Clinical Trial Details (PDF Generation Date :- Thu, 22 Oct 2020 19:51:09 GMT)

CTRI Number	CTRI/2020/06/026196 [Registered on: 28/06/2020] - **Trial Registered Prospectively**
Last Modified On	17/08/2020
Post Graduate Thesis	No
Type of Trial	Interventional
Type of Study	Drug Surgical/Anesthesia Preventive
Study Design	Randomized, Parallel Group, Multiple Arm Trial
Public Title of Study	Prevention of Respiratory Complications In At Surgery in COVID-19 Pandemic
Scientific Title of Study	Preventing Pulmonary Complications In Surgical Patients At Risk Of COVID-19

Secondary IDs if Any

Secondary ID	Identifier
2020-001448-24	EudraCT

Details of Principal Investigator or overall Trial Coordinator (multi-center study)

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Source of Monetary or Material Support

Source of Monetary or Material Support
> Christian Medical College Ludhiana
> University Of Birmingham, UK

Primary Sponsor

Primary Sponsor Details	
Name	University Of Birmingham
Address	Research Governance Team University of Birmingham Birmingham, B152TT
Type of Sponsor	Research institution

Details of Secondary Sponsor

Name	Address
NIL	NIL

Countries of Recruitment

List of Countries
Benin
Ghana
India
Italy
Mexico
Nigeria
Rwanda
South Africa
United Kingdom

Sites of Study

Name of Principal Investigator	Name of Site	Site Address	Phone/Fax/Email
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Details of Ethics Committee

Name of Committee	Approval Status	Date of Approval	Is Independent Ethics Committee?
All India Institute Of Medical Sciences Bhubhaneshwar	Approved	14/08/2020	No
All India Institute Of Medical Sciences Jodhpur	Approved	29/07/2020	No

Christian Medical College Ludhiana	Approved	24/06/2020	No
Datta Meghe Institute Of Medical Sciences Wardha	Approved	12/06/2020	No

Regulatory Clearance Status from DCGI

Status	Date
Not Applicable	No Date Specified

Health Condition / Problems Studied

Health Type	Condition
Patients	Coronavirus as the cause of diseases classified elsewhere
Patients	Medical and Surgical

Intervention / Comparator Agent

Type	Name	Details
Intervention	Lopinavir-Ritonavir	Lopinavir is a HIV-1 (Human Immunodeficiency Virus 1) protease inhibitor, normally used as part of combined drug therapy for HIV. Ritonavir is added to Lopinavir to enhance efficacy by increasing serum availability [3]. In-vitro experiments show viral susceptibility to the drug. A published series of patients treated with this Lopinavir-Ritonavir showed improved outcomes at 21 days after diagnosis, compared to historical controls. Lopinavir-Ritonavir has previously been shown to improve outcomes in animal models (marmosets) infected with MERS-CoV. A trial including 194 patients with advanced COVID-19 infection showed a small difference in time to clinical improvement, suggesting the need for further trials evaluating this drug. Though early studies have not shown any difference in post treatment viral load, some centres are using this drug combination off-label to treat COVID-19 patients. No work has yet looked at the impact of these drugs on pre-infection or pre-symptomatic treatment (or in vulnerable patients). Robust evidence is needed to prove or exclude the benefit of Lopinavir-Ritonavir use to prevent pulmonary complications in patients undergoing surgery.
Intervention	Hydroxychloroquine	Hydroxychloroquine is usually used as an antimalarial drug and in auto-immune diseases

		such as Lupus and Rheumatoid Arthritis. Promising laboratory studies have shown that chloroquine decreases COVID-19 entrance and replication within cells, together with its known anti-inflammatory effect. From small early phase clinical trials in China that included more than 100 patients being treated for COVID-19 pneumonia, chloroquine was associated with a shorter course of disease and less pneumonia exacerbation. A subsequent small non-randomised study from France showed reduction of viral load with hydroxychloroquine. It has been used widely for many years without any major safety concerns. The Summary of Product Characteristics (SPC) lists all the reported adverse effects (section 4.8) but does not identify any commonly occurring adverse events which are specifically problems for surgical patients.
Intervention	Hydroxychloroquine plus Lopinavir-Ritonavir	Lopinavir 400mg-Ritonavir 100mg by mouth every 12 hours for 10 days or until discharge, whichever occurs first AND Hydroxychloroquine 400mg BD day 1; then 400mg daily day 2-5 or until discharge, whichever occurs first. There are no dual toxicity effects. Patients should undergo perioperative care according to each hospital's normal practice, the main factors of which will be recorded. Potential interactions will be checked on a case by case basis. Discontinuation rates will be monitored.
Comparator Agent	Control (normal practice; neither trial drug)	Treatment without the trial drugs. Patients will be treated as per hospital routine practice without receiving any of the drugs given in the intervention arms. The control arm may change over the course of the trial and will be monitored by the TMG and DMC.

Inclusion Criteria

Inclusion Criteria	
Age From	16.00 Year(s)
Age To	80.00 Year(s)
Gender	Both

Details	1. Patients aged 16 years and over. 2. Planned to undergo any type of elective or emergency inpatient surgery requiring general or regional anaesthesia (such as vulnerable patients undergoing surgery for a fractured neck of femur). 3. Asymptomatic of COVID-19, including patients with: those not tested, negative test results, positive test but no symptoms 4. Informed patient consent.

Exclusion Criteria

Exclusion Criteria	
Details	1. Procedures under local anaesthesia. 2. Symptomatic COVID-19 infection (by confirmed COVID-19 test or a clinical diagnosis) 3. Existing regular preoperative treatment with trial drugs. 4. Known history of adverse reaction/contraindication to trial drugs. 5.Pregnancy (including caesarean section). • Actively breastfeeding.

Method of Generating Random Sequence	Computer generated randomization
Method of Concealment	Centralized
Blinding/Masking	Open Label

Primary Outcome

Outcome	Timepoints
One of the following COVID-19 specific, inpatient, postoperative pulmonary complications: Pneumonia, Acute respiratory distress syndrome, Death	All randomised participants will be followed up until death, discharge from hospital, or 30 days post-randomisation (whichever is sooner). Longer-term follow-up (e.g. 5 years) will be sought as appropriate to each participating country's settings.

Secondary Outcome

Outcome	Timepoints
Pneumonia, ARDS, and death will be presented and analysed separately as secondary outcomes. Unexpected ventilation Postoperative diagnosis of proven COVID-19 pulmonary complications Overall SARS-CoV-2 infected rate Duration of hospital stay (including time spent in intensive care, time ventilated) Pulmonary function in keeping with the WHO Solidarity Trial outcome scale	Secondary outcome measures will be recorded on the index hospital admission up to 30 days following surgery

Target Sample Size	**Total Sample Size=**6400 **Sample Size from India=**1100 **Final Enrollment numbers achieved (Total)=**Applicable only for Completed/Terminated trials **Final Enrollment numbers achieved (India)=**Applicable only for Completed/Terminated trials
Phase of Trial	Phase 3/ Phase 4
Date of First Enrollment (India)	15/08/2020
Date of First Enrollment (Global)	15/08/2020
Estimated Duration of Trial	**Years=**1 **Months=**6 **Days=**0
Recruitment Status of Trial (Global)	Not Yet Recruiting

Recruitment Status of Trial (India)	Not Yet Recruiting
Publication Details	No Publications yet
Brief Summary	***Background:*** Surgical patients represent a highly vulnerable patient group, who are at particular risk of COVID-19 exposure and complications whilst in hospital for essential surgical treatment. They are vulnerable because of their underlying comorbidity and also because they will be subjected to artificial ventilation at the time of surgery. There are currently no interventional trials looking to prevent or mitigate the pulmonary complications associated with concurrent COVID-19 infection acquired either just before surgery or during the postoperative stay in hospital. ***Primary objectives:*** To provide reliable estimates of the effect of study treatments on postoperative pulmonary complications during the COVID-19 pandemic. ***Secondary objectives:*** To assess the effects of study treatments on: • Post-operative proven COVID-19 pulmonary complications • Overall SARS-CoV-2 infected rate • Duration of intensive care and total hospital stay • Pulmonary function in keeping with WHO Solidarity Trial outcome scale (detailed in Appendix 2) • Safety and tolerability of study treatments ***Design:*** Adaptive platform design, multi-centre, open-label, randomised controlled trial. The interim trial results will be monitored by an independent Data Monitoring Committee (DMC), who will periodically assess whether the randomised comparisons in the study have provided evidence on postoperative pulmonary complications that is strong enough to influence global treatment guidelines. Trial arms will be amended on recommendation from the DMC and new arms can be added if a new drug or vaccine is released during the study that requires evaluation. ***Centre eligibility:*** Any hospital performing elective or emergency adult surgery that has recorded at least one case of COVID-19. ***Participants*** **Inclusion:** Adults aged 16 years and over listed to undergo any type of inpatient surgery requiring general or regional anaesthesia (such as vulnerable patients undergoing surgery for a fractured neck of femur). who are asymptomatic of COVID-19 infection (including patients with: those not tested, negative test results, positive test but no symptoms) and are able to give informed consent. **Exclusion:** Procedures under local anaesthesia; patients who have symptoms of COVID-19 infection (by confirmed COVID-19 test or a clinical diagnosis); existing regular preoperative treatment with trial drugs; known history of adverse reaction

or contraindication to trial drugs; pregnant patients (including caesarean section).

Interventions and randomisation: The trial drugs are Lopinavir-Ritonavir and Hydroxychloroquine. Patients will be randomised 1:1:1:1 to (A) Control (normal practice; neither trial drug), (B) Lopinavir-Ritonavir only, (C) Hydroxychloroquine only, (D) both Lopinavir-Ritonavir and Hydroxychloroquine.

Primary Outcome*:* Any one of the following COVID-19 specific, inpatient, postoperative pulmonary complications: pneumonia; acute respiratory distress syndrome (ARDS); or death.

Secondary Outcomes:

- Unexpected ventilation (unexpected inability to extubate and wean patient from ventilation after general anaesthesia, or reintubation and ventilation by 30 days after surgery)
- Postoperative diagnosis of proven COVID-19 pulmonary complications
- Overall SARS-CoV-2 infected rate (symptomatic and/or asymptomatic)
- Duration of hospital stay (including time spent in intensive care, time ventilated)
- Pulmonary function in keeping with the WHO Solidarity Trial outcome scale

***Sample size*:**

The trial uses a Bayesian adaptive platform design, allowing for termination of arms if their superiority to standard care is established, and addition of new treatment arms. The detailed statistical design of the trial will be described in a Statistical Analysis Plan.

The adaptive platform design does not have a fixed sample size. We will set a maximum sample size for each arm of 1600; which is similar to the number needed for a traditional frequentist 2-arm

comparison to achieve p<0.05 with 90% power, with event rates of 16% in the control group and 12% in the intervention arm. Interim analyses will be conducted every 200 patients, starting when 250 patients per arm have reached the end of follow-up. All analyses will use Bayesian methods, with weakly informative priors, which will allocate very low probability to unrealistic treatment effects. New treatment arms will be added as more interventions are proposed and they will be compared only with controls recruited contemporaneously. Data from earlier control patients will be used in a more informative prior for the control group in these comparisons.