RECOVERY UK Clinical Trial Pharmacy Briefing Document

(Based on Protocol V28.0 30-June-2025)

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

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.

Initial supply should be 30 packs. Before stock falls to 10 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 30 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

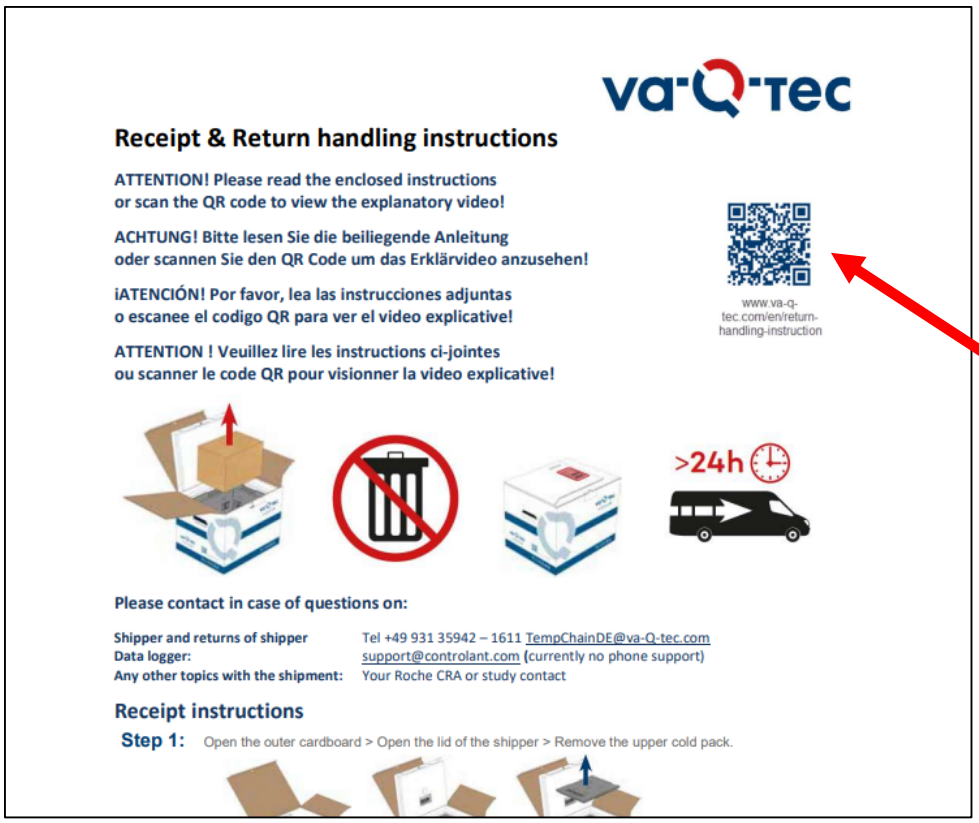
Shipments are sent at ambient temperature and include a reusable cloud-based temperature monitor with real time data tracking (Smart Sensor data logger). Upon receipt of the shipment:

1) Check that the shipment appears intact and complete

2) Locate:
- The Smart Sensor
- The 'Delivery Note/Consignment Request' document
- The 'Receipt and Return handling instructions' document

The Receipt and Return handling instructions are also available on the RECOVERY EU webpage in the 'pharmacy documents' section (www.recoverytrial.net/eu).

3) Stop the Smart Sensor. The Receipt and Return handling instructions explain how to do this 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 Oxford trial team (recoverytrial@ndph.ox.ac.uk) for guidance. A QR code on the instructions links to an explanatory video.



va-Q-tec

Receipt & Return handling instructions

ATTENTION! Please read the enclosed instructions or scan the QR code to view the explanatory video!

ACHTUNG! Bitte lesen Sie die beiliegende Anleitung oder scannen Sie den QR Code um das Erklärvideo anzusehen!

¡ATENCIÓN! Por favor, lea las instrucciones adjuntas o escanee el codigo QR para ver el video explicative!

ATTENTION ! Veuillez lire les instructions ci-jointes ou scanner le code QR pour visionner la video explicative!

www.va-q-tec.com/en/return-handling-instruction

>24h

Please contact in case of questions on:

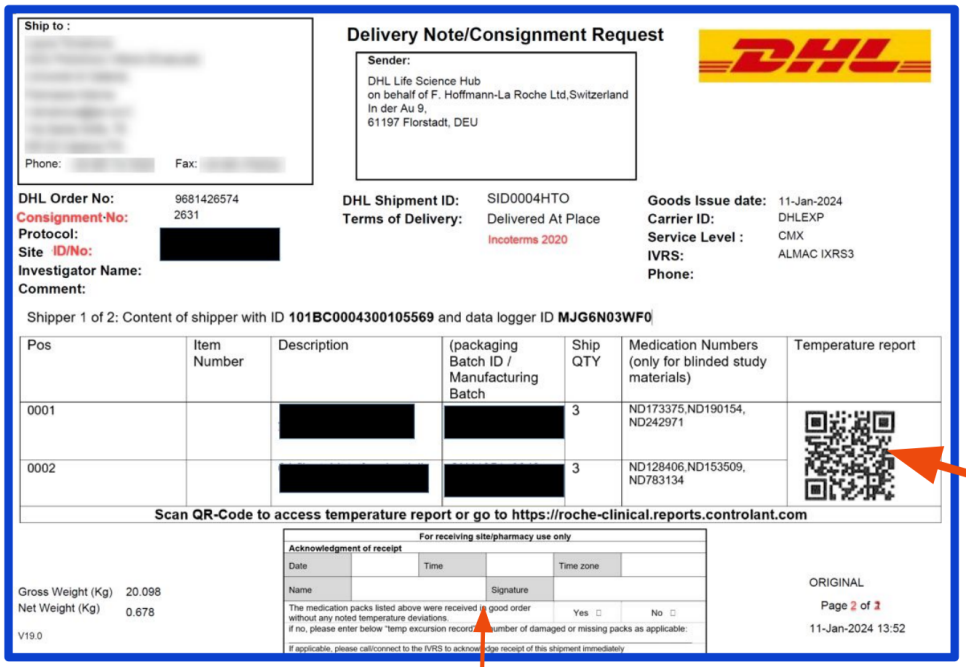
Shipper and returns of shipper	Tel +49 931 35942 – 1611 TempChainDE@va-Q-tec.com
Data logger:	support@controlant.com (currently no phone support)
Any other topics with the shipment:	Your Roche CRA or study contact

Receipt instructions

Step 1: Open the outer cardboard > Open the lid of the shipper > Remove the upper cold pack.

QR code with link to explanatory video

4) Record details of the shipment receipt on the Delivery Note, in the box indicated below.



Ship to :

[redacted]

Phone: [redacted] Fax: [redacted]

Delivery Note/Consignment Request

Sender:

DHL Life Science Hub
on behalf of F. Hoffmann-La Roche Ltd,Switzerland
In der Au 9,
61197 Florstadt, DEU

DHL

DHL Order No: 9681426574
Consignment No: 2631
Protocol:
Site ID/No: [redacted]
Investigator Name:
Comment:

DHL Shipment ID: SID0004HTO
Terms of Delivery: Delivered At Place
Incoterms 2020

Goods Issue date: 11-Jan-2024
Carrier ID: DHLEXP
Service Level : CMX
IVRS: ALMAC IXRS3
Phone:

Shipper 1 of 2: Content of shipper with ID **101BC0004300105569** and data logger ID **MJG6N03WF0**

Pos	Item Number	Description	(packaging Batch ID / Manufacturing Batch	Ship QTY	Medication Numbers (only for blinded study materials)	Temperature report
0001		[redacted]	[redacted]	3	ND173375,ND190154, ND242971	
0002		[redacted]	[redacted]	3	ND128406,ND153509, ND783134	

Scan QR-Code to access temperature report or go to https://roche-clinical.reports.controlant.com

For receiving site/pharmacy use only

Acknowledgment of receipt

Date		Time		Time zone	
Name			Signature		

The medication packs listed above were received in good order without any noted temperature deviations. Yes ☐ No ☐

if no, please enter below "temp excursion record" number of damaged or missing packs as applicable:

if applicable, please call/connect to the IVRS to acknowledge receipt of this shipment immediately

Gross Weight (Kg) 20.098
Net Weight (Kg) 0.678

V19.0

ORIGINAL
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QR code for downloading temperature report

Box for recording details of shipment receipt

5) Scan the QR code on the Delivery Note to download the temperature report. A copy of the temperature report and the Delivery Note should be kept in the Investigator Site File (electronic or physical copies can be kept, according to local preference). The temperature report can also be obtained by emailing the trial team if necessary. Note the instructions may say 'record the shipment in IxRS (as applicable)', but this system is not used for RECOVERY shipments.

6) Follow the Receipt and Return handling instructions to prepare the shipper and Smart Sensor for return.

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

Two doses of baloxavir marboxil, administered by mouth or feeding tube. The first dose is to be given on day 1 and the second dose on day 4. Treatment should be started as soon as possible after the patient is randomised, aiming for a delay of no more than 6 hours. This two-dose regimen is based on evidence from a previous trial in hospitalised patients, and is different to the one-dose regimen licensed for uncomplicated influenza.

If the patient is discharged before the course is complete, they should be provided with the 2nd dose to take at home. The trial follow-up form will record whether or not this happened, but site teams do not need record whether or not the 2nd dose was actually taken by the patient after discharge.

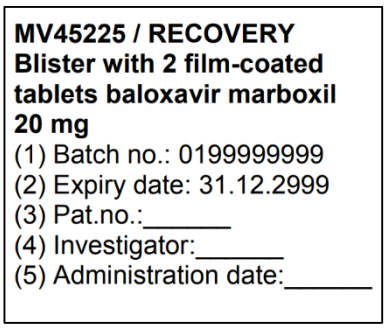
Dosing of baloxavir marboxil depends on the patient's weight:

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

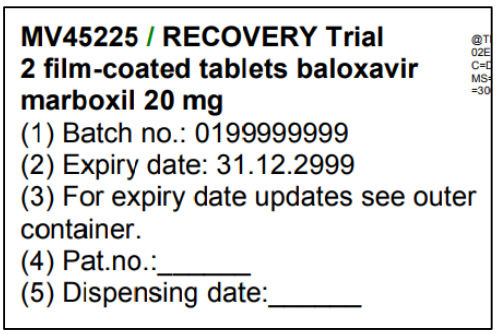
1) Check that the IMP has not passed its expiry date.

2) The following information should be written on the front page of the box and blister label booklets, in the spaces provided:

- 'Pat no.' (this can be RECOVERY participant ID or local hospital number)
- 'Investigator' (name of site Principal Investigator, on box only)
- 'Dispensing date' or 'Administration date' (write the dispensing date for both, as this is also the intended administration date)

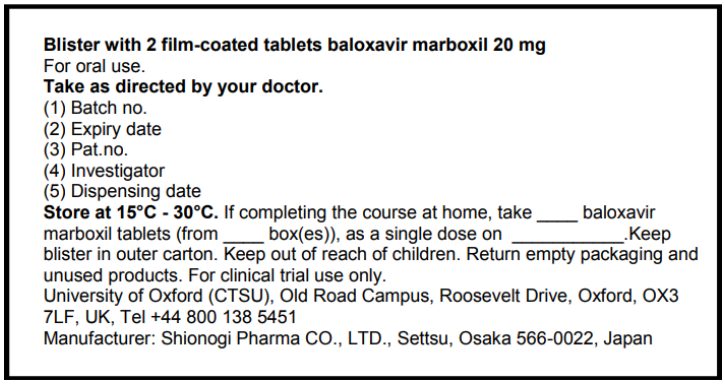


Box



Blister

3) Instructions for the second dose should be written on the relevant language page of the box label booklet. The labelling includes spaces to write instructions for the second dose:


Blister with 2 film-coated tablets baloxavir marboxil 20 mg
For oral use.
Take as directed by your doctor.
(1) Batch no.
(2) Expiry date
(3) Pat.no.
(4) Investigator
(5) Dispensing date
Store at 15°C - 30°C. If completing the course at home, take ____ baloxavir marboxil tablets (from ____ box(es)), as a single dose on _____.Keep blister in outer carton. Keep out of reach of children. Return empty packaging and unused products. For clinical trial use only.
University of Oxford (CTSU), Old Road Campus, Roosevelt Drive, Oxford, OX3 7LF, UK, Tel +44 800 138 5451
Manufacturer: Shionogi Pharma CO., LTD., Settsu, Osaka 566-0022, Japan

For example, the label would be completed as follows for a patient randomised on 28/11/2025 (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 _1/12/2025_"
- **If patient weighs ≥80kg** "If completing the course at home, take _4_baloxavir marboxil tablets (from _2_ box(es)), as a single dose on _1/12/2025_"

The second dose should be dispensed with the first if possible, so the complete course is held on the ward with the patient. If the patient is discharged before the course is complete, they should be discharged with the second dose to take at home. Pharmacies should ensure that dispensing the trial treatment doesn't delay discharge from hospital (as this could introduce bias to the trial results for duration of hospital stay).

3.4 Returns and Destruction

Any remaining stock at the end of the trial should be disposed of according to local pharmacy procedures. No sponsor approval is required before destruction, but the sponsor should be informed afterwards that all remaining trial baloxavir marboxil has been destroyed (email recoverytrial@ndph.ox.ac.uk).

3.5 Recalls, complaints or use of expired IMP

In the event of a recall, the Oxford trial team will email the PI and pharmacy contact and ask them to quarantine the material immediately, and to provide confirmation of action taken. We will then arrange for the material to be collected.

In case of any IMP-related issues, complaints, or the use of expired IMP, please contact the Oxford trial team (recoverytrial@ndph.ox.ac.uk).

3.6 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
25.0	01-Oct-2025	Updated baloxavir initial supply to 30 packs instead of 12, removed reference to protocol V27 and replaced with protocol V28. Added note about recalls (section 3.5)
25.1	10-Nov-2025	Updated baloxavir section in line with EU pharmacy briefing document (elaboration on baloxavir procedures including receiving shipment and dispensing)
25.2	12-Nov-2025	Further minor updates to wording in baloxavir section in line with EU pharmacy briefing document