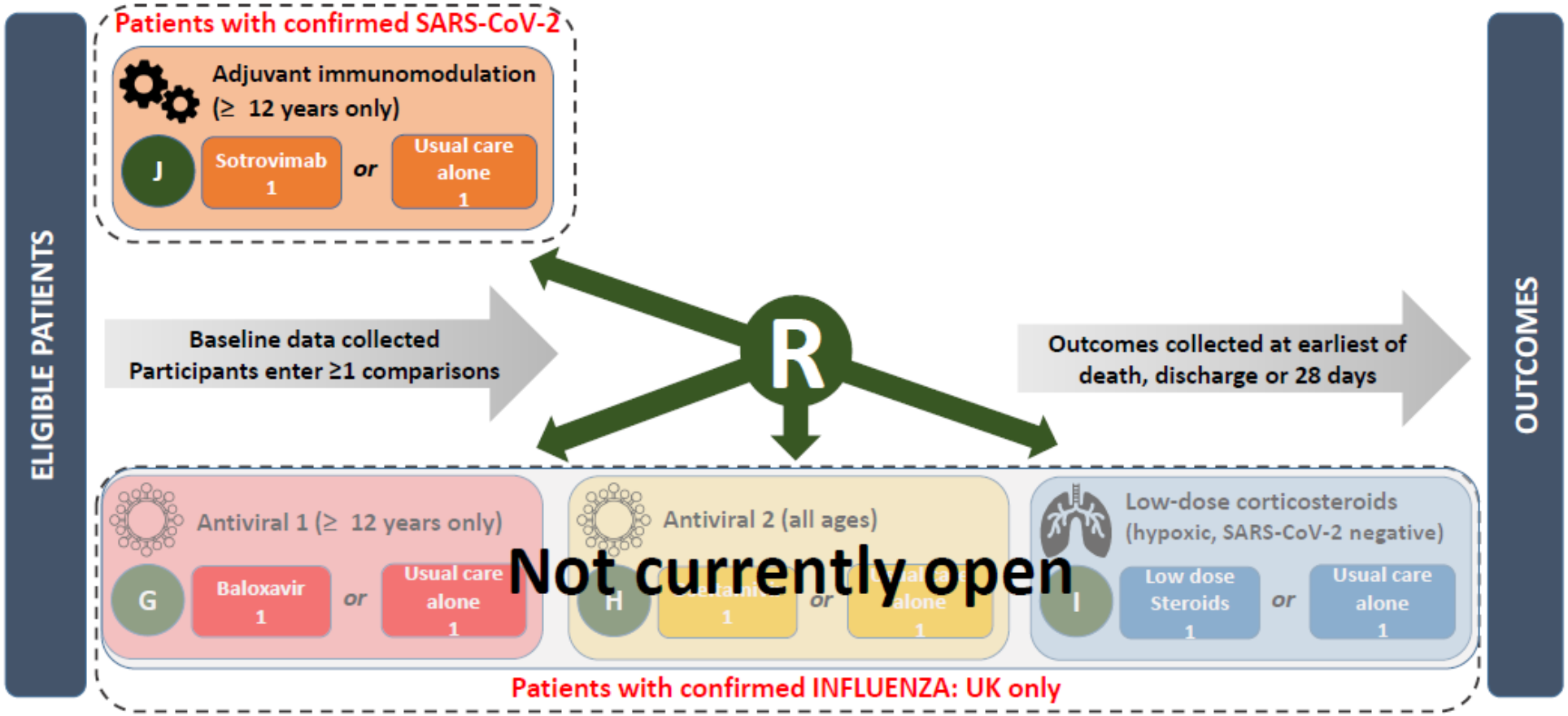
Paediatric Patients

Adapted for paediatric patients

	RECOVERY	
Eligibility		**See page 2 to 6 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		**Not currently open**
PIMS-TS Randomisation	Not relevant to adults	**Randomisation has closed.**
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):
   Randomisation has closed. Randomisation stage 1 (comparing steroids, intravenous immunoglobulin, and no additional treatment) closed on the 16th July 2021. Second stage randomisation (tocilizumab *vs* anakinra *vs* standard of care) closed on the 18th March 2022.

   Influenza: Not currently open.

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**	**R (≥12 years and ≥40 kg only)**	**Recruitment has closed**	N/A
	Sotrovimab			
Influenza interventions randomisation	**No additional treatment**	N/A	N/A	**Not currently open**
	Baloxavir marboxil			
	Oseltamivir			
	Low-dose Corticosteroids[1]			

[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.

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?** No current treatment options in RECOVERY as randomisation arms have closed.

6. **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

7. **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.

8. **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.

FAQ – Clinical management

9. **Is any dose adjustment required in a child with renal impairment?** No dosage adjustment is required for sotrovimab.

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

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.

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.

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.

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
Version 14 (10th May 2022)	Remove of PIMS-TS information as randomisation is now closed Minimised randomisation information on influenza as these arms currently remain inactive.