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CHALLENGES IN CONDUCTING BIOEQUIVALENCE STUDIES DURING THE COVID-19 PANDEMIC: AN OVERVIEW

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ABSTRACT

Since the late 2019, there has been a rapid spread of coronavirus named SARS-CoV-2, leading to global pandemic. Due to this, there is a significant impact on the economy and has created panic among the humans. Currently, the world is witnessing a steep surge in number of cases and the virus is spreading from human to human at a greater speed. This pandemic has impacted businesses including biopharmaceutical industry and Clinical Trial industry. While various measures are currently being taken to control the spread of this virus across various workplaces, there are huge challenges in the successful conduct of clinical research involving human research participants. This overview outlines the possible measures that can be adapted to contain the spread of virus among the research staff and research participants with particular reference to conducting Bioavailability / Bioequivalence studies in the wake of rapidly evolving situation and to enable CROs to prepare a strong ground for facing even more challenges that may arise in future.

INTRODUCTION

In the month of December 2019, a group of patients were identified with a novel coronavirus infection in the city of Wuhan, Hubei province, in China[1]**.** The Virus was initially named as 2019 novel coronavirus (shortened as 2019 nCoV), and subsequently the virus has been named SARS-CoV-2 by ICTV (International Committee of Taxonomy of Viruses)[2] and the disease which the virus causes has been named as "Coronavirus Disease 2019" COVID-19. The COVID-19 is an infectious disease that is caused by a newly discovered coronavirus, SARS-COV-2. The SARS-CoV-2 virus is an etiological agent of COVI-19 and primarily spreads through respiratory droplets and contact routes (WHO, 2020).[3]

The outbreak of this respiratory disease caused by this novel coronavirus, resulted in millions of people infected within a brief period of time and has posed as a huge public health challenge across the globe. US-HHS issued declaration of a public health emergency related to COVID-19 and mobilized the Operational Divisions in the month of January, 2020[4]. On March 11, 2020, COVID-19 was declared as pandemic by WHO, owing to the serious economic losses and the panic it has caused in human race.[5] COVID-19 is highly transmittable and pathogenic and the current data indicates that the virus spreads primarily between people who are in close contact with each other. A person may be infected when respiratory droplets or aerosols containing the virus are inhaled or come directly in contact with the eyes, nose or mouth. The virus may also spread in

poorly ventilated and/or crowded indoor settings, where people spend longer periods of time. These are because of aerosols that remain suspended in the air. It was also observed that some of the patients have developed gastrointestinal symptoms such as vomiting and diarrhoea, reinforcing the conclusion that the virus can survive in digestive tract as well.[7] Common symptoms of a person infected with coronavirus are cough, fever, shortness of breath or difficulty in breathing, repeated shaking with chills, chills, muscle pain, sore throat, headache, and loss of taste/smell.

The currently available information indicates that the transmission from human-to-human occurs primarily through physical contact and/ or through respiratory droplets from coughs or sneezes.[7] It was shown that the virus can survive on contaminated surfaces for several days.[8] Human to Human infection can occur indirectly by touch transfer of virus from these surfaces or hands to the mucosa of the mouth, nose or eyes. Therefore, high level of infection control measures such as sanitizing surfaces, maintaining good personal and hand hygiene are important to limit the spread of the virus, which is playing havoc with human lives. A team from Sun- Yat Sen University confirmed that faecal samples from few positive SARS CoV-2 patients, were tested positive by nucleic acid detection, which provided substantial evidence that this virus has the likelihood of faecal-oral transmission.[7]

Current pandemic has severely impacted several countries, communities, and businesses in the most intense way that humanity has witnessed in the last several decades. Global health agencies, governments, healthcare work forces, and volunteers from various NGOs, have come together to fight and limit community transmission of this virus.

However, based on the experience, the authors of this overview have outlined the practical difficulties currently the CRO industry faces and suggested possible preventive measures to mitigate the transmission of the virus among the study participants, CRO Staff and provide insights towards successful conduct of studies. This overview is basically intended to share the information based on challenges, which could help framing an agenda for research into a number of unaddressed questions. Eventually, the overview also outlines practical implications, based on the existing knowledge for containing the spread of coronavirus with particular reference to the research participants, scientific community involved in clinical trials and bioequivalence studies.

Current Scenario:

As we write this overview, there has been steep increase in number of cases across the globe and also in India. As of 28th August, 2020, coronavirus has infected more than ~23 million people world-wide out, of which ~3 million cases have been reported in India, which is now in third position globally after USA and Brazil.[9,10] India recorded a new-single-day high of 4.09 lakh cases during the third week of May 2021 and the total number of deaths have now risen to 283,248 and counting, according to ministry of health data, Government of India.[11] The new variant of virus, has a new set of symptoms and appear to be more contagious and dangerous. The variant is not only impacting the old and middle-aged, but also affecting the younger age groups. The number of infections has grown exponentially during the last 12 months and on the contrary, there are an increasing number of investigational drugs/ vaccines that are in various phases of trials and clinical development and few vaccines have been approved for emergency use and were rolled out to the general population.[6] It is also believed across various countries around the globe, that the pre-pandemic normalcy never returns until a global robust vaccination program with effective vaccine that works against various mutant strains are in place.

To address a pandemic, the magnitude of the necessity of the trained medical army goes multi-fold. During the month of March 2020, a wide variety of preventive measures have been implemented to reduce the transmission, which include complete lockdowns, travel and mobility restrictions, various social distancing measures such as closure of educational institutions, crowded places, shopping malls etc to mitigate/ prevent the transmission of the virus. In this pandemic situation, most of the people are staying at home to prevent the spread of the virus. Over a period of time, various states have eased the lockdown and started opening up various businesses in a phased manner. However, till date, governments have not opened educational institutions, and other public places. The number of cases saw a decline during January 2021, and subsequently during March 2021, India saw a steep rise in the number of cases and deaths at a faster rate than ever before. Many countries across the globe started vaccinating the population with emergency use approvals to protect the human race. Till an effective vaccine/ treatment option is in place, the world needs to adhere to the safety measures laid down by global and local health authorities, from time to time with a focus to prevent the spread of the disease and eventually to witness a virus-free world.

Like other industrial sectors, the Covid-19 situation has also impacted the pharmaceutical industry big time, than ever before and is witnessing a significant impact in the conduct of clinical trials and bioequivalence studies of drugs destined for various global regulatory agencies. The pharmaceutical and Contract Research Organization (CRO) industry were allowed to start operations as essential services, with reduced manpower to minimize the social contact to avoid the spread of virus.

This overview mainly focuses on the challenges in conducting bioequivalence studies in these critical times and the authors wish to draw some attention to the preventive measures that need to be taken to minimize the spread of COVID-19 virus and the impact it has on the study volunteers /patients and study staff and eventually on the study conduction. The main challenges that arose in this situation includes closure of study sites, quarantines, restriction in travel, supply chain interruptions for the proposed medicinal products to be investigated / generic medicinal product or the reference listed drug product, availability of site personnel and study volunteers/subjects becoming infected with COVID-19. In addition to this, frequent interruptions and re-initiating the studies called for protocol revisions and eventually impacting the project timelines. These led to challenges in meeting pre-defined protocol procedures, including usage of the investigational medicinal product or administering or comply with protocol-mandated return visits and diagnostic/laboratory testing, while safeguarding the rights, safety and well-being of research participants.

Various regulatory agencies such as EMA, USFDA and ICMR have laid down guidelines on conducting clinical trials in this pandemic situation. This overview highlights some of the key points from these guidelines while suggesting possible solutions for the real-time challenges currently CROs face in conducting bioequivalence studies.

Current ICMR Recommendations: [12]

The Indian Council for Medical Research published guidelines intended for ethics committees that review biomedical and health research during this current Covid -19, pandemic, in the month of April 2020. While all the stakeholders are required to follow the guidelines in totality, some of the key points relevant to the CRO settings, are outlined in this overview.

Educating the volunteers/patients:

Educating volunteers/ subjects/ patients on the coronavirus situation and its impact are of paramount importance. All efforts to be made to educate the research

participants about this COVID-19 pandemic and its impact, every effort should be in place to prevent the spread of negative information or sensationalising news, making false claims or promises, or spreading negativity or creating a scare.

Biosafety in laboratories and hospitals:

While the guideline outlines the biosafety measures in laboratories and hospitals, these safety precautions are applicable to the CRO and attached labs as well. In case of any suspected case during the time of recruitment/conduct of the study, the CRO shall refer the volunteer/subject to the nearest designated laboratory/testing centre. The laboratory should ensure adequate labelling and specimens handling and appropriate biosafety precautions and regulatory standards to safeguard the individuals and the environment / testing at NABL certified laboratories. As prescribed by the Department of Biotechnology (DBT) and Ministry of Environment and Forests, Govt. of India, regulatory requirements for bio-safety labs should be strictly followed.

The CRO staff must be adequately trained on various additional precautions, sanitizing with appropriate disinfectants, hand hygiene, use of personal protective equipment (PPE), or other physical barriers, handling of biomedical waste to minimize the risk of exposure.

Ethics committee reviews:

The Ethics Committee members should receive training and adopt / include a Standard Operating Procedure, (SOP) and usage of electronic platform for research review in this COVID-19 pandemic. Electronic copy of research protocol and relevant documents need to be submitted for screening and for their completeness and categorization into various categories such as exempt / expedited review / emergency or full committee review depending on the urgency and need by Secretariat.

The Ethics Committees should adapt to the new normal, such as handling / reviewing electronic documents with truncated timelines with accelerated procedures. To ensure social distancing, the ECs should, as far as possible, switch over to Virtual or tele / video conferences. While keeping the agenda for virtual meetings short, Ethics committees may conduct fast track meetings for review more frequently within 24 to 48 hours. Prior to main meeting, EC need to plan a review by subject experts/obtain clarifications from researchers. EC may also call independent consultants for meeting (who are non-voting members) or representative (s) from specific patient group as special invitee (s).

Prior to final decision is made, the special invitee(s) in the web-meeting may be requested to leave. In case of a study that is currently underway, if the concerned principal investigator (PI) is indisposed for a specific duration, parts of PI duties may need to be temporarily delegated to others / co-investigator while appropriately documenting and reporting to Ethics Committee at the earliest through electronic mode of communication.

Safety of the staff involved in the study conduction:

In view of this current pandemic, safety of staff must get due attention as rapid spread of infection to even one member in a lab or clinical setting could unduly interrupt the entire program / project. Therefore, ensuring adequate safety is the primary responsibility of the CRO, sponsors and local authorities, since research team may be constantly subjected to various disturbing instances such as trauma, humiliation and threats of violence, while carrying-out research.

Various additional precautions need to be taken such as prioritizing key research activities and scheduling activities to prevent overcrowding, imparting adequate training, taking adequate biosafety precautions, exposure of minimal number of researchers, communicating via electronic platforms, adequate protection gear/PPE and infrastructure to undertake research,

safety measures against any possible assault from general public or other individuals, insurance coverage etc.

Psychological and mental health:

Volunteers or staff who tested positive for COVID-19, their family members, health workers who constantly get in contact with COVID positive cases, must be provided adequate psychosocial support wherever possible. Psychosocial counselling may be provided for COVID-19 positive patients and their family members according ICMR guidance. There is a basic necessity to show respect, empathy and compassion and should not subject them to any kind of discrimination or stigma. Individuals may face enormous stress and anxiety when in isolation or quarantine. Management of the mental health and psychosocial well-being is of paramount importance. The organization should ensure enough access to psychosocial and emotional support, good and transparent communication, flexible work hours, and ways and means to ensure physical, psychological well-being and mental health of those who are going through the crisis.

EMA Guidance on Management of Clinical Trials:

To manage clinical trials during the Covid -19 (coronavirus), EMA issued a guidance ver.03 in month of April 2020. The guidance outlines the importance of having pragmatic and harmonized actions to protect the integrity of trials, ensuring well-being, rights and safety of research study participants and also to ensure safety of study staff during this global public health crisis. This guidance is primarily intended for all the stakeholders who are involved in clinical trial activities during this current pandemic situation.

This EMA guidance is meant predominantly for patient based clinical trials and addresses the measures to be taken with respect to initiating new trials, changes to be made to ongoing trials, safety reporting, risk assessment, communication with authorities, agreements with and between sponsors, trial sites and trial participants, changes to informed consent forms, changes in distribution of investigational medicinal products (IMPs), changes in the mode of supply of medical devices and *in-vitro* diagnostic, changes to monitoring, auditing, protocol deviations, reimbursement of exceptional expenses and commencement of new clinical trials that are aimed to test newer treatments for covid-19 and protection of rights of trial participants' during remote source data verification.[13]

USFDA-Guidance for Industry-

US-FDA issued a guidance to provide sponsors and investigators with considerations for approaches on how common COVID-19 related symptoms can be measured and analysed in clinical trials evaluating biological products or drugs, during September 2020, for the prevention or treatment of COVID-19 in out-patient and adolescent subjects. The guidance was issued to enable the sponsors to help identify symptoms across the subjects when designing clinical trials of drugs to treat or prevent COVID-19 in adult or adolescent subjects.

The data to be identified from subjects are in the form of questionnaire that was adopted from the information provided by Centers for Disease Control by US-FDA.[14] According to FDA, eICF options may also be explored where feasible to minimize the volunteer contact with the study staff as far as possible.

Measures to be taken at CRO:

The first priority the CRO need to address is on awareness programs for the site staff at all levels. The entire CRO staff need be trained on the basics of Epidemiology of Coronavirus and preventive measures to be considered to arrest the spread of the COVID-19. Refresher programs to be conducted for staff from time to time, based on the current updates from the global and local health

authorities. Clear-cut guidelines / procedures for the staff to be in place, and the CRO management should ensure that the staffs are trained on these guidelines and procedures from time to time and are updated as and when newer information is available. The CROs can explore hiring expertise in pulmonary medicine/ emergency/ critical care medicine for training the CRO Investigators and other allied staff on awareness on coronavirus and its management.

Pre-screening and screening activities:

After completion of all the pre-study activities and scheduling the screening activities, the screening team/volunteer mobilization team may contact the volunteers telephonically to obtain basic information such as signs and symptoms of COVID such as fever, cough, throat infection/irritation, muscle ache, loss of smell/taste, shortness of breath or difficulty breathing, Headache and chest pain,[13] information about their place of living, whether it is designated as a containment zone and whether his or her close contacts were tested positive for COVID-19 in the recent past, before calling them for screening activities at the site. Volunteers' COVID-19 vaccination details may also be obtained at the time of screening, and vaccination status can also be considered as an enrolment criteria.

Volunteers with any of these symptoms and those residing in containment zones, should not be allowed to visit the study centre for screening activities. Those subjects who have recovered from COVID-19, and had tested negative, should be cautioned to remain isolated at home for a further period of at least two weeks before calling them for screening activities. It has been reported in a study, that though the respiratory samples are negative in Covid-19 test, their faecal samples are positive for Covid-19 after ~35 days from the onset of symptoms. However, the local guidelines have not included faecal tests in the patients who tested negative in respiratory samples through RT-PCR tests.

Updated information about Covid-19 preventive measures needs to be sent to the volunteers via SMS and social media platforms, in a simple language that is easily understood by them. Volunteers, who meet the above-mentioned criteria, may be called and strictly instructed to visit the CRO facility with a face mask.

The CROs should earmark separate entry areas for volunteers in order to prevent mix up with other staff entry areas and make arrangements to maintain social distance at all the areas. Every volunteer / staff should be monitored for body temperature using infrared thermometer and oxygen saturation levels at the security area prior to entering into the facility. If their body temperature is more than 99.0°F or 37.22°C, and oxygen saturation levels below 90%, the volunteers/staff are requested to consult his/her physician and isolate themselves at home and seek necessary medical attention. The social distancing should be maintained in all the procedures according to standard guidelines laid down from time to time.

The staff whoever is required to be in close contact with research participants, should be required to use appropriate PPE such as face mask, face shield, goggles, shoe covers and gloves and all other necessary equipment during the conduction of activity (ies). If the local regulations permit, a valid COVID-19 test also needs to be considered during screening activities.

Clinical phase:

When the volunteers/study staff visit the facility, they should be informed to maintain adequate social distance (at least 6 feet) between themselves. The volunteers should be enquired about COVID-19 symptoms before entering into the facility. Alcohol based sanitizers should be made available at the facility at various accessible places, and security/concerned staff to ensure that all the volunteers/subjects are sanitized before entering into the facility.

Adequate hygiene practices need to be in place at all times.

The CRO may display various measures such as Do's and Don'ts published by health authorities at various places in the facility and volunteers should be well-informed about these measures at time of screening and at the time of entry during subsequent return visits. Blood C-reactive protein (CRP) and Chest X-ray should be mandatorily included during the screening and if possible in subsequent periods. The staff and subjects should be instructed to maintain the social distancing at all times. Frequent check of body temperature and oxygen saturation levels should be done at least 6 hours during the entire duration of clinical conduction. The subjects should be given clear instructions on the preventive measures at the time of check-out of the facility during each period and periodically instruct them via SMS and other social media platforms. The subjects also need to be informed about any new developments concerning the COVID-19, for their information.

In-house Sanitization:

In-house sanitization procedures should be more frequent, particularly in high-touch areas of the facility. It has been reported that the SARS-CoV-2 is viable various media/objects such in aerosols for ~ 3 hours, on stainless steel and plastic surfaces for up to 72 hours, up to 4 hours on copper, and on cardboard up to 24 hours. More washrooms need to be provided for subjects and hygiene should be maintained with frequent cleaning and disinfection with high quality proven disinfecting agents that are effective against a variety of pathogens.

Recently, in a study by *Wu et al*, revealed that Covid-19 asymptomatic patient's fecal samples were detected for SARS-CoV-2 RNA and it was believed to be present in high concentration for longer duration, which is an indicator of active replication in the GI tract, however, till date, faecal transmission were not reported. It is also reported that the Covid-19 patients who were cured of the respiratory symptoms, can shed the virus in faeces for days.

A study was conducted in early 2020, between January and March, in which 98 patients were enrolled in whom, both faecal and respiratory samples were collected in ~76% of the enrolled patients. Of these, SARS CoV-2 RNA was negative in 45% of patients, whereas their respiratory swab samples remained positive for ~15.4 days from the date of appearance of first symptom. The 55% of the remaining patients who were enrolled, were tested positive for SARS CoV-2 RNA in their respiratory and faecal samples remained positive for ~16.7 days and ~27.9 days respectively, after onset of first symptom i.e., for ~ 11.2 days longer than for respiratory samples.[15]

This study data indicates that shedding of virus in faeces was observed for ~ 35 days after the respiratory swab samples were negative for SARS-CoV-2 RNA. Although the current understanding about the viability of SARS-CoV-2 is rudimentary, the virus appears to remain viable in the environment for several days, which could possibly lead to faecal–oral transmission, as observed in other types of viruses such as Middle East respiratory syndrome CoV and severe acute respiratory virus CoV.[15]

Based on this, it is highly recommended to conduct routine stool sample testing with RT-PCR even after testing negative in respiratory swab samples. If any of the subjects who were in hospital or under self-quarantine tested positive in their faecal samples, strict precautions to be taken to prevent the transmission.

Though there is a minimal risk of contracting COVID-19, from the faeces of a subject, who recently recovered from Covid-19 and tested negative, initial investigations suggest that the virus may be present in faeces in some cases for days.[15] But this possibility cannot be ruled out and the CROs should exercise caution. The

spread of SARS CoV-2 through Respiratory source is still the primary route and sufficient evidence is not in place to put forth practical measures for the group of patients/ subjects with negative results from respiratory swab sample, but positive in faecal samples.[16]

In view of this, wash-rooms (toilets) should be regarded as a potential source of infections. Improper usage of wash-rooms may lead to cross-infection through fecal-oral route, if proper preventive measures are not taken. Extensive studies were carried out by Yu-Yun Li *et al*.,(2020) on computational fluid dynamics to explore and visualize the characteristics of flow of fluid during flushing of wash-room (toilets) and the role of flushing on the spread of virus aerosol particles. These results from simulation studies indicated that there is a massive upward movement and transport of virus particles, with approximately between 40 and 60% of particular movement reaching above the toilet seat, eventually leading to spread of virus. The authors from this study have also given suggestions for safe toilet use and have provided recommendations for better toilet design.[17]

In the wake of these findings, it is suggested that the CROs should improve the sanitary safety in toilet use, which are *hitherto* insufficient. In the wake of Covid-19 scenario, and possible evidence of fecal transmission of virus, the frequency of cleaning with high-quality disinfectants before and after use of toilets needs to be carried out, with particular reference to touch areas such as flush button and door handle where the possibility of presence of virus is high. A toilet hygiene guideline needs to be in place for both study participants as well as the staff. Specimen collections, transport and testing procedures, in case of any suspected subject during the study, should be in accordance with the current guidelines.[19]

Bio-analytical phase:

The entry, sanitization procedures and social distancing measures should be maintained similar to those followed during clinical phase conduction. The work shifts can be planned to prevent crowding at the bench in the laboratory, and the number of workplaces at each bench can be limited. Partitions can be placed between workstations for protection. As some of the staff are working from home or working at site on shifts, the existing staff may be spread over the facility to maintain a safe distance. Disinfecting bio-analytical areas is a challenge as there is a continuous work ongoing in shift systems and there is a possible mix up of disinfectants sprays with laboratory reagents. The laboratory should lay down procedures so that the routine reagents/chemicals are not contaminated with disinfecting agents.

CONCLUSION:

The coronavirus situation is evolving. Globally, the biopharmaceutical companies are working hard to find potential treatments/vaccine options to combat this virus. The global regulatory agencies are also working in tandem with the industry to enable accelerated approvals for candidate treatments wherever possible. Current clinical trials that are being conducted across the globe and the data generated thus far, appear to be promising and till a potential candidate vaccine is in place, the COVID-19 measures continue to take a centre stage and the clinical trial industry continues to face challenges. These suggested measures, if effectively implemented, would make the organisations better prepared in a much more critical situations, in case it arises.

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Conflicts of interest

No conflicts of interest

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Disclaimer:

The views expressed in this overview are those of the authors based on the current knowledge and their experiences and are not those of the organization they work for. The term 'Volunteers' /' subjects/ patients' are used interchangeably in this overview and it refers to human research participants.