RECOVERY
Randomised Evaluation of COVID-19 Therapy

Paediatric Patients

	RECOVERY - Adults		Adaption for paediatric patients
Eligibility	In the original protocol, patients were eligible if all they were: - Aged at least 18 years - Hospitalised - SARS-CoV-2 infection (clinically suspected or laboratory confirmed) - No medical history that might, in the opinion of the attending clinician, put the patient at significant risk if he/she were to participate in the trial		Children and infants of all ages are included in RECOVERY **Please see FAQs "Recruitment and randomisation" on page 2 and 3 for details on which children should be offered participation in RECOVERY**.
1st stage Interventions	Randomisation part A - No additional treatment - Lopinavir-Ritonavir - Corticosteroid Hydroxychloroquine - Azithromycin	Randomisation part B - No additional treatment - Convalescent plasma	Same options (including no additional treatment) but: - Lopinavir-Ritonavir arm will not be open to preterm infants with a corrected gestation age of <42 weeks or any neonates with postnatal age of < 14 days. - Corticosteroid arm will include different corticosteroid options (dexamethasone, prednisolone or methylprednisolone) at the discretion of the treating clinician. For infants with a corrected gestation age of < 40 weeks, hydrocortisone is recommended. - Hydroxychloroquine arm will not be open to infants with postnatal age of < 180 days.
	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.		
2nd stage Interventions	- No additional treatment - Tocilizumab		Same option of 2 arms. Not open to children before 1st birthday.
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, if appropriate) - Hospitalisation status (inpatient/ discharged, with date of discharge, if appropriate) - Use of ventilation (none/ previous/ ongoing, with days of use and type, if appropriate) - Use of renal dialysis or haemofiltration (none/ previous/ ongoing)		Same outcome measures.

FAQ - General

1. **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.
2. **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.
3. **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

1. **Should a child who has laboratory confirmed SARS-CoV-2 but only displaying mild symptoms be recruited?** No.
2. **Which child should be considered for RECOVERY?** The **RCPCH guidance (click to link to pdf**) should be used to guide the decision about treatment and therefore consider enrolment into RECOVERY:

   The RCPCH guidance recommends that treatment with antivirals may be considered in those with signs of severe disease. The RCPCH criteria should also be used to consider whether the RECOVERY trial should be offered to the family:

   - Unventilated requiring FiO2 >40% to maintain saturation 88-97%

   and/or

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

   For older children with shock but without severe respiratory compromise see FAQ 5 below.

3. **Which neonates should be considered for RECOVERY?** For neonates, the presence of any of the following should be used to consider whether the RECOVERY trial should be offered to the family:
   - A significant increase in respiratory support to maintain oxygen saturations within agreed acceptable limits that is new or above a baby's baseline
   - Signs of sepsis with shock
   - Encephalopathy
   - Multi-organ failure
4. **Can children be enrolled if they have suspected COVID-19, but a negative SARS-CoV2 PCR on a respiratory sample?** Yes, children with suspected or confirmed COVID-19 may be enrolled in RECOVERY. This includes children presenting with evidence of severe inflammation with single or multi-organ dysfunction, who test negative for SARS-CoV2, but who are suspected of having COVID-19.

5. **What if the child has suspected "Paediatric multisystem inflammatory syndrome temporally associated with COVID-19" (click to link to RCPCH case definition and guidelines)?** The patient can be entered into the trial. For COVID-19 positive patients, first line enrolment can happen at any time. For COVID-19 negative patients with this syndrome, they will usually be enrolled **following** initial treatment with intravenous immunoglobulin +/- high dose aspirin (if Kawasaki Disease-like presentation) **and if** there is no clinical improvement **or** there is clinical deterioration. If a >1 year old patient is seriously unwell (treated on PICU), 2nd line randomisation can occur immediately following 1st line randomisation. As the trial is open label, clinicians will be aware of randomisation and will be able to consider further or additional therapies considered clinically necessary (discuss with local paediatric infectious diseases, rheumatology or intensive care specialists on call).

6. **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 next section on "Randomisation: intervention-specific considerations" for additional guidance (page 6 – 7).

7. **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 from the receiving site. If required, the patient can be entered into the second randomisation (tocilizumab vs. standard of care) by the receiving site (refer to the section on "Second randomisation of paediatric participants" – page 11).

8. **Are the drugs safe for children?** The paediatric group for the trial has reviewed the safety literature (Annex A), and experience around using these drugs for other conditions, and consider that participation in the trial is reasonable for children. The regulators (MHRA and HRA) did not raise objections to the inclusion of children.

9. **What if the child is already taking antiretroviral drugs**? The patient can be entered into the trial but will not be randomised to the lopinavir-ritonavir arm.

10. **Clarification on lopinavir-ritonavir age limits**
    - Preterm infants with a corrected gestation age of <42 weeks would be unsuitable.
    - A neonate born at 42 weeks but 7 days old would be unsuitable.
    - A neonate born at 41 weeks and 8 days old would be unsuitable.

11. **What if the child is currently receiving or has received a recent course of corticosteroid?** The patient can be entered into the trial, and the corticosteroid arm remains an option for the 1st stage randomisation. However, if the attending clinician intends to prescribe e.g. pulse methylprednisolone followed by additional systemic corticosteroid (e.g. a further 2-3 week course of prednisolone following the pulse of methylprednisolone), the corticosteroid arm should be indicated as "unsuitable" (The child will be randomised to the other available arms and corticosteroid can be given as part of standard of care).

12. **What if the child is already taking hydroxychloroquine**? The patient can be entered into the trial but will not be randomised to the hydroxychloroquine or azithromycin arm as co-administration may increase the risk of cardiac side effects.

13. **What if the child is already taking azithromycin or other macrolides (prophylaxis or treatment dose)**? The patient can be entered into the trial but will not be randomised to the hydroxychloroquine or azithromycin arm as co-administration may increase the risk of cardiac side effects.

14. **Can we proceed directly to the second randomisation (standard care vs. tocilizumab)?** No, the patient must go through the mandatory 1st randomisation. Once you have completed the 1st randomisation online, the option for the 2nd randomisation will appear. You can start the two allocated interventions at the same time.

15. **What if the child is on regular tocilizumab**? The patient can only be entered into 1st randomisation. The patient cannot be entered into the 2nd randomisation if there has been treatment with anti-interleukin 6, anti-interleukin 6 receptor antagonists, or Janus Kinase inhibitors within the 30 days prior to 2nd randomisation.

16. **Can a child who has already received IVIG take part in the second randomisation (standard care vs. tocilizumab)?** Yes

17. **What if the child is nil by mouth?** The patient can be entered into the trial, but the attending clinician should indicate on the randomisation page that lopinavir-Ritonavir and hydroxychloroquine are unsuitable for the patient. (Note: select azithromycin as well if intravenous azithromcyin supply is not available). The patient will then be randomised to the remaining arms.

18. **What if the child has a profound diarrhoea?** The patient can be entered into the trial, but the attending clinician should consider how this may impact on medication absorption. The clinician may then wish to indicate on the randomisation page that lopinavir-Ritonavir and hydroxychloroquine are unsuitable for the patient. (Note: select azithromycin as well if intravenous azithromcyin supply is not available). The patient will then be randomised to the remaining arms.

FAQ – Clinical management

1. **If the child is randomised to lopinavir-ritonavir, should we wait for HIV testing result before starting treatment?** HIV testing should be done in all children randomised to lopinavir-ritonavir, but do not delay treatment while waiting for results.
2. **The child is randomised to hydroxychloroquine and we have carried out the baseline ECG, do we need to repeat the ECG?** Repeat ECGs should be considered depending on the patient's baseline risk and carried out if it has been deemed clinically necessary. We recommend that repeat ECG is carried out if baseline ECG shows QTc at the upper limit of normal (https://www.mdcalc.com/corrected-qt-interval-qtc).
3. **Can the route of administration of the intervention be switched during the 10 days if clinically indicated?** Yes
4. **My patient has not been randomised to the corticosteroid arm. Can we still add in corticosteroid?** Yes, the attending 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.
5. **The child has been randomised to the corticosteroid arm. Can we use additional corticosteroid (e.g. intravenous high dose pulse methylprednisolone 10 - 30 mg/kg) if it was considered clinical necessary by the attending clinician?** Yes, pulsed methylprednisolone (usually 10 - 30 mg/kg for 3 days) can be given at the discretion of the attending clinician. However, if the attending clinician intends to prescribe e.g. pulse methylprednisolone followed by additional systemic corticosteroid (e.g. a further 2-3 week course of prednisolone following the pulse of methylprednisolone), the corticosteroid arm should be indicated as "unsuitable" (The child will be randomised to the other available arms and corticosteroid can be given as part of standard of care).
6. **The child has not been randomised to the azithromycin arm. Can we still add in azithromycin or a macrolide?** Yes, the attending clinician can add in azithromycin or a macrolide if it has been deemed clinically necessary and the patient can continue to be treated as per the RECOVERY clinical trial. However, clinicians should consider potential drug-drug interactions, in particular for patients randomised to hydroxychloroquine arm due to possible increased risk of cardiac side effects.
7. **What if the child vomits**? If the child vomits less than 30 minutes after taking an oral dose, give the same dose again if it has been clinically appropriate.

Randomisation: intervention-specific considerations

In additional 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
Lopinavir-Ritonavir Kaletra®	Select "Yes" to question A14 to reflect that lopinavir-ritonavir is **unsuitable** for the patient if any of the following circumstances apply: - Corrected gestation age of < 42 weeks - Patient with postnatal age of < 14 days - Known HIV infection - Severe hepatic insufficiency - The route of drug administration for the patient is limited to parenteral route only. - Known hypersensitivity to lopinavir-ritonavir - Patient is on a drug which interacts (clinically significantly) with lopinavir-ritonavir which cannot be stopped: https://www.covid19-druginteractions.org/ - Patient is being given drugs using polyurethane feeding tube and non-polyurethane tube cannot be sourced. For question A15 which relates to the availability of lopinavir-ritonavir at your site, please remember to check with pharmacy the availability of your required formulation first. For example, if the patient requires oral solution and there is no stock of oral solution, select "No" to A15 relating to lopinavir-ritonavir.
Corticosteroid	No additional considerations
Hydroxychloroquine	Select "Yes" to question A14 to reflect that hydroxychloroquine is **unsuitable** for the patient if any of the following circumstances apply: - Patient with postnatal age of < 6 months - Known prolonged QTc interval or other cardiac problems - Known hypersensitivity to 4-aminoquinoline compounds - The route of drug administration for the patient is limited to parenteral route only. - Patient is on a drug which interacts (clinically significantly) with hydroxychloroquine which cannot be stopped: https://www.covid19-druginteractions.org/

Randomisation: intervention-specific considerations

Drug	Additional considerations relating to randomisation
Azithromycin	Select "Yes" to question A14 to reflect that azithromycin is **unsuitable** for the patient if any of the following circumstances apply: - Known prolonged QTc interval - Known hypersensitivity to any macrolide or ketolide antibiotic - Patient is on prophylaxis azithromycin or other macrolides - Patient is on a drug which interacts (clinically significantly) with azithromycin which cannot be stopped For question A15 which relates to the availability of azithromycin at your site, please remember to check with pharmacy the availability of your required formulation first. For example, if the patient cannot be given drug enterally and there is no stock of intravenous infusion, select "No" to A15 relating to azithromycin.
Tocilizumab	Select "Yes" to question A14.1 to reflect that tocilizumab is **unsuitable** for the patient if any of the following circumstances apply: - Patient < 1 year - Known hepatitis B, hepatitis C or tuberculosis infection - Known hypersensitivity to tocilizumab - Patient received treatment with anti-interleukin 6, anti-interleukin 6 receptor antagonists, or Janus Kinase inhibitors within the 30 days prior to 2nd randomisation.

Paediatric dosing information

Duration of treatment (apart from tocilizumab) = 10 days or until discharge from hospital

Arm	Route	Weight [#]	Dose (Duration for all arms = 10 days or until discharge from hospital)
No additional treatment	-	-	-
Lopinavir-Ritonavir (Kaletra®) - 80/20mg in 1mL oral solution - 100/25mg tablet - 200/50mg tablet Tablets must NOT be crushed	Oral or Nasogastric	Preterm infants with a corrected gestation age of <42 weeks or neonates with postnatal age of < 14 days excluded	
		≤ 5 kg	0.2 mL/kg every 12 hours
		6 - 9 kg	1.5 mL every 12 hours
		10 - 13 kg	2 mL every 12 hours
		14 - 19 kg	2.5 mL every 12 hours or 200/50 mg every 12 hours
		20 - 24 kg	3 mL every 12 hours or 200/50 mg every 12 hours
		25 - 34 kg	4 mL every 12 hours or 300/75 mg every 12 hours
		≥ 35 kg	5 mL every 12 hours or 400/100 mg every 12 hours
Corticosteroid - Oral solution* - Tablet* - Soluble tablet* - Solution for injection* *various strengths available	Oral or Nasogastric or Intravenous	All Including pre-term neonates	**Hydrocortisone (IV) – additional option for Preterm infants with a corrected gestation age of <40 weeks:** 0.5 mg/kg every 12 hours for 7 days and then 0.5mg/kg once daily for 3 days or **Prednisolone (Oral/NG):** 1 mg/kg once daily (max: 40 mg; doses can be rounded as per routine clinical practice) or **Methylprednisolone sodium succinate (IV):** 0.8 mg/kg once daily (max: 32 mg) or **Dexamethasone (Oral/NG/IV):** 150 micrograms/kg (as base) once daily (max: 6 mg)

[#] Weight to be rounded to the nearest kg unless dosage expressed as mg/kg or mL/kg.

Duration of treatment (apart from tocilizumab) = 10 days or until discharge from hospital

Arm	Route	Weight [#]	Dose (Duration for all arms = 10 days or until discharge from hospital)
Hydroxychloroquine sulfate Dose expressed as hydroxychloroquine sulfate - 200mg tablet (tablets may be crushed and dispersed in water to allow for aliquot dosing – see note below) **A baseline ECG (to check QTc interval) is recommended for paediatric patients randomised to hydroxychloroquine.**	Oral or Nasogastric	Infants with postnatal age of <180 days excluded	
		5 - 10 kg	Initial dose: 100 mg 6 hours after initial dose: 100 mg 12 hours after initial dose: 50 mg 24 hours after initial dose: 50 mg Then 50 mg every 12 hours
		11 - 20 kg	Initial dose: 200 mg 6 hours after initial dose: 200 mg 12 hours after initial dose: 100 mg 24 hours after initial dose: 100 mg Then 100 mg every 12 hours
		21 - 39 kg	Initial dose: 400 mg 6 hours after initial dose: 400 mg 12 hours after initial dose: 200 mg 24 hours after initial dose: 200 mg Then 200 mg every 12 hours
		≥ 40 kg	Initial dose: 800 mg 6 hours after initial dose: 800 mg 12 hours after initial dose: 400 mg 24 hours after initial dose: 400 mg Then 400 mg every 12 hours
Azithromycin - 40mg in 1mL oral suspension - 250mg tablet/capsule - 500mg tablet/capsule - 500mg powder for solution for infusion	Oral or Nasogastric or Intravenous	≤ 16 kg Including preterm neonates	10 mg/kg once daily
		17 - 25 kg	200 mg once daily
		26 - 35 kg	300 mg once daily
		36 - 45 kg	400 mg once daily
		≥ 46 kg	500 mg once daily
Convalescent Plasma	Intravenous		5 mL/kg of ABO compatible convalescent plasma intravenous up to standard adult dose of 275 mLs per day on study days 1 and 2. Minimum of 12 hour interval between 1st and 2nd units. Convalescent plasma for neonates and infants up to one year of age needs to be ordered on a named patient basis from the relevant National Blood Service to ensure the unit meets neonatal requirements. Data transfer storage and retention will be in line with NHSBT standard procedures and protocols.

[#] Weight to be rounded to the nearest kg unless dosage expressed as mg/kg or mL/kg.

Second stage randomisation (Patients < 1 year of age will NOT be eligible)

Arm	Route	Weight	Dose
No additional treatment	-	-	-
Tocilizumab	Intravenous	Infants < 1 year excluded	
		< 30 kg	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	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.

Second randomisation of paediatric participants

The RECOVERY protocol includes a second randomisation for participants who fulfil the following criteria:

(i) Randomised into the RECOVERY trial no more than 21 days ago

(ii) Clinical evidence of progressive COVID-19:

  a. oxygen saturation <92% on room air or requiring oxygen
  (or in children (age <18 years), significant systemic disease with persistent pyrexia, with or without evidence of respiratory involvement)[1]; and

  b. C-reactive protein ≥75 mg/L

(iii) No medical history that might, in the opinion of the attending clinician, put the patient at significant risk if he/she were to participate in this aspect of the RECOVERY trial.

The organisation of children's services for COVID-19 will involve transferring children to regional tertiary units for specialist services and/or paediatric intensive care should their condition satisfy the above criteria, where interventions like tocilizumab (hence this second randomisation) will be considered. A copy of the RECOVERY trial consent form and first randomisation allocation sheet should be sent with the child on transfer.

The current trial web-based computer system only allows participants to be "second randomised" at the site where they were first recruited into the trial. Therefore the following procedure must be followed to allow children who have been recruited at a referring hospital and subsequently transferred to a tertiary centre to be entered into this second randomisation.**The RECOVERY paediatric lead at the tertiary centre/PICU will assume trial responsibility for the child upon arrival.**

Procedure

1. **Tertiary centre/PICU RECOVERY team** contact referring hospital RECOVERY team (ideally the referring hospital's RECOVERY paediatric lead if possible) to discuss second randomisation and agree that it is reasonable to proceed.

2. If agreed, **Tertiary Centre/PICU RECOVERY team** send baseline information required for second randomisation to referring hospital. This information includes:
   - Name of treating clinician (at PICU)
   - Current oxygen and ventilation requirements
   - Whether participant has significant systemic disease with persistent pyrexia
   - Latest laboratory results for CRP, ferritin and creatinine (copies of laboratory reports)

   The participant's study ID should be added to these documents. This information should be shared using NHSmail whenever possible. If other e-mail is used then any identifiers should be redacted.
3. **Referring hospital RECOVERY team** complete second randomisation on trial web-based randomisation system (indicating the name of the tertiary/PICU clinician and hospital in response to question A2 "Name of treating clinician").

4. **Referring hospital RECOVERY team** share PDF of allocation notification with tertiary unit/ PICU.

[1] A small number of children (age <18 years) present with atypical features, including a hyperinflammatory state and evidence of single or multi-organ dysfunction. Some do not have significant lung involvement.
(see: https://www.rcpch.ac.uk/sites/default/files/2020-05/COVID-19-Paediatric-multisystem-%20inflammatory%20syndrome-20200501.pdf)

5. **Referring hospital RECOVERY team** store data received from tertiary unit/PICU in participant's medical record along with entry to describe second randomisation and a copy of the allocation notification from the RECOVERY trial web-based randomisation system.

6. **Tertiary unit/PICU RECOVERY team** prescribe tocilizumab if necessary and document second randomisation process in medical record (with copy of allocation notification).

7. 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 administration

Drug	Specific administration issues
Lopinavir-Ritonavir Kaletra®	**Tablets** - Do NOT crush tablets as administration of crushed lopinavir/ritonavir tablets to children significantly reduced lopinavir and ritonavir exposure by up to 47%. (DOI: 10.1097/QAI.0b013e318232b057) **Oral solution** - Should be given with food to enhance absorption. If no food, continue with dose administration. - Considering Kaletra® oral solution should be given with food, administration with breast/formula milk in neonates is not anticipated to pose any issues (although specific data is not available). - Medicines used in neonates sometimes contain alcohol and propylene glycol. Each mL of Kaletra® contains 356.3 mg of alcohol (42.4% v/v) and 152.7 mg of propylene glycol (15.3% w/v). - Has a very bitter taste. The following strategies may help but check patient's food allergy history first: mix with small amount of chocolate milk; give ice chips/frozen fruit juice to dull the taste buds; give peanut butter to coat the mouth; give strong tasting foods/drinks after administration. - Not recommended for use with polyurethane feeding tubes due to potential incompatibility. Check feeding tube material before administration. Enteral GBUK manufacture Carefeed® tube which is made of PVC (http://www.gbukenteral.com/products/carefeed- feeding-and-drainage-tubes/).
Corticosteroid	Corticosteroid arm will include different corticosteroid options (dexamethasone, prednisolone or methylprednisolone) at the discretion of the treating clinician. For infants with a corrected gestation age of < 40 weeks, hydrocortisone is recommended. **Dexamethasone -** prescribed in units of dexamethasone **base**. **Prednisolone -** If soluble prednisolone tablet or oral solution is not available, prednisolone tablets may be crushed and dispersed in water.
Hydroxychloroquine	- Hydroxychloroquine should be prescribed in units of **hydroxychloroquine sulfate**. - Has a bitter taste. The following strategies may help but check patient's food allergy history first: give ice chips/frozen fruit juice to dull the taste buds; give strong tasting foods/drinks after administration. **Doses less than 200mg** - Crush and disperse one 200mg tablet in 10mL of water; stir-well and leave for 5 minutes. - Measure a proportion to obtain the required dose using an oral/enteral syringe.

Trial drugs administration

<table>
<tr><th>Drug</th><th>Specific administration issues</th></tr>
<tr><td>Azithromycin</td><td>
Oral suspension

Reconstitute with water as per manufacturer’s instructions.
Shelf-life of reconstituted suspension: as per manufacturer’s instructions.
Considering azithromycin may be taken together with food, administration with breast/formula milk in neonates is not anticipated to pose any issues (although specific data is not available).

Powder for solution for infusion 500 mg (Brand: Zedbac)

Add 4.8 ml of sterile water for injections to the 500 mg vial and shaking the vial until all the drug is dissolved.
Reconstituted solution contains 100 mg azithromycin per mL.
Dilute the reconstituted solution as follow using a suitable diluent (0.9% sodium chloride, 5% glucose or 0.45% sodium chloride):

<table>
<tr><th>Dose</th><th>Amount of reconstituted solution</th><th>Amount of diluent</th></tr>
<tr><td>< 100 mg</td><td>1 mL</td><td>49 mL*</td></tr>
<tr><td>100 to 199 mg</td><td>Required amount between 1 to 1.9 mL</td><td>100 mL</td></tr>
<tr><td>200 mg</td><td>2 mL</td><td>100 mL</td></tr>
<tr><td>300 mg</td><td>3 mL</td><td>250 mL</td></tr>
<tr><td>400 mg</td><td>4 mL</td><td>250 mL</td></tr>
<tr><td>500 mg</td><td>5 mL</td><td>250mL</td></tr>
</table>
*For doses < 100mg, the diluted solution contains 100mg in 50mL. Measure the required volume to deliver the required dose.

Set the infusion pump and administer as an intravenous infusion over 60 minutes.
After dilution, the prepared solution for infusion is physically and chemically stable at 25°C for 24 hours (storage at 2 - 8°C would be preferred).

Medusa recommends that the drug should not be infused with any other medicines. Additional Y-site compatibility information available via DynaMed (some common drugs are provided here):

Compatible: amikacin, fluconazole, methylprednisolone, milrinone
Incompatible: Midazolam,
Caution: ceftriaxone, cefotaxime, clindamycin, gentamicin

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</table>

Trial drugs administration

Drug	Specific administration issues
Tocilizumab	Based on vial size availability, doses can be rounded in accordance to the Roche dosing guide in order to minimise wastage and to allow doses to be measured accurately. Refer to page 7: 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).

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.

Lopinavir-Ritonavir (Kaletra®)

Dosing is broadly based on SmPC licensed posology for the treatment of HIV infection in children 14 days or older. To facilitate administration, paediatric HIV dosing endorsed by Children's HIV association has been adopted (https://www.chiva.org.uk/guidelines/paediatric-dosing-2019/). The high alcohol and propylene glycol content in the oral solution formulation is thought to be the primary reason why it is not suitable for preterm neonates or neonates < 14 days old.

Corticosteroid

Similar to adults, the value of corticosteroids as adjuvant therapy in acute respiratory distress syndrome in children is widely debated (DOI: 10.21037/atm.2019.07.77). WHO has prioritised the evaluation of corticosteroids in clinical trials to assess safety and efficacy (https://www.who.int/blueprint/priority-diseases/keyaction/Global_Research_Forum_FINAL_VERSION_for_web_14_feb_2020.pdf?ua=1).

For preterm infants with a corrected gestation age of <40 weeks: As clinical experience with the choice of corticosteroids vary across paediatric subgroups, the choice of corticosteroids is at the discretion of the clinical team except in preterm infants (corrected gestation age of < 40 weeks) where hydrocortisone is recommended. The dose of hydrocortisone for preterm neonates 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.

Hydroxychloroquine

Hydroxychloroquine is a hydroxylated version of chloroquine, and the two drugs have a similar mechanism of action. Hydroxychloroquine is considered better tolerated than chloroquine. Adverse effects of hydroxychloroquine usually relate to long term cumulative use of the drug.

Products containing hydroxychloroquine marketed in the UK are licensed for juvenile idiopathic polyarthritis, discoid and systemic lupus erythematosus in "children". In the US and Canada, it is also licensed for the treatment of malaria in "children".

- US hydroxychloroquine sulfate licensed posology for the treatment of malaria in "children": 13 mg/kg (10 mg/kg base), not to exceed 800 mg (620 mg base) followed by 6.5 mg/kg (5 mg/kg base), not to exceed 400 mg (310 mg base), at 6 hours, 24 hours and 48 hours after the initial dose. Therefore, cumulative dose administered over 3 days = 25 mg/kg base.

- UK licensed posology of hydroxychloroquine sulfate for juvenile idiopathic polyarthritis, discoid and systemic lupus erythematosus in "children": 5 mg/kg base daily (max 310mg base) based on ideal body weight.
- Hydroxychloroquine sulfate is also used in the treatment of interstitial lung disease in children including neonates at a dose of 5 - 7.7 mg/kg base daily. This is off-label use of the drug.
- UK chloroquine phosphate licensed posology for the treatment of malaria: 10 mg/kg base, followed by 5 mg/kg base, at 6 hours, 24 hours and 48 hours after the initial dose. Therefore, cumulative dose administered over 3 days = 25 mg/kg base. The licensed posology is also presented by age bands. By age bands, cumulative dose over 3 days is equivalent to approx. 15 - 50 mg/kg base depending on the weight of the child.
- A number of published studies have also investigated the use of higher dose chloroquine in paediatric patients and it was generally reported as well tolerated:

Ursing et al. (2020)	DOI: 10.1128/aac.01846-19	50mg/kg base over 3 days and 70mg/kg base over 5 days
Ursing et al. (2019)	DOI: 10.1128/AAC.01111-08	77-81 mg/kg base over 5 days
Ursing et al. (2011)	DOI: 10.1093/infdis/jiq001	50mg/kg base over 3 days
Kofoed et al. (2007)	DOI: 10.1016/j.trstmh.2006.05.008	50mg/kg base over 3 days
Kofoed et al. (2007)	DOI: 10.4269/ajtmh.2002.67.28	50mg/kg base over 3 days
Scragg & Powell (1968)	DOI: 10.1136/adc.43.227.121	15 mg/kg base daily for 3 weeks
Scragg & Powell (1966)	DOI: 10.1136/adc.41.219.549	15 mg/kg base daily for 3 weeks
Cañete et al. (2010)	West Indian Med J. 2010 Dec; 59(6):607-11.	10 mg/kg base twice daily for 5 days

Azithromycin

Azithromycin is licensed for the treatment of bacterial infection in "children and adolescents", although SmPC indicates limited data for under 1 year. The intravenous formulation is not licensed in children <18 years. While bioavailability after oral administration is approximately 37% in both adults and children, licensed posology in adults is the same (500mg once daily) for both oral and intravenous formulations; this possibly reflects the severity of infection requiring intravenous formulation.

The standard treatment duration is 3 days in the UK (5 days tend to be used in the US). In clinical practice, treatment of up to 17 days is recommended in children with lyme disease, and azithromycin 3 times a week is recommended in the treatment of chronic pseudomonas aeruginosa infection in cystic

fibrosis patients. The use of intravenous azithromycin at 10-20 mg/kg/day in preterm babies for management of chronic lung disease for up to 10 days has previously been studied, with an on-going NIHR funded trial (AZTEC trial: https://aztec-trial.uk/) using similar doses.

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.

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