.
Technological supports	Foundation of far-off access for some frameworks, for example, the establishment of remote access to the hospital laboratory system and also centres to monitor COVID-19 patients. Remote/digital access for CRF, so that staff can work in the clinic and stay away from each other. An online GCP program is necessary.
Participant engagement	Contact with subjects to ensure retention is vital. A phone exclusive to study related should be carried by one member of the team to cover 24/7 contact from participants and should be shared amongst the trial team, i.e., trial managers, research nurses, PIs and co-PIs.
Communication	Communication strategy within the host institution/clinical research facilities to keep staff occupied and involved. Considering of meetings by Skype/Zoom/Teams study training sessions, and for sharing information online. Online telephone group for the team, e.g., WhatsApp, is important for the social support of staff. Establishment of virtual meetings by Skype/Zoom/MS Teams study for virtual coffee/social support (non-workrelated activities)

GCP: Good clinical practices, CRF: Case record form

Regulations for Conducting Clinical Trials:

The US FDA^[11] issued several guidelines to aid clinical investigators in deciding whether to continue or “temporarily” suspend a study, some important ones are mentioned below:

- ⇒ The vital/key consideration: safety of trial participants.
- ⇒ Principal Investigator should assess the risk-benefit ratio. This decision should be made in considering whether local transmission of COVID-19 is controlled, keeping in mind the patients’ medical status, clinical response, investigational product availability, and regulations.
- ⇒ Investigators may consider virtual visits and telemedicine as alternatives. If diagnostic assessments (e.g., labs and imaging) or administering medications are required, then doing so in a health care setting, local centres/providers could be an alternative.
- ⇒ The FDA instructed researchers and sponsors to "determine the protection of a participant's safety, and rights are best served by continuing a study participant in the trial as per the protocol or by discontinuing the administration or use of the investigational product or even participation in the trial". Also calls on investigators and sponsors to coordinate with institutional review boards and ethics committees on changes to the protocol as early as possible.
- ⇒ Investigators should document, and sponsors should include data on related variables in the clinical trial datasets, whether an assessment was conducted in person or remotely (including the type of technology used), as well as the date of the assessment and the person who conducted the assessment.
- ⇒ When feasible, a traditional method of obtaining and documenting informed consent using a signed paper copy of the

consent form is recommended, or use of electronic informed consent or a photograph of the signed informed consent document can be transmitted to the trial staff^[12]

Any deviations in a protocol are usually not implemented before review and approval by the Institutional Review Board (IRB)/Institutional Ethics Committee (IEC), and in some cases, by FDA. Sponsors and investigators are encouraged to engage with IRBs/IEC as soon as possible when urgent or emergent changes to the protocol or informed consent are expected due to the pandemic. Changes to protocol or investigational plan to minimize immediate hazards or to protect life and well-being of research participants may be implemented without IRB approval or before filing an amendment to the investigational new drug (IND) or investigational device exemption (IDE), but should be reported afterwards^[11].

Decentralized Clinical Trial

Decentralized clinical trials (DCTs) include least or no 'in-person associations' between the patient and the site staff including the investigator. The virtual examination 'direct-to-patient model is the core theme around which DCTs rotate. They are site less, subsequently, the information is gathered distantly through associated gadgets, telemedicine, and portable medical services suppliers.^[13]

Clinical trials evolved slowly in the past few years and traversed an interesting journey starting from site-based traditional trials to site-less decentralized trials

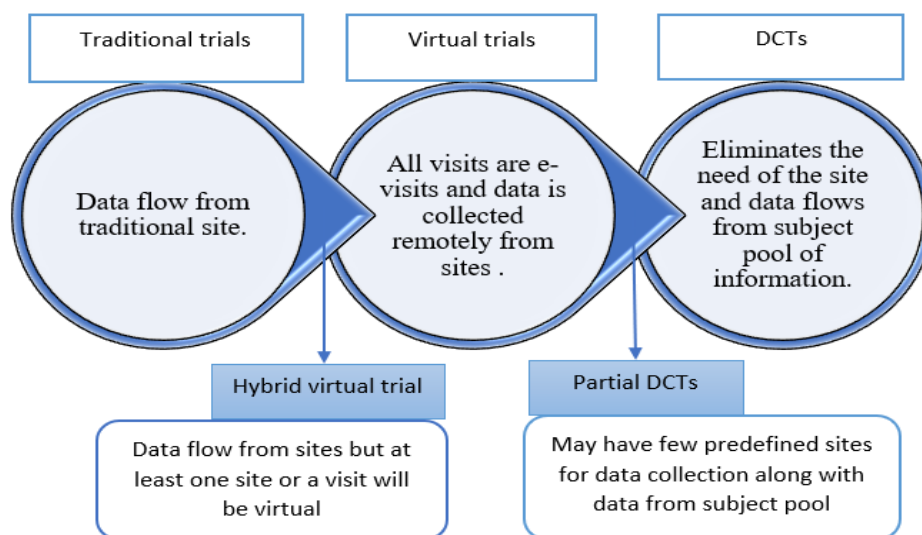


Fig 4: Depiction of thin demarcation in each type of clinical trial

Decentralized clinical trials may be the fate of clinical research and trials. These are site-less and visit-less. All exercises beginning from the preliminary enrolment to patient exit is preferably done distantly, at the comfort of the patient's home. The best possibility for this sort of study is late phase trials.

Now and then, there might be an incomplete execution of DCT wherein a portion of the indicative tests, for example, X-ray, CT Scan, MRI and so on are being done at the site or central labs while for other people, for example, checking of glucose level or fundamental PFTs, information may be gathered from patient's pool of data^[13].

Advantages of DCT:

As Per the present-day situation, we don't have any committed vaccine to stop this flare-up. Clinical trials for vaccines are the need of an hour in order to end the reckless virus and the troubles caused by it. Trial recruitment and execution including different tests to be done is a difficult assignment, as everybody will undoubtedly remain at their homes. In this situation, DCTs are the best choice accessible to scientists for late phase studies.

- + With the assistance of online media tuning in and other comparable techniques, enrolment should be possible.
- + Patient consent can be taken utilizing electronic informed consent forms

followed by distant screening and enlistment rather than paper-based methodology taken at the trial sites.

- + Utilizing advancements dependent on biosensor empowered data collection gadgets, medical tests can be managed without the requirement of any local labs.
- + Safety of clinical data management will also be straightforward as information can flow well within stipulated timelines as required by authorities

Hence, DCT offers comfort, consistency, and compliance while helping in avoidance of the additional spread of illness by keeping up social distancing between already stressed people on these troublesome occasions.

Impact on Trials in the Future

It has taken a pandemic and a relentless virus for the medical community to start thinking critically about various aspects of patient care and clinical trials. Through the necessary reforms executed for medicine to survive in this crisis, we hope that we can find a silver lining in improving how to execute clinical trials going forward for the betterment of cancer patients or patients with chronic debilitating conditions^[14]

It is difficult to foresee the continuous effect upon daily existence, including how clinical trials might be planned and managed later on. Processes to comply with regulatory and ethical frameworks

have been incorporated to support new trials and trial amendments at a speed unheard of. For example, the RECOVERY (Randomised Evaluation of COVID-19 Therapy) Trial, aims to identify treatment option that may be beneficial for people hospitalised with suspected or confirmed COVID-19, was set up in only 9 days—this has never been achieved before^[15].

While the pandemic has made numerous difficulties and an amazing effort from trial supervisory groups who have had to execute new procedures, processes and revisions in a critical period, some lessons can be learnt in managing trials later on. It is notable that clinical trials can be confounded and costly and along these lines, efficiencies in trial design and conduct are pivotal.^[16,17] We are hopeful that the lessons learnt during these unprecedented times can be carried forward to clinical trials in the future, though a measured approach is required to ensure participant safety and adherence with relevant ethical and legislative requirements.

Will COVID-19 hold us back?

Again, the answer here is no! Saying that COVID-19 is posing a variety of challenges to the world is not right. The depth and expanse of difficulties that this disease is throwing at the world are unprecedented. As experts predicted, the pandemic has run through 2020 into 2021.

“Research on COVID-19 is proceeding quickly. There is some amazing work going on. The rapidity with which new information, new data becomes available, new studies become published is quite impressive. In some respects, it’s like something that we’ve never seen.” - According to Lauer[9].

What does the future hold?

The utilization of innovation/technology in clinical trials has hugely expanded. This will proceed later on too in any event, when this pandemic gets over. We need to conduct our trials

quicker taking their quality into account. Going ahead, learning lessons from COVID-19, we need to make our study designs, conduct, analysis, and reporting catastrophe-proof. Our future clinical trials will need to have the inbuilt necessary safeguards and processes to guarantee that no disturbances happen to the patients' wellbeing or trial integrity if such things were to happen once more.

At long last, all stakeholders should altogether upgrade clinical investigations in India because the patients are sitting tight for more up to date treatment choices for their infections!^[18]

Conclusion

Clinical trials are essential for research, but COVID-19 exposed ways that in a way, their design, conduct, and reporting could be changed for the betterment. The express designing and launch of trials to research COVID-19 have shown that certain areas and practices of clinical trials could be improved, modified, or modernized in ways that would benefit patients and practitioners. In the future, it will be important for conducting researches to incorporate those lessons to ensure the highest quality of research.

Conducting clinical trials is a multifaceted job, and numerous challenges arise, even in "normal" circumstances. Managing trials during a pandemic adds a layer of complexity. Further research is necessary to document the workload of clinical trial managers, to fully understand their role and its critical interface with clinical trial participants, sponsors, regulatory authorities and other clinical trial staff. We recommend that in the future when seeking ethical and regulatory approval, all studies should have a contingency plan for situations where participant movement may be restricted^[10].

Amidst all this, we should remember that,

*The long-term effects
on research are unclear.*

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