RECOVERY Clinical Trial Pharmacy Briefing Document

(Based on Protocol V6.0 14/05/2020)

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

Randomisation Part A

Medicine	Formulation	Source	Accountability logs	Prescribed	IMP Annex 13 labelling
Standard of Care	Any	Licensed products – Standard Pharmaceutical Wholesalers	No	Yes	No
Dexamethasone	Tablet/ soluble tablet/oral liquid or intravenous	Licensed products -Standard Pharmaceutical Wholesalers (DHSC via Immform in due course)	No	Yes	No
Prednisolone	Tablet	Licensed products -Standard Pharmaceutical Wholesalers	No	Yes	No
Hydrocortisone	Intravenous	Licensed products -Standard Pharmaceutical Wholesalers	No	Yes	No
Methylprednisolone Sodium Succinate	Intravenous	Licensed products – Standard Pharmaceutical Wholesalers	No	Yes	No
Lopinavir/ritonavir (MHRA approved stock)	Oral tablet / liquid*	DHSC via Immform	No	Yes	No
Hydroxychloroquine	Oral tablet	DHSC via Immform	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

Second Randomisation

Tocilizumab	Intravenous	DHSC via Immform	No	Yes	No

*Liquid may not be available at the start of the trial

** 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 lopinavir/ritonavir and hydroxychloroquine 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 Dexamethasone

2.1 Initial supply and re-ordering

Dexamethasone can be sourced by local pharmacy procurement team via their normal routes until the stock is available through PHE as below. For the purpose of this study dexamethasone tablets, soluble tablets or oral liquid can be used.

Dexamethasone (MHRA approved stock specifically for this study) will be available in the near future by local pharmacy procurement team from PHE. PHE have ring fenced stock for this clinical trial. Initially PHE only have tablets, oral solution and intravenous ampoules in stock: dexamethasone 2mg tablets (pack size 50 tablets), dexamethasone 2mg/5mL oral solution (pack size 150mL bottle or 75mL bottle) and dexamethasone 3.3mg/mL intravenous ampoules (pack size 10 1mL ampoules).

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 vaccines. 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’.

2.1.1 Storage

As per SmPC

All sites will need to ensure clear storage separation between stock for this study and general stock, 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 reporting of temperature excursions required.

2.2 Dispensing quantities

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 on 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. **Please do NOT dispense whole packs**.

For dexamethasone 2mg tablets: dosage three tablets once a day for 10 days, patients should be dispensed 30 tablets. This is assuming no dose modification.

For dexamethasone 2mg/5mL oral solution: dosage 15mL once a day for 10 days. Patients should be initially dispensed 75mL to avoid wastage if the patient needs to be switched to alternative formulation. This is assuming no dose modification.

For dexamethasone 3.3mg/mL intravenous 1ml ampoules: dosage 1.8mL once a day for 10 days, patients should be initially dispensed 10 ampoules to avoid wastage if the patient can be switched to an oral formulation earlier. This is assuming no dose modification.

2.3 Returns and Destructions

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

2.4 FAQs

Q. How is dexamethasone to be prescribed as there are different salts available?

A. To be prescribed as dexamethasone 6mg base

Q. Is the dose the same for oral and IV for dexamethasone despite differences in bioavailability?

A. Yes, the dose will be 6mg base for both IV and oral.

Q. The IV dose of dexamethasone base of the 3.3mg/mL comes to 1.82mL which cannot be measured accurately in a 2mL syringe. What do we do?

A. Volume to be rounded to 1.8mL which is measurable.

Q. Our normal hospital practice is to dissolve dexamethasone 2mg tablets instead of using soluble tablets or oral liquid, is this permitted?

A. Yes. If sites cannot source the soluble tablets or liquid, then the 2mg tablets can be dissolved in 10mL of water. There are no issues with this going down a fine bore nasogastric tubes (Reference: Handbook of Drug Administration via Enteral Feeding Tubes).

Q. Is IV dexamethasone to be given as an IV bolus or infusion?

A. Either is acceptable, treating clinician to decide.

3 Prednisolone

3.1 Initial supply and re-ordering

Prednisolone should be sourced by local pharmacy procurement team via their normal routes.

3.2 Storage

As per SmPC

No reporting of temperature excursions required.

3.3 Returns and Destructions

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

4 Hydrocortisone

4.1 Initial supply and re-ordering

Hydrocortisone should be sourced by local pharmacy procurement team via their normal routes.

4.2 Storage

As per SmPC

No reporting of temperature excursions required.

4.3 Returns and Destructions

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

4.4 FAQs

Q. Does it matter which hydrocortisone salt we use in this study?

A. No. Please use whichever product is normally used in your Trust.

5 Methylprednisolone Sodium Succinate

5.1 Initial supply and re-ordering

Methylprednisolone sodium succinate should be sourced by local pharmacy procurement team via their normal routes.

5.2 Storage

As per SmPC

No reporting of temperature excursions required.

5.3 Returns and Destructions

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

6 Lopinavir/Ritonavir

6.1 Initial supply and re-ordering

Lopinavir/ritonavir (MHRA approved stock specifically for this study) is to be procured by local pharmacy procurement team from PHE. PHE have ring fenced stock for this clinical trial. At present PHE only have tablets in stock: Lopinavir 100mg/Ritonavir 25mg (pack size 60 tablets) and Lopinavir 200mg/Ritonavir 50mg (pack size 60 tablets).

Supplies of lopinavir/ritonavir liquid have been procured and will be made available on ImmForm soon. However, please note that this stock will be non-UK (foreign) livery (see FAQ below for management of non-UK livery stock).

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 vaccines. 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'.

PIL inside the MHRA approved packs are not suitable for patients; all doses will be given by healthcare professionals.

6.2 Storage

Tablets are usually stored at room temperature (<25°C) and supplied as blister packs.
Tablets from Mylan® come in bottles; these are stable out of the original container for up to 120 days.

The following information was provided by the manufacturer (Hetero Lab Limited): We have a hold time data conducted in simulated container (HDPE container) for coated tablets before packaging. It is established for 45 days. Apart from we have freeze thaw study and in use stability study. Hence it is stable out of the packaging.

Liquid can be stored outside of the refrigerator (<25°C) for up to 42 days. The date of removal from the refrigerator needs to be added to the bottle.

All sites will need to ensure clear storage separation between stock for this study and general stock for HIV 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 Dispensing quantities

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 on 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. **Please do NOT dispense whole packs**.

For lopinavir/ritonavir 200mg/50mg tablets: dosage two tablets twice a day for 10 days, patients should be dispensed 40 tablets. This is assuming no dose modification.

For lopinavir/ritonavir 100mg/25mg tablets: dosage four tablets twice a day for 10 days patients should be dispensed 80 tablets. This is assuming no dose modification.

For Kaletra® 400mg/100mg in 5ml liquid: dosage 5ml twice a day for 10 days, in view of limited supply, supply initially one 60ml bottle and switch back to oral tablets as soon as possible, to limit wastage.

6.4 Returns and Destructions

During the study if any patient returns or if any lopinavir/ritonavir 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. Can we use our own existing stock of lopinavir/ritonavir for this study?

A. No. NHSE have advised that all UK licensed stock of Kaletra® (and generics) already in wholesalers and hospitals should be protected for HIV patients already receiving this treatment.

Q. What is the alcohol content in Kaletra® liquid?

A. Kaletra® 400/100 liquid contains 42% v/v alcohol. Patients would be expected to take 5mL twice a day.

Q. How can Kaletra® liquid be made more palatable for patients to take?

A. The solution has a bitter after taste than can persist. The following strategies can improve palatability:

- Eating salty or savoury food eg peanut butter, crisps takes away the taste better than sweet
- Administer using an oral syringe rather than a spoon and direct the syringe towards the back of the tongue where there are fewer taste buds
- Mix the solution with a small quantity of chocolate milk

Q. Where can I find information regarding drug interactions and administration of lopinavir/ritonavir?

A. The Liverpool HIV drug interaction site has been proactive in creating some documents around interactions for possible COVID-19 treatments as well as how to administer HIV drugs via different routes (http://www.covid19-druginteractions.org/). Interactions can also be checked at website: https://www.hiv-druginteractions.org/checker

Q. If we can't source Kaletra® liquid can we crush the tablets?

A. Lopinavir and ritonavir levels are significantly reduced by crushing, so it is not advised (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3205189/). Also it is not easy to crush the tablets, so the subsequent 'suspension' may block an enteral tube.

AbbVie Ltd. have produced a guidance document on how to dissolve their tablets in water to make an aqueous suspension. To prepare a suspension for feeding tube administration, full intact tablets of the appropriate dose should be dissolved in a sufficient volume of drinking water (at least 10mL per tablet; 2 tablets in at least 20mL water) at room temperature until completely dissolved. No agitation or stirring is needed. Do not crush or grind the tablet(s) prior to mixing with water. Dissolution of the Kaletra/Aluvia tablets will take several hours (at least 4 hours). AbbVie Ltd. recommends initiating preparation of the suspension 6 to 12 hours in advance of administration. Following slow, full dissolution, the milky suspension should be carefully stirred or swirled, and then the entire volume of the resultant milky suspension may then be administered via a feeding tube as a whole dose. Partial dosing less than that of the original tablet should not be attempted. A water rinse may be necessary to assure complete dosing. The resulting suspension must be used within 24 hours of preparation. Please note that for the resulting suspension, pharmacokinetic studies have not been conducted and the bioequivalence is not known. Therefore, the decision to dissolve tablets in this manner will be up to the participating site. We would recommend close monitoring of the patient for potential increased adverse effects.

The dose of lopinavir/ritonavir does not need to be increased or modified if the site decides to dissolve the tablets to form the aqueous suspension.

Q. What feeding tubes are suitable for use with Kaletra® liquid?

A. Kaletra® liquid is not compatible with polyurethane feeding tubes, however it is compatible with PVC or silicone feeding tubes. Please check material of your feeding tubes.

If sites are struggling to find a compatible feeding tube, then there is a product by Enteral GBUK called the Carefeed® tube which is made of PVC (http://www.gbukenteral.com/products/carefeed-feeding-and-drainage-tubes/).

Q. What supportive medications are considered appropriate for lopinavir/ritonavir patients?

A. This is at the discretion of the managing team, but we would not recommend routine prescribing (but rather respond to side-effects if they occur).

Q. I've heard that lopinavir/ritonavir tends to cause diarrhoea, what should I do?

A. This is a frequently reported side effect in patients with HIV, but the frequency is not known in COVID-19 patients. If the patient is able to eat and drink, taking with food can reduce the risk of gastrointestinal side effects. If patients get diarrhoea, loperamide can be used in the usual doses.

Q. If my patient moves to ICU should the lopinavir/ritonavir be stopped?

A. It is likely that lopinavir/ritonavir will have to be stopped as the tablets cannot be crushed and administered down a feeding tube, also the liquid is not compatible with most hospitals feeding tubes and it also interacts with drugs commonly used in ICU such as midazolam.

Q. Is there anything that we need to do if the stock received is considered non-UK (foreign) livery?

A. PHE has supplied some batches of lopinavir/ritonavir that have non-UK (foreign) livery and therefore the MHRA have stated that:

"Non-UK livery is acceptable provided the IMP is labelled such as to ensure protection of the subject and traceability, to enable identification of the produce and trial, and to facilitate proper use of the IMP."

Therefore, sites must take appropriate action to ensure that this is followed for any non-UK livery stock going forward. For example sites could issue stock on an individual named patient basis ensuring that on the inpatient label the following are recorded: patient name, trial name, batch number and expiry, ward area and quantity dispensed. If sites are using an electronic prescribing system, then they could see if their electronic prescribing system has the facility to allow the nurse to record the batch number of the lopinavir/ritonavir given at administration. For ease sites may decide to follow this process for all lopinavir/ritonavir stock.

7 Hydroxychloroquine

7.1 Initial Supply and re-ordering

Hydroxychloroquine (MHRA approved stock specifically for this study) is to be procured by local pharmacy procurement team from PHE.

PHE have ring fenced stock for this clinical trial pack size: 200mg x 60 tablets.

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 vaccines. 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'.

7.2 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.

7.3 Dispensing quantities

Hydroxychloroquine dosage is 12 tablets in first 24 hours and then 2 tablets twice a day for 9 days ie a total of 200mg x 46 tablets. This is assuming no dose modification.

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. **Please do NOT dispense whole packs**.

7.4 Returns and Destructions

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

7.5 FAQs

Q. Can you crush and disperse hydroxychloroquine if a patient cannot swallow the tablets?

A. Yes, tablets can be crushed and dispersed in 15mL to 30mL water (NEWT guidelines).

Q. My patient is already on hydroxychloroquine for a pre-existing condition, can they be entered into the trial?

A. Yes, but not into the hydroxychloroquine arm.

8 Azithromycin

8.1 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'.

8.2 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.

8.3 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.

8.4 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.

8.5 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.

9 Tocilizumab

9.1 Initial Supply and re-ordering

Tocilizumab (MHRA approved stock specifically for this study) is to be procured by local pharmacy procurement team from PHE. PHE have ring fenced stock for this clinical trial. At present PHE has: tocilizumab 200mg/10mL vials (pack size 1 vial) and tocilizumab 400mg/20mL vials (pack size 1 vial).

Only sites that have been selected to open the paediatric tocilizumab arm will also be able to order the 80mg/4mL vials (pack size 1 vial).

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 vaccines. 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.

There is currently only a limited supply of stock. Therefore there will only be a limited number of sites open to this arm. An initial maximum supply of 8 x 200mg/10mL vials and 16 x 400mg/20mL vials can be ordered per site initially.

For the selected paediatric sites an initial order of 2 x 400mg/20mL vials, 2 x 200mg/10mL and 8 x 80mg/4mL vials (double the amount is available for Evelina, GOSH and Birmingham Children's Hospital). If your site is also an adult tocilizumab site, please ONLY order the 80mg/4mL vials. The 400mg/20mL and 200mg/10mL vials can be used for either adult or paediatric patients.

9.2 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.

9.3 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^{o}C) for up to 24 hours or as per local policy. (see Tocilizumab SmPC and Medusa for guidance).

9.4 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.

9.5 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.

10 Convalescent plasma

10.1 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.

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

11 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 dexamethasone, prednisolone, methylprednisolone and hydrocortisone 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. Lopinavir/ritonavir, hydroxychloroquine, azithromycin, dexamethasone and tocilizumab are supplied via PHE, and will be free of charge.

Q. There is a recommendation from Surviving Sepsis Campaign for COVID-19 regarding using steroids for adult respiratory distress syndrome (ARDS) patients on mechanical ventilation (recommendation 42), but my patient has not been randomised to the dexamethasone arm. Can we still add in steroid therapy?

A. Yes, the treating clinician can add in steroid therapy if it has been deemed clinically necessary and the patient can continue to be treated as per the RECOVERY clinical trial.

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.