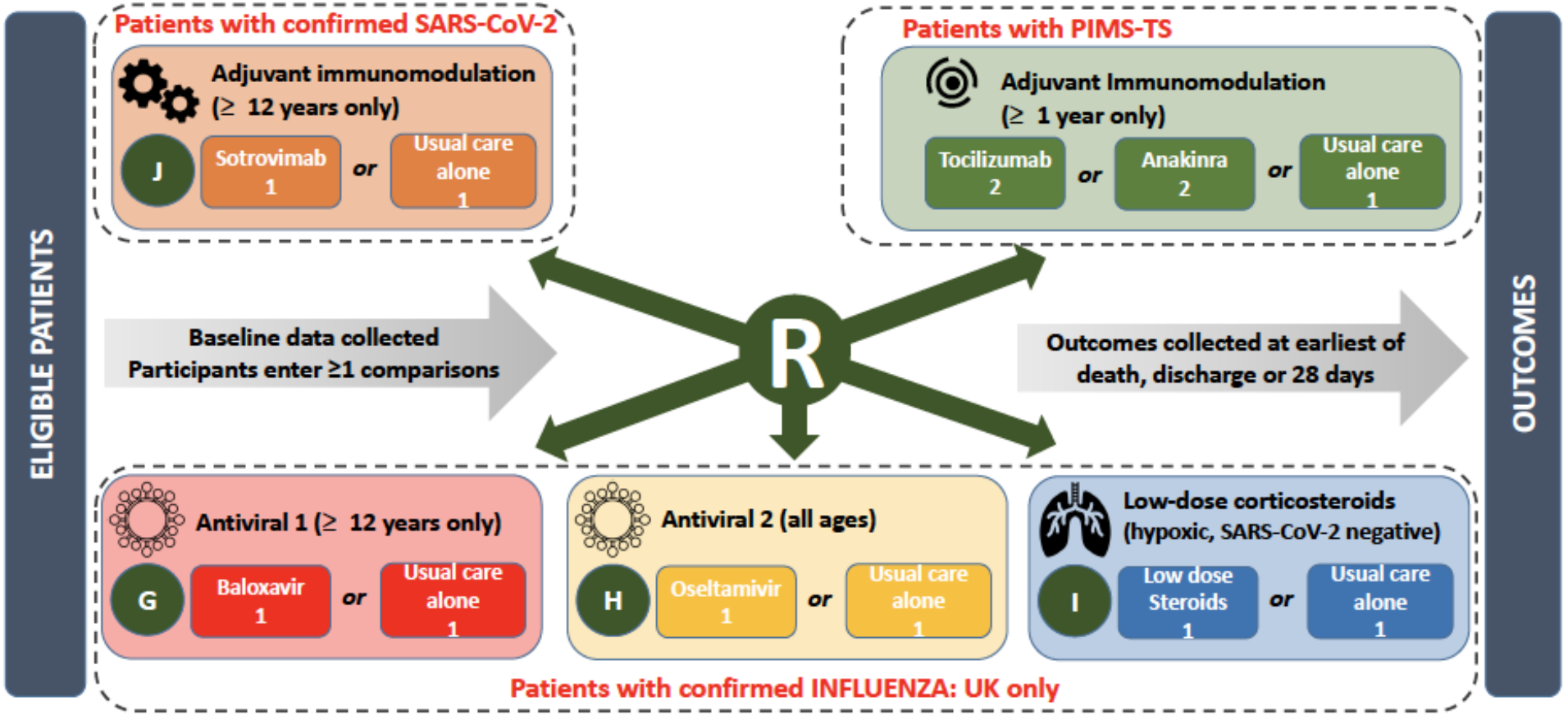
	RECOVERY FOR CHILDREN	**Paediatric Patients** **Adapted for paediatric patients**
Eligibility		**See page 2 to 7 for details on which children should be offered participation in RECOVERY.**
COVID-19 Randomisation (RESPIRATORY)	Randomisation consists of different parts to allow for the factorial design. The available arms are different between adults and children. If one or more of the active drug treatments is not available at the hospital or is believed, by the attending clinician, to be contraindicated (or definitely indicated) for the specific patient, then this fact will be recorded via the web- based form prior to randomisation; random allocation will then be between the remaining arms.	**Children with respiratory COVID phenotype (≥12 years and ≥40 kg):** - No additional treatment - Sotrovumab Note: No current options for children <12 years
Influenza randomisation		**Children with influenza will be randomised to:** - No additional treatment - Baloxavir (age ≥12 years only) - Oseltamivir - Low-dose corticosteroids
PIMS-TS Randomisation	Not relevant to adults	**Children (≥1 year) with severe PIMS-TS who have not responded to therapy with intravenous immunoglobin (IVIg) and/or corticosteroids (or if IVIg or corticosteroids are not considered indicated) randomised 2:2:1 to:** - No additional treatment - Tocilizumab - Anakinra Note: see page 7 for other exclusion criteria
Follow-up/outcomes	Ascertained at the time of death or discharge or at 28 days after randomisation (whichever is sooner): - Vital status (alive/ dead, with date and presumed cause of death) - Hospitalisation status (inpatient/ discharged, with date of discharge) - Use of ventilation (none/ previous/ ongoing, with days of use and type) - Use of renal dialysis or haemofiltration (none/ previous/ ongoing)	Same outcome measures. **Follow-up form 6-8 weeks after discharge for PIMS-TS patients only**



Notes:

- Patients eligible for randomisation to the low-dose corticosteroid arm must be with influenza infection, **without** suspected or confirmed SARS-CoV-2 infection.

FAQ - General

- **Who has endorsed the trial?** The trial itself has been endorsed by all of the UK Chief Medical Officers and NHS England Medical Director. Inclusion of children has been endorsed by NHS England, the Royal College of Paediatrics and Child Health, and the NIHR CRN: Children.
- **Who should take consent for inclusion in the trial?** Any healthcare professional with appropriate training (completed online) and knowledge of the trial can take consent.
- **Who can take part?** There are no special approvals needed for including children. If the site Principal Investigator is not a paediatric healthcare professional, one will be identified, to work alongside them.

FAQ – Recruitment and randomisation: COVID-19 (respiratory), COVID-19 (PIMS-TS) and INFLUENZA

1. **Should a child who has laboratory confirmed SARS-CoV-2 but only displaying mild symptoms of COVID-19 be recruited?** No.
2. **Which child should be considered for RECOVERY?**

   Respiratory presentations of acute COVID-19 and ≥12 years: The **RCPCH guidance** **(click to link to pdf**) should be used to guide the decision about thresholds for treatment and therefore consideration of enrolment into RECOVERY. These criteria include (but are not limited to**):

   - Unventilated requiring FiO2 >40% to maintain saturation 88-97% (or clinical concern regarding deterioration)

   or

   - Ventilation: Oxygenation index: 4 ≤ 16 / Oxygenation saturation index: 5 ≤ 12.3

   AND

   Laboratory confirmed SARS-CoV-2 infection (note change to previous guidance)

   ** can consider randomisation even with lower O_2 requirement – early administration of monoclonal antibody may be of benefit, may consider randomisation locally if considered unwell enough to have started low dose dexamethasone.

   Paediatric multisystem inflammatory syndrome temporally associated with COVID-19 (PIMS-TS): Children can specifically be recruited to RECOVERY if they have suspected PIMS-TS.
   Randomisation stage 1 (comparing steroids, intravenous immunoglobulin, and no additional treatment) closed on the 16th July 2021.
   Currently, only 2nd stage randomisation (tocilizumab *vs* anakinra *vs* standard of care) remains open for children who have severe PIMS-TS (those who have not responded to therapy with IVIg and/or corticosteroids or if IVIg or corticosteroids are not considered indicated).
   For PIMS-TS a positive laboratory test for SARS-CoV-2 is not required.

Influenza: Children can be recruited if they have clinical evidence of viral pneumonia requiring hospitalisation (or if they develop viral pneumonia due to influenza while in hospital for another reason) **AND** test-confirmed influenza (polymerase chain reaction or rapid antigen tests). The diagnosis of viral pneumonia is based in clinical assessment and supporting chest X-ray findings are NOT a requirement. RECOVERY does not require CXR in children.

The table below shows potential clinical scenarios and randomisation options within RECOVERY for each clinical scenario.
R= recommended option

		Acute respiratory presentation of COVID-19	PIMS-TS	Influenza
	Phenotypes	**Primarily respiratory symptoms**	**Severe PIMS-TS Children (those who have not responded to therapy with IVIg and/or corticosteroids or if IVIg or corticosteroids are not considered indicated) AND ≥1 years**	**Clinical evidence of viral pneumonia requiring hospitalisation (or viral pneumonia due to influenza while in hospital for another reason) and laboratory-confirmed influenza (polymerase chain reaction or rapid antigen tests).**
1st stage COVID-19 interventions randomisation	**No additional treatment** **Sotrovimab**	**R** **(≥12 years and ≥40 kg only)**	Proceed directly to 2nd stage.	N/A
2nd stage PIMS- TS Interventions randomisation	**No additional treatment** **Tocilizumab** **Anakinra**	No option to 2nd stage randomisation. Manage as clinically indicated	**R** **(≥1 year only)**	N/A
Influenza interventions randomisation	**No additional treatment** **Baloxavir marboxil** **Oseltamivir** **Low-dose Corticosteroids[1]**	N/A	N/A	**R** **(≥12 years only for baloxavir)**

[1] without suspected or confirmed SARS-CoV-2 infection

3. **Which neonates/infants should be considered for RECOVERY?** No current treatment options in RECOVERY for neonates/infants with COVID-19 or PIMS-TS. Low-dose corticosteroid and oseltamivir as a treatment option are available in RECOVERY for neonates/infants with test-confirmed influenza.

4. **Can children be enrolled if they have suspected acute respiratory COVID-19, but a negative SARS-CoV2 PCR on a respiratory sample?** No, a diagnosis of respiratory COVID-19 with confirmed positive SARS-CoV2 PCR is now part of the inclusion criteria.

5. **Can children be enrolled if they are suspected of having PIMS-TS, but a negative SARS-CoV2 PCR on a respiratory sample?** Yes, children who test negative for SARS-CoV2, who are suspected of having PIMS-TS may be enrolled in RECOVERY.

6. **Can a child be enrolled to both COVID-19 AND Influenza treatment arms?** Children can be enrolled in RECOVERY and randomised to standard of care vs. oseltamivir vs. baloxavir. They are **not** eligible for randomisation to the low dose corticosteroid arm.

7. **Can a child be enrolled if one (or more) of the intervention arms is contra-indicated for that patient?** Yes, the child can be entered into the trial. The attending clinician would be asked to record on the web-based form which treatment(s) are unsuitable for the patient prior to randomisation. Random allocation will then be between the remaining arms. Refer to the table above and the next section on "Randomisation: additional intervention-specific considerations" for additional guidance (page 7).

8. **Can a child be included for randomisation to the sotrovimab arm if they have received a recent course of antibody treatment against SARS-CoV2?** Yes

9. **Should blood sample be taken for serology testing prior to administration of sotrovimab?** Yes, a sample should be taken but do not delay treatment while waiting for results.

10. **If the child is transferred from one centre to another, can they remain in the trial**? Yes. They can remain in the trial and the trial drugs will be provided by the receiving site.

11. **Baloxavir is only available as tablets, can a child be enrolled if they are unable to swallow tablets**? The criteria are:
    - Baloxavir:
        - In children without enteral tube, we recommend that baloxavir is selected as unsuitable. They can be randomised between standard of care, oseltamivir, and low-dose corticosteroid.
        - In children with enteral tube in situ and an administration volume of 100mL is clinically unacceptable, we recommend that baloxavir is selected as unsuitable. They can be randomised between standard of care, oseltamivir, and low-dose corticosteroid.

- In children with enteral tube in situ and an administration volume of 100mL is clinically acceptable, see page 13 for administration instructions.

12. **Should children be screened for tuberculosis and hepatitis before inclusion for randomisation for tocilizumab or anakinra?** The RECOVERY trial protocol does not require screening for tuberculosis or hepatitis given the short treatment duration. Screening can be carried out at the discretion of the attending clinician but do not delay treatment while waiting for results.

FAQ – Clinical management

20. **Is any dose adjustment required in a child with renal impairment?** No dosage adjustment is required for sotrovimab, tocilizumab and anakinra. For oseltamivir, please refer to dosing table.

21. **For children who have received tocilizumab or anakinra, what is the advice on live and live attenuated vaccines?** Limited data are available on the response to vaccination with live vaccines in children receiving these drugs. We recommend that live and live attenuated vaccines (BCG, rotavirus vaccine, MMR vaccine, live attenuated influenza vaccine (nasal spray)) be avoided for at least 12 weeks.

Randomisation: ADDITIONAL intervention-specific considerations

In addition to the information provided below, the attending clinician can, based on their clinical judgement, indicate on the web-based form that one or more of the interventions is deemed **unsuitable** for the specific patient.

Drug	Additional considerations relating to randomisation
Sotrovimab	Select "Yes" to reflect that this drug is **unsuitable** if any of the following circumstances apply: - Patient < 12 year - Known hypersensitivity to sotrovimab or to any of the excipients
Tocilizumab	Select "Yes" to reflect that this drug is **unsuitable** if any of the following circumstances apply: - Patient < 1 year - Known hypersensitivity to tocilizumab or to any of the excipients - Known hepatitis B, hepatitis C or tuberculosis infection - Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3 x Upper Limit of Normal - Received biologic immunomodulators or Janus Kinase inhibitors within the 30 days prior to randomisation.
Anakinra	Select "Yes" to reflect that this drug is **unsuitable** if any of the following circumstances apply: - Patient < 1 year - Known hypersensitivity to anakinra or E. coli derived proteins or to any of the excipients - Known hepatitis B, hepatitis C or tuberculosis infection - Absolute neutrophil count <1.5 x 10^9/L - Received biologic immunomodulators or Janus Kinase inhibitors within the 30 days prior to randomisation.
Oseltamivir	Select "Yes" to reflect that this drug is **unsuitable** if any of the following circumstances apply: - Hypersensitivity to the oseltamivir or to any of the excipients
Baloxavir marboxil	Select "Yes" to reflect that this drug is **unsuitable** if any of the following circumstances apply: - Hypersensitivity to the baloxavir marboxil or to any of the excipients - Known hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption - Unable to swallow tablet and not suitable for enteral administration
Low-dose corticosteroids	Select "Yes" to reflect that this drug is **unsuitable** if any of the following circumstances apply: - Laboratory confirmed SARS-CoV2 infection.

Paediatric dosing information

Children with respiratory COVID phenotype (≥12 years and ≥40 kg)

Arm	Route	Age/Weight	Dose
Sotrovimab	Intravenous	≥ 12 years and ≥ 40 kg	1000 mg as a single dose No dose adjustment is required in patients with renal or hepatic impairment.

Children with severe PIMS-TS who have not responded to therapy with intravenous immunoglobin (IVIg) and/or corticosteroids (or if IVIg or corticosteroids are not considered indicated)

Arm	Route	Age/Weight	Dose
Tocilizumab	Intravenous	Infants < 1 year excluded	
		< 30 kg	For children with PIMS-TS: 12 mg/kg A second dose may be given ≥12 and ≤24 hours later if, in the opinion of the attending clinicians, the patient's condition has not improved.
		≥ 30 kg	For children with PIMS-TS: 8 mg/kg (max 800 mg) A second dose may be given ≥12 and ≤24 hours later if, in the opinion of the attending clinicians, the patient's condition has not improved.
Anakinra	Subcutaneous (Intravenous route if clinically required)	Infants < 1 year or <10 kg excluded	
		≥ 10 kg	For children with PIMS-TS: 2 mg/kg daily for 7 days or until discharge, whichever is sooner

Children with influenza

<table>
<tr><th>Arm</th><th>Route</th><th>Weight/Age</th><th>Dose</th></tr>
<tr><td rowspan="3">Oseltamivir

- 30, 45 and 75 mg capsules

- Oral suspension [a]</td><td rowspan="3">Oral
<u>or</u>
Other enteral routes</td><td>Less than 36 corrected gestational age</td><td>1 mg/kg twice daily for 5 days [b]</td></tr>
<tr><td>0 - 12 months (≥36 corrected gestational age) [c]</td><td>3 mg/kg twice daily for 5 days [b]</td></tr>
<tr><td>≥ 1 year [c]</td><td><table><tr><th>Weight (kg)</th><th>Dose</th></tr><tr><td>≥ 10 to 15</td><td>30 mg twice daily for 5 days [b]</td></tr><tr><td>> 15 to 23</td><td>45 mg twice daily for 5 days [b]</td></tr><tr><td>> 23 to 40</td><td>60 mg twice daily for 5 days [b]</td></tr><tr><td>> 40</td><td>75 mg twice daily for 5 days [b]</td></tr></table>
Those within significant renal impairment (CrCl 10 - 30 mL/min) should receive once daily dosing. Those with CrCl <10 ml/min should receive only a single dose on day 1.</td></tr>
<tr><td>Baloxavir marboxil

- 20 and 40 mg tablets</td><td>Oral
<u>or</u>
Other enteral routes</td><td>≥ 12 years old</td><td><table><tr><th>Weight (kg)</th><th>Dose</th></tr><tr><td><40</td><td>Not eligible</td></tr><tr><td>≥ 40 to < 80</td><td>40 mg on day 1 and day 4</td></tr><tr><td>≥ 80</td><td>80 mg on day 1 and day 4</td></tr></table></td></tr>
<tr><td rowspan="2">Low dose corticosteroids</td><td rowspan="2">Oral
<u>or</u>
Other enteral routes
<u>or</u>
Intravenous</td><td>Less than 36 corrected gestational age</td><td>Hydrocortisone (IV)
0.5 mg/kg every 12 hours for 7 days and then 0.5mg/kg once daily for 3 days</td></tr>
<tr><td>≥0 month (≥36 corrected gestational age)</td><td>Dexamethasone:
150 micrograms/kg (as base) once daily (max: 6 mg once daily) for 10 days (or until discharge if sooner)</td></tr>
</table>

[a] Public Health England advises that oseltamivir oral suspension should be reserved for children under the age of 1 year. Children over 1 year of age, those with swallowing difficulties, and those receiving nasogastric oseltamivir, should use capsules which can be opened and mixed into an appropriate sugary liquid.

[b] 10 days if immunocompromised

[c] Children 1 year or over weighing less than 10 kg, 3mg/kg twice daily should be used.
Children between 0 – 12 months weighing more than 10 kg, 30 mg twice daily should be used.

Transfer of paediatric participants

The organisation of children's services for may involve transferring children to regional tertiary units for specialist services and/or paediatric intensive care should their condition deteriorate. A copy of the RECOVERY trial consent form and randomisation allocation sheet should be sent with the child on transfer.

The RECOVERY paediatric lead at the tertiary centre/PICU will assume trial responsibility for the child upon arrival.

Procedure

- The trial drugs will be provided by the receiving site.
- At the earliest of discharge, death or 28 days after first randomisation, Tertiary/**PICU RECOVERY team** contact referring hospital RECOVERY team to support completion of trial follow-up form (unless child has been transferred back to referring hospital prior to discharge).

Trial drugs supply and administration

Drug	Specific administration issues
Sotrovimab	Sotrovimab will be supplied by the sponsor via Fisher. Sites are to re-order supplies of sotrovimab when stock levels are running low by emailing the RECOVERY trial team: recoverytrial@ndph.ox.ac.uk Sotrovimab is available as 500mg in 8mL vials, 1 vial per carton. **Preparation** 1. Allow 2 vials of sotrovimab to equilibrate to room temperature, protected from light, for approximately 15 minutes. 2. Obtain 1 x 100 mL sodium chloride 0.9% or glucose 5% infusion bag. 3. Sites must ensure that the brand of infusion bag being used can hold an additional volume of 16mL safely and that there is no additional risk of spillage/inadvertent loss when the ward nurse spikes the bag. If this cannot be confirmed, withdraw 16 mL from the infusion bag and discard. 4. Visually inspect each vial to ensure it is a clear, colourless or yellow to brown solution, free from visible particles and that there is no visible damage to the vial. 5. Gently swirl each vial several times before use without creating air bubbles. Do not shake or vigorously agitate the vials. 6. Withdraw 16 mL of sotrovimab. 7. Add 16 mL of sotrovimab to the 100 mL sodium chloride 0.9% or glucose 5% infusion bag. 8. Gently rock the infusion bag back and forth 3 to 5 times. Do NOT invert the infusion bag. Avoid forming air bubbles 9. The diluted solution should be administered immediately. If not possible then it may be stored at room temperature (up to 25°C) for up to 6 hours or refrigerated (2 – 8°C) for up to 24 hours from the time of dilution until the end of administration. **Administration** - A single 1000mg dose to be administered as an intravenous infusion using a 0.2micron low protein binding in-line filter. - Set the infusion pump and administer as an intravenous infusion over 60 minutes.

Tocilizumab	Approval has been given for sites to use tocilizumab from local hospital stock by NHSE (and equivalent bodies in devolved nations). Charged via specialised commissioning (no blueteq required) Based on vial size availability, doses can be rounded. Refer to Roche dosing guide in order to minimise wastage and to allow doses to be measured accurately. Refer to page 7 of https://www.medicines.org.uk/emc/rmm/1393/Document **Concentrate for solution for infusion 20 mg/mL** **< 30 kg** - Calculate the volume of tocilizumab concentrate required for the patient's dose. - Withdraw a volume of sodium chloride 0.9% from a 50 mL infusion bag, equal to the volume of tocilizumab concentrate required for the patient's dose. - The required amount of tocilizumab concentrate should be withdrawn from the vial and placed in the 50 mL infusion bag. Set the infusion pump and administer as an intravenous infusion over 60 minutes. The infusion rate can be adjusted in line with local practice. **≥ 30 kg** - Calculate the volume of tocilizumab concentrate required for the patient's dose. - Withdraw a volume of sodium chloride 0.9% from a 100 mL infusion bag, equal to the volume of tocilizumab concentrate required for the patient's dose. - The required amount of tocilizumab concentrate should be withdrawn from the vial and placed in the 100 mL infusion bag. - Set the infusion pump and administer as an intravenous infusion over 60 minutes. The infusion rate can be adjusted in line with local practice. After dilution, the prepared solution for infusion is physically and chemically stable at 30°C for 24 hours (storage at 2 - 8°C would be preferred).

Anakinra	Anakinra will be sourced by local pharmacy procurement team via their normal routes. Charged via specialised commissioning (no blueteq required) Instructions for intravenous administration (if clinically required): Round dose to the nearest 5mg. Dilute in a suitable volume of sodium chloride 0.9% (10mL would be a suitable volume but 5mL may be used if very fluid restricted) and administer as intravenous bolus over 3 to 5 minutes. Can be given peripheral or central line but it should not be mixed with other drugs.
Oseltamivir	Oseltamivir will be sourced by local pharmacy procurement team from Alliance Health Hospital system free of charge. Where supply is limited, UKHSA (formerly PHE) advises that oseltamivir oral suspension should be reserved for children under the age of 1 year. Children over 1 year of age, those with swallowing difficulties, and those receiving nasogastric oseltamivir, should use capsules which can be opened and mixed into an appropriate sugary liquid.
Baloxavir marboxil	Baloxavir marboxil will be sourced by local pharmacy procurement team from Alliance Health Hospital system free of charge. - Baloxavir marboxil tablets must be swallowed whole with or without foods. - It should not be taken with products that contain polyvalent cations such as laxatives, antacids or oral supplements containing iron, zinc, selenium, calcium or magnesium. In those with swallowing difficulties and have an enteral tube in situ, using the following methods: 1. Baloxavir marboxil tablets can be disintegrated (must not be crushed or split). 2. Continuous stirring with a spoon for ~ 10 minutes in 100 mL of water at ambient temperature (Do NOT mix with food or juice). Note: 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 suspension is bioequivalence to baloxavir tablet, and the suspension is a simple 2mg/mL 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.
Corticosteroid	Dexamethasone will be sourced by local pharmacy procurement team from UKHSA (formerly PHE). Dexamethasone is available as 2mg tablets in packs of 50 tablets, 2mg/5mL oral solution in 75mL or 150mL bottles, and 3.3mg/mL intravenous 1mL ampoules in packs of 10. Hydrocortisone should be supplied from local hospital stock (any brand with marketing authorisation) and refer to individual SmPC for administration information.

Annex A: Trial drugs in children

There is clinical experience around using all the listed trial drugs for other conditions in children. The trial website provides broader discussions on the different interventions and their rationale with respect to COVID-19 (https://www.recoverytrial.net/for-site-staff/site-teams). Information relating to paediatric dosing is summarised below.

Sotrovimab - Sotrovimab is a human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody which includes a 2 amino acid "LS" modification in the Fc domain of the antibody to extend its's half-life. This "LS" modification is also reputed to enhance distribution to the respiratory mucosa. While the current regulatory submission package did not include data on paediatric patients, the regulators have considered it acceptable to extrapolate to adolescents of 40 kg or above based on data on similar products. Sotrovimab is licensed for the treatment of symptomatic adults and adolescents (aged 12 years and over and weighing at least 40 kg) with acute covid-19 infection; the licensed dose is a single 500 mg intravenous infusion. Of note, the range of body weight for adults treated in the adult COMET-ICE trial was 36-165 kg. Due to the emergence of the omicron variant, a higher dose of 1000 mg is being tested in the RECOVERY protocol. This provides a safety margin of approximately 30-fold with respect to the NOAEL of 500 mg/kg observed in repeat-dose toxicity study.

Tocilizumab - Tocilizumab is licensed for the treatment of juvenile idiopathic polyarthritis and chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome (CRS) in children 2 years of age and older. A phase I PK study (n=11) showed tocilizumab 12mg/kg every 2 weeks provide comparable PK, PD and efficacy (with respect to JIA) between patients younger than 2 years (range: 0.8 - 1.8) and those aged 2 to 17 years (https://doi.org/10.1186/s12969-019-0364-z), although there is possibly a higher incidence of serious hypersensitivity in under 2.

Anakinra – Anakinra is licensed in children (aged 8 months and older with a body weight of 10 kg or above) for the treatment of cryopyrin-associated periodic syndromes, familial mediterranean fever, and Still's disease.

Oseltamivir - Oseltamivir is licensed for the treatment of influenza in children including full term neonates. The indication in infants below the age of 1 year is based upon extrapolation of efficacy data from older children and the recommended posology is based upon pharmacokinetic modelling data indicating that a dose of 3 mg/kg provides plasma concentrations of the pro-drug and active metabolite that are anticipated to be clinically efficacious with a safety profile comparable to that seen in older children and adults. Limited data exist on dosing oseltamivir in premature babies; there is a single pharmacokinetic study in 12 infants from a single centre; dosing for preterm neonates is therefore based on Public Health England guidance. The most frequently (very common and common) reported side effects of oseltamivir are nausea, vomiting, stomach ache, stomach upset, headache and pain.

Baloxavir marboxil – Baloxavir is licensed for the treatment of influenza in patients aged 12 years and above. The licensed dose is a single dose of baloxavir marboxil taken as soon as possible within 48 hours of symptom onset. The dosing recommendation is based on two Phase III studies in largely healthy patients with uncomplicated influenza. Repeat dose regimen (single dose on day 1 and 4) was investigated in one Phase III trial (https://adisinsight.springer.com/trials/700300072) in hospitalised patients (aged ≥ 12 years) with severe influenza. Seriously ill patients who are hospitalized with influenza demonstrate prolonged viral shedding compared with otherwise healthy patients with influenza. Therefore, the repeat-dose regimen is to ensure that plasma baloxavir concentrations remain above a target-threshold concentration for a longer duration in severely ill patients owing to the greater potential of a protracted influenza illness.

Corticosteroid – Corticosteroid is licensed in children for the treatment of a range of conditions in which anti-inflammatory and immunosuppressive effects are required. The choice and dose of corticosteroid depend on the condition. For methylprednisolone, a dosage of 10-30 mg/kg/day to a maximum of 1 g/day for up to 3 days are recommended for the treatment of haematological, rheumatic, renal and dermatological conditions. For pre-term neonates, the dose of hydrocortisone has been extrapolated from the PREMILOC trial (DOI: 10.1016/S0140-6736(16)00202-6) which assessed the use of hydrocortisone in the management of bronchopulmonary dysplasia.

Change control

Version	Changes
Version 2 (6th May2020)	Eligibility adaptation for paediatrics – signposting to FAQs New and amended FAQs: Recruitment and randomisation Q1, Q2 and Q3 New FAQ: Clinical management Q1
Version 3 (21st May 2020)	Clarification on hydrocortisone option New FAQs: Recruitment and randomisation Q7, Q10, and Q11 New FAQ: Clinical management Q5 Inclusion of dosing tables from protocol version 6 Minor non-substantive edits made for consistency and clarity
Version 4 (27th May 2020)	Update: Recruitment and randomisation Q7 New section: Second randomisation of paediatric participants
Version 5 (2nd July 2020)	Hydroxychloroquine and lopinavir-ritonivir info removed from FAQ Hydroxychloroquine and lopinavir-ritonivir info removed from section - Randomisation: intervention-specific considerations Hydroxychloroquine and lopinavir-ritonivir info removed from section - Trial drugs administration Hydroxychloroquine and lopinavir-ritonivir info removed from Annex A New FAQ: Clinical management Q6 and Q7 (dose adjustment in renal impairment and infusion rate for convalescent plasma) New FAQs: Recruitment and randomisation Q9 and Q10 (updated for dexamethasone and convalescent plasma)
Version 6 (23 July 2020)	Randomisation arms have been updated. Amendment of corticosteroid dosing for children with PIMS-TS phenotype. New FAQs on intravenous immunoglobulin and high dose methylprednisolone Intravenous immunoglobulin info added to section - Randomisation: intervention-specific considerations Trial drugs administration section changed to Trial drugs supply and administration Intravenous immunoglobulin info added to section - Trial drugs supply administration Intravenous immunoglobulin and high dose methylprednisolone info added to Annex A Scenario flowcharts
Version 7 (06 Oct 2020)	Addition of randomisation arm: Synthetic neutralising antibodies (REGN10933 + REGN10987) New FAQ: Recruitment and randomisation Q13 Dosing table – minor amendments for clarification
Version 8 (16th Dec 2020)	Information on azithromycin removed as this arm has now closed.

	Option to proceed to 2nd stage randomisation if a child with PIMS-TS has already received a dose of intravenous immunoglobulin (IVIg) and steroids New FAQ to provide clarification on IVIg dose calculation and administration. Approval from NHSE to allow the use of hospital stock of tocilizumab.
Version 9 (13th Jan 2021)	Additional consideration when assessing suitability for tocilizumab randomisation: Children with alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3 x Upper Limit of Normal are unsuitable.
Version 10 (28 Jan 2021)	Information convalescent plasma removed Addition of baricitinib information Addition of anakinra information
Version 10.1	Correct exclusion criteria for baricitinib; "<1.5 x 10^9/L" correct to <0.5 x 10^9/L. Additional intravenous preparation instructions for anakinra Flowcharts moved to page 2 and 3 Removed reference to randomisation part A/B/C/D to minimise confusion Removed "no additional treatment" from table on paediatric dosing information.
Version 11 (25 Aug 2021)	Randomisation stage 1 (comparing steroids, intravenous immunoglobulin, and no additional treatment) closed on the 16th July 2021. Synthetic neutralising antibodies (REGN10933 + REGN10987) arm is closed.
Version 12 (25th Nov 2021)	Addition of influenza randomisation information Amended second randomisation section to reflect the closure of randomisation stage 1 (comparing steroids, intravenous immunoglobulin, and no additional treatment) for PIMS-TS.
Version 13 (10th Jan 2022)	Remove of baricitinib information as randomisation is now closed Addition of new randomisation arm of Sotrovimab