RECOVERY Clinical Trial Pharmacy Briefing Document

(Based on Protocol V10.1 04-Nov-2020)

1 Introduction

The following medicines are listed as IMPs for this study. The supply arrangements for each arm is different (see table 1 below).

This clinical trial is being run to make it as easy as possible, while ensuring that the outcome data from the patients is collected to inform future care of patients with Covid-19.

Table 1: Medicines for Recovery Clinical Trial

Medicine	Formulation	Source	Accountability logs	Prescribed	IMP Annex 13 labelling
Randomisation Part A					
Standard of Care	Any	Licensed products – Standard Pharmaceutical Wholesalers	No	Yes	No
Azithromycin	Oral tablet/capsule/ oral liquid/ intravenous**	DHSC via Immform	No	Yes	No
Randomisation Part B					
Convalescent Plasma	Intravenous	UK Blood Service	No	Yes	No
REGN10933&REGN10987 (synthetic neutralising antibodies)	Intravenous	Regeneron	Yes	Yes	Yes
Randomisation Part C					
Aspirin	Oral tablet/dispersible tablet/suppositories	NHS stock. Licensed products – Standard Pharmaceutical Wholesalers	No	Yes	No
Second randomisation					
Tocilizumab	Intravenous	DHSC via Immform	No	Yes	No

** Capsules and intravenous preparations may not be available at the start of the trial

Standard of care for this study is best supportive care. There should be provisions put in place by local sites to prevent doctors prescribing tocilizimab to patients whom have not consented to the RECOVERY study for the treatment of Covid-19.

The MHRA is aware and have approved the study to allow any doctor working within the hospital to prescribe for this study (this can include FY1 doctors under supervision as per local practice), without having GCP training or being on a delegation log. Similarly GCP trained research staff to take consent of the patient for this trial is not required. However, it is expected that all staff will complete online Recovery study training.

Further information regarding paediatric dosing and administration can be found on a separate document (RECOVERY Paediatric Guidance Document)

2 Azithromycin

2.1 Initial supply and re-ordering

Azithromycin (MHRA approved stock specifically for this study) is to be procured by local pharmacy procurement team from PHE. However, until such stocks are available, NHS England and equivalent bodies in Wales and Scotland have approved the use of NHS stocks for the RECOVERY trial.

PHE have ring fenced stock for this clinical trial. Initially PHE have oral liquid and tablets in stock: azithromycin 200mg/5mL powder for oral suspension (pack size 30mL bottle) and azithromycin 500mg tablets (pack size 3). The liquid is only to be used in paediatrics due to the limited supply.

There are discussions being held currently with suppliers around procuring the capsules and intravenous preparations.

Pharmacy purchasing teams are to order the medicine using ImmForm via Movianto, which teams should be familiar with as they should be using this system to order other study treatments. If they do not already have an existing account, then email helpdesk@immform.org.uk to set up an account.

PHE have stated that they can order Monday to Friday with deliveries for the next working day as long as orders are placed before 11:55. Orders placed before cut-off on a Friday will be delivered on a Monday; any orders after cut-off will be delivered on a Tuesday.

DHSC are determining the amount of stock that will be sent to each site, but it is likely to be sufficient for 100 patients for 10 day course each. See under heading below ‘Dispensing’.

2.2 Storage

As per SmPC

All sites will need to ensure storage separation between stock for this study and general stock for patients, as well as having some way of identifying the difference between stock when dispensing and checking. This could be done via a number of ways such as adding an additional label on

receipting of stock stating to be used in the 'RECOVERY trial only' and storing in different areas of pharmacy.

No temperature excursion reporting required.

2.3 Dispensing quantities

Azithromycin dosage is 500mg once daily for 10 days; patients should be dispensed 10 x 500mg tablets or 20 x 250mg capsules. This is assuming no dose modifications.

There is a need to either dispense the required number of tablets for a patient or allocate to a 'ward/area' stock holding for Covid-19 patients that can be used for more than one patient. If dispensing for individual patients the clinical trial specified quantities must be dispensed for each patient to ensure that supplies last as long as possible.

2.4 Returns and Destructions

During the study if any patient returns or if any azithromycin expires or there is still stock at end of study, this can be destroyed on site. No approval from Sponsor is required.

2.5 FAQs

Q. My patient has been allocated to another arm, but as part of our standard of care we would prescribe them azithromycin. Can they be on both?

A. If after randomisation a doctor wishes to prescribe a macrolide for a participant on hydroxychloroquine this is allowed, but the doctor should consider the potential interaction between these two drugs and the QT interval. For patients in other arms, macrolides can also be used.

Q. My patient is already on azithromycin can they still be entered into the study?

A. Yes, they can still be enrolled. You will be asked to indicate if they are on a macrolide antibiotic already and if they are then they will not be allocated azithromycin (or hydroxychloroquine).

Q. As the liquid formulation is not available from PHE for use in adults, can we crush the tablets or open the capsules for NG administration?

A. We currently do not have data to support the crushing of tablets or the opening of capsules of NG administration. There is anecdotal evidence of tablets being crushed and dispersed in water. The decision to crush and disperse tablets would have to be made by each individual site and we would advise close monitoring of the patient for potential increased adverse effects.

3 Convalescent plasma

3.1 Initial Supply and re-ordering

Convalescent plasma to be ordered via NHSBT.

Not all sites will be opened to this arm due to limited supplies of convalescent plasma. Sites that will be taking part initially will be contacted by the RECOVERY team.

The convalescent plasma is to be handled and administered in the same way as frozen plasma.

4 REGN10933 & REGN10987 (Synthetic neutralising antibodies)

4.1 General

See Pharmacy manual for REGN10933 and REGN10987 on the RECOVERY website for further information regarding supply, storage, drug preparation and administration.

As REGN10933 and REGN10987 are novel drugs, these need to be treated in pharmacy as per any type C clinical trial. Therefore, full accountability, temperature monitoring and Annex 13 compliant labelling will be required.

Not all sites will be opened to this arm. Sites that will be taking part initially will be contacted by the RECOVERY team.

4.2 FAQs

Q. Is there any expectation from the sponsor for any additional temperature monitoring whilst transporting either the REGN10933 & REGN10987 vials from one site to another, or when transporting the final infusion bag from the aseptic unit to the ward?

A. Sponsor's permission is not required for the transport of REGN10933 and REGN10987 vials from one site to another, but temperature monitoring is required for such transfers. Temperature monitoring is not required when transporting the final infusion bag from the aseptic unit to the ward (unless the ward is on a separate site in which case temperature monitoring is recommended, except where a validated shipper is used). The transport and temperature monitoring of stock or final prepared product should be carried out as per site's local SOPs.

Q. Can the REGN10933 & REGN10987 infusion be made on the ward by nurses?

A. This would have to be an individual site decision based on the outcome of a documented risk assessment; retained within trial file. Please see Oxford University Hospitals NHS Foundation Trust (OUH) local risk assessment in the Pharmacy Manual. The NPSA risk score is 6 (red) and the health and safety risk is moderate; .therefore, OUH have assessed that locally the infusion will be prepared within the aseptic unit. Please read Pharmacy Manual for further information.

Sites will also need to consider that wherever the drug is being prepared or infused, that staff have access to a monoclonal antibody spillage kit or similar eg cytotoxic one.

Q. Do patients need to be treated with any pre-medications prior to receiving the REGN10933 & REGN10987 infusion?

A. No, we are not recommending any pre-medication prior to infusion.

Q. What are the major drug-drug interactions for REGN10933 and REGN10987?

A. There are currently no known drug-drug interactions with REGN10933 and REGN10987. All reactions must be reported to the Central Coordinating Centre as detailed in the protocol.

Q. Does the mixing of 2 separate mAbs together in the same infusion bag count as manufacturing?

A. No, a senior pharmaceutical advisor at the MHRA has confirmed that the reconstitution of REGN-COV2 does not count as manufacturing. Therefore, this reconstitution process can be done within an unlicensed aseptic unit. Please read Pharmacy Manual for further information.

5 Aspirin

5.1 Initial supply and re-ordering

Aspirin will be sourced by local pharmacy procurement team via their normal routes. For the purpose of this study aspirin tablets, enteric coated/gastro-resistant tablets, dispersible tablets or suppositories can be used.

5.2 Storage

As per SmPC

No temperature excursion reporting required.

5.3 Dispensing quantities

Aspirin dosage is 150mg once daily for the duration of the hospital admission.

5.4 Returns and Destructions

During the study if any patient returns or if any aspirin expires or there is still stock at end of study, this can be returned to stock in the usual way or destroyed on site. No approval from Sponsor is required.

5.5 FAQs

Q. My patient is already on aspirin. Can they participate in this part?

A. No. Current use of aspirin (or other antiplatelets like clopidogrel, prasugrel, ticagrelor) will be recorded on the randomisation form and exclude the participant from this comparison.

Q. My patient is on warfarin or a DOAC. Can they participate in this part?

A. Yes. However, there is an increased risk of bleeding which should be taken into consideration.

Q. Should we modify their VTE prophylaxis if they are allocated aspirin?

A. No. Hospital VTE prophylaxis should continue as normal (see Protocol section 2.4.3).

Q. What about gastro-protection?

A. This can be used according to the discretion of the managing doctor.

6 Tocilizumab

6.1 Initial Supply and re-ordering

All trial stock is now distributed to sites so no further stock can be ordered through Movianto.

6.2 Storage

As per SmPC

All sites will need to ensure storage separation between stock for this study and general stock for patients, as well as having some way of identifying the difference between stock when dispensing and checking. This could be done via a number of ways such as adding an additional label on receipting of stock stating to be used in the 'RECOVERY trial only' and storing in different areas of pharmacy.

No temperature excursion reporting required.

6.3 Dose Preparation Guide

Tocilizumab doses should be prepared in an IV infusion bag containing sodium chloride 0.9%. Do not use infusion bags containing any other diluents.

Calculate the appropriate volume of tocilizumab solution for infusion to be added to the sodium chloride 0.9% infusion bag.

Prior to the addition of the tocilizumab to the IV bag, remove the equivalent volume of saline from the sodium chloride 0.9% IV bag.

The required volume of tocilizumab should be withdrawn from the vial(s) and added to the saline IV bag. To mix the solution, gently invert the infusion bag to avoid foaming. Inspect the bag for particulates and discard if present.

If not used immediately, the prepared tocilizumab infusion may be stored in the fridge (2 – 8°C) for up to 24 hours or as per local policy. (see Tocilizumab SmPC and Medusa for guidance).

6.4 Returns and Destructions

During the study if any tocilizumab expires or there is still stock at end of study, this can be destroyed on site. No approval from Sponsor is required.

6.5 FAQs

Q. My patient is already on tocilizumab; can they still be entered into the second randomisation?

A. No, they cannot be entered into the second randomisation. Patients on other biologics need careful consideration.

Q. Is there any expectation from the sponsor for any additional temperature monitoring whilst transporting either the tocilizumab vials from one site to another, or when transporting the final infusion bag from the aseptic unit to the ward?

A. No additional temperature monitoring required by sponsor. The transport of stock or final product to be done as per the site's local SOPs.

Q. Can we use our own existing stock of tocilizumab?

A. No. NHSE have advised that all UK licensed stock of tocilizumab already in wholesalers and hospitals should be protected for patients already receiving this treatment.

Q. For pregnant women do we use the pre-pregnancy weight to calculate the tocilizumab dose?

A. Yes, the tocilizumab dose should be calculated using the pre-pregnancy weight. For further information regarding pregnancy please see Recovery Intervention Sheet - tocilizumab (https://www.recoverytrial.net/files/recovery-intervention-sheet-tocilizumab-v1-0.pdf) and Recovery for Pregnant and Postpartum Women (https://www.recoverytrial.net/files/recovery-information-for-pregnant-patients-v2-0.pdf)

Q. Can the tocilizumab infusion be made on the ward by nurses?

A. This would have to be an individual site decision based on the outcome of a risk assessment. Please see Oxford University Hospitals NHS Foundation Trust (OUH) local risk assessment attached for reference. The NPSA risk score is 4 (amber) and the health and safety risk is low. Therefore, OUH have assessed that locally with appropriate risk mitigation strategies such as creating a worksheet for the nurses to follow and for nurses to wear the appropriate PPE, the infusion can be prepared on the ward. There is available a preparation worksheet that can be adapted for local use.

Q. Tocilizumab is a biological agent does the batch number need to be recorded in the patient's healthcare record?

A. Yes, if the sample worksheet is used it records this information and the document should then be stored in the notes. If you have an electronic healthcare record with medicines administration section with the ability to record the batch number; it should be recorded here as well.

Q. The SmPC for tocilizumab states that if patients were to weigh less than 30Kg then the infusion should be made up in a 50mL infusion bag. What should I do in this situation?

A. Yes, that is fine for the infusion to be made in a 50mL sodium chloride 0.9% infusion bag.

Q. What are the major drug-drug interactions for tocilizumab?

A. Tocilizumab can increase metabolism of warfarin, phenytoin and ciclosporin so these may need levels monitoring and dose adjustment. Further details are in the SmPC.

Q. Do patients need to be treated with any pre-medications prior to receiving the tocilizumab infusion?

A. No, we are not recommending any pre-medication prior to infusion.

7 General FAQs

Q. What happens if our site does not have one of the medications used in the study in stock?

A. The co-ordinating centre should be informed (e-mail to recoverytrial@ndph.ox.ac.uk). It is possible to indicate on the randomisation form if a treatment is unavailable (and this can be set at a site level), so participants would not be assigned it.

Q. How will the cost of IMPs be covered?

A. The low cost of aspirin could be covered by assigning to the government's COVID-19 cost centre as part of their overall treatment costs. Please liaise with your finance department to identify the mechanism set-up on how to claim for these extra COVID-19 costs. Azithromycin and tocilizumab are supplied via PHE, and will be free of charge. REGN10933&REGN10987 (synthetic neutralising antibodies) are supplied by Regeneron.

Q. Can patients treated according to local pathway/protocol guidance still be considered for the RECOVERY trial further down the line?

A. All patients should receive standard care according to their local protocol. Randomisation is in addition to that.

Q. Are you allowing co-enrolment into other clinical trials of COVID-19?

A. Yes, as long as the clinical trial does not directly conflict with RECOVERY. Please see the trial website for further information.

Q. To ensure consistency for all patients, can the sponsor provide some guidance on how urgent (hours) the trial patient needs to receive the first dose of treatment?

A. We have no specific guidance on this, but within 6 hours would be ideal.

Q. Is Sponsor happy for sites to 'pre-pack' tablets into patient courses?

A. Yes

Q. If patients are discharged earlier than 10 days are pharmacy expected to use the left over medication to maximise stock (if sites SOPs allow)?

A. Yes if local site SOPs allow

Q. Are sites able to add their own dispensing/additional labels to manage the study as they feel is most appropriate?

A. Yes

Q. Can non-medical prescribers be utilised to prescribe trial medications?

A. Yes if local SOPs allow

Q. If a patient has suspected COVID-19, but the test results come back negative are they expected to come off the study?

A. If COVID swabs come back negative, but the treating clinician feels that clinically the patient does have COVID-19 then the patient can continue on study. However, the patient should stop if it is thought that the symptoms are due to another cause.

Q. What do we do with the remaining stock of dexamethasone, hydroxychloroquine and lopinavir/ritonavir?

A. The remaining stock of dexamethasone and hydroxychloroquine can be moved into hospital's own stock, if appropriate. The remaining stock of lopinavir/ritonavir needs to be ring fenced and kept for now as there may be future UPH trials which may require it.