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INVITED ARTICLE

CONDUCTING CLINICAL RESEARCH DURING PANDEMIC ERA: PROBLEMS AND PROSPECTS.

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ABSTRACT

The COVID-19 pandemic has significantly affected ongoing clinical research, as conducting clinical research is often seen as secondary to addressing the immediate health needs of patients by healthcare providers. Pandemics create operational challenges and raise scientific and ethical issues for clinical research activities. The benefit of clinical research in terms of opportunities for patients suffering from various diseases, and ability to investigate new therapies to address pandemics cannot be overlooked. This review summarizes the challenges that arise during a pandemic while conducting clinical research along with solutions for addressing these challenges.

Key Words: Clinical trial, clinical research, pandemic, COVID-19, CRO, sponsor

Introduction

The ongoing Covid-19 pandemic has rapidly affected 20.1 million people (as of 12th August, 2020) around the globe with around 7 lacs deaths.[1] Each pandemic faced by the world till date is different with regard to their transmission, affected population, mortality and morbidity rates, epidemics, and available treatments.[2] Clinical research is the greatest need in response to these pandemics to find treatments, a way to prevent the disease, and to prevent a pandemic from arising again.[3] To conduct clinical research involving human subjects, there are well-established scientific and ethical principles that must be followed to assure that the

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obtained results are scientifically sound and reliable. For example, as per the Declaration of Helsinki, the investigators must obtain "freely given informed consent" from research subjects, "the health of patient will be first consideration", medical research "must conform to generally accepted scientific principles", "be preceded by careful assessment of the predictable risks and burdens to the individuals and groups involved" etc. However, pandemics create different challenges and raise scientific and ethical issues for conducting clinical research activities.[4,5] Hence, there is a need to identify and understand these challenges to accelerate the clinical research activities and to strengthen research outcomes for improvement of patient care in the midst and after the pandemics. The present review summarizes the challenges that arise due to pandemic during conducting clinical research, and discusses possible strategies to overcome these challenges.

2. Material and Methods

A search for research articles, review articles, and text-books was conducted using electronic databases "PubMed", "ScienceDirect" and "Google Scholar" with combination of various keywords like pandemic, COVID-19, clinical research, challenges during clinical trial etc. The most relevant articles were identified manually and retrieved. Critical analysis of the literature was carried out by all authors and presented in the current form.

3. Role of investigators, clinical research organizations (CRO) and sponsors during Pandemics

Due to the ongoing COVID 19 pandemic, hospitals and health care centres have been flooded with COVID-19 patients, which has led to a major health risk for research personnel and study participants, especially who are immune-compromised. The pandemic has also raised several challenges in conducting clinical trials as discussed below.[6]

Should non-pandemic clinical trials be continued or suspended/stopped during pandemics?

Because of the associated health risk, mandatory lock down in various regions, and the need to maintain social distancing as well as quarantine, one approach to tackling clinical research in a pandemic situation is to suspend or discontinue those clinical trials that are non-essential or those that do not provide immediate benefits to enrolled patients. However, it is difficult to identify which trials are essential as associated long-term benefits and risks must be considered, which cannot be predicted before the trial is completed, and data is analysed. Sustaining ongoing trials have potential benefits to millions of patients suffering from various chronic diseases that will once again be important once the pandemic ends. Moreover, suspension of clinical trials for longer duration raises questions related to data integrity or may lead to trial failure. Discontinuation of ongoing trials causes

wastage of invested resources, time and efforts of research personnel as well as participants. It also raises ethical questions for study participants, who have already agreed for the potential risk in exchange of societal benefits that will no longer be meaningful as the study has been discontinued.[6,7]

Suspension or discontinuation of clinical trials related to various life threatening diseases may have adverse impact on these patients. For example, cancer patients who miss a dose or two of an investigational product, have increased risk of their disease worsening and even death. The risk from diseases that were most important causes of morbidity and mortality in the pre-pandemic era, will remain the same in the post-pandemic era. Thus, suspension or discontinuation of their clinical trials may lead to "collateral damage" from pandemics for individuals in future.

Therefore, instead of discontinuation of trials, mass, efforts and resources should be directed towards continuing clinical trials using innovative and thoughtful methods and proactive planning.[7]

Which are the challenges faced by investigators, CRO and* sponsors *during pandemics?

During the ongoing COVID-19 pandemic, the hurdles faced by CROs and sites are due to several reasons, the most prominent ones being- hospitals across the globe have been transformed into COVID-19 facilities, prioritizing patient care and trials related to COVID-19, thus, leading to reduced flow of study participant visits to clinical trial sites. The pandemic prompted complete and long-term lockdowns in several countries including India limiting movement of patients and clinical trial supplies. Due to the lockdown, patients could not visit the healthcare facilities for non-COVID-19 consultations, which led to minimal or no new enrolments, as well as missed or delayed follow up visits by trial participants. Patients are afraid to visit clinical sites due to the fear of contracting the disease as well. Plummeting movement of drugs and essential supplies led to missed or delayed doses leading to protocol deviations, at places leading to adverse effects on participant's wellbeing.

The CROs had a tough time fulfilling their obligations of trial oversight of ongoing trials, which typically involves on-site visits for source data review and verification. During the long lockdowns, scheduled monitoring visits were not undertaken as planned and review of critical aspects of trial activities such as informed consent, eligibility criteria verification, investigational product related documents, and safety of participants were significantly delayed. All these detours in the course of a trial increase the burden on CROs in terms of documentation of the delays and deviations from the protocols, and assessing their impact on the participants and the trial at large.

Several trials which are being planned are anticipating significant delay due to the pandemic. Anticipated challenges leading

to delayed start-up of trial include delayed availability of clinical trial sites, interrupted communications and coordination with ECs and regulatory agencies, truncated pool of potential patients for enrolments, challenges for onsite monitoring, and study supply chain disruptions.

The most critical part for many CROs is to meet the requests for on time IP delivery to the trial sites and to ensure that the participants received their doses on time. As can be understood, the temperature sensitive shipments have suffered due to the trans-state transport lock down which in turn have resulted in delay in delivery of the study medication. Such missed doses have several consequences, the most important being compromised safety of the participant.

Most prominent global regulatory agencies set up dynamic guidelines to address the changing pace of the pandemic, with the expectation that the sponsor, CROs and investigators will align with the guidelines. Though these guidelines brought in some sense of legitimacy to the ground reality, it increased stress on the stakeholders to keep abreast with the regulatory expectations.

The long-term challenges faced by clinical researchers include shifted focus of clinical trials towards pandemic related clinical research rather than other diseases. Change in protocol and maintenance of data integrity are also important considerations during pandemics. Another challenge is to be ready for future pandemic situations to conduct clinical research within desired time duration.

What are the best ways to address the challenges?

Sponsors and CROs must communicate proactively with site teams and extend all possible support to avoid derailing of ongoing trials. Clear communication and proper precautions are necessary to assure the safety of patients as well as staff conducting clinical research. It is important to convey to the site staff that sponsors and CROs are a pillar for their support. Medical and paramedical personnel should be motivated. Guidelines regarding precautions to be taken during encounters with patients should be provided to the sites. As a goodwill gesture safety kits, tools to document deviations should also be provided. Support in terms of home care professionals should be offered to support sites, especially when the sites are overwhelmed with pandemic and need help in legwork.

Sponsors and CROs can create simple, graphic patient training material, which can help patients understand the importance of the trial visits and compliance to the study procedures. These messages can be relayed by the site to patients.

Sponsor can support the sites by providing for transportation of patients from their homes to sites or for site staff (CRA/phlebotomist/pharmacist) to patients' homes to address periodic study

visits for study medication dispensation or laboratory sample collection or for collection of vital data that may be critical for a particular trial.

Sponsors and CROs can take a staggered approach, addressing the most pressing needs in terms of data. Collection of data needs thoughtful consideration during a pandemic. The outcome should be ranked as the priority, and primary outcome should be ranked first in priority whereas outcomes that are not pre-specified should be eliminated temporarily.

Out of box solutions such as use of artificial intelligence (AI) in clinical trials can save the day (Figure 1).[8] An AI based solutions can help in multiple different ways and several sponsors are adopting virtual trials methodology.[9-11]

However, use of AI, remote monitoring or web-based solutions can highlight the possibilities of break in data integrity. Therefore, prior to implementation, it's important to implement certain checks on the provisions of the consent provided by the study participants.

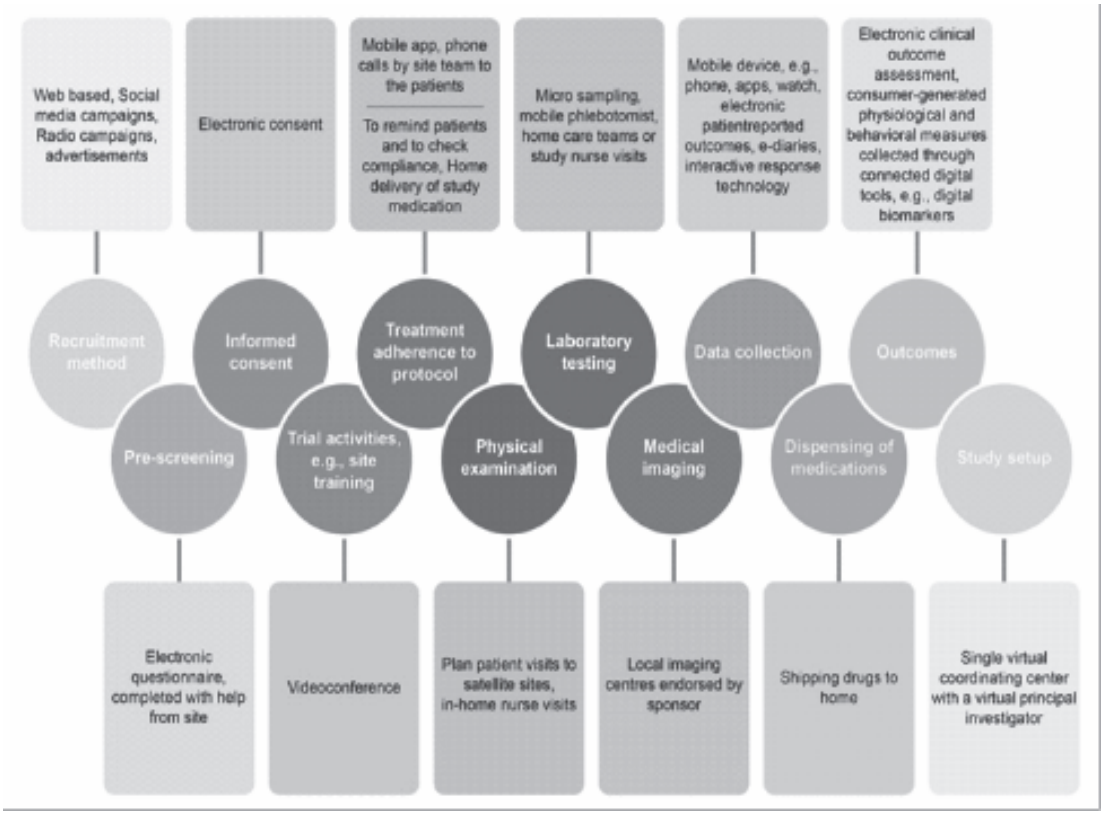

Figure 1: Solutions for conducting clinical trials virtually

Pandemic causes uncertainty during clinical research, therefore, revised statistical methods should be developed to present results, assure the data integrity and to overcome uncertainty due to pandemics. For example, the analysis should stratify the data by method of data collection. The focus of clinical trials should be on clinical end-points than just achieving targets. It is advisable to use adaptive trial designs.

Various observations adopted in practice by sites/CROs are mentioned below.

In certain situations, some sponsors have shipped study medication directly to the participant's home – the authors of this article caution on this approach and if this approach needs to be undertaken, several checks and balances need to be in place before deciding on this option.

Sponsors and CROs have come up with out of box ideas to get on with business in this time of pandemic.

Ethics committee's meetings are increasingly being held electronically using on line platforms to ensure timely review of ongoing studies as well as new studies. The process needed some fine-tuning at the end of the stakeholders, which the sponsors and CROs are helping with.

Site training has gone online as well, using online platforms, and going by this author's experience, it has been very successful.

In order to fulfil monitoring obligations, sponsors and CROs have relied heavily upon central and remote monitoring during the pandemic. With help of information technology and various web-based tools, many companies have successfully moved on to remote monitoring approaches.

4. Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs)

Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) should thoroughly review whether the scientific and ethical conductance of clinical research is as per regulatory guideline or not. IRB/IEC should review benefit to risk related to clinical trials during pandemic, and should evaluate the best way to preserve a participant's safety, welfare, and rights i.e. by continuing the clinical trial as per protocol, by discontinuing the use of IP, or by suspending the participation in the trial. The investigators/CRO sponsors should consult and inform IRBs/IEC as early as possible when urgent or emergent deviations from protocols are required due to pandemic situation. The changes in protocol should be closely monitored by IRB/IEC to assure participant safety, and should ensure the changes would not raise questions on the integrity of the data when inspected. Necessary changes to minimize or eliminate risk or to safeguard life and wellbeing of participants may be implemented without prior approval of IRB/IEC, but, should be reported afterwards.

5. Regulatory guidance

Various regulatory agencies have rapidly developed guidelines to assist investigators/CRO sponsors for conducting clinical trials in pandemic situations. The Food and Drug Administration (FDA) has issued guidance on "Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency. Guidance for Industry, Investigators, and Institutional Review Boards" and "COVID-19: Developing Drugs and Biological Products for Treatment or Prevention. Guidance for Industry". [12,13] The European Medicines Agency (EMA) has issued, "Guidance on the management of clinical trials during the covid-19 (coronavirus) pandemic".[14]

In India, Central Drugs Standard Control Organisation (CDSCO) has issued notice, "Conduct of clinical trial in present situation due to outbreak of COVID-19" to assist clinical trial sponsors, investigators, and ethics committees in ensuring the safety and well-being of trial participants as well as trial data integrity.[15] Indian Council of Medical Research (ICMR) has also developed guideline, "National Guidelines for Ethics Committees Reviewing Biomedical & Health Research during COVID-19 Pandemic", which covers general ethical issues, review procedures for both COVID-19 related and non-COVID related research, informed consent, and vulnerability.[16]

Each guideline urges investigators/ CROs/ sponsors of clinical trial to assure the safety of study participants using various precautions while maintaining good clinical practice (GCP) guidelines and minimizing risk to the trial integrity during the COVID-19 pandemic. Also, all guidelines suggest that investigators/ CROs/ sponsors/ IRB/ IEC should consider establishing and implementing or revising policy and procedures to safeguard and minimize or eliminate risk to health and wellbeing of study participants during COVID-19. Depending upon the nature of the changes described above, a protocol amendment may be done as per applicable regulatory guideline.

6. Conclusion

During an unprecedented pandemic, clinical research faces abundant challenges to continue with ongoing projects as well as to fast track COVID-19 related trials. Addressing these challenges with innovative solutions is essential. All stakeholders of clinical trials need to align themselves and address the situation with proper safety pre-cautions, adaptive policies and procedures, and using technologies. This approach can help to conduct clinical research without risk to patient or data integrity. Adoption of technology in clinical research has been a welcoming practice during the pandemic and is likely to continue beyond this pandemic. Considering the success of centralised and remote monitoring, this may become standard practice.

7. **Conflicts of Interest/ Competing Interests:** None.

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