Paediatric Patients

	RECOVERY - Adults		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 - Azithromycin	Randomisation part B - No additional treatment - Convalescent plasma - **Synthetic neutralising antibodies**	Same options but in randomisation part A, the arms for paediatric patients are: - No additional treatment - Corticosteroid arm **remains open** with different dosing options for patients with PIMS-TS phenotype (high dose methylprednisolone) and for neonates/infants <=44 weeks gestation with acute respiratory COVID-19 (low dose steroids). - Intravenous immunoglobulin - Azithromycin Lopinavir-Ritonavir and hydroxychloroquine arms are **closed.**
	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 of COVID-19 be recruited?** No.
2. **Which child should be considered for RECOVERY?**

   Respiratory presentations of acute COVID-19: 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:

   - Unventilated requiring FiO2 >40% to maintain saturation 88-97%
     and/or
   - Ventilation: Oxygenation index: 4 ≤ 16 / Oxygenation saturation index: 5 ≤ 12.3

   Paediatric multisystem inflammatory syndrome temporally associated with COVID-19 (PIMS-TS): Children can specifically be recruited to RECOVERY if they have suspected PIMS-TS. Following the NHS England national consensus process (publication pending), additional arms have been added to randomisation 1 to address areas of equipoise identified for the treatment of children with PIMS-TS. Randomisation 1 allows the comparison of high-dose steroids (10mg/Kg once/day for 3 days) vs no additional treatment (in presence and absence of IVIg) and IVIg (2g/Kg single dose) vs no additional treatment (in presence and absence of steroids).

   This design:
   - Allows investigators to use steroids or IVIg as standard care if deemed necessary (but also to recruit moderate cases to no additional treatment)
   - Allows effects of steroids and IVIg to be compared with no additional treatment separately (in presence and absence of other drug)
   - Allows wide spectrum of severity to be recruited because some treatment can be guaranteed but not absolutely required
   - Second randomisation to tocilizumab is still available

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

Potential clinical scenarios (>44 weeks gestation – 18th birthday): protocol allows randomisation 1A or 1B or both.

(N.B. Neonates/infants (corrected gestational age of ≤44 weeks) can be recruited to the low dose steroid arm – do not use this table)

R= recommended option; Unsuitable = not recommended by paediatric working group

		Acute respiratory presentation of COVID-19	Acute respiratory presentation with evolving inflammatory phenotype	PIMS-TS			
	Phenotypes	**Primarily respiratory symptoms**	**Initially respiratory symptoms (dexamethasone given, any doses), now deteriorating with features of PIMS-TS**	**Moderate PIMS-TS (nothing given so far)**	**Severe PIMS-TS (methylpred* given before randomisation or current treatment) * or >=2mg/kg of prednisolone or equivalent**	**Severe PIMS-TS (IVIg given before randomisation)**	**Severe PIMS-TS ((IVIg and methylpred* given before randomisation) * or >=2mg/kg of prednisolone or equivalent**
1st stage interventions, randomisation A	**No additional treatment**	R	R	R	R	R	R (option to be able to move to 2nd stage randomisation)
	Azithromycin	R	R	Unsuitable unless acute respiratory COVID suspected	Unsuitable unless acute respiratory COVID suspected	Unsuitable unless acute respiratory COVID suspected	R (option to be able to move to 2nd stage randomisation)
	Steroid (high dose)	Unsuitable	R	R	Unsuitable	R	Unsuitable
	IVIg	Unsuitable	R	R	R	Unsuitable	Unsuitable
1st stage interventions, randomisation B	**No additional treatment**	R	R	R	R	R	R
	Convalescent plasma	R	R	Caution. See FAQ 12 below	Caution. See FAQ 12 below	Caution. See FAQ 12 below	Caution. See FAQ 12 below
	Synthetic neutralising antibodies	R (age restriction) See FAQ 13	Unsuitable	Unsuitable	Unsuitable	Unsuitable	Unsuitable
2nd stage interventions	**No additional treatment**	R	R	R	R	R	R
	Tocilizumab	R, if failure to respond following 1st stage interventions	R, if failure to respond following 1st stage interventions	Probably unsuitable, unless deterioration or failure to respond following 1st stage interventions. See FAQ 16	R, if failure to respond following 1st stage interventions. See FAQ 16	R, if failure to respond following 1st stage interventions. See FAQ 16	R, if failure to respond following 1st stage interventions. See FAQ 16

3. **Which neonates/infants should be considered for RECOVERY?** For neonates/infants with a corrected gestational age of <=44 weeks, 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

    N.B. Neonates/infants with corrected gestational age <=44 weeks should not be recruited to IVIg or high dose methyl prednisolone arms, options available are: no additional treatment, azithromycin, low dose steroids (according to neonatal dosing schedule).

4. **Can children be enrolled if they have suspected acute respiratory COVID-19 or PIMS-TS, but a negative SARS-CoV2 PCR on a respiratory sample?** Yes, children with clinically suspected or confirmed COVID-19 may be enrolled in RECOVERY. This includes children who test negative for SARS-CoV2, who are suspected of having PIMS-TS or have clinically suspected COVID-19 (typical symptoms and compatible CXR).

5. **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 on page 3 and the next section on "Randomisation: intervention-specific considerations" for additional guidance (page 6).

6. **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. 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 11-12).

7. **Dexamethasone is now the NHS standard of care for patients with COVID-19 needing oxygen. Why is corticosteroid still part of the RECOVERY protocol for children?** Children (outside of the neonatal period) admitted to hospital with acute COVID-19 respiratory disease requiring oxygen should be considered for treatment with dexamethasone as part of standard of care. Neonates/infants (corrected gestational age of ≤44 weeks) can be recruited to the low dose steroid arm in RECOVERY. Where a child has been diagnosed with PIMS-TS, the NHS England national consensus process (publication pending) has demonstrated equipoise regarding the role of high dose steroids, which are now included in the first stage interventions in RECOVERY, for children over corrected gestational age of 44 weeks and younger than 18 years old.

8. **What if a child with respiratory COVID phenotype is currently receiving or has received a recent course of low dose of corticosteroid but is now showing signs suggestive of inflammatory phenotype?** The patient can be entered into the trial – see FAQ 2 table above, page 3.

9. **Why are neonates/infants with a corrected gestational age of <=44 weeks excluded from the intravenous immunoglobulin (IVIg) arm?** This arm of the study is specifically included for patients with PIMS-TS phenotype. There are no reports of neonates <=44 weeks gestational age with PIMS-TS at the current time.

10. **What if the child has already received a dose of intravenous immunoglobulin (IVIg)?** The patient can be entered into the trial but will not be randomised to the IVIg arm, this should be marked as unsuitable. The patient will be randomised to the other available arms (standard of care, intravenous methylprednisolone, and azithromycin) unless the clinician has indicated any of these arms are "unsuitable".

11. **What if the child has already received a dose of steroids? If the patient has received >=2mg/kg of prednisolone (or equivalent),** the patient can be entered into the trial but will not be randomised to the methylprednisolone arm, this should be marked as unsuitable. The patient will be randomised to the other available arms (standard of care, IVIG, and azithromycin) unless the clinician has indicated any of these arms are "unsuitable".

12. **Can children be randomised to the convalescent plasma arm of RECOVERY?** Yes, individual investigators may choose to randomise neonates, infants and children to convalescent plasma, where it is available in a specific research site and local investigators consider this appropriate for that child. Specific scenarios are considered below:

    Acute respiratory presentation of COVID-19: Yes, all neonates, infants and children diagnosed with acute COVID-19 can be randomised to receive convalescent plasma or standard of care as part of RECOVERY, if available at the research site and local investigators consider this appropriate for that child, see table on page 3.

    Children with PIMS-TS: The receipt of IVIg either prior to randomisation or as the allocated 1st stage intervention means investigators should reserve convalescent plasma in PIMS-TS as a potential entry to RECOVERY for those children who have received both IVIg and high dose methyl prednisolone as treatment prior to consideration of entry to RECOVERY (see table on page 3).

    While to date there are no safety concerns reported for convalescent plasma in children or adults, the RECOVERY paediatric working group have not yet achieved consensus on the relative risks and benefits of convalescent plasma in children with COVID-19 or PIMS-TS phenotype. This is because of both the potential, but as yet unproven, antibody-mediated contribution to the pathogenesis of PIMS-TS and because there is still enhanced safety monitoring around its use in adult disease.

13. **Can children be randomised to the synthetic neutralising antibodies arm of RECOVERY?**
Yes, individual investigators may choose to randomise children (≥12 years and ≥40kg) to synthetic neutralising antibodies for children with acute respiratory presentation of COVID-19, where it is available in a specific research site and local investigators consider this appropriate for that child. Synthetic neutralising antibodies are contra-indicated in children who have received IVIg during current admission. In addition, for children with PIMS-TS, this should be marked as unsuitable.

14. **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 azithromycin arm, this should be marked as unsuitable.

15. **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, if necessary.

16. **Are all patients with PIMS-TS suitable for the second randomisation (standard care vs. tocilizumab)?** No. Children with mild-moderate PIMS-TS are likely to be unsuitable for randomisation to 2nd stage interventions, unless they clinically deteriorate or there is failure to respond to 1st stage randomisation, with evidence of ongoing fever and inflammation. Children with more severe disease would be suitable for 2nd stage randomisation, if they fail to respond to 1st stage interventions, with ongoing evidence of fever and inflammation.

17. **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.

FAQ – Clinical management

1. **Can the route of administration of the intervention be switched during the treatment period if clinically indicated?** Yes
2. **My patient has been randomised to hydrocortisone but no longer has intravenous access?** Off protocol steroids can be given by alternative route as clinically necessary; this should be recorded in the paediatric case report form.
3. **The child has been randomised to the corticosteroid arm and received 3 days of methylprednisolone according to protocol. Can we give a further 2-3 week course of prednisolone if considered clinically necessary by the attending clinician?** Additional steroids are not recommended and weaning is not considered necessary after 3 days of high dose methylprednisolone. Please consider 2nd stage randomisation, or alternative therapies. However, if the attending clinician still deems this clinically necessary, receipt of additional corticosteroids should be listed in the paediatric case report form.

4. **My patient has not been randomised to the corticosteroid arm. Can we still add in corticosteroid?** Off protocol steroids are not recommended. Please consider 2nd stage randomisation, or alternative therapies, prior to using off protocol corticosteroids unless deemed absolutely clinically necessary (for example if a child is randomised to SOC in both first and second stage randomisations and clinicians feel corticosteroids are clinically necessary at that stage). If additional corticosteroids are given, this should be recorded in the paediatric case report form.

5. **My Patient has been randomised to the IVIg arm and has received a total of 2g/kg of IVIg, according to protocol. Can we give further infusions of IVIg?** Repeat doses of IVIg are not recommended in the protocol, above a maximum of 2g/kg (which may be given as a single infusion or divided over more than one day). Please consider 2nd stage randomisation, prior to using off protocol infusions of IVIg, unless deemed absolutely clinically necessary. If off-protocol IVIg is given, this should be recorded in the paediatric case report form.

6. **My patient has not been randomised to the IVIg arm. Can we still use IVIg?** Use of off protocol IVIg is not recommended. Please consider 2nd stage randomisation, or alternative therapies, prior to using off protocol IVIg unless deemed absolutely clinically necessary (for example if a child is randomised to SOC in both first and second stage randomisations and clinicians feel IVIg is clinically necessary at that stage). If off-protocol IVIg is given, this should be recorded in the paediatric case report form.

7. **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 and receipt of azithromycin should be noted in the paediatric case report form.

8. **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.

9. **Is any dose adjustment required in a child with renal impairment?** No dosage adjustment is required for corticosteroids, azithromycin or tocilizumab. For IVIg and convalescent plasma, this should be managed as clinically necessary.

10. **What is the infusion rate for convalescent plasma?** Convalescent plasma should be administered in line with standard clinical practice. The Joint United Kingdom (UK) Blood Transfusion and Tissue Transplantation Services Professional Advisory Committee **(click to link to guidance)** recommends a typical infusion rate of 10-20 mL/kg/hr.

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
Corticosteroid	No additional considerations
Intravenous Immunoglobulin (IVIg)	Select "Yes" to question A14 to reflect that IVIg is **unsuitable** for the patient if any of the following circumstances apply: - Hypersensitivity to the active substance (human immunoglobulins) or to any of the excipients. - Patients with selective IgA deficiency who have **known** antibody against IgA.
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 prophylactic 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.
Synthetic neutralising antibodies	Select "Yes" to question A14 to reflect that Synthetic neutralising antibodies is **unsuitable** for the patient if any of the following circumstances apply: - Patient < 12 year or weight <40kg - Patient received treatment with IVIg during current admission
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

First stage randomisation – Part A

Arm	Route	Weight	Dose (Duration for all arms = 10 days or until discharge from hospital)
No additional treatment	-	-	-
Corticosteroid - Solution for injection* *various strengths available	Intravenous	All Including pre-term neonates	Neonates/infants with a corrected gestational age of ≤44 weeks **Hydrocortisone** (IV): 0.5 mg/kg every 12 hours for 7 days and then 0.5mg/kg once daily for 3 days
	Intravenous	All	For all other children (with PIMS-TS): **Methylprednisolone sodium succinate** 10 mg/kg (as base; max 1 gram) once daily for 3 days No additional oral corticosteroid should be prescribed to follow the 3 day treatment course.
Human normal immunoglobulin (IVIg) - solution for infusion *various strengths available	Intravenous	All	For children with corrected gestational age >44 weeks and <18 years with PIMS-TS phenotype: 2 g/kg as a single dose (Dose should be based on ideal body weight in line with NHS England guidance.)
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

First stage randomisation – Part B

Arm	Route	Weight	Dose
No additional treatment	-	-	-
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.
Synthetic neutralising antibodies (REGN10933 + REGN10987)	Intravenous	≥ 12 years And ≥ 40 kg	8 g (4 g of each monoclonal antibody)

Second stage randomisation (Patients < 1 year of age will <u>NOT</u> 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 supply and administration

Drug	Specific administration issues
Corticosteroid	All corticosteroid products should be supplied from local hospital stock (any brand with marketing authorisation) and refer to individual SmPC for administration information. **Note**: Version 8 of the protocol contains a typographical error. The route of administration with respect to hydrocortisone (for neonates/ infants with a corrected gestational age of <=44 weeks) should read by intravenous route only.
Intravenous Immunoglobulin (IVIg)	- Approval has been given for sites to use IVIg from local hospital stock by NHSE (and equivalent bodies in devolved nations). - Any brand with marketing authorisation can be used. - Dose should be calculated based on ideal body weight in line with NHSE guidance and refer to individual SmPC for administration information. - A diagnosis of PIMS-TS is listed on the National IVIg database with a **red** panel indication: • Kawasaki/Paediatric inflammatory multisystem syndrome (PIMS-TS) with confirmed Covid-19 • Kawasaki/Paediatric inflammatory multisystem syndrome (PIMS-TS) with suspected Covid-19 - Completion of the National IVIg database is mandatory.
Azithromycin	**Supply: DHSC via Immform** **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).

<table>
<tr>
<td>Azithromycin (continued)</td>
<td>
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
</td>
</tr>
<tr>
<td>Synthetic neutralising antibodies
(REGN10933 + REGN10987)</td>
<td>
Supply: Regeneron

- Preparation instructions: refer to RECOVERY pharmacy manual. The IMP preparation should preferably be undertaken by pharmacy within an aseptic unit. However, preparation on ward level can be made by individual site based on local risk assessment.
</td>
</tr>
</table>

continued **Synthetic neutralising antibodies** **(REGN10933 + REGN10987)**	Administration instructions - No pre-medication is recommended prior to infusion. - If required, allow the drug solution to equilibrate to room temperature. - Administer by intravenous infusion over 60 minutes. However, the infusion time may be extended to enhance tolerability but infusion must be completed within 4 hours (from time of preparation). - A sterile, non-pyrogenic, low-protein binding 0.2 or 0.22 micron in-line or add-on filter must be used. The filter membrane must be made of polyethersulfone (PES) membrane. - Do not infuse with any other medicines. - When the administration is complete, flush the infusion line with sufficient volume of sodium chloride 0.9% at the same infusion rate to ensure that all the drug solution has been administered. The flush volume should be greater than the priming volume of the infusion line. The infusion of synthetic neutralising antibodies should be interrupted if any of the following are observed (or worsen during the infusion): sustained/severe cough, rigors/chills, rash, pruritus, urticaria, diaphoresis, hypotension, dyspnoea, vomiting, or flushing. The reactions should be treated symptomatically, and the infusion may be restarted at 50% of the original rate once all symptoms have ceased (or returned to baseline) and at the discretion of the managing physician. If the managing physician feels there is medical need for treatment or discontinuation of the infusion other than described above, they should use clinical judgment to provide appropriate response according to typical clinical practice.
Tocilizumab	**Supply: DHSC via Immform** 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 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.

continued **Tocilizumab**	**≥ 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.

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 neonates/ infants with a corrected gestational age of <=44 weeks**, 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.

Intravenous Immunoglobulin (IVIg) – IVIg is licensed for replacement and immunomodulation therapy in children 0-18 years.

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.

Synthetic neutralising antibodies (REGN10933 + REGN10987) are two monoclonal antibodies under development by Regeneron Pharmaceuticals, Inc. The two antibodies bind specifically to the receptor binding protein of the spike glycoprotein of SARS-SoC-2 blocking viral entry into host cells. Currently, there is no data available in children.

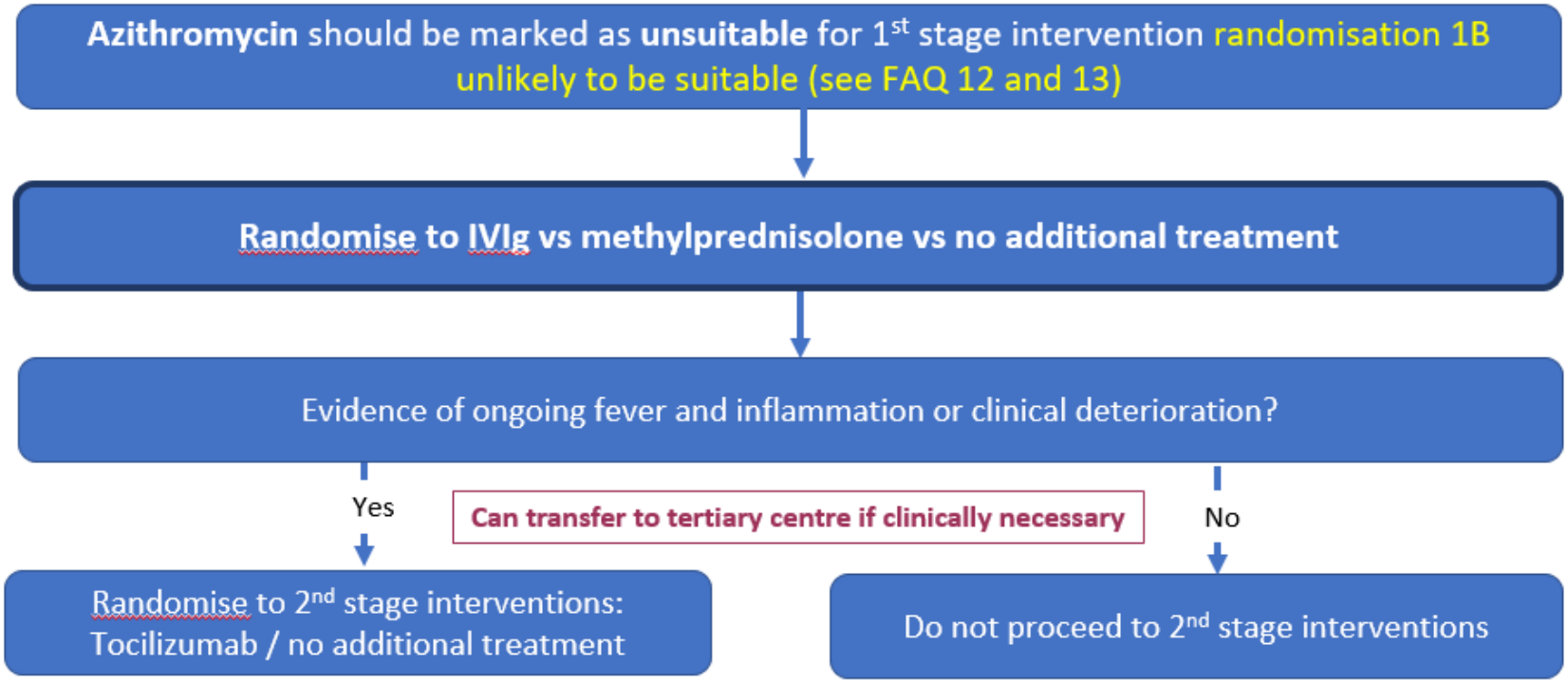
Change control

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

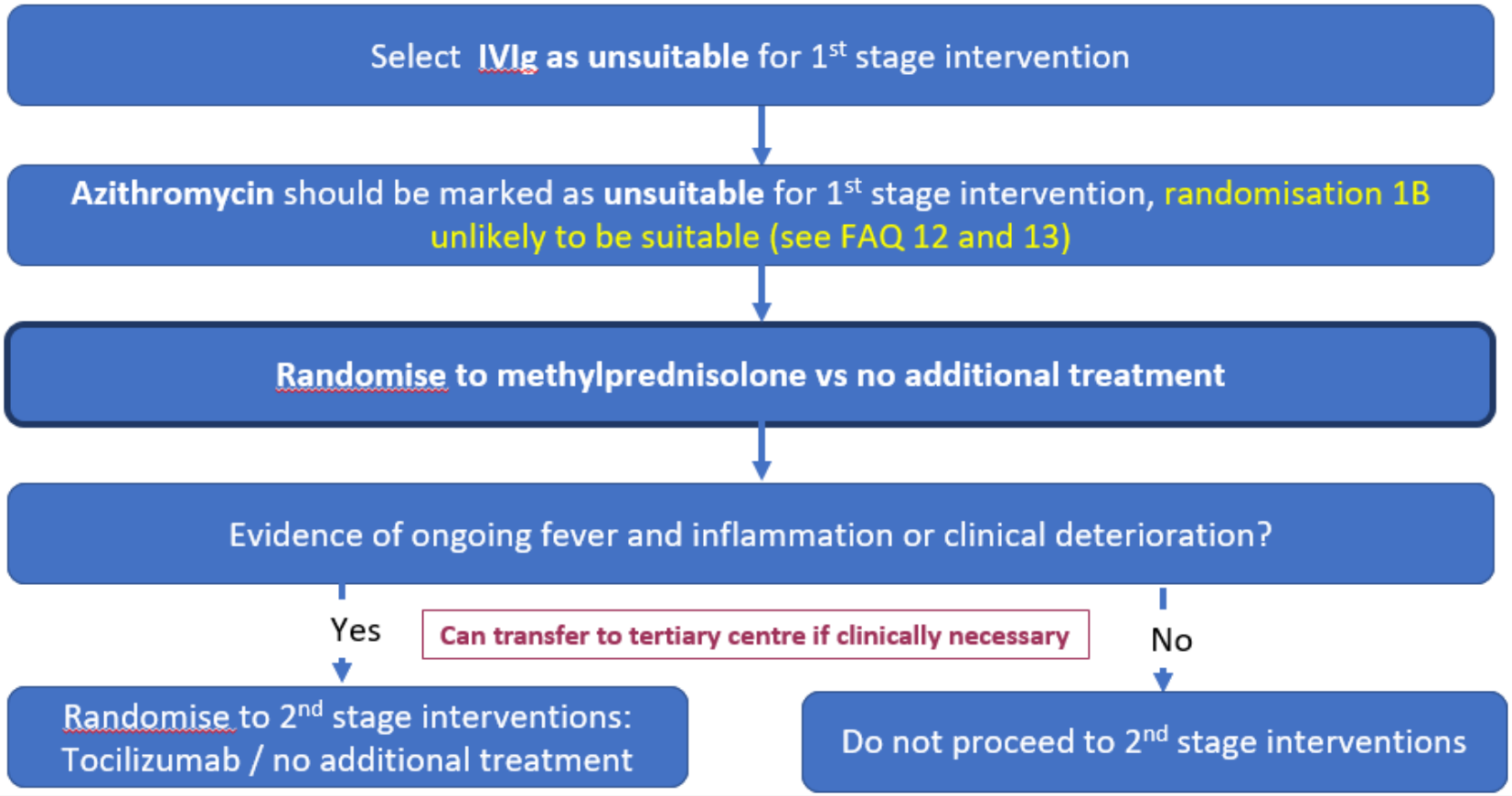
Scenario 1: Patient with PIMS-TS who has not received treatment* prior to enrolment

*IVIg, methylprednisolone or equivalent to ≥ 2mg/kg prednisolone

RECOVERY
Randomised Evaluation of COVID-19 Therapy



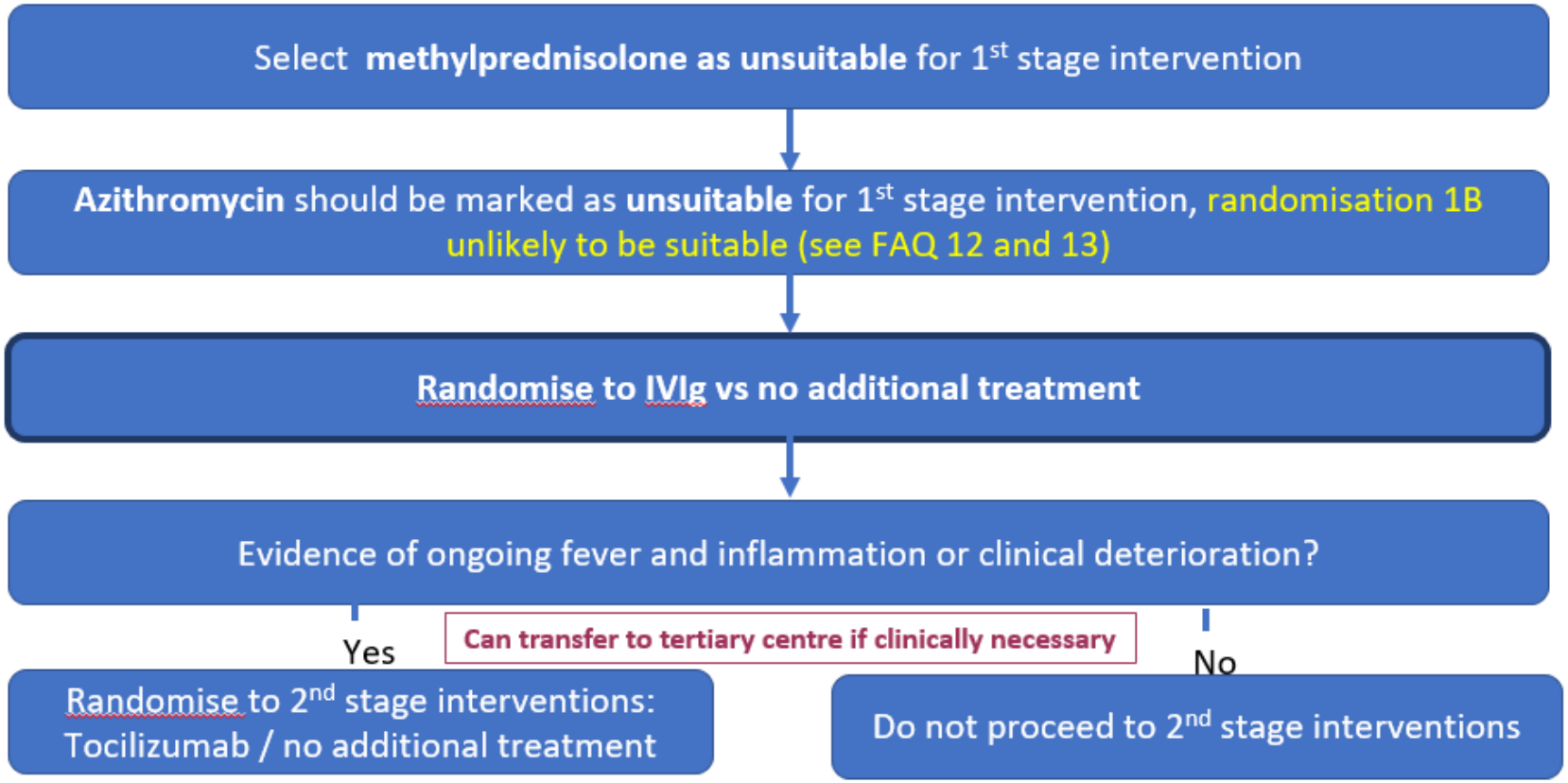
Scenario 2: Patient with PIMS-TS who has already received IVIg prior to enrolment



Scenario 3: Patient with PIMS-TS who has already received methylprednisolone* prior to enrolment

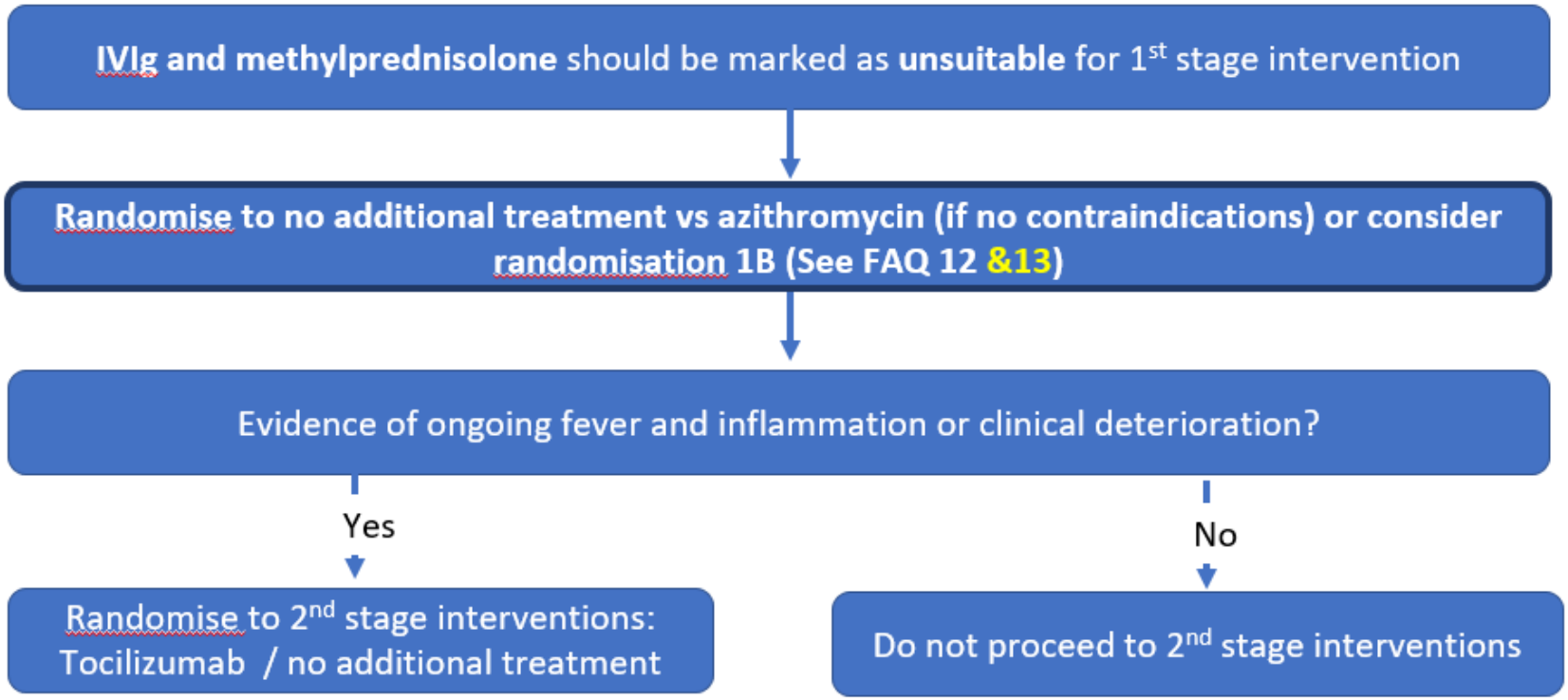
*** (or equivalent to ≥ 2mg/kg prednisolone)**

RECOVERY
Randomised Evaluation of COVID-19 Therapy



Scenario 4: Patient with PIMS-TS who has already received IVIg AND methylprednisolone* prior to enrolment * (or equivalent to ≥ 2mg/kg prednisolone)

RECOVERY
Randomised Evaluation of COVID-19 Therapy



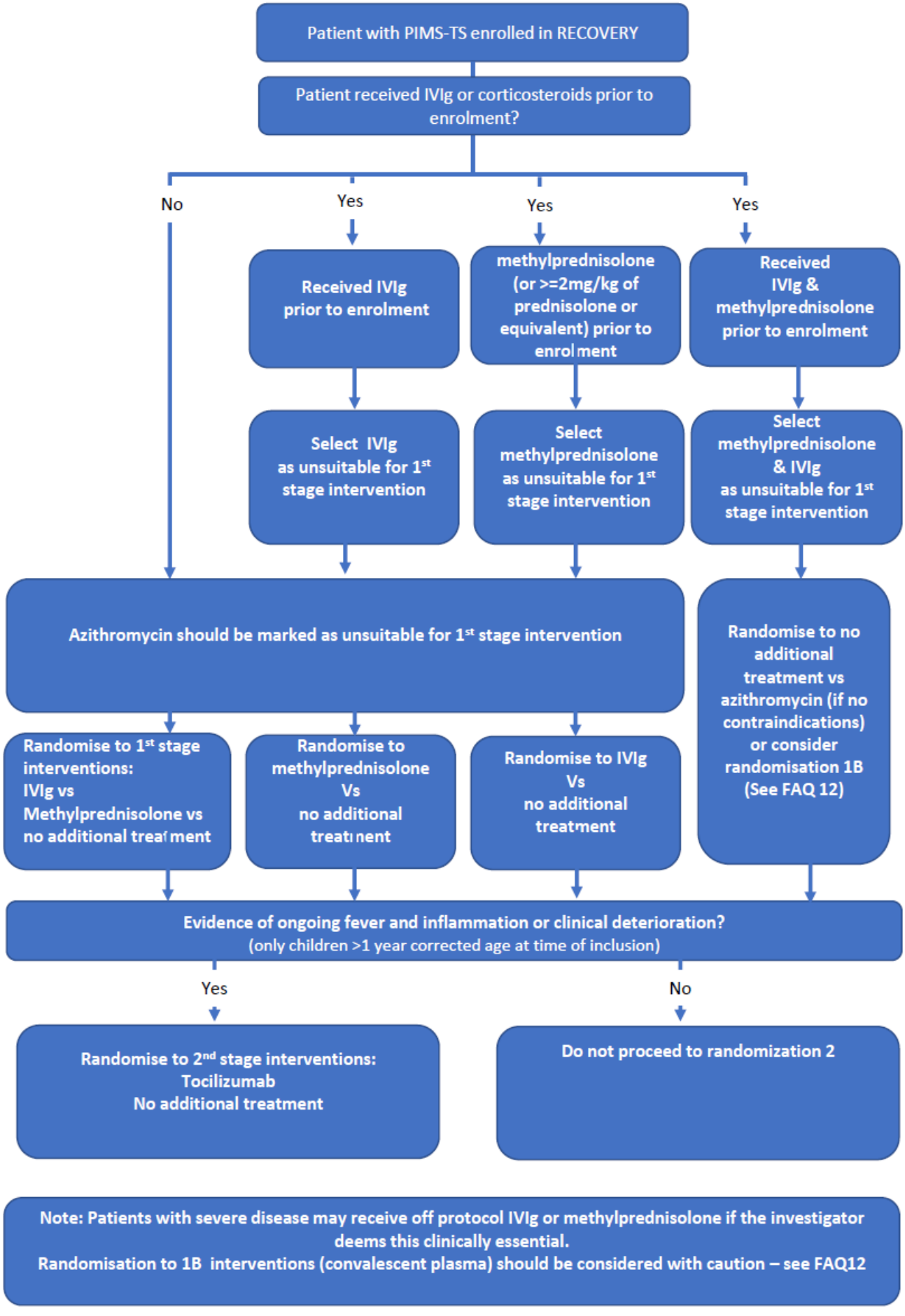
PIMS-TS Scenarios 1-4

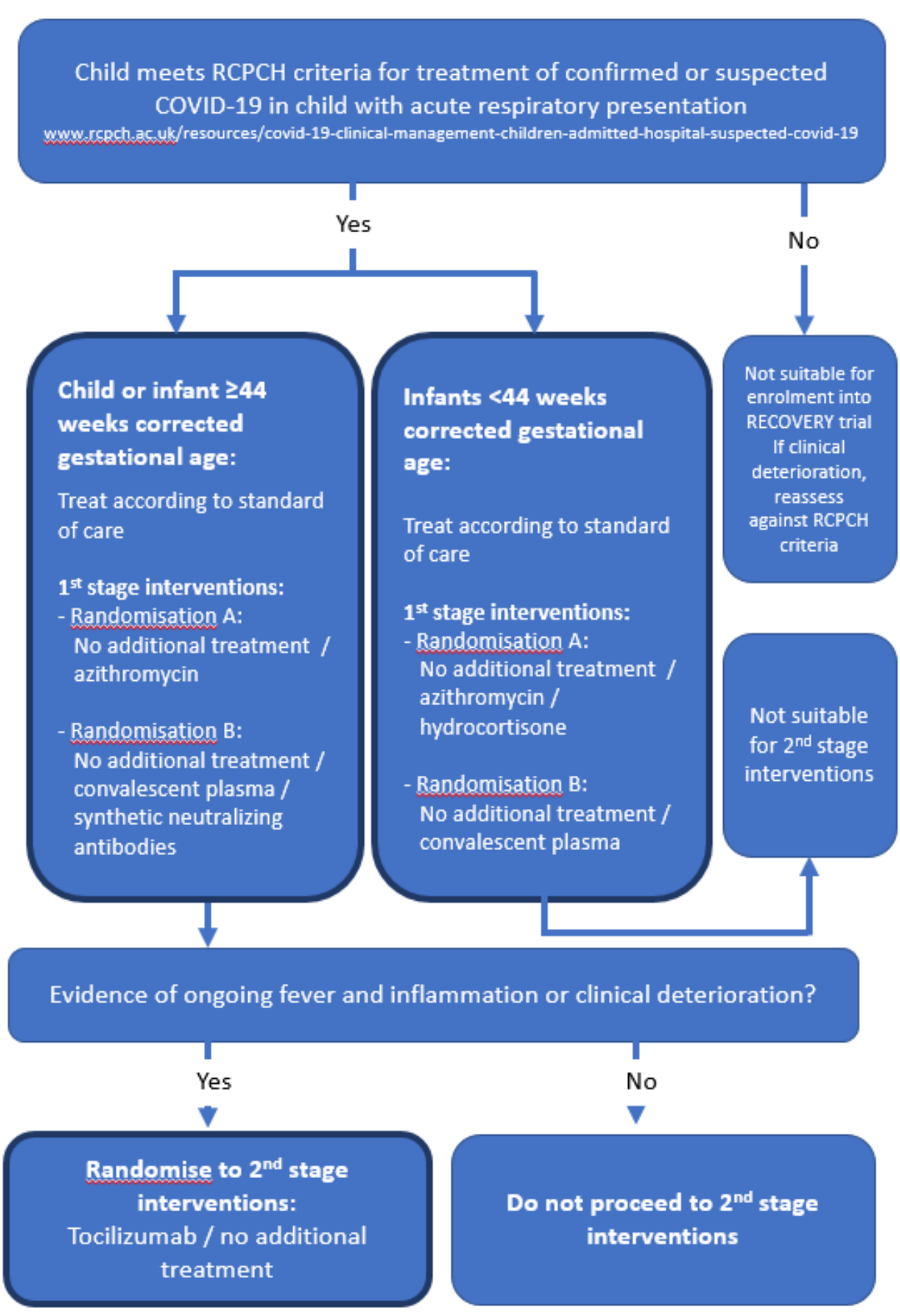
RECOVERY
Randomised Evaluation of COVID-19 Therapy

Patients with severe disease may receive off protocol IVIg or methylprednisolone if the investigator deems this clinically essential

Where possible, use 2nd stage interventions instead of off protocol treatments, or alternatively convalescent plasma could be used in place of a second dose of IVIg

Use the paediatric case report form to record all use of immunomodulation (both on and off protocol)


Patient with PIMS-TS enrolled in RECOVERY
Patient received IVIg or corticosteroids prior to enrolment?
No
Yes
Yes
Yes
Received IVIg prior to enrolment
methylprednisolone (or >=2mg/kg of prednisolone or equivalent) prior to enrolment
Received IVIg & methylprednisolone prior to enrolment
Select IVIg as unsuitable for 1st stage intervention
Select methylprednisolone as unsuitable for 1st stage intervention
Select methylprednisolone & IVIg as unsuitable for 1st stage intervention
Azithromycin should be marked as unsuitable for 1st stage intervention
Randomise to 1st stage interventions: IVIg vs Methylprednisolone vs no additional treatment
Randomise to methylprednisolone Vs no additional treatment
Randomise to IVIg Vs no additional treatment
Randomise to no additional treatment vs azithromycin (if no contraindications) or consider randomisation 1B (See FAQ 12)
Evidence of ongoing fever and inflammation or clinical deterioration?
(only children >1 year corrected age at time of inclusion)
Yes
No
Randomise to 2nd stage interventions: Tocilizumab No additional treatment
Do not proceed to randomization 2
Note: Patients with severe disease may receive off protocol IVIg or methylprednisolone if the investigator deems this clinically essential.
Randomisation to 1B interventions (convalescent plasma) should be considered with caution – see FAQ12


Child meets RCPCH criteria for treatment of confirmed or suspected COVID-19 in child with acute respiratory presentation
www.rcpch.ac.uk/resources/covid-19-clinical-management-children-admitted-hospital-suspected-covid-19
Yes
No
Child or infant ≥44 weeks corrected gestational age:
Treat according to standard of care
1st stage interventions:
- Randomisation A:
No additional treatment / azithromycin
- Randomisation B:
No additional treatment / convalescent plasma / synthetic neutralizing antibodies
Infants <44 weeks corrected gestational age:
Treat according to standard of care
1st stage interventions:
- Randomisation A:
No additional treatment / azithromycin / hydrocortisone
- Randomisation B:
No additional treatment / convalescent plasma
Not suitable for enrolment into RECOVERY trial If clinical deterioration, reassess against RCPCH criteria
Not suitable for 2nd stage interventions
Evidence of ongoing fever and inflammation or clinical deterioration?
Yes
No
Randomise to 2nd stage interventions:
Tocilizumab / no additional treatment
Do not proceed to 2nd stage interventions