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Impacts of COVID-19 Pandemic on the Conduct of Clinical Trials

Inamdar Sanobar M, Bhasale Sakshi S, Wakchaure Sayali M, Chaugule Ashiya M, Bhalerao Pooja A
Samarth Institute of Pharmacy, Belhe, Maharashtra., India

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ABSTRACT

The main objective of this study was to explore the effects of the coronavirus disease 2019 epidemic on the ongoing and upcoming all the clinical trials. The coronavirus (SARS-CoV-2) is a strain of Coronavirus that affected worldwide. The COVID-19 pandemic has Impacted all sectors of life including the conduct of clinical Trials of medicinal products globally. The COVID-19 had caused major disruptions to the all clinical trial mainly the non-COVID trails. An estimated 80% of non-COVID-19 trials were stopped or has been interrupted as a result of the COVID-19 pandemic.The effect of pandemic challenges will depend on the severity duration of each wave of the COVID 19 pandemic the duration of the trial. Therefore, in this study, we analysed the impact of COVID-19 on clinical trials, and alternative steps to continue non-COVID clinical trials.

Keywords :- SAR-CoV -2 , Pandemic, COVID-19, Clinical trails

I. INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic is having an enormous impact on our various activities. Starting from health systems to overall economic conditions around the world have been severely damaged; therefore, there is a concern about the development of future medical technology, including the development of new drugs, will also be hindered. The COVID related restrictions resulted in difficulties in continuing the ongoing trials. As per reported by ClinicalTrials.gov registered 1773 trials that were suspended between March 2020 and April 2021 and the COVID-19 pandemic being the reason for this majority of non- COVID-19 Clinical trails to disrupted.

Which has lead to the initiation of large number of trials for the test the safety and efficacy of COVID 19 Vaccines around the globe according to (Kim et al., 2021). This article focus on the effects of the COVID 19 pandemic on the non- Clinical trials. The challenges that were faced by the Sponsors and investigators were mainly due to lockdowns, Individual quarantines, conversion of trial sites into CCOVID Treatment facilities thereby, forcing the temporary closures of sites, travel restrictions, disruptions to the supply chain and the investigational product, or other considerations if trial subjects became infected with COVID-19.

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These all the COVID-19 restrictions affected trial monitoring, data collection, and also drug supply activities, and specially the participants were not willing to visit the trial sites (hospitals) by Public transport where they may come in contact with COVID -19 infected patients. And in many cases they might have not been able to visit the site during the scheduled visits due to health issues related to COVID-19 infection, for example they may have been self-isolation, quarantine or hospitalise COVID-19.

Many researchers has see a significant decrease in the number of trails funding opportunities. The global impact of the crisis will have on the economy of the world makes it hard to imagine that future research will not be substantially affected. During this COVID-19, many of the resources were understandably redirected toward preparing and caring for COVID-19 affected patients, this has lead to the collateral damage to so many patients with non-COVID-19 medical conditions that did not receive on time proper medical resources, or failed to seek, treatment.

The COVID-19 pandemic has great impact on massive disruptions to clinical trial research across the world. In Other aspects the virus has severely affected the ability to conduct trials in safe and effective ways. The effect of COVID-19 has been enormous, around 80% of non-COVID-19 trials has been stopped or interrupted, according to Michael Lauer, deputy director for extramural research at the US National Institutes of Health. But the effect extends beyond just trials. This has major effects on all biomedical research across the world that is not directly related to COVID. Lauer told The Lancet. “Laboratories are closed. Also the communications have been shut down, many of the conferences have been cancelled, supply chains for equipment have been lost, and resources have been lost. There have been widespread financial losses within academic medical centres that have had spill over effects on their research operations.” The effect has also been felt by those who conduct research. During this crises period many of the researchers were pulled away from working on clinical trials to work in emergency medical care, especially during the first months of the pandemic in places where the pandemic threatened.

a) Pre-COVID-19 vs post-COVID-19 – clinical trial challenges revealed:-

During the pandemic the industry continues to focus on the development of vaccines, therapies and all the other possible alternative treatment in response to COVID-19, the crisis has had a considerable impact on clinical trials in sectors of therapy areas, particularly on cardiovascular, dermatology and the metabolic .On the other hand significant regulatory agencies, such as the FDA and EMEA, have been involved in promoting the guidelines and measures for maintaining the integrity of the trials that attempted to guarantee the safety, rights and wellbeing of patients and healthcare staff during this COVID-19 pandemic, maintaining clinical trials has been severely challenging.

The COVID-19 pandemic has clearly changed the consequences on the conduct of clinical trials :-

- There has been delayed enrolments of patients due to concerns about the safety of patients as well as with the reallocation and hence lack of staff or resources to house these patients.
- Central laboratory has faced the problem of disrupted supply chain due to closed borders, also affecting shipment of clinical trial samples to be tested .
- During recruitment there has been seen a extension of the duration of the trial, as the study was either slowed down or interrupted during pandemic.
- The overstretched hospitals, system and resources.

- Patients were prevented from entering trails and visiting hospitals ,new study initiation were placed on hold by the industry itself or forced by regional lockdowns.
- There was the conversion of physical visits of the patients into virtual visits during this pandemic.
- Many of the recruited patients having to leave the trials .
- Many of the vendors and contractors where unable to visit distribution obligations, such as delivering drugs sites.

b) Guidelines and Alternative for Clinical trails:-

The suspension of non- clinical trials has a significant impact on many of the patients especially those with end-stage diseases such as stage IV cancer that have not responded to traditional treatment regimens; for these patients, the drugs offered by clinical trials was only their hope for potential survival. Patients who live with debilitating chronic conditions like cardiovascular diseases stand to lose the potential therapeutic benefits offered by clinical trials.

Data Integrity:-

The Data integrity is defined as the extent to which all trial data are complete, consistent, accurate, trustworthy, and reliable throughout the data lifecycle mentioned by (WHO 2019). During the pandemic period, it is essential to adopt methods of data collection to manage with clinical trials that will increase the validity of assessments of safety and efficacy (T. R. Fleming, 2011).

Trail Integrity:-

The Trail integrity is another broader trial conduct-related concept, which encompasses data integrity and refers to the ability of a trial to produce results that are reliable and valid. This implies that results are not affected by (unknown) biases. The data collected and the conclusions made from a Clinical trial are directly affected by the and trial integrity. To avoid loss of data integrity, sponsors should has to consider other approaches for data collection that will be helpful such as electronic data capture by patients at home, telecommunication, or Telemedicine (McDermott & Newman). Home visits by the site staff, or use of local Instead of central laboratories ,Centralized Data monitoring, are some of the other options Available for the continuation of data collection during the Pandemic. Home delivery of the trial medication could be done through courier by the site staff, Ensuring the stability of the medication and to keep the Confidentiality of the participants.

Adverse event reporting:-

The CDSCO and ethics committee should be reported by the Sponsor about the any SAE both unexpected and for which there is a Reasonable possibility that the investigational product Caused the SAE, i.e., there is evidence to suggest a causal Relationship between the drug and the adverse event, There is a possibility that the participants gets infected with COVID 19 during the trial may develop SAEs That are associated with the disease and not due to the Investigational product or the participant may have become More susceptible to developing SAE due to COVID 19 Infection. The report should be checked that whether the SAE is causally related or unrelated the investigational product may be decided only after Analysis of the unblinded data and it is responsibility of The Data Monitoring Committee (DMC).

Expert opinion:-

Experts suggested to avoid such unsatisfactory conditions in the future, a couple of lessons may be helpful: Regulators should coordinate their actions at least within the EU. A minimal core data set, follow-up standardizing the baseline, and outcome variables, its measurement and documentation is still urgently needed. The same is true for the efficacy and effectiveness endpoints and the safety assessment. Will provide great platform to inform investigators

about relevant questions of the research and to enable investigators to find suitable collaborators for their projects will be helpful, too, collaboration is needed among the national drug authorities and EMA to avoid parallel trials investigating more or less the same hypotheses resulting in too small samples, and trials with inappropriate designs. Therefore, there is a need for responsibilities.

Resumptions of Clinical trails:-

As the world adapts to the pandemic and many countries pass the peak of COVID-19 infections and deaths, and, lockdown restrictions are being eased worldwide, this could allow for the resumption of all clinical trials. For resuming the trails continuation the following COVID guidelines also the same guidelines that govern the continuation of clinical trials could be followed. The many of the key factors are assessing the risk of disease transmission while conducting of trails to both the study participants and staff in light of the clinical benefit of the conduct of trial and the number of positive cases .

During the initiation Pandemic wave in U.S there was a total of 62,252 trial activations examined and; over 58,000 were non-COVID-19 trial activations. The non-COVID-19 activations included oncology (49.8%), cardiovascular (27.5%), mental-health (19.2%), and multiple disease studies (3.4%). Most studies with known data consisted of treatment trials (68.5%) that evaluated systemic therapies (48.9%). Also, 3,364 COVID-19 trial activations were examined. The research team found that the US monthly trial activations were 57% of the expected estimate if the pandemic had not occurred .The decrease for non-US based trials, in contrast, was less pronounced, with monthly trial activations at 77% of the expected rate had the pandemic not occurred. Thus, the reduction for US-based trials was 27% greater than for impact on the initiation of new clinical research studies for non-COVID-19 diseases. Our aim was to examine the association of the COVID-19 outbreak with conduct of non COVID-19 clinical trials.

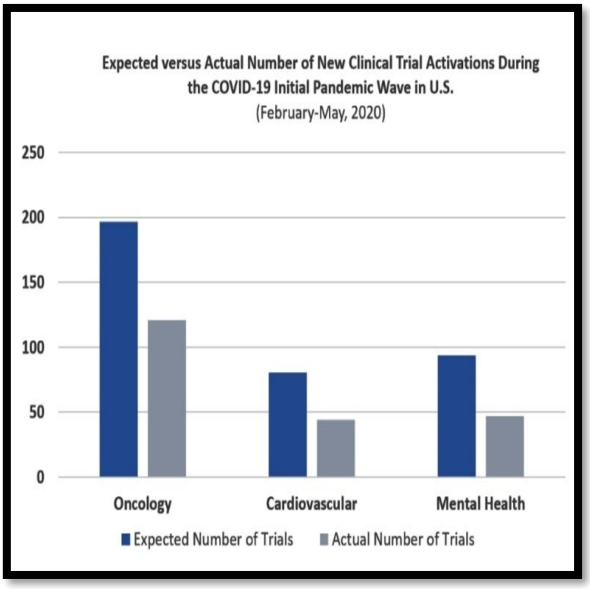

Fig 1 - Expected Vs. Actual Number of Clinical Trial Activations During the COVID-19 Initial Pandemic Wave in US

Table 1-Challenges & Potential Supportive Strategies for the initiation & conduct of clinical trails in India during COVID-19 pandemic

Challenges	Potential Supportive Strategies
There were delays in approval from regulatory agencies.	• For review of proposals streamline regulatory approval processes with prescribed timelines. • Trials of public health importance initiated by the Priorities investigator. • Eliminate redundancy in approval processes • For addressing questions of public health importance Expedite review of academic trials that
During the trials conduct there was lack of previous experience and digital platforms.	• Training on the various use of electronic case report forms. • For the core trial staff regular good clinical practice training and simulation activities should be done. • Incorporation of research into medical and nursing curriculum.
Due to travel restrictions there were limited scope for site visits by trial management team	There should be supervision of the clinical trails by the local site-level investigators with remote virtual monitoring.
Issues with delegation of site-level site set-ups and responsibilities	Develop internal capacity Hospitals to recognise research as a public health need
Ensuring data integrity and source data verification.	• In electronic case report forms the Real-time data entry is to be done with validation rules. • For source document verification use of virtual tools.

II. RESULTS AND DISCUSSION

The COVID-19 pandemic has caused severe interruptions in Conducting non-COVID-19 clinical trials. As in recent research into COVID-19 treatments has increased, a key question is whether the landscape of clinical research for non-COVID-19 diseases has also changed. Clinical trials are an essential tool in medical research, but due to COVID-19 pandemic has exposed ways that their design, conduct, and reporting could be improved. Nowadays the management of the clinical trails is important since advances in new treatments for patients rely on the conduct of clinical trials, which represent in proving the efficacy or effectiveness of new therapies. Thus interruptions in the conduct of non COVID-19 clinical trial research could slow down the development of new treatments for common illness.

III. CONCLUSION

This interruption in the continuation of the clinical trails and reduction in new trial activations for non-COVID-19 diseases is likely to slow the development of clinical research and on the treatment to non-COVID patients and new drug discovery, with long-term negative consequences on the patients health .The study examined the effects of COVID-19 on conduct of clinical during the COVID-19 crises by gathering insights and perceptions from clinical operations professionals from pharmaceutical companies in the United States. The goal was to study and understand the modifications and alternative step that organizations have made in response to the pandemic, especially with regard to remote or virtual approaches. Now an important question for researchers and policy-makers is whether the renewed outbreak period of winter will have a similarly negative impact on the initiation of new clinical research studies for non-COVID-19 diseases. Our aim was to examine the association of the COVID-19 outbreak with conduct of non COVID-19 clinical trials.

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