RECOVERY TRIAL PROTOCOL:

Region-Specific Appendix for Nepal

Summary

This region-specific appendix provides further details of RECOVERY trial procedures in Nepal, and should be read together with the core RECOVERY protocol. This appendix includes information relating to region-specific eligibility criteria, trial procedures, governance, and safety information.

The Oxford University Clinical Research Unit Nepal (OUCRU Nepal) is the Regional Coordinating Centre for RECOVERY in Nepal. OUCRU Nepal can be contacted with questions about the protocol or trial procedures.

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ABBREVIATIONS

CAP	Community-acquired pneumonia
CCO	Central Coordinating Office
CoI	Conflict of Interest
COVID-19	Corona Virus Disease 2019, the disease caused by SARS-CoV-2
CT	Computed Tomography
DDA	Department of Drug Administration
eCRF	Electronic Case Report Form
GCP	Good Clinical Practice
ICH	International Council for Harmonisation
LAR	Legally Acceptable Representative
OxTREC	Oxford Tropical Research Ethics Committee
PCR	Polymerase Chain Reaction
PI	Principal Investigator
PJP	Pneumocystis jirovecii pneumonia
QA	Quality Assurance
RCC	Regional Coordinating Centre
RSA	Region-Specific Appendix
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SmPC	Summary of Product Characteristics
STIDH	Sukraraj Tropical and Infectious Disease Hospital
TB	Tuberculosis

1. VERSION HISTORY

The version of this Nepal Region-Specific Appendix (RSA) is given in the footer and in the table below. The current versions of Nepal RSA and core protocol should always be used, and can be confirmed by checking the study website (www.recoverytrial.net). This Nepal RSA will not necessarily be updated with core protocol amendments if they have no impact on this document (so the current Nepal RSA can be used with subsequent core protocol versions).

Nepal RSA Version	Date	Brief Description of Changes
1.0	18-Jan-2024	Initial version. Aligned with core protocol V27.0 (13-Sep-2023)

2. NEPAL CONTEXT

The core protocol describes a multinational randomised trial among patients hospitalised for pneumonia, including influenza, and community-acquired pneumonia related to other pathogens. The trial is being conducted in Nepal as well as in other countries around the world, although no COVID-19 treatment are currently being evaluated in Nepal. In Nepal we will be randomizing patients admitted with in influenza and community-acquired pneumonia and the details of the comparison arms are provided in Table 1.

Table 1: Treatments under evaluation in RECOVERY in Nepal

Condition	**Randomised comparisons, each vs. usual care alone**	**Eligibility criteria specific to comparison**
Influenza	Baloxavir	
	Oseltamivir	
	Low-dose Corticosteroids	hypoxia; without suspected or confirmed SARS-CoV-2 infection
Community-acquired pneumonia	Low-dose corticosteroids	without suspected or confirmed SARS-CoV-2, influenza, TB[a] or PJP[b]
[a] active pulmonary tuberculosis; [b] Pneumocystis jirovecii pneumonia		

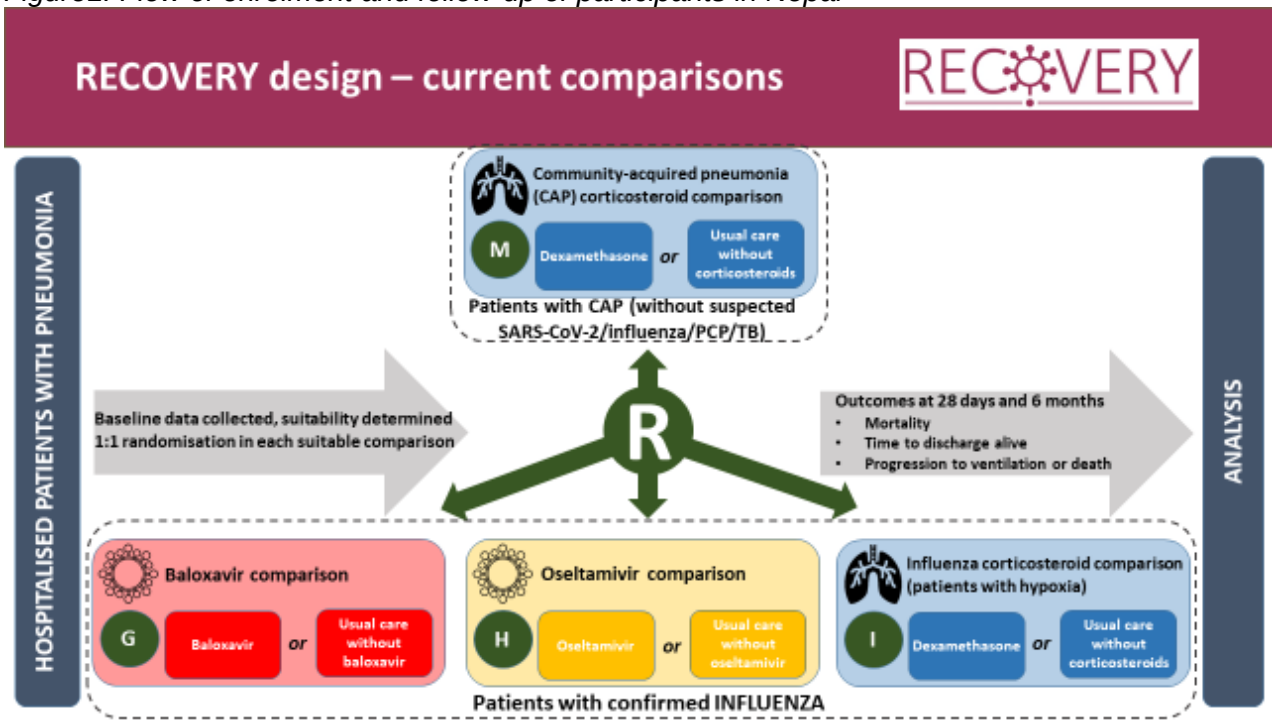
2.1 RECOVERY trial design in Nepal

Adult patients, 18 year and above, hospitalized with, pneumonia and influenza in selected hospitals who meet inclusion criteria will be randomised in the study.

The prospective study sites for Nepal are as follows:

- Sukraraj Tropical and Infectious Disease Hospital (STIDH), Teku, Kathmandu
- Nepal APF Hospital, Balambu, Kathmandu
- National Academy of Medical Sciences, Bir Hospital, Mahaboudha, Kathmandu

Figure1: Flow of enrolment and follow-up of participants in Nepal



2.2 Governance in Nepal

The trial will be conducted in compliance with the approved protocol, the Declaration of Helsinki and the principles of Good Clinical Practice (GCP). The protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to OxTREC, local ethics committees and respective IRC of the designated hospitals for written approval. Approval of study drugs will also be obtained from the Department of Drug administration (DDA)

All efforts will be made to conduct the research in a way that is sensitive to the Nepali culture and the social values. The participant study related materials (information sheet, consent forms, etc) will be printed in Nepali.

RECOVERY is registered with clinicaltrials.gov, study number NCT04381936.

3. NEPAL CORE PROTOCOL CLARIFICATIONS

Nepal-specific clarifications to the core protocol are listed below, with reference to the sections affected.

3.1 Core protocol Section 2: Design and Procedures

The schedule of assessments for participants in Nepal is shown below.

Table 2: RECOVERY Schedule of assessments

Procedure	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D28	D180
Eligibility assessment	X											
Consent	X											
Baseline data collection & randomisation	X											
Concomitant medication assessment[a]	X										X[c]	

Procedure	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D28	D180
Study treatment (oseltamivir)	X	X	X	X	X							
Study treatment (Baloxavir)	X			X								
Study treatment (corticosteroids)	X	X	X	X	X	X	X	X	X	X		
28-day follow-up (medical records +/- call to participant)											X[c]	
6-month follow-up (medical records +/- call to participant)												X
Adverse event monitoring[b]	X	X	X	X	X	X	X	X	X	X		

[a] use of medication will be subject to standard medication reviews (typically within 48 hours of enrolment) which will guide modifications to both the study treatment and use of concomitant medication (e.g. in the case of potential drug interactions)
[b] Participants are monitored for serious adverse reactions to study treatment by their clinical team
c Follow-up data will be collected on discharge if patients leave hospital before day 28 (in this case patients or their next of kin will be contacted to determine vital status on day 28).

3.2 Core protocol Section 2.1: Eligibility

Patients aged < 18 and patients with COVID-19 are not included in Nepal.

Inclusion Criteria

Patients are eligible for the study in Nepal if all of the following are true:

i) Hospitalised

ii) Pneumonia syndrome (clinically suspected or laboratory confirmed)

In general, pneumonia should be suspected when a patient presents with:

a) typical symptoms of a new respiratory infection (e.g. influenza-like illness with fever and muscle pain, or respiratory illness with cough and shortness of breath); and
b) objective evidence of acute lung disease (e.g. consolidation or ground-glass shadowing on X-ray or CT, hypoxia, or compatible clinical examination); and
c) alternative causes have been considered unlikely or excluded (e.g. heart failure).

However, the diagnosis remains a clinical one based on the opinion of the managing doctor (the above criteria are just a guide).

iii) One of the following diagnoses:

a) Confirmed influenza A or B infection (including patients with SARS-CoV-2 co-infection and/or hospital-acquired infection)
b) Community-acquired pneumonia with planned antibiotic treatment (excluding patients with suspected or confirmed SARS-CoV-2, influenza, active pulmonary tuberculosis or *Pneumocystis jirovecii* pneumonia)

iv) 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

v) Age ≥ 18 years old

Exclusion Criteria

i) Patients who have been previously recruited into RECOVERY less than 6 months ago*
ii) Known contra-indication to any of the active drug treatment arms

iii) If the patient should definitely be receiving one of the active drug treatment arms then that arm will not be available for randomisation for that patient
iv) Patients who lack capacity, an advanced directive or behaviour that clearly indicates that they would not wish to participate in the trial

*Note: Patients who have been previously recruited into RECOVERY are eligible to be recruited again as long as their previous randomisation was >6 months ago. Patients will not be recruited into the same randomised comparison on more than one occasion, regardless of how far apart they occur.

3.3 Core protocol Section 2.2: Consent

Clarification of consent process

Written Participant Information and Informed consent forms will be presented to the patients detailing no less than: the exact the nature of the study; what it will involve for the patient; the implications and constraints of the protocol; and the known side effects of the medicines under evaluation and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal.

Informed consent will be obtained from each patient 18 years and above before enrolment into the study. Patients who lack capacity to consent due to severe disease (e.g. needs ventilation) or a prior condition, consent will be taken from legally acceptable representative (LAR). If they regain capacity, such participants should be provided with information about the trial (ideally prior to discharge, but otherwise as soon as possible thereafter), what their rights are and how to exercise them, but it is not necessary to obtain their written consent.

For illiterate patients, the consent process should be witnessed by an impartial witness (who is not a relative of the participant, is not associated with the research and has no CoI). The witness should be able to understand the language of the prospective participant so that he/she can read as well as communicate the information to the participant or LAR effectively for them to make an informed decision.

The patient will be allowed as much time as required to consider the information as long as they remain eligible and within the time-frame for recruitment into the study, and the opportunity to question the Investigator or other independent parties to decide whether they will participate. The person who obtained the consent must be suitably qualified and experienced and have been authorised to do so by the site PI. A copy of the signed Informed Consent will be given to the patient. The original signed form will be retained at the study site.

A clinician, even if they are independent of the trial, cannot act as a legal representative in Nepal.

3.4 Core protocol Section 2.3.1: Baseline sample collection

Participants do not require baseline sample collection, although if the influenza diagnosis was based on a rapid antigen test alone then a nose or throat swab will be collected for influenza PCR at a clinical laboratory (if this testing is locally available). This swab will be collected after obtaining consent and prior to randomisation, and patients with a positive antigen test may proceed to randomisation before results of influenza PCR are available. Samples will not be retained after influenza PCR testing.

No Baseline samples are required for participants with community -acquired pneumonia in Nepal

3.5 Core protocol Section 2.4: Randomised allocation of treatment for COVID-19

These comparisons are not open in the Nepal.

3.6 Core protocol section 2.7: Administration of allocated treatment

As stated in the core protocol "The patient's own doctors are free to modify or stop study treatments if they feel it is in the best interests of the patient without the need for the patient to withdraw from the study", so trial treatment allocation should never override the best interests of the patient.

To clarify, if the attending doctor considers that continuing a trial treatment is no longer in the best interest of the participant for any reason after randomisation, for example because of a suspected adverse reaction, then the treatment should be stopped. Conversely, if the attending doctor considers that a trial treatment becomes indicated after randomisation, then this should be given regardless of randomised allocation. If the participant is allocated corticosteroids in RECOVERY and a different systemic corticosteroid regimen becomes indicated, this should replace the allocated treatment (with trial treatment reintroduced afterwards if needed to complete the planned duration of treatment). For example, if dexamethasone treatment were indicated in a pregnant woman for fetal lung maturation, this should replace prednisolone or hydrocortisone given as part of RECOVERY.

3.7 Core protocol Section 2.8: Collecting follow-up information

Consent will be obtained to access the participant's medical records held by the admitting hospital.

3.8 Core protocol Section 2.8.1: Follow-up swab samples

No follow-up samples will be collected in Nepal.

3.9 Core protocol Section 3.1.3: Safety and other outcomes for evaluation of all treatments

Virological outcomes which include viral RNA levels in the nasopharynx and the frequency of detection of resistance markers will not be assessed in Nepal.

3.10 Core protocol Section 4.2: Central assessment and onward reporting of Suspected Severe Adverse Reactions

The recording and reporting process will be same in Nepal as mentioned in the core protocol section 4.1 and 4.2. In addition, all confirmed SUSARs will also be reported to the local ethics within 48 hours of site awareness.

3.11 Core protocol Section 5.2: Training and monitoring

Standardised procedures will be in place to train staff before site initiation, which may include face-to-face meetings, online meetings, and online self-study materials. A site initiation visit will usually be conducted before site activation by the Nepal RCC (here RCC refers to OUCRU Nepal). As described in the core protocol, the study will use a risk-based monitoring approach. The Quality assurance (QA) team from OUCRU Nepal will monitor the study according to a detailed monitoring plan. A monitoring report will be prepared following each site visit, followed by debriefing sessions to the study site team.

Medical records, any other relevant source documents and the site investigator file must be made available to the QA team for these visits during the course of the study and at the completion of the study as needed.

3.12 Core protocol Section 5.3: Data Management

Data collected for the RECOVERY study will be entered into secure, password protected web-based eCRFs designed by programmers at the CCO (here CCO refers to University of Oxford), and will be stored on servers located in the United Kingdom. Each subject is allocated a unique trial number.

The RECOVERY Data Management Plan contains details of data management, privacy and protection within the RECOVERY study, and was produced in accordance with University of Oxford and Nuffield Department of Population Health data management policies.

3.13 Core protocol Section 6.6: End of trial

RECOVERY is planned as a perpetual platform trial for patients admitted to hospital with pneumonia, and promising new treatments may be added to the trial in future. There is no planned end date, but the trial may be terminated at the discretion of the sponsor, for example because of inadequate funding or recruitment.