RECOVERY Clinical Trial Pharmacy Briefing Document

(Based on Protocol V27.0 13-Sep-2023)

Contents

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 influenza and community-acquired pneumonia (CAP) caused by other pathogens.

Table 1: Medicines for RECOVERY Clinical Trial

Medicine	Formulation	Source	Accountability logs	Prescribed	IMP Annex 13 labelling
Randomisation Part G (influenza)					
No additional treatment					
Baloxavir marboxil	Oral tablet	Roche trial specific stock	No	Yes	Yes
Randomisation Part H (influenza)					
No additional treatment					
Oseltamivir	Oral capsule, Oral suspension	NHS stock. Licensed products – Standard Pharmaceutical Wholesalers	No	Yes	No
Randomisation Part I (dexamethasone for influenza)					
No additional treatment					
Dexamethasone	Oral tablet, oral suspension, intravenous ampoules	NHS stock. Licensed products – Standard Pharmaceutical Wholesalers	No	Yes	No
Randomisation Part M (dexamethasone for community-acquired pneumonia)					
No additional treatment					
Dexamethasone	Oral tablet, oral suspension, intravenous ampoules	NHS stock. Licensed products – Standard Pharmaceutical Wholesalers	No	Yes	No

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). 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.

2 Dexamethasone

2.1 Initial supply and re-ordering

Dexamethasone will be sourced by local Pharmacy Procurement team via their normal routes.

2.2 Storage

As per SmPC

No temperature excursion reporting required. Follow Trust SOPs to manage temperature excursions.

2.3 Dispensing quantities

Randomisation Part I (dexamethasone for influenza) and **Randomisation Part M** (dexamethasone for CAP): Dexamethasone **6mg** (base) once daily by mouth, nasogastric tube or intravenously for **10**

days, discontinued on discharge from hospital if this happens sooner. See below for details of alternative corticosteroids for use in pregnant women.

Children aged under 18 years (Randomisation Part I only)

Greater than 36 weeks corrected gestational age: Dexamethasone 150 micrograms/kg (as base) once daily (max: 6 mg once daily) for 10 days (or until discharge if sooner). Enteral or intravenous route.

Less than 36 weeks corrected gestational age: Hydrocortisone (IV) 0.5 mg/kg every 12 hours for 7 days and then 0.5mg/kg once daily for 3 days. Enteral or intravenous route.

2.4 Returns and Destructions

Not applicable as stock is supplied via local pharmacy.

2.5 FAQs

Also see the intervention sheets here https://www.recoverytrial.net/for-site-staff/site-teams

Q. My patient is pregnant or breastfeeding can they be treated with dexamethasone?

A. No. Pregnant or breastfeeding women should be prescribed oral prednisolone 40mg once a day or intravenous hydrocortisone (sodium succinate) 80mg twice daily. Refer to protocol Appendix 4 for information about recruiting pregnant women.

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

A. To be prescribed as dexamethasone base

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

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

Q. How should the oral dose be taken?
Dexamethasone should be taken with or after food to minimise irritation to the gastrointestinal tract. Drinks containing alcohol or caffeine should be avoided.

Q. The IV 6mg 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 6mg/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 Baloxavir marboxil

3.1 Initial supply and re-ordering

Baloxavir marboxil will be sourced by local Pharmacy Procurement team free of charge from Roche. Baloxavir is available as packs of 2 x 20mg tablets, labelled as a clinical trial IMP.

Note baloxavir received by sites before 19-December 2024 was packaged differently, as this was commercial stock and came in packs of 1x40mg tablet. Any remaining 1x40mg packs should be used for trial patients before switching to the new baloxavir supply. There are no trial specific requirements for dispensing the 1x40mg packs, and this should be done according to usual pharmacy practice.

Initial supply should be 12 packs. Before stock falls to 4 packs of baloxavir tablets (2 x 20mg), please re-order by emailing the Oxford trial team at recoverytrial@ndph.ox.ac.uk with your request, making sure you state:

- Your Trust
- The hospital address for delivery
- The amount of baloxavir required (maximum stock holding should usually be 12 packs, but please discuss with the trial team if this creates problems because of high recruitment)

The trial team will place orders using the Roche clinical trial distribution system (STRIDE), and we expect deliveries to arrive within 2-3 working days of the order being placed, although this can take up to a week.

Receiving shipments
Shipments are sent at ambient temperature and include a reusable cloud-based temperature monitor with real time data tracking (Smart Sensor data logger). Upon receipt of the shipment, check that the shipment appears intact and complete, and locate the Smart Sensor along with the handling instructions. The handling instructions are also on the RECOVERY pharmacy page www.recoverytrial.net/uk/for-site-staff/pharmacy.

The instructions explain how to stop the Smart Sensor and recognise if the alarm light indicates a temperature excursion. If a temperature excursion has occurred (alarm light is blinking), quarantine the material and contact the trial team (recoverytrial@ndph.ox.ac.uk) for guidance.

After the Smart Sensor has been stopped, follow instructions to download a temperature report from the Roche website for filing in the site file (this report can also be obtained by emailing the trial team if necessary). Note the instructions say ‘record the shipment in IxRS (as applicable)’, but this system is not used for RECOVERY shipments.

After stopping the Smart Sensor, place inside the protective pouch, seal, and place into empty shipper along with all cold packs. Return the shipper with Smart Sensor for re-use.

3.2 Storage

Store at 15-30°C. No trial-specific temperature monitoring or temperature excursion reporting is required once the material is received by the pharmacy (the material is equivalent to commercial baloxavir, which has no temperature storage requirements). Follow Trust SOPs to manage

temperature excursions. If a problem in the storage conditions of the material is identified, then quarantine the material and notify the trial team as above.

All sites will need to ensure clear storage separation between stock for this study and general hospital stock for flu patients or stock used for other clinical trials.

3.3 Dispensing quantities

Adults and adolescents (≥ 12 years of age)

<40kg	Not eligible for baloxavir comparison
40kg to <80kg	Baloxavir 40mg by mouth on day 1 and day 4
≥80kg	Baloxavir 80mg by mouth on day 1 and day 4

When dispensing baloxavir the following information should be written on the box and blister labels in the spaces provided:

- RECOVERY participant ID or NHS/hospital number ('pat no.')
- Investigator (name of PI)
- Dispensing date

If the participant is discharged before the course is complete, they should be provided with medication to complete the course at home. The clinical trial labelling on 2x20mg packs includes spaces to write instructions for the second dose, which can be filled in when the initial request is dispensed. These would be completed as follows for a patient randomised on 28/11/2024 (day 1):

- **If patient weighs <80kg** "If completing the course at home, take _2_baloxavir marboxil tablets (from _1_ box(es)), as a single dose on _1/12/2024_"
- **If patient weighs ≥80kg** "If completing the course at home, take _4_baloxavir marboxil tablets (from _2_ box(es)), as a single dose on _1/12/2024_"

(Note this does not apply if using any remaining 1x40mg stock, and instructions for taking the 2nd dose of this stock can be determined by the pharmacist according to their usual practice).

3.4 Returns and Destructions

Any remaining stock at the end of the trial should be disposed of according to local pharmacy procedures. No sponsor approval is required.

3.5 FAQs

Also see the baloxavir intervention sheet https://www.recoverytrial.net/for-site-staff/site-teams

Q. Can baloxavir tablets be cut or crushed for patients who have swallowing difficulties or who have a feeding tube?

A. The tablets must **not** be crushed or split. If administering via a feeding tube, the tablets can be dissolved in 100ml water. While the company's in house data on dispersing tablet has not been tested for enteral administration, baloxavir suspension is licensed in the US for administration via enteral feeding tube, suggesting drug interaction with tubing is unlikely to be an issue. Given the licensed baloxavir 2mg/mL suspension is bioequivalent to baloxavir tablet, and the suspension is a simple suspension formulation (excipients: non-colloidal silicon dioxide, hypromellose, maltitol,

mannitol, povidone K25, sodium chloride, strawberry flavour, sucralose and talc), the administration of dispersed tablet suspension is likely to have minimal impact on bioavailability.

For patients who cannot swallow tablets and who do not have a feeding tube, tablets may be dissolved in 100ml water. However this cannot be mixed with anything to improve taste or alter consistency (e.g. thickener).

Q. How should the tablets be taken?
A. The tablets must be swallowed whole with or without food.
Baloxavir should not be taken with products that contain polyvalent cations such as laxatives, antacids or oral supplements containing iron, zinc, selenium, calcium or magnesium

Q. Do tablets contain lactose?
The tablets contain lactose as an excipient, so patients who are lactose intolerant should not be randomised to receive this medicine.

Q. My patient is pregnant or breastfeeding can they be treated with baloxavir?

A. Yes; pregnant or breastfeeding women can be randomised to receive baloxavir in this trial, but see the advice in the intervention sheet, and refer to protocol Appendix 4 for information about recruiting pregnant women.

4 Oseltamivir

4.1 Initial supply and re-ordering

Oseltamivir will be sourced by local Pharmacy Procurement team via their normal routes.

4.2 Storage

As per SmPC. No temperature excursion reporting required. Follow Trust SOPs to manage temperature excursions.

4.3 Dispensing quantities

Adults or children weighing >40 kg:
Oseltamivir 75mg capsules twice daily by mouth for 5* days.

Adults and children aged ≥ 1 year - dose for those weighing ≤40kg:

Body Weight	Recommended dose for 5* days
<10 kg	3 mg/kg twice daily
≥10 kg to 15 kg	30mg twice daily
>15 kg to 23 kg	45mg twice daily
>23 kg to 40 kg	60mg twice daily

Children aged 0-12 months (≥36 weeks corrected gestational age):

Body Weight	Recommended dose for 5* days
<10 kg	3 mg/kg twice daily
≥10kg	30mg twice daily

Neonates less than 36 weeks corrected gestational age:
1 mg/kg twice daily for 5* days.

*Course can be extended to 10 days for immunosuppressed patients at the managing clinician's discretion. If the participant is discharged before the course is complete, the participant should be provided with medication to complete the course at home.

4.4 Returns and Destructions

Not applicable as stock is supplied via local pharmacy.

4.5 FAQs

Also see the oseltamivir intervention sheet https://www.recoverytrial.net/for-site-staff/site-teams

Q. My patient has renal impairment, can they receive oseltamivir?

A. Yes; the twice a day dose should be reduced if renal function is impaired (this dose is 75mg in adults and children weighing >40kg, but a lower dose should be used in those weighing <40kg, as above):

- eGFR ≥10 to <30mL/min/1.73m^2 dose to be given once daily
- eGFR <10mL/min/1.73m^2 single dose to be given on day 1

Note renal dose adjustment in RECOVERY differs from that in the SmPC.

Q. My patient is pregnant or breastfeeding can they be treated with oseltamivir?

A. Yes; pregnant or breastfeeding women can be randomised to receive oseltamivir. Refer to protocol Appendix 4 for information about recruiting pregnant women.

5 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. Baloxavir will be free of charge from Roche. Corticosteroids and oseltamivir are provided by the site and are not directly reimbursed, but are treated as research costs in the SoECAT.

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

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 the sponsor happy for sites to 'pre-pack' tablets into patient courses?

A. Yes for use within one trust, with appropriate documentation and checks.
It is not legal to pre-pack for another Trust, unless the trust holds the relevant MHRA licenses.

Q. If patients are discharged early are pharmacy expected to use the left over medication to maximise stock?

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

6 Version History

Version number	Date	Brief Description of Changes
23.0	29-Jun-2023	Removal of empagliflozin, Paxlovid & molnupiravir comparisons. Update of section 5.2 & Appendix 1 to reflect sotrovimab expiry extension to 36 months.
24.0	14-Dec-2023	Addition of Part M (community-acquired pneumonia dexamethasone comparison). Minor update to baloxavir & oseltamivir re-ordering.
24.1	19-Feb-2024	Update of section 5.2 & Appendix 1 to reflect sotrovimab expiry extension to 48 months. Addition of version history.
24.2	17-Sep-2024	Update baloxavir packaging and disposal, update oseltamivir disposal, removal of covid comparisons (sotrovimab and high dose steroids)
24.3	01-Dec-2024	Change to baloxavir supply and ordering. Oseltamivir supply changed to NHS stock.
24.4	20-Dec-2024	Updated details about baloxavir receipt and dispensing.
24.5	09-Jan-2025	Updated shipping details for baloxavir with information on Smart Sensor temperature monitoring via STRIDE