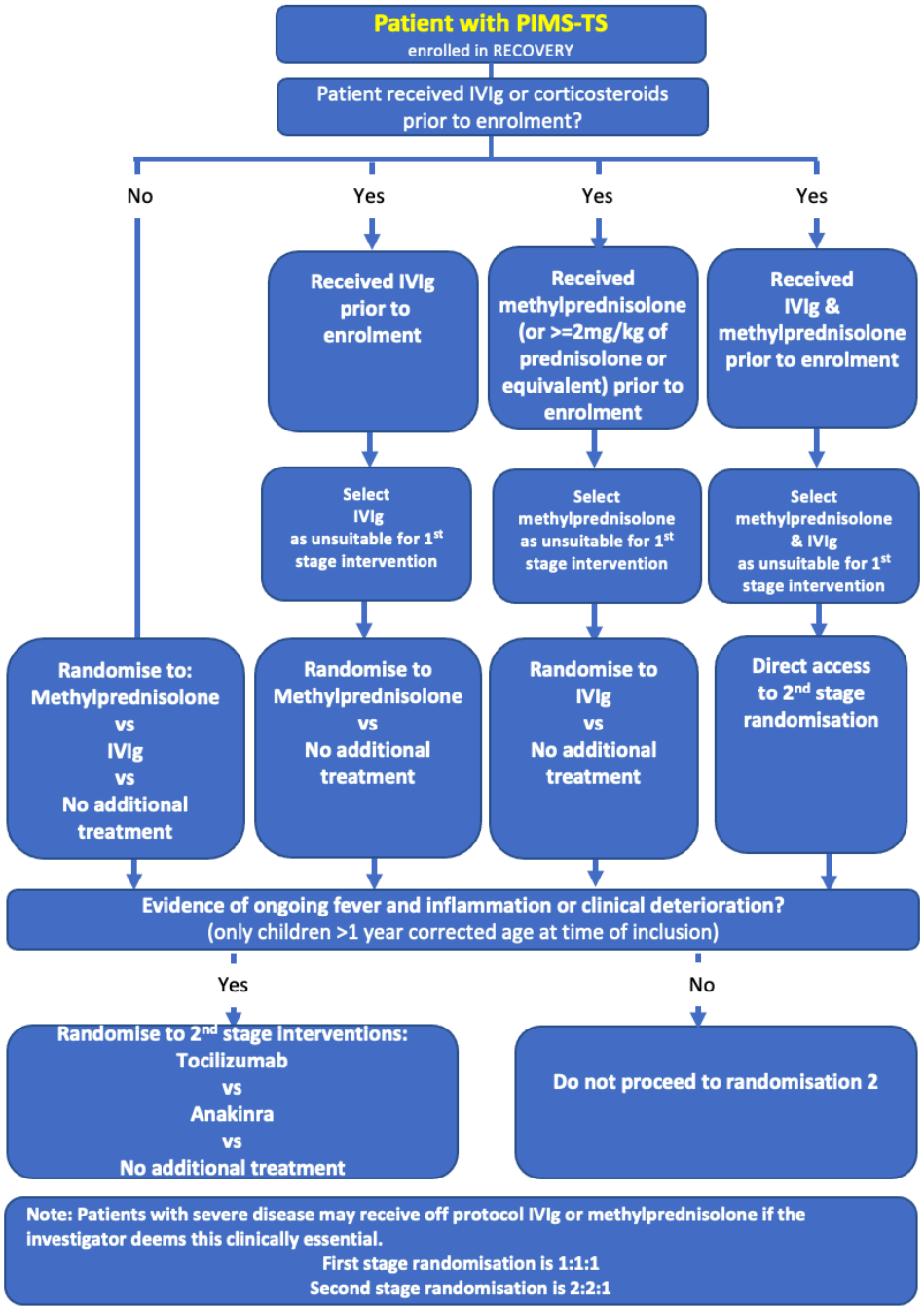
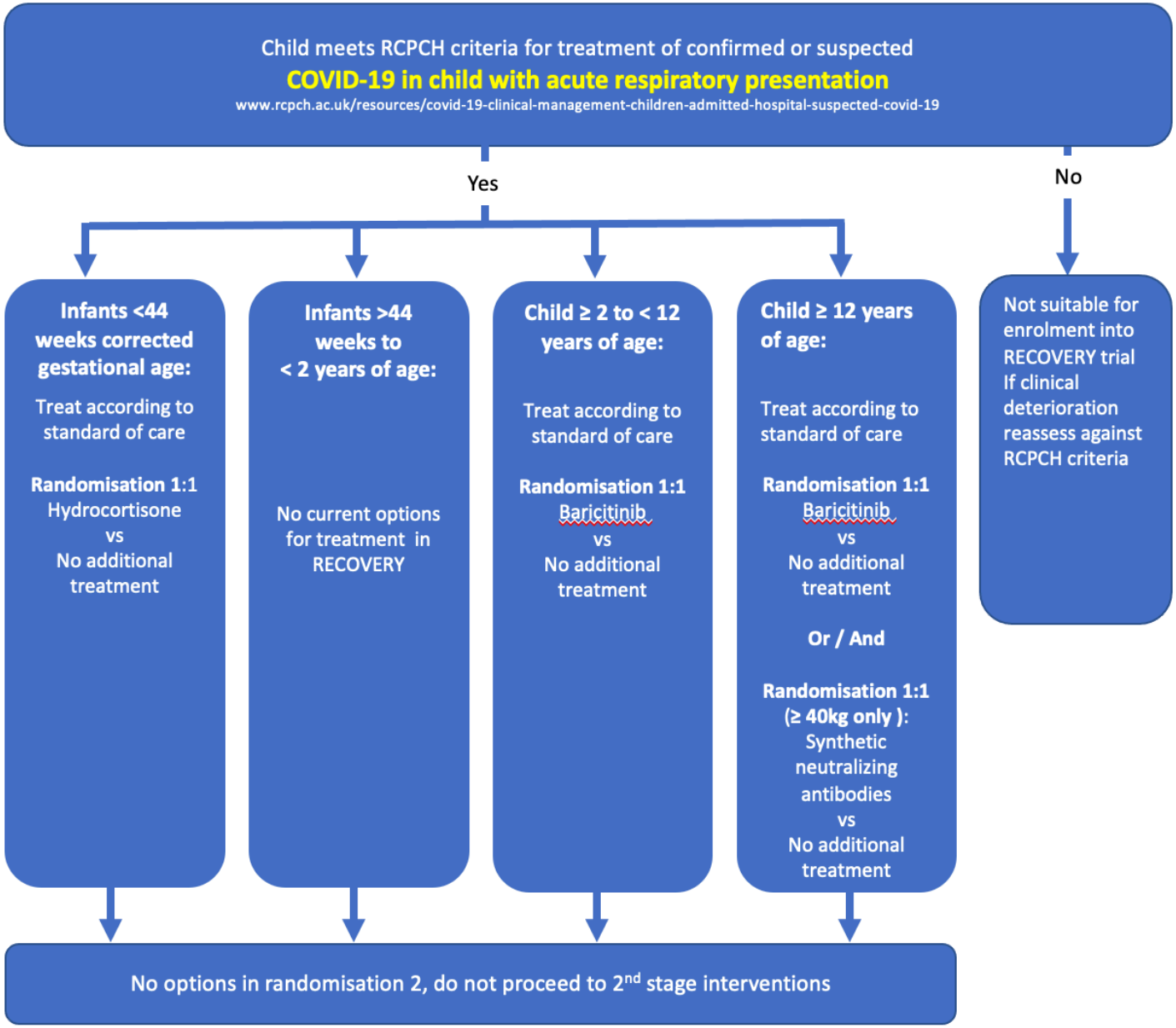
	RECOVERY - Adults	**Paediatric Patients** **Adapted for paediatric patients**
Eligibility	In the original protocol, patients were eligible if all they were: - Aged at least 18 years - Hospitalised - SARS-CoV-2 infection (clinically suspected or laboratory confirmed) - No medical history that might, in 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 4 to 8 for details on which children should be offered participation in RECOVERY**.
1st stage Interventions	1st stage 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 PIMS-TS (Corrected gestational age >44 weeks):** - No additional treatment - High dose methylprednisolone - Intravenous immunoglobulin (IVIg) **Children with respiratory COVID phenotype (<12 years):** - No additional treatment - Low dose hydrocortisone (≤44 weeks gestation) - Baricitinib (≥2 years) Note: No current options for children >44 weeks and <2 years **Children with respiratory COVID phenotype (≥12 years):** - No additional treatment - Baricitinib Or / And - No additional treatment - Synthetic neutralising antibodies (≥40 kg only)
2nd stage Interventions		**Children with PIMS-TS randomised 2:2:1 to:** - Tocilizumab (≥1 year) - Anakinra (≥1 year) - No additional treatment Note: see page 10 for other exclusion criteria
Follow-up/outcomes	Ascertained at the time of death or discharge or at 28 days after randomisation (whichever is sooner): - Vital status (alive/ dead, with date and presumed cause of death) - Hospitalisation status (inpatient/ discharged, with date of discharge) - Use of ventilation (none/ previous/ ongoing, with days of use and type) - Use of renal dialysis or haemofiltration (none/ previous/ ongoing)	Same outcome measures.


Patient with PIMS-TS
enrolled in RECOVERY
Patient received IVIg or corticosteroids prior to enrolment?
No
Yes
Yes
Yes
Received IVIg prior to enrolment
Received 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
Randomise to: Methylprednisolone vs IVIg vs No additional treatment
Randomise to Methylprednisolone vs No additional treatment
Randomise to IVIg vs No additional treatment
Direct access to 2nd stage randomisation
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 vs Anakinra vs No additional treatment
Do not proceed to randomisation 2
Note: Patients with severe disease may receive off protocol IVIg or methylprednisolone if the investigator deems this clinically essential.
First stage randomisation is 1:1:1
Second stage randomisation is 2:2:1


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
Infants <44 weeks corrected gestational age:
Treat according to standard of care
Randomisation 1:1
Hydrocortisone
vs
No additional treatment
Infants >44 weeks to < 2 years of age:
No current options for treatment in RECOVERY
Child ≥ 2 to < 12 years of age:
Treat according to standard of care
Randomisation 1:1
Baricitinib
vs
No additional treatment
Child ≥ 12 years of age:
Treat according to standard of care
Randomisation 1:1
Baricitinib
vs
No additional treatment
Or / And
Randomisation 1:1
(≥ 40kg only):
Synthetic neutralizing antibodies
vs
No additional treatment
Not suitable for enrolment into RECOVERY trial
If clinical deterioration reassess against RCPCH criteria
No options in randomisation 2, do not proceed to 2nd stage interventions

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

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%

   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 (Harwood 2020 Lancet Child & Adolescent Health), 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 or anakinra 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):

Notes: Neonates/infants (corrected gestational age of ≤44 weeks) can be recruited to the low dose steroid arm – do not use this table
No current options for children >44 weeks and <2 years of age with respiratory COVID phenotype.

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

		Acute respiratory presentation of COVID-19	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	**No additional treatment**	R	R	R	R	R	**Option to recruit to RECOVERY 2nd stage if IVIg and methylprednisolone have been given prior to randomisation.** See FAQ 13
	Steroid (high dose)	Unsuitable	R	R	Unsuitable	R	
	IVIg	Unsuitable	R	R	R	Unsuitable	
	Baricitinib	R	Unsuitable	Unsuitable	Unsuitable	Unsuitable	Unsuitable
1st stage interventions, randomisation	**No additional treatment**	R	No options for randomisation	No options for randomisation	No options for randomisation	No options for randomisation	No options for randomisation
	Synthetic neutralising antibodies	R (age restriction) See FAQ 15					
2nd stage interventions	**No additional treatment**	No option to 2nd stage randomisation. Manage as clinically indicated	R, if failure to respond following 1st stage interventions. See FAQ 12-14	Probably unsuitable, unless deterioration or failure to respond following 1st stage interventions. See FAQ 12-14	R, if failure to respond following 1st stage interventions. See FAQ 12-14	R, if failure to respond following 1st stage interventions. See FAQ 12-14	R, if failure to respond following 1st stage interventions. See FAQ 12-14
	Tocilizumab						
	Anakinra						

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 and 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 5 and the next section on "Randomisation: additional intervention-specific considerations" for additional guidance (page 10).

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 2nd stage randomisation (tocilizumab *vs* anakinra *vs* standard of care); the randomisation is carried out by the referring site (see section on "Second randomisation of paediatric participants" – page 13-14).

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 (150 micrograms/kg (as base) once daily; max 6mg; duration 10 days or stop at discharge) 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 (Harwood 2020 Lancet Child & Adolescent Health) 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.

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, and intravenous methylprednisolone) 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 and IVIg) unless the clinician has indicated any of these arms are "unsuitable".

12. **Are all patients with PIMS-TS suitable for the second randomisation (standard care *vs* tocilizumab *vs* anakinra)?** 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. Tocilizumab and anakinra are only suitable for children ≥ 1 year of age. Also, see page 10 for other exclusion criteria.

13. **Can we proceed directly to the 2nd stage randomisation (standard care *vs* tocilizumab *vs* anakinra)?** If a child with PIMS-TS has already received a dose of intravenous immunoglobulin (IVIg) and steroids, the patient can be entered into the trial but will not be randomised to the IVIg or methylprednisolone arm, this should be marked as unsuitable. From December 2020, there is now the option to randomise directly to 2nd stage randomisation in children with PIMS-TS.

14. **What if the child is on regular biologic immunomodulators (monoclonal antibodies) or Janus Kinase inhibitors**?

    - For children with PIMS-TS, they can only be entered into 1st stage randomisation.
    - For children with acute respiratory presentation of COVID-19, they can only be entered to 1st stage randomisation between synthetic antibodies and no additional treatment.

15. **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. This option is not available for children with PIMS-TS.

16. **Can a child with respiratory phenotype who is considered unsuitable for baricitinib proceed to 1st stage randomisation between synthetic antibodies and no additional treatment?** The patient can be entered into the trial but will not be randomised to the baricitinib arm, this should be marked as unsuitable. The patient (≥12 years and ≥ 40 kg) will be randomised between standard of care and synthetic neutralising antibodies.

17. **Can we randomise children (with respiratory phenotype) to the baricitinib arm if they have an absolute lymphocyte count of less than 0.5 x 10^9 cells/L?** Yes, they can be included for randomisation to the baricitinib arm. Lymphopaenia is a risk marker for severe COVID-19 so this would potentially exclude the participants who had the most to gain from baricitinib therapy.

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

19. **The child is female of child-bearing potential, is a pregnancy test required prior to randomisation to baricitinib**? Yes, baricitinib should be marked as unsuitable if a pregnancy test has not been done or is positive in a female considered of childbearing potential.

FAQ – Clinical management

20. **Can the route of administration of the intervention be switched during the treatment period if clinically indicated?** Yes

21. **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.

22. **A child with PIMS-TS 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.

23. **A child with PIMS-TS has <u>not</u> 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.

24. **A child with PIMS-TS 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.

25. **A child with PIMS-TS has <u>not</u> 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.

26. **How should ideal body weight be calculated for IVIg?** Ideal body weight should be calculated according to your local clinical practice.

27. **In routine clinical practice, we prescribe IVIg using actual body weight. Is it mandatory to use ideal body weight?** The recommendation to use ideal body weight is in line with NHSE guidance although we recognise that their current wording is generic. We have also been informed that this is a topic currently being reviewed by NHSE and reference to ideal body weight will include children in the next version. If your Trust allows the use of actual body weight to calculate IVIg dose, we have no objection to your site following your current practice.

28. **Can we give the total IVIg dose over 2 days?** The IVIg dose should be given as a single dose unless there are clinical concerns with volume overload.

29. **Is any dose adjustment required in a child with renal impairment?** No dosage adjustment is required for corticosteroids, tocilizumab and anakinra. For IVIg, this should be managed as clinically necessary. For baricitinib, please refer to dosing table.

30. **A child has been randomised and started on baricitinib. However, the patient is now presenting with evolving inflammatory phenotype. Can we proceed to 2nd stage randomisation?** The 2nd stage randomisation is only available to children with PIMS-TS diagnosis at trial enrolment**.** If the clinical decision is to start tocilizumab, we recommend that baricitinib is stopped (half-life of baricitinib in adults is 12 hours). The use of toculizumab will be considered off-protocol and should be recorded in the paediatric case report form.

31. **For children who have received IVIg, synthetic neutralising antibodies, baricitinib, tocilizumab or anakinra, what is the advice on live and live attenuated vaccines?** Limited data are available on the response to vaccination with live vaccines in children receiving these drugs. We recommend that live and live attenuated vaccines be avoided for at least 12 weeks.

Randomisation: ADDITIONAL intervention-specific considerations

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

Drug	Additional considerations relating to randomisation
Corticosteroid	No additional considerations
Intravenous Immunoglobulin (IVIg)	Select "Yes" to question A14 to reflect that this drug is **unsuitable** 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.
Baricitinib	Select "Yes" to question A14 to reflect that this drug is **unsuitable** if any of the following circumstances apply: - Patient < 2 year - Known hypersensitivity to baricitinib - Known hepatitis B, hepatitis C or tuberculosis infection - Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3 x Upper Limit of Normal - Received biologic immunomodulators or Janus Kinase inhibitors within the 30 days prior to randomisation. - Absolute neutrophil count <0.5 x 10^9/L - On renal replacement therapy - Positive pregnancy test or breast feeding
Synthetic neutralising antibodies	Select "Yes" to question A14 to reflect that this drug is **unsuitable** 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 to reflect that this drug is **unsuitable** if any of the following circumstances apply: - Patient < 1 year - Known hypersensitivity to tocilizumab - Known hepatitis B, hepatitis C or tuberculosis infection - Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3 x Upper Limit of Normal - Received biologic immunomodulators or Janus Kinase inhibitors within the 30 days prior to randomisation.
Anakinra	Select "Yes" to question A14 to reflect that this drug is **unsuitable** if any of the following circumstances apply: - Patient < 1 year - Known hypersensitivity to anakinra or E. coli derived proteins - Known hepatitis B, hepatitis C or tuberculosis infection - Absolute neutrophil count <1.5 x 10^9/L - Received biologic immunomodulators or Janus Kinase inhibitors within the 30 days prior to randomisation.

Paediatric dosing information

First stage randomisation

<table>
<tr><th>Arm</th><th>Route</th><th>Age/Weight</th><th>Dose</th></tr>
<tr><td rowspan="2">Corticosteroid
- Solution for injection*

*various strengths available</td><td>Intravenous</td><td>-</td><td>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</td></tr>
<tr><td>Intravenous</td><td>-</td><td>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.</td></tr>
<tr><td>Human normal immunoglobulin (IVIg)

- solution for infusion

*various strengths available</td><td>Intravenous</td><td>Corrected gestational age >44 weeks</td><td>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.)</td></tr>
<tr><td>Baricitinib

- 2 and 4 mg tablets</td><td>Oral/ other enteral routes</td><td>≥ 2 years</td><td>For children ≥ 2 years with respiratory presentation of COVID-19:

Once daily for 10 days or until discharge, whichever is sooner

<table><tr><th>eGFR</th><th>2 to < 9 yr</th><th>≥ 9 yr</th></tr><tr><td>≥ 60</td><td>2mg</td><td>4mg</td></tr><tr><td>30 to <60</td><td>2mg alt day</td><td>2mg</td></tr><tr><td>15 to <30</td><td>Excluded</td><td>2mg alt day</td></tr></table>
Those on renal replacement therapy are excluded</td></tr>
<tr><td>Synthetic neutralising antibodies
(REGN10933 + REGN10987)</td><td>Intravenous</td><td>≥ 12 years
And
≥ 40 kg</td><td>For children ≥ 12 years and ≥ 40 kg with respiratory presentation of COVID-19:

8 g (4 g of each monoclonal antibody)</td></tr>
</table>

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

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

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 **PIMS-TS**:

- significant systemic disease with persistent pyrexia[1]; and
- 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.

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.

[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)

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

<table>
<tr><th>Drug</th><th>Specific administration issues</th></tr>
<tr><td>Corticosteroid</td><td>All corticosteroid products should be supplied from local hospital stock (any brand with marketing authorisation) and refer to individual SmPC for administration information.</td></tr>
<tr><td>Intravenous Immunoglobulin (IVIg)</td><td>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 <u>red</u> 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.</td></tr>
<tr><td>Baricitinib</td><td>Baricitinib will be sourced by local pharmacy procurement team via their normal routes. Baricitinib is available as 2mg and 4mg film coated tablets. A Blueteq form will need to be completed for each patient to ensure that costs can be reimbursed to hospital trusts. The Blueteq form can be completed in retrospect.

Instructions for administration for patients who are unable to swallow whole tablets:
- The dispersion volume is listed as per table below.
- Disperse the required number of tablets in water with gentle swirling.
- Tablets may be crushed to facilitate dispersion.
- Dispersed tablets are stable in water for up to 4 hours.
- Ensure the tablet(s) are sufficiently dispersed to allow free passage through the tip of the syringe.
- Withdraw the required volume from the container into an appropriate size syringe and administer.
- Rinse container (rinse volume as per table below), withdraw the contents into the syringe and administer.
<table>
<tr><th>Administration via</th><th>Dispersion volume</th><th>Container rinse volume</th></tr>
<tr><td>Oral dispersion</td><td>10 mL (5 mL minimum)</td><td>10 mL (5 mL minimum)</td></tr>
<tr><td>Gastrostomy tube</td><td>15 mL (10 mL minimum)</td><td>15 mL (10 mL minimum)</td></tr>
<tr><td>Nasogastric tube</td><td>30 mL</td><td>15 mL</td></tr>
</table>
</td></tr>
</table>

	Mixing with food: In adults, administration of baricitinib with meals was not associated with a clinically relevant effect on exposure. Therefore, mixing with a small amount of juice or squash would be considered expectable to aid administration. There is no data on NJ administration.
Synthetic neutralising antibodies **(REGN10933 + REGN10987)**	**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. 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	Approval has been given for sites to use tocilizumab from local hospital stock by NHSE (and equivalent bodies in devolved nations). Charged via specialised commissioning (no blueteq required) Based on vial size availability, doses can be rounded. Refer to Roche dosing guide in order to minimise wastage and to allow doses to be measured accurately. Refer to page 7 of https://www.medicines.org.uk/emc/rmm/1393/Document **Concentrate for solution for infusion 20 mg/mL** **< 30 kg** - Calculate the volume of tocilizumab concentrate required for the patient's dose. - Withdraw a volume of sodium chloride 0.9% from a 50 mL infusion bag, equal to the volume of tocilizumab concentrate required for the patient's dose. - The required amount of tocilizumab concentrate should be withdrawn from the vial and placed in the 50 mL infusion bag. Set the infusion pump and administer as an intravenous infusion over 60 minutes. The infusion rate can be adjusted in line with local practice. **≥ 30 kg** - Calculate the volume of tocilizumab concentrate required for the patient's dose. - Withdraw a volume of sodium chloride 0.9% from a 100 mL infusion bag, equal to the volume of tocilizumab concentrate required for the patient's dose. - The required amount of tocilizumab concentrate should be withdrawn from the vial and placed in the 100 mL infusion bag. - Set the infusion pump and administer as an intravenous infusion over 60 minutes. The infusion rate can be adjusted in line with local practice. After dilution, the prepared solution for infusion is physically and chemically stable at 30°C for 24 hours (storage at 2 - 8°C would be preferred).
Anakinra	Anakinra will be sourced by local pharmacy procurement team via their normal routes. Charged via specialised commissioning (no blueteq required) Instructions for intravenous administration (if clinically required): Round dose to the nearest 5mg. Dilute in a suitable volume of sodium chloride 0.9% (10mL would be a suitable volume but 5mL may be used if very fluid restricted) and administer as intravenous bolus over 3 to 5 minutes. Can be given peripheral or central line but it should not be mixed with other drugs.

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.

Baricitinib – Baricitinib is licensed in adults for the treatment of rheumatoid arthritis and atopic dermatitis at a recommended dose of 2 to 4mg once daily. Limited data informing baricitinib dosing (at doses 1 to 4mg once daily) in paediatric patients comes from ongoing clinical trials for the treatment of chronic autoimmune disorders requiring long-term treatment including different forms of juvenile idiopathic arthritis and atopic dermatitis. Through an expanded access program, baritictinib is also being used in the management of patients with type 1 interferonopathies (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6026004/). Paediatric patients with type 1 interferonopathies typically receive doses higher than 4 mg once daily dose (mean dose of 6 mg/day) and have been monitored over an extended period of time (up to 7 years).

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

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

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

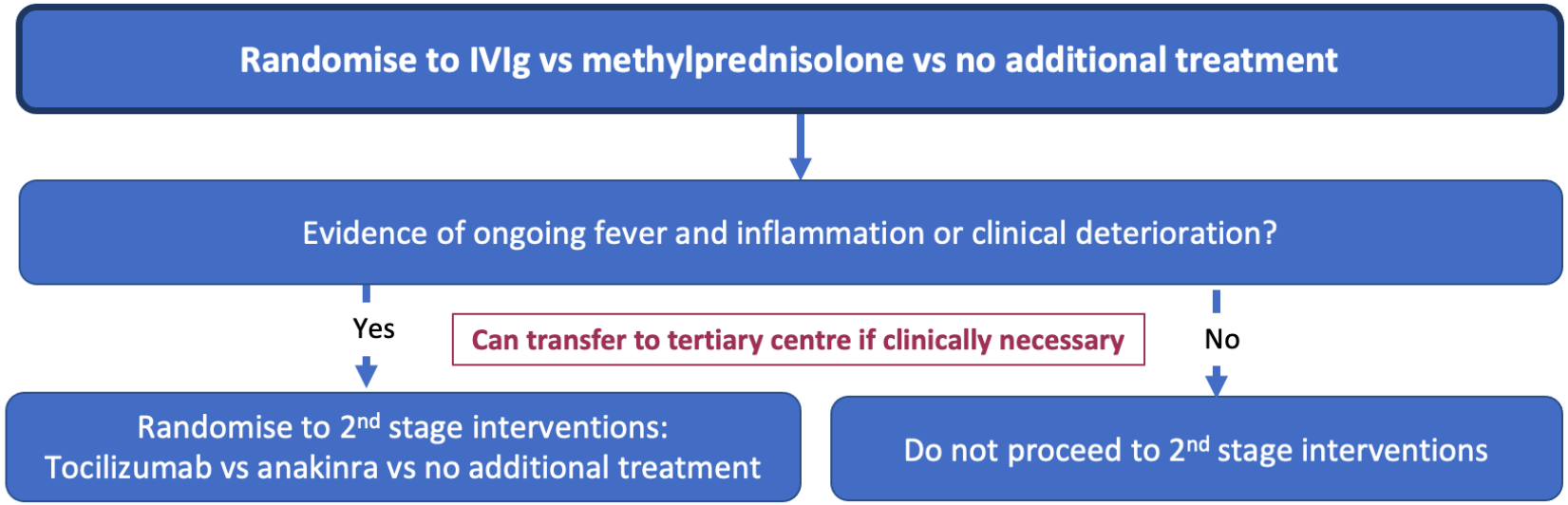
Version	Changes
Version 2 (6th May2020)	Eligibility adaptation for paediatrics – signposting to FAQs New and amended FAQs: Recruitment and randomisation Q1, Q2 and Q3 New FAQ: Clinical management Q1
Version 3 (21st May 2020)	Clarification on hydrocortisone option New FAQs: Recruitment and randomisation 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

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.

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

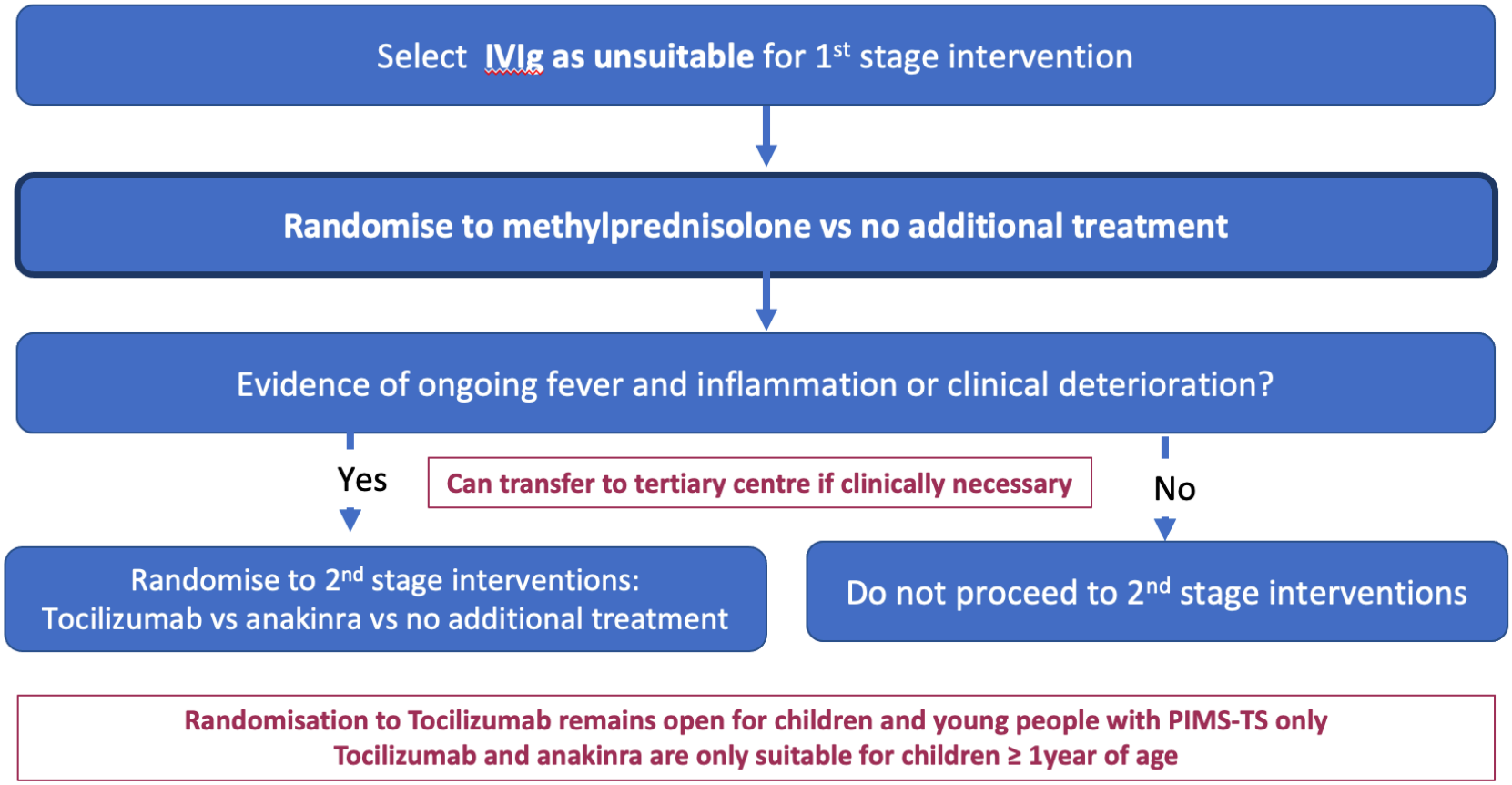
***IVIg, methylprednisolone or equivalent to ≥ 2mg/kg prednisolone**

RECOVERY
Randomised Evaluation of COVID-19 Therapy



Randomisation to Tocilizumab remains open for children and young people with PIMS-TS only
Tocilizumab and anakinra are only suitable for children ≥ 1year of age

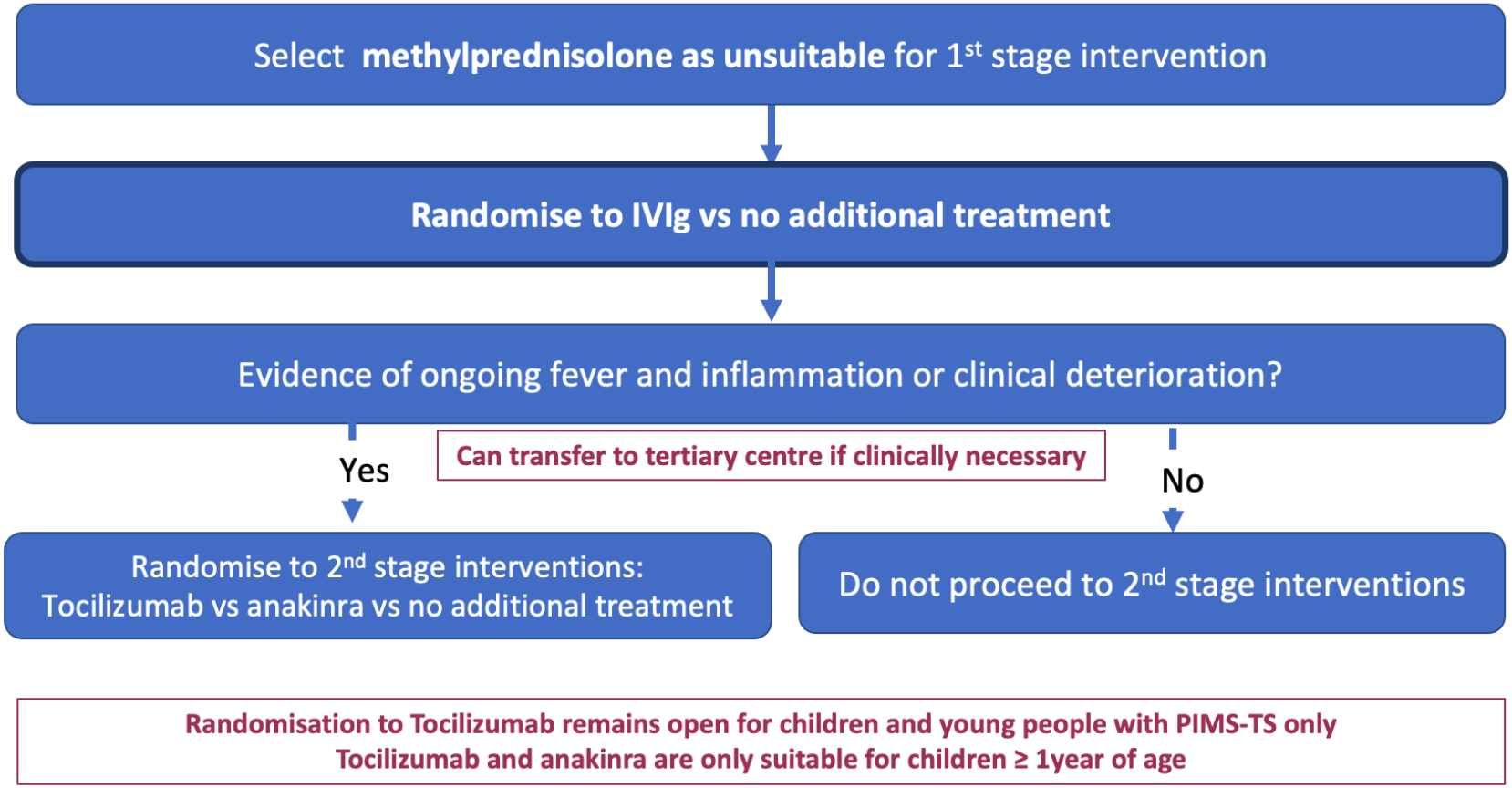
Scenario 2: Patient with PIMS-TS who has already received IVIg prior to enrolment



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

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

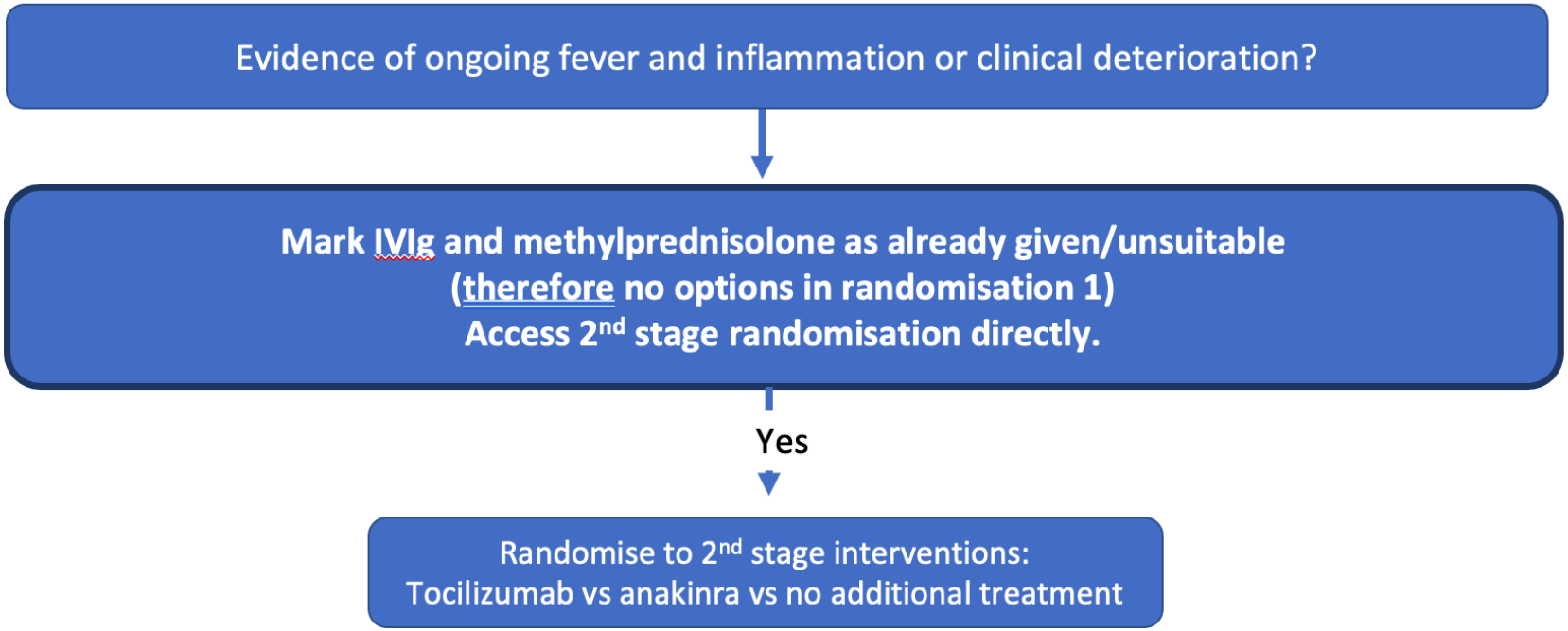
RECOVERY
Randomised Evaluation of COVID-19 Therapy



Randomisation to Tocilizumab remains open for children and young people with PIMS-TS only
Tocilizumab and anakinra are only suitable for children ≥ 1year of age

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



Randomisation to Tocilizumab remains open for children and young people with PIMS-TS only
Tocilizumab and anakinra are only suitable for children ≥ 1year of age

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, before or after first stage randomisation

Where possible, use 2nd stage interventions (tocilizumab vs anakinra vs standard of care) rather than off protocol treatments

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