Pattern of clinical research in the era of COVID-19 pandemic: A new learning experience for the present as well as future

The COVID-19 pandemic, a public health emergency, has affected 29,185,976 lives worldwide and 4,846,427 people across India. It has affected day-to-day life of each and every individual (health, social, and economy). Among various sectors, biomedical and health research has also been affected by this pandemic. COVID-19 has brought with it a number of challenges in the conduct of research during this pandemic. To fight against this pandemic, the Ministry of Home Affairs announced the “Disaster Management Act” with suspension on transportations and closure of institutions, such as education, training, and coaching centers.

Nevertheless, it is research that has to be given prime importance to overcome this pandemic. Further, it is to be taken into account that on-going research that is already being carried out might require some inevitable protocol deviations and novel ways to overcome the challenges.

Recent Trend of Articles during COVID-19

At present, research can be categorized into the following categories:

a. New research that is associated with COVID-19
b. On-going research not associated with COVID-19
c. New research not associated with COVID-19.

Research review needs to be prioritized on the basis of urgency and essential steps need to be taken that will enable new research’s review and carry on the on-going research after amendments are made as per the need considering social distancing norms.

The major challenges posed during the conduct of research are social distancing norms, quarantine, restrictions in travel, transportation of samples, hindrance in the production, as well as supply chain of different materials required for carrying out research, and the most challenging one is the chance of participants as well as researchers getting infected with SARS-CoV-2 virus.

Decisions regarding on-going studies

It is important to consider the influence of COVID-19 on on-going studies, recruitment, and continued participation of participants. The requirements for research studies other than COVID-19 which are on-going/near-term/have direct benefits and in case stopped can pose risk to the patients; hence, such circumstances must be wisely assessed. Such studies can either be continued, or mechanisms for continuation can be suggested. The measures that are considerable include temporary termination of study either at few clinical trial sites or at all; suspension or delaying the study or activation of sites that are yet to be initiated without any compromise of safety and wellness of participants; continuing study with restricted parameters; phone or video calls instead of physical visits; delay or cancellation of visits to make certain that visits that are too necessary are performed at sites; it may be required to take re-consent of patients who are already enrolled in an on-going study for the implementation of urgent changes; which can be accomplished through phone/video calls/oral consents accompanied by e-mail confirmation. Furthermore, restricting travel, confinement of participants, and workforce to perform visits need to be considered.

Review of new non-COVID research

Research other than COVID-19 should not be affected because of COVID-19 and studies that will assess treatment for communicable diseases/chronic conditions/injuries/others can also be given consideration for review by ethical committee (EC) because these conditions also require utmost importance. EC needs to review and evaluate the negative influence that any planned study may have on safety of participants or enhance risk to them because of COVID-19 and decide whether to permit or not. It can also suggest added safety measures for the conduct of research in this emergency. The review can also be done via virtual EC meetings and ensure proper scientific and ethical review as well as satisfying quorum requirements.

Types of Research Regarding COVID-19 That Could be Undertaken

New research directly related to:

a. Development of new diagnostic tools: Standardized diagnostics provide sensitive and specific identification among suspects, whereas lack of proper diagnostic methods may cause delay in the
identification of the pathogen. Local availability of diagnostics can control the outbreak at the start point itself
b. Development of strategies to fight against the pandemic: Development of antiviral agents, vaccines, immunomodulation, prophylaxis, and supportive therapy
c. Online surveys of front-line workers concerned to their mental status, social, and economic security, etc. However, feasibility of research is the most important factor that has to be borne in mind while planning or carrying a clinical trial during a pandemic
d. For studies requiring conventional methods of data collection, alternative methods such as electronic formats such as mails, questionnaire-based surveys, and calls via telephone or video may also be adopted
e. Appropriate training should be given to all healthcare workers involved in COVID-19 research. Priority to safety of health workers should be given as the general public requires their service during a pandemic.

For on-going non-COVID-19 research, strategies such as extension of study duration can be done; conduct of the study can be narrowed down by reducing the parameters to be assessed; conventional methods of data collection and informed consent can be replaced by electronic means. Only the visits that are absolutely essential at research sites should be allowed with all the necessary precautions. These methods can be followed with the prior approval of the EC.[4]

Feasibility in the conduct of clinical trials should also be verified during a pandemic.

The follow-up visits to the investigational site as per the protocol may not be feasible during a pandemic. Hence, they can be replaced by any electronic means as mentioned earlier or investigations can be performed at a local laboratory if required. COVID-19 screening should be made mandatory for all the participants. In case of any deviations in the protocol, sponsors and clinical investigators should communicate with the EC as soon as possible. Missing data due to missed visits or study discontinuation due to COVID-19 may be considered as “last follow-up data carry forward,” and such data must be summarized in the clinical report. Assessment of parameters can be done virtually by telephone or video calls.

Role of Ethics Committee

EC to ensure all clinical trials, biomedical, and health research to be registered on the Clinical Trial Registry of India (CTRI) with appropriate approval from regulators. Fast-track reviews may be done within 24–48 h if the EC meets frequently. Non-COVID-19 research should not suffer due to “COVID-19.”

Current Evidence of Pattern of Research during COVID-19

There has been an enormous spike in research articles on COVID-19 since the outbreak of this pandemic. A review article published in the previous issue has focused in detail on different aspects of COVID-19 as per the current evidence.[5] We observe that there has been a change in the pattern of research because of COVID-19 pandemic. Therefore, in the present editorial, we have focused on the pattern of research, various challenges faced, and few strategies to overcome the challenges. Table 1 Number of Clinical Trials registered with various databases (as of 3rd September, 2020).

Diagnostics

Among other pandemic control management strategies, diagnostics are also at priority to focus on for advancement. Standardized diagnostics give sensitive and specific identifications among suspects, whereas lack of proper diagnostic methods cause delay in the identification of the pathogen. Local availability of diagnostics can control the outbreak at start point.

As of September 3, 176 trials are registered for diagnosis of COVID-19 at ClinicalTrial.gov. Among these, 15 interventional and observational studies are completed. From all these studies, an approximately 30% are based on the conventional RT-PCR technique and 33% on rapid diagnostic tests with approximately 90% on antibody detection tests. 20% are based on radiological analysis using CT scan and ultrasound findings. Around nine studies were based on self-test/home test for the detection of COVID-19. According to a systematic review by Mahendiratta et al., RT-PCR is a gold standard test for COVID-19 till date. However, drawbacks of the technique such as false-negative result have also been mentioned as limitations of the technique.[6]

Repurposing of Conventional Drugs

Chloroquine and hydroxychloroquine

FDA has given approval for the use of chloroquine and hydroxychloroquine (CQ and HCQ) in COVID-19 with some limited circumstances through the EUA.[7] The role of CQ and HCQ in COVID-19 has been discussed in detail by Mahalmani et al.[7] As of September 3, 2020, 212 HCQ trials (179 randomized) are registered at ClinicalTrials.gov out of which seven clinical trials (Phase III) and one nonrandomized trial have been completed. One of the Phase III randomized trials has been terminated and four
suspended. 16 randomized parallel-group multiple-arm trials of HCQ are registered at CTRI. Similarly, 38 CQ trials (31 randomized) are registered at ClinicalTrials.gov; two clinical trials (Phase II) and one nonrandomized trial have been completed. One of the Phase II randomized trials has been suspended and one (Phase IV) terminated. Two randomized parallel-group multiple-arm trials of CQ are registered with CTRI.

Ivermectin
Ivermectin is an FDA-approved antiparasitic drug that has shown antiviral activity against various RNA as well as DNA viruses.[8,9] As of September 3, 2020, 36 ivermectin trials (30 randomized) are registered at ClinicalTrials.gov, of which two randomized trials (Phase I, Phase II/Phase III) and one observational study have been completed. Seven trials of ivermectin are registered at CTRI.

It has potential for use in COVID-19 and is safe at higher doses and frequent regimens.[10] An in vitro study by Caly et al. has shown that 5 µM of ivermectin is effective in reducing viral RNA, with an IC₅₀ value of ~2 µM.[8] However, well-controlled dose–response study needs to be considered for carrying out a clinical trial of ivermectin because in vitro inhibitory concentrations (5 µM/L) are not probable to be achievable in humans.[11] Various studies have reported clinical efficacy of ivermectin in COVID-19 patients.[12-15]

Antivirals
Various antivirals that have shown their potential effect for use in COVID-19 target RNA-dependent RNA polymerase, papain-like proteinase, 3-chymotrypsin-like proteinase (3CLpro), S protein, and TMPRSS2. As of September 3, 2020, 32 lopinavir/ritonavir trials (27 randomized) are registered at ClinicalTrials.gov of which one randomized trial (Phase II) and one nonrandomized trial have been completed. A Phase III randomized trial of lopinavir/ritonavir has been withdrawn, and also, a Phase II randomized trial has been terminated. Two randomized trials of lopinavir/ritonavir are registered at CTRI.

Twenty-four remdesivir trials (17 randomized) are registered at ClinicalTrials.gov of which three randomized trials (Phase III) and a nonrandomized trial have been completed. One of the Phase III randomized trials has been terminated and one suspended. One randomized parallel-group multiple-arm trial of remdesivir is registered at CTRI.

Twenty-nine favipiravir trials (27 randomized) are registered with ClinicalTrials.gov from which five randomized trials (4 Phase I trials and a Phase III trial) and a nonrandomized trial have been completed. Three randomized trials of favipiravir are registered with CTRI.

Corticosteroids
Corticosteroids have been used for the treatment of SARS-CoV and MERS and at present are used for SARS-CoV-2. As of September 2, 2020, 17 dexamethasone trials (15 randomized) are registered at ClinicalTrials.gov of which one randomized trial and an observational study have been completed. One of the Phase III randomized trials has been terminated and one Phase IV trial has been suspended. Two randomized trials of dexamethasone are registered at CTRI. 17 methylprednisolone trials (14 randomized) are registered at ClinicalTrials.gov of which two randomized and two observational studies have been completed. A randomized trial of methylprednisolone is registered at CTRI. Studies have shown efficacy of prednisolone in SARS-CoV-2-infected patients. As of September 3, 2020, two prednisolone trials (1 randomized) are registered at ClinicalTrials.gov.

Janus kinase inhibitors
As of September 3, 2020, 12 baricitinib trials (6 randomized) and 20 ruxolitinib trials (7 randomized) are registered at ClinicalTrials.gov from which one Phase II/Phase III study of baricitinib has been completed. One Phase II study of ruxolitinib has been discontinued.

Biologicals

Monoclonal antibody
As of September 3, 2020, 46 studies have been registered at ClinicalTrials.gov of which 32 are in recruiting phase, 3 in active, not recruiting phase, and 1 was suspended. Out of the studies that are going on, single study is in early Phase I, 12 studies in Phase I, 23 in Phase II, 7 in Phase III, and 2 studies in Phase IV.

Mesenchymal stromal/stem cells
As of September 3, 2020, 53 studies have been registered at ClinicalTrials.gov of which 23 are in recruiting phase, 4 in active, not recruiting phase, and 2 are completed. Out of the studies that are going on, 4 are in early Phase I, 27 studies are in Phase I, 34 in Phase II, and 2 in Phase III.

As the key for the treatment of SARS-CoV-2 infection lies in the management of cytokine storm, mesenchymal stromal/stem cells (MSCs) are considered to have a potential role in COVID-19 by virtue of their immunomodulatory and anti-inflammatory properties.[16] Liang et al., in a case report of a critically ill COVID-19 patient, showed that on treating with allogeneic human umbilical cord MSC, the patient improved within 5 days of her second cell infusion. The
patient was off the ventilator and able to walk along with improvement in T-cell counts with no obvious side effects.[17]

Another study by Leng et al. revealed that intravenous transplantation of MSCs was safe and effective in critically ill severe COVID-19 pneumonia. However, the sample size is limited only to seven patients.[18] Despite the lack of robust clinical evidence, currently, a number of promising trials are underway.

**Convalescent plasma therapy**

As of September 3, 2020, 131 convalescent plasma therapy trials are registered at ClinicalTrials.gov of which nine studies (4 randomized) have been completed. One Phase II study has been withdrawn. Eleven trials of convalescent plasma therapy are registered with CTRI.

**Vaccines**

As of September 3, 2020, 72 vaccine trials have been registered at ClinicalTrials.gov., out of them 32 are in recruiting phase, 13 are active, not recruiting phase, a study is terminated, and 2 studies have been completed. Out of the studies that are going on, 2 are in early Phase II, 22 are Phase I, 22 in Phase II, 27 in Phase III, and 4 studies are in Phase IV.

Phase II clinical trials of the Oxford University-AstraZeneca vaccine candidate for COVID-19, manufactured by Serum Institute of India, will probably begin soon in the month of August. ChAdOx1 nCoV-19 (AZD1222) has exhibited encouraging results in early human trials. Pune-based Serum Institute, the world’s largest manufacturer of vaccines, is conducting Phase II/III clinical trials, which has been named as “Covishield” in India.[19]

Bharat Biotech in collaboration with the Indian Council of Medical Research-National Institute of Virology has developed an India’s indigenous COVID-19 vaccine “COVAXIN.”[20] However, these trials are currently on-going and the government has permitted fast-tracking of regulatory clearances for the vaccine.

**Dietary Supplements**

As of September 3, 2020, 17 clinical trials are registered at ClinicalTrials.gov for zinc, Vitamin C, and magnesium. 12 are in combination of Zinc with CQ, HCQ, Vitamin D, and Vitamin C in which two are in Phase IV and two are in Phase III.

**Traditional Indian Medicine**

Various studies are initiated to observe the effect of traditional Indian medicines (Ayurveda, Unani, Siddha, and Homeopathic [AYUSH]) in COVID-19 pandemic. In majority of the clinical trials, traditional Indian medicines (TIMs) for use in COVID-19 are studied as an add-on therapy in addition to standard of care medicines or as a prophylactic/preventive measure in high-risk population. TIM is studied as stand-alone in asymptomatic patients or patients with mild-to-moderate disease. In CTRI, around 16 AYUSH interventional trials are registered for the treatment of the disease are ongoing on several Ayurveda formulations such as AYUSH-64, Ashwagandha and Shunti capsule, Arsenicum Album, Guduchi Ghan Vati, and Maha-Sudarshana Ghan Vati.

As of September 3, 2020, 123 trials of TIM are registered with CTRI and 7 with ClinicalTrials.gov.

**Traditional Chinese medicine**

Traditional Chinese medicine (TCM) may prevent the entry of SARS-CoV-2 into the host cell by targeting ACE-2 or inhibit its replication and assembly inside the cells by targeting 3CLpro. In China, it is recommended to use TCM in combination with conventional treatment for COVID-19. It was shown that intervention of TCM in COVID-19 improved cure rate, reduced course of disease, delayed progression of disease, and decreased death rate. Huang et al. suggested that quercetin, kaempferol, luteolin, isorhamnetin, baikalein, naringenin, and wogonin are the important ingredients of TCM for the management of COVID-19.[21] As of September 3, 2020, 24 trials of TCM are registered with ChiCTR and 8 with ClinicalTrials.gov.

**Conclusion**

In view of the current situation of COVID-19, carrying out effective clinical research is very crucial. However, the pandemic has affected the research especially the on-going research experiments and clinical trials. All the researchers are recommended to work in context of gathering more clinical data and actual ground base studies for COVID-19. With restricted resources and work force, every country is suffering in research. However, let’s not give up and join hands together to overcome the challenges we are facing at present. With the combined efforts, we will definitely win this battle. Every beginning has an end and so is this pandemic too.

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### Table 1: Number of Clinical Trials registered with various databases (as of September 3, 2020)

| Database                                    | Number of clinical trials |
|---------------------------------------------|---------------------------|
| ClinicalTrials.gov                          | 3201                      |
| ICTRP                                       | 2361                      |
| CTRI                                        | 471                       |
| ChiCTR                                      | 699                       |
| European Union Clinical Trials Register     | 313                       |
| ANZCTR                                      | 116                       |

*ICTRP=International Clinical Trial Registry Platform, CTRI=Clinical Trial Registry of India, ChiCTR=Chinese Clinical Trial Registry, ANZCTR=Australian New Zealand Clinical Trials Registry*
Mahalmani, et al.: Pattern of clinical research in the era of COVID-19 pandemic

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