भारतीय आयुर्विज्ञान अनुसंधान परिषद
स्वास्थ्य अनुसंधान विभाग, स्वास्थ्य और परिवार
कल्याण मंत्रालय, भारत सरकार

Indian Council of Medical Research
Department of Health Research, Ministry of Health
and Family Welfare, Government of India

Date: 09/07/2021

Call for Expression of Intent to participate as a study site for India-UK RECOVERY

ICMR, Delhi along with University of Oxford is proposing to conduct a multi-centre, adaptive platform trial in COVID-19 patients, titled 'India-UK RECOVERY (**R**andomised **E**valuation of **COV**id-19 th**ER**ap**Y**).

An expression of intent is sought from institutions/hospitals with the facilities and capacity available to participate in the above-mentioned clinical trial, which will enroll participants admitted in their hospitals. The intervention arm of the trial will include baricitinib. The control arm will receive local standard of care.

The trial will be initiated only after obtaining requisite regulatory and ethics approvals. A brief synopsis of the study plan is attached herewith. Institutions which are interested to collaborate with ICMR on undertaking this trial, may express their interest by providing the details through the following link: https://forms.gle/afgz8Su3W2MYYsjd6

The call will close on **20th July, 2021**

For further details please contact:
Dr. Aparna Mukherjee
Scientist E
Clinical Studies, Trial & Projection Unit
Epidemiology and Communicable Diseases,
ICMR, New Delhi
recovery.icmr.secretariat@gmail.com

PROTOCOL SYNOPSIS

RANDOMISED EVALUATION OF COVID-19 THERAPY (RECOVERY) India-UK RECOVERY trial

Background: In early 2020, as this protocol was being developed, there were no approved treatments for COVID-19, a disease induced by the novel coronavirus SARS-CoV-2 that emerged in China in late 2019. The UK New and Emerging Respiratory Virus Threats Advisory Group (NERVTAG) advised that several possible treatments should be evaluated, including Lopinavir-Ritonavir, low-dose corticosteroids, and Hydroxychloroquine (which has now been done). A World Health Organization (WHO) expert group issued broadly similar advice. These groups also advised that other treatments will soon emerge that require evaluation. Currently, in discussion with the RECOVERY team, it has been decided that India will participate in evaluating the role of baricitinib in COVID-19.

Eligibility and randomisation: This protocol describes a randomised trial among patients hospitalised for COVID-19. All eligible patients are randomly allocated between several treatment arms, each to be given in addition to the usual standard of care in the participating hospital. To begin with, at the Indian sites, all participants aged 18 years or older will be allocated (1:1) to baricitinib vs. no additional treatment.

Adaptive design: The interim trial results will be monitored by an independent Data Monitoring Committee (DMC). The most important task for the DMC will be to assess whether the randomised comparisons in the study have provided evidence on mortality that is strong enough (with a range of uncertainty around the results that is narrow enough) to affect national and global treatment strategies. In such a circumstance, the DMC will inform the Trial Steering Committee who will make the results available to the public and amend the trial arms accordingly. Regardless, follow-up will continue for all randomised participants, including those previously assigned to trial arms that are modified or ceased. New trial arms can be added as evidence emerges that other candidate therapeutics should be evaluated.

Outcomes: The main outcomes will be death, discharge, need for ventilation and need for renal replacement therapy. For the main analyses, follow-up will be censored at 28 days after randomisation. Additional information on longer term outcomes may be collected through review of medical records or linkage to medical databases where available.

Simplicity of procedures: To facilitate collaboration, even in hospitals that suddenly become overloaded, patient enrolment and all other trial procedures are greatly streamlined. Informed consent is simple and data entry is minimal. Randomisation via the internet is simple and quick, at the end of which the allocated treatment is displayed on the screen and can be printed or downloaded. Key follow-up information is recorded at a single time point and may be ascertained by contacting participants in person, by phone or electronically, or by review of medical records and databases.

Data to be recorded: At randomisation, information will be collected on the identity of the randomising clinician and of the patient, age, sex, major co-morbidity, pregnancy, COVID19 onset date and severity, and any contraindications to the study treatments. The main outcomes will be death (with date and probable cause), discharge (with date), need for ventilation (with number of days recorded) and need for renal replacement therapy. Reminders will be sent if outcome data have not been recorded by 28 days after randomisation. Suspected Unexpected Serious Adverse Reactions (SUSARs) to one of the study medications (e.g., Stevens-Johnson syndrome, anaphylaxis, aplastic anaemia) will be collected and reported in an expedited fashion. Other adverse events will not be recorded but may be available through linkage to medical databases.

Numbers to be randomised: The larger the number randomised the more accurate the results will be, but the numbers that can be randomised will depend critically on how large the epidemic becomes. If substantial numbers are hospitalised in the participating centres, then it may be possible to randomise several thousand with mild disease and a few thousand with severe disease, but realistic, appropriate sample sizes could not be estimated at the start of the trial. It is estimated that about 2000 patients will need to be randomised from India.

DESIGN AND PROCEDURES

Inclusion Criteria:

I. Hospitalised
II. SARS-CoV-2 infection associated disease (clinically suspected or laboratory confirmed)
In general, SARS-CoV-2 disease should be suspected when a patient presents with:
    a) Typical symptoms (e.g. influenza-like illness with fever and muscle pain, or respiratory illness with cough and shortness of breath); and
    b) Compatible chest X-ray findings (consolidation or ground-glass shadowing); and
    c) alternative causes have been considered unlikely or excluded (e.g. heart failure, influenza). However, the diagnosis remains a clinical one based on the opinion of the managing doctor

III. No medical history that might, in the opinion of the attending clinician, put the patient at significant risk if he/she were to participate in the trial

Exclusion Criteria:

I. Pregnant or breastfeeding women.
II. eGFR <15 mL/min/1.73m2 (including participants on dialysis/haemofiltration)
III. Neutrophil count <0.5 x 109/L
IV. Evidence of active TB infection

Baricitinib will only be included in the randomisation of women of child-bearing potential if they have had a negative pregnancy test since admission. A woman of childbearing potential is defined as a post-menarchal, pre-menopausal female capable of becoming pregnant. This includes women on oral, injectable, or mechanical contraception; women who are single; women whose male partners have been vasectomized or whose male partners have received or are utilizing mechanical contraceptive devices

Consent

Informed consent should be obtained from each patient before enrolment into the study. However, if the patient lacks capacity to give consent due to the severity of their medical condition (e.g. acute respiratory failure or need for immediate ventilation) or prior disease, then consent may be obtained from a relative acting as the patient's legally designated representative or – if a suitable relative is not available after reasonable efforts to locate one – an independent doctor. Further consent will then be sought with the patient if they recover sufficiently. Witnessed consent may be obtained over the telephone or web video link if hospital visiting rules or parental infection mean a parent/guardian cannot be physically present.

Baseline information The following information will be recorded on the web-based form by the attending clinician or delegate:

- Patient details (e.g. name or initials, date of birth, sex)
- Clinician details (e.g. name)
- COVID-19 symptom onset date
- COVID-19 severity as assessed by need for supplemental oxygen, non-invasive ventilation or invasive mechanical ventilation/extracorporeal membrane oxygenation (ECMO)
- Oxygen saturations on air (if available), and S/F94 ratio (if participating in early phase assessment; see Section 2.7.1)
- Latest routine measurement of creatinine, C-reactive protein, and D-dimer (if available)
- SARS-CoV-2 PCR test result (if available)
- Major co-morbidity (e.g. heart disease, diabetes, chronic lung disease) and pregnancy (including pregnancy test result in all women of child-bearing potential[e])
- Use of relevant medications (corticosteroids, remdesivir, antiplatelet and anticoagulant therapy)
- Date of hospitalisation
- Contraindication to the study treatment regimens (in the opinion of the attending clinician)
- Name of person completing the form

The person completing the form will then be asked to confirm that they wish to randomise the patient and will then be required to enter their name and e-mail address.

Main randomisation

In addition to receiving usual care, eligible patients will be allocated using a central web based randomisation service (without stratification or minimisation). The eligible patients may be randomised to one of the following treatment arms:

- No additional treatment
- Baricitinib, **4 mg once daily** by mouth or nasogastric tube for 10 days in total. (Treatment will be discontinued in case the patient is discharged earlier)

Cautions:

- Dose should be reduced in presence of renal impairment
  - eGFR ≥30 <60 mL/min/1.73m2: 2 mg once daily
  - eGFR ≥15 <30 mL/min/1.73m2: 2 mg on alternate days
- Dose should be halved in patients also taking probenecid
- Baricitinib and tocilizumab may be co-administered, but the managing clinician should consider the risk of infection and gastrointestinal perforation (which may present atypically due to suppressed C-reactive protein production and concomitant corticosteroids)