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Supplementary appendix

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Immunomodulatory therapy in children with paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS, MIS-C; RECOVERY): a randomised, controlled, open-label, platform trial

SUPPLEMENTARY APPENDIX

RECOVERY Collaborative Group

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Supplementary Methods

Study organization

The RECOVERY trial is an investigator-initiated, individually randomised, open-label, controlled trial to evaluate the efficacy and safety of a range of putative treatments in patients hospitalized with COVID-19 or PIMS-TS. The protocol is available at www.recoverytrial.net. The trial is being conducted at 177 National Health Service (NHS) hospital organizations in the United Kingdom. The trial is coordinated by a team drawn from the Clinical Trial Service Unit and the National Perinatal Epidemiology Clinical Trials Unit within the Nuffield Department of Population Health at University of Oxford, the trial sponsor. Support for local site activities is provided by the National Institute for Health Research Clinical Research Network.

Access to relevant routine health care and registry data is supported by NHS DigiTrials, the Intensive Care National Audit and Research Centre, Public Health Scotland, National Records Service of Scotland, and the Secure Anonymised Information Linkage (SAIL) at University of Swansea.

Protocol changes

RECOVERY is a randomised trial among patients hospitalized with PIMS-TS. All eligible patients receive usual standard of care in the participating hospital and are randomly allocated between no additional treatment and one of several active treatment arms. Over time, additional treatment arms have been added (see Table).

The final protocol (V16.1) which included all the PIMS-TS treatment comparisons are included in the supplementary material to this publication, together with summaries of the changes made.

Table. Protocol changes to PIMS-TS treatment comparisons

Protocol version	Date	Randomisation	Treatment arms
8.0	03-Jul-2020	Main (part A)	No additional treatment Intravenous immunoglobulin[b] High-dose corticosteroid[b]
		Second[a]	No additional treatment Tocilizumab
13.0	26-Jan-2021	Main (part A)[c]	No additional treatment Intravenous immunoglobulin[b] High-dose corticosteroid[b]
		Second[a]	No additional treatment Tocilizumab Anakinra
17.1	10-Aug-2021	Second[a]	No additional treatment Tocilizumab Anakinra
23.0	08-Mar-2022	PIMS-TS comparisons removed	

[a] for patients with (a) oxygen saturation <92% on air or requiring oxygen or children with significant systemic disease with persistent pyrexia; and (b) C-reactive protein ≥75 md/L)
[b] Enrolment ceased 8 July 2021.
[c] from protocol version 12.1, children could enter the second randomisation regardless of whether they were included in the main randomisation. Enrolment ceased 8 March 2022.

Main and second randomisation for children with PIMS-TS

All RECOVERY trial participants received usual standard of care. On study entry, participants initially underwent the Main Randomisation. Children with significant systemic disease (defined as C-reactive protein ≥75 mg/L) could be considered for the Second Randomisation at any time up to 21 days after the initial randomisation, and regardless of initial treatment allocation(s). From protocol V12.1, children could enter the second randomisation regardless of whether they were included in the main randomisation. A web-system was used to provide simple randomisation (without stratification or minimisation) with allocation concealment until randomisation had been completed.

Over time, treatment arms were added and removed from the protocol, and not all treatments were available at every hospital. Similarly, not all treatments were deemed by the attending clinician to be suitable for some patients (e.g. due to comorbid conditions or concomitant medication). In any of these cases, randomisation involved fewer arms.

Part A (from 13 August 2020)

Eligible participants could be randomised to one of the following arms:

Treatment arm	Arm opened	Arm closed
No additional treatment	13 August 2020	16 July 2021
High-dose methylprednisolone	13 August 2020	16 July 2021
Intravenous immunoglobulin	13 August 2020	16 July 2021

Second randomisation for children with PIMS-TS (from 14 April 2020)

From 14 April 2020, a participant could be randomised to one of the following arms and thus receive 0 or 1 treatment on top of those allocated in the initial randomisation and usual standard of care:

Treatment arm	Arm opened	Arm closed
No additional treatment	13 August 2020	18 February 2022
Tocilizumab	13 August 2020	18 February 2022
Anakinra	2 February 2021	18 February 2022

Ascertainment and classification of study outcomes

Information on baseline characteristics and study outcomes was collected through a combination of electronic case report forms (see below) completed by members of the local research team at each participating hospital and (in the UK) linkage to National Health Service, clinical audit, and other relevant health records. Full details are provided in the RECOVERY Definition and Derivation of Baseline Characteristics and Outcomes Document (see Appendix 3).

Randomisation forms

The (main) Randomisation form (shown below) was completed by trained study staff. It collected baseline information about the participant (including demographics, COVID-19 history, comorbidities and suitability for the study treatments) and availability of the study treatments. Once completed and electronically signed, the treatment allocation was displayed. A second Randomisation form was completed for any children entering these comparisons.

The following modifications pertinent to children with PIMS-TS were made to the Randomisation forms during the trial:

Randomisation form version	Date of release	Major modifications from previous version
8.0	13-Aug-20	For protocol V8.0 • Addition of low-dose and high-dose corticosteroids and intravenous immunoglobulin for children
12.0	22-Dec-20	For protocol V12.1 • Allow children to enter trial without entering main randomisation
13.0	02-Feb-21	For protocol V13.0 • Anakinra added as treatment

RECOVERY
Randomised Evaluation of COVID-19 Therapy

Sample Form (v15.00 - 11/05/21)

Randomisation Program

Call Freefone **0800 138 5451** to contact the RECOVERY team for **URGENT** problems using the Randomisation Program or for medical advice. All **NON-URGENT queries** should be emailed to **recoverytrial@ndph.ox.ac.uk**

Logged in as: **RECOVERY Site**

Section A: Baseline and Eligibility

Date and time of randomisation: 11 May 2021 14:00

Treating clinician

A1. Name of treating clinician

Patient details

A2. Patient surname

Patient forename

A3. NHS number ☐Tick if not available

A4. What is the patient's date of birth? 01 / May / 2019 Age: 2y

A4.3 What is this child's weight? kg
Use estimated weight if necessary

A5. What is the patient's sex?

Inclusion criteria

A6. Has consent been taken in line with the protocol?
If answer is No patient cannot be enrolled in the study

A7. Does the patient have proven or suspected SARS-CoV-2 infection?
If answer is No patient cannot be enrolled in the study

A7.5 Does the patient have probable PIMS-TS syndrome? Yes

A8. Does the patient have any medical history that might, in the opinion of the attending clinician, put the patient at significant risk if they were to participate in the trial?

A9. COVID-19 symptom onset date: / /

A10. Date of hospitalisation: / /

A11. Does the patient require oxygen?

A12. Please select one of the following to describe the current level of ventilation support

A12.1 Enter latest oxygen saturation measurement (%)

A12.2 Enter latest CRP measurement since admission to hospital (mg/L) ☐Tick if not measured
Enter 0 if below the limit of measurement ☐Tick if greater than limit of measurement

A12.3 Enter latest creatinine measurement since admission to hospital µmol/L ☐Tick if not measured

A12.4 Enter latest D-dimer measurement since admission to hospital ng/mL ☐Tick if not measured
Enter 0 if below the limit of measurement ☐Tick if greater than limit of measurement

A12.5 Has the patient received a COVID-19 vaccine?

Does the patient have any CURRENT comorbidities or other medical problems or treatments?

A13.1 Diabetes

A13.2 Heart disease

A13.3 Chronic lung disease

A13.4 Tuberculosis

A13.5 HIV

A13.6 Severe liver disease

A13.7 Severe kidney impairment (eGFR<30 or on dialysis)

A13.8 Known long QT syndrome

A13.9 Current treatment with macrolide antibiotics which are to continue
Macrolide antibiotics include clarithromycin, azithromycin and erythromycin

A13.10 Antiplatelet therapy
Includes aspirin, clopidogrel, ticagrelor, prasugrel, dipyridamole

A13.12 Has received tocilizumab therapy during this admission

Are the following treatments UNSUITABLE for the patient?
If you answer Yes it means you think this patient should NOT receive this drug.

A14.1 High-dose corticosteroids (methylprednisolone)

A14.2 Intravenous immunoglobulin

A14D.1 Baricitinib
NB Baricitinib is NOT suitable if patient (i) is pregnant; (ii) has eGFR <15 ml/min or is on dialysis/haemofiltration; (iii) has active TB; or (iv) has neutrophil count <0.5
Must be Yes if patient has probable PIMS-TS syndrome Yes

Are the following treatments available?

A15.1 High-dose corticosteroids (methylprednisolone)

A15.2 Intravenous immunoglobulin

A15D.1 Baricitinib

Current medication

A16.1 Is the patient currently prescribed remdesivir?

A16.2 Is the patient currently prescribed systemic corticosteroids (dexamethasone, prednisolone, hydrocortisone, methylprednisolone)?
Please do not include topical or inhaled treatments

A16.25 Has the patient received high-dose (10 mg/kg methylprednisolone or equivalent) corticosteroids on this admission?

A16.3 Has the patient received intravenous immunoglobulin on this admission?

A16.4 Is the patient currently on warfarin or a direct oral anticoagulant?
Includes apixaban, rivaroxaban

A16.5 What venous thromboembolism prophylaxis is the patient receiving?
Standard = usual for hospitalised patients (not increased due to COVID-19); Higher dose = treatment dose or increased prophylaxis due to COVID-19

Please sign off this form once complete

Surname:

Forename:

Professional email:

Continue

Cancel

Home

Sample Form (v13.00 - 01/02/21)

Randomisation Program

Call Freefone **0800 138 5451** to contact the RECOVERY team for **URGENT** problems using the Randomisation Program or for medical advice. All **NON-URGENT queries** should be emailed to **recoverytrial@ndph.ox.ac.uk**

Logged in as: **RECOVERY Site**

Section A: Baseline and Eligibility

Date and time of second randomisation: 1 Feb 2021 00:47

Patient details

Study no	1234567
Name	Forename Surname
Date and time of main randomisation	31 Jan 2021 12:00
A1. What is the patient's date of birth?	/ /

Treating clinician

A2. Name of treating clinician	

Inclusion criteria

A3. Does the patient require oxygen?	
A4. Please select one of the following to describe the current level of ventilation support	
A5. Enter latest oxygen saturation measurement (%)	
A6. Enter latest CRP measurement since admission to hospital (mg/L) Enter 0 if below the limit of measurement	Tick if not measured Tick if greater than limit of measurement
A6.1 Does the patient have significant systemic disease with persistent pyrexia?	
A7. Enter latest ferritin measurement since admission to hospital (ng/mL) Enter 0 if below the limit of measurement	Tick if not measured Tick if greater than limit of measurement
A8. Enter latest creatinine measurement since admission to hospital (µmol/L)	Tick if not measured
A8.5 Is the patient currently prescribed systemic corticosteroids (dexamethasone, prednisolone, hydrocortisone, methylprednisolone)? Please do not include topical or inhaled treatments	
A8.6 Has the patient received high-dose (10 mg/kg methylprednisolone or equivalent) corticosteroids on this admission?	
A8.7 Has the patient received intravenous immunoglobulin on this admission?	
A9. Does the patient have any medical history that might, in the opinion of the attending clinician, put the patient at significant risk if they were to participate in this aspect of the trial?	

Are the following treatments unsuitable for the patient?

A10.1 Tocilizumab	
A10.2 Anakinra	

Are the following treatments available?

A11.1 Tocilizumab	
A11.2 Anakinra	

Please sign off this form once complete

Surname:	
Forename:	
Professional email:	

Continue

Cancel

Follow-up form

The Follow-up form (shown on the next page) collected information on study treatment adherence (including both the randomised allocation and use of other study treatments), vital status (including date and provisional cause of death if available), hospitalisation status (including date of discharge), respiratory support received during the hospitalisation, occurrence of any major cardiac arrhythmias and renal replacement therapy received.

The following modifications pertinent to children with PIMS-TS were made to the Follow-up form during the trial:

Follow-up form version	**Date of release**	**Modifications from previous version**
8.0	10-Jul-20	Information on new treatments for children adherence
10.0	06-Nov-20	Capture of thrombotic and bleeding events added Information of enrolment into other studies added
11.0	16-Nov-20	Minor changes to in-form validation
14.0	24-Feb-21	Additional information on infections
16.0	28-Jul-21	Capture of metabolic complications
17.0	20-Aug-21	Additional information on metabolic complications
20.0	28-Mar-22	Information on liver function tests and seizures

Follow-up

Date of randomisation

Please only report events that occurred from first randomisation until 28 days later on this form (except for Q2).

Patient's date of birth *

yyyy-mm-dd

» Vital Status

0. What is the patient's vital status? *

- ◯ Alive
- ◯ Dead

0.1 What is the patient's current hospitalisation status? *

- Inpatient
- Discharged

The patient has been enrolled in the trial for **NaN** days

0.1.1 Date follow-up form completed

yyyy-mm-dd

0.1.1 What was the date of discharge? *

yyyy-mm-dd

0.1 What was the date of death? *

yyyy-mm-dd

0.2 What was the underlying cause of death? *

This can be obtained from the last entry in part 1 of the death certificate

- ◯ COVID-19
- ◯ Other infection
- ◯ Cardiovascular
- ◯ Other

Please give details

» Treatments

1. Which of the following treatment(s) did the patient definitely receive as part of their hospital admission after randomisation? *

(NB Include RECOVERY study-allocated drug, only if given, PLUS any of the other treatments if given as standard hospital care)

- ☐ No additional treatment
- ☐ Lopinavir-ritonavir

- [ ] Corticosteroid (dexamethasone, prednisolone, hydrocortisone or methylprednisolone)
- [ ] Hydroxychloroquine
- [ ] Azithromycin or other macrolide (eg, clarithromycin, erythromycin)
- [ ] Tocilizumab or sarilumab
- [ ] Remdesivir
- [ ] Intravenous immunoglobulin
- [ ] Synthetic monoclonal antibodies (REGN10933+REGN10987)
- [ ] Aspirin
- [ ] Colchicine
- [ ] Baricitinib
- [ ] Anakinra
- [ ] Favipiravir
- [ ] Empagliflozin
- [ ] Ivermectin
- [ ] Oseltamivir
- [ ] Other neuraminidase inhibitor (e.g. zanamivir, laninamivir)
- [ ] Baloxavir
- [ ] Sotrovimab
- [ ] Molnupiravir
- [ ] Paxlovid

Please select number of days the patient received corticosteroid (dexamethasone, prednisolone, hydrocortisone or methylprednisolone) (of any dose)

○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ 6 ○ 7 ○ 8 ○ 9 ○ 10

Dosing information:

6 mg dexamethasone is equivalent to 40 mg prednisolone or 160 mg hydrocortisone or 32 mg methylprednisolone.

10 mg dexamethasone is equivalent to 67 mg prednisolone or 267 mg hydrocortisone or 53 mg methylprednisolone

20 mg dexamethasone is equivalent to 133 mg prednisolone or 534 mg hydrocortisone or 106 mg methylprednisolone

Please indicate the highest dose received on a single day during the 10 days after randomisation

- ○ <6 mg dexamethasone
- ○ 6 mg dexamethasone
- ○ >6 mg and <=10 mg dexamethasone
- ○ >10 mg and <20 mg dexamethasone
- ○ 20 mg dexamethasone
- ○ >20 mg dexamethasone

Please select number of doses of tocilizumab or sarilumab the patient received

○ 1 ○ >1

Please select number of days the patient received remdesivir

○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ 6 ○ 7 ○ 8 ○ 9 ○ 10

Please select number of days the patient received baricitinib

1 2 3 4 5 6 7 8 9 10

Please select number of days the patient received anakinra

1 2 3 4 5 6 7

Please select the proportion of days the patient received empagliflozin during the first 28 days after randomisation (or from randomisation to date of discharge if this is sooner)

Most days (≥90%) Some days (≥50% <90%) Few days (<50% of days, but not zero) None

Please select number of days the patient received oseltamivir

1 2 3 4 5 6 7 8 9 10

Please select number of doses of baloxavir the patient received

1 2

Did the participant experience an infusion reaction during or within 2 hours after the sotrovimab infusion? *

Yes

No

How severe was the reaction? *

Mild (no intervention required)

Moderate (eg, antihistamines or steroids required)

Severe (adrenaline required)

Was the infusion completed? *

Yes

No

Please select the number of days the patient received molnupiravir

1 2 3 4 5 6

Was the participant provided with treatment to complete the course at home?

Yes

No

Please select the number of days the patient received Paxlovid

1 2 3 4 5 6

Was the participant provided with treatment to complete the course at home?

Yes

No

Only required if Q17.0 and or Q17.1 on the Randomisation form were answered Yes

Was the baseline serum sample collected?

Yes

No

Was the baseline swab samples collected? *

- Yes
- No

Was the DAY 3 follow-up swab sample collected? *

- Yes
- No
- Swab sent home with patient

Was the DAY 5 follow-up swab sample collected? *

- Yes
- No
- Swab sent home with patient

» Ventilation

4. Did the patient require any form of assisted ventilation (ie, more than just supplementary oxygen) from day of randomisation until 28 days later? *

- Yes
- No

Please answer the following questions:

4.1 For how many days did the patient require assisted ventilation? *

4.2 What type of ventilation did the patient receive?

	Yes	No	Unknown
CPAP alone	◯	◯	◯
Non-invasive ventilation (eg, BiPAP)	◯	◯	◯
High-flow nasal oxygen (eg, AIRVO)	◯	◯	◯
Mechanical ventilation (intubation/tracheostomy)	◯	◯	◯
ECMO	◯	◯	◯

Total number of days the patient received invasive mechanical ventilation (intubation/tracheostomy) from randomisation until discharge/death/28 days after randomisation

» Cardiac arrhythmia

5. Has the patient been documented to have a NEW cardiac arrhythmia at any point since the main randomisation until 28 days later? *

- ◯ Yes
- ◯ No
- ◯ Unknown

5.1 Please select all of the following which apply

- ☐ Atrial flutter or atrial fibrillation
- ☐ Supraventricular tachycardia
- ☐ Ventricular tachycardia (including torsades de pointes)
- ☐ Ventricular fibrillation
- ☐ Atrioventricular block requiring intervention (eg, cardiac pacing)

» Renal outcomes

6. Did the patient require use of renal dialysis or haemofiltration from main randomisation until 28 days later? *

- ◯ Yes
- ◯ No

6.1 Please enter the highest creatinine level recorded after randomisation until 28 days later. *	Unit *	Date recorded *	Select if creatinine level not available *
.....	◯ µmol/L ◯ mg/dL	yyyy-mm-dd	◯ Not available

» Thrombosis and bleeding

7. During the first 28 days after randomisation (or until discharge if sooner), did the participant have a thrombotic event? *

- ◯ Yes
- ◯ No
- ◯ Unknown

7.1 Please indicate the type of thrombotic event

Select all that apply

- ☐ Pulmonary embolism
- ☐ Deep-vein thrombosis
- ☐ Ischaemic stroke
- ☐ Myocardial infarction
- ☐ Systemic arterial embolism
- ☐ Other

8. During the first 28 days after randomisation (or until discharge if sooner), did the participant experience clinically-significant bleeding ie, intra-cranial bleeding or bleeding that required intervention (eg, surgery, endoscopy or vasoactive drugs) or a blood transfusion? *

- ◯ Yes
- ◯ No

◯ Unknown

8.1 Please indicate the site(s) of bleeding *

Select all that apply

☐ Intra-cranial

☐ Gastrointestinal

☐ Other

8.2 Please indicate which interventions were required to manage the bleed *

Select all that apply

☐ Blood transfusion

☐ Surgery

☐ Endoscopy

☐ Vasoactive drugs (e.g. inotropes on ICU)

☐ None of the above

» Other infections

9. During the first 28 days after randomisation (or until discharge if sooner), did the participant develop another infection? *

◯ Yes

◯ No

◯ Unknown

9.1 Please indicate the type of infection

Select all that apply

☐ Pneumonia

☐ Urinary tract

☐ Biliary

☐ Other intra-abdominal

☐ Blood stream

☐ Skin

☐ Other

Pneumonia - please indicate the putative organism

◯ Bacterial ◯ Fungal ◯ Viral ◯ Other ◯ Unknown

Please indicate the virus

NB do not record the virus leading to study entry

☐ SARS-CoV-2 ☐ Influenza ☐ Other/unknown

Urinary tract - please indicate the putative organism

◯ Bacterial ◯ Fungal ◯ Other ◯ Unknown

Biliary - please indicate the putative organism

Biliary - please indicate the putative organism

Bacterial Fungal Other Unknown

Intra-abdominal - please indicate the putative organism

Bacterial Fungal Other Unknown

Blood stream - please indicate the putative organism

Please only select this if positive blood culture but no known anatomical site found

Bacterial Fungal Other Unknown

Skin - please indicate the putative organism

Bacterial Fungal Viral Other Unknown

Other - please indicate the putative organism

Bacterial Fungal Other

Unknown

Please describe the anatomical site

» Metabolic complications

10. During the first 28 days after randomisation (or until discharge if sooner), did the participant have any of the following?

		Yes	No	Unknown
Ketoacidosis *Ketoacidosis is defined as (i) ketosis (blood ketones ≥1.5 mmol/L or urine ketones ≥2+) AND (ii) metabolic acidosis (eg, bicarbonate <15 mmol/L) AND (iii) no obvious alternative cause of acidosis*	*	◯	◯	◯
Hyperglycaemic hyperosmolar state	*	◯	◯	◯
Other hyperglycaemia requiring new use of insulin	*	◯	◯	◯
Severe hypoglycaemia *Hypoglycaemia causing reduced conscious level requiring another person to help recover.*	*	◯	◯	◯

» Other safety outcomes

11. Did the participant experience a seizure after randomisation? *

Yes

No

Unknown

11.1 Does the patient have a history of seizures or epilepsy?

Yes

No

Unknown

11.2 Please enter the highest ALT (or AST) level recorded after randomisation until 28 days later. If below the limit of detection, enter 0

Date *	Result *	Upper limit of normal *	Units

yyyy-mm-dd			◉ IU/L or U/L ○ µmol/L ○ µkat/L

11.3 Please enter the highest bilirubin level recorded after randomisation until 28 days later. If below the limit of detection, enter 0

Date *	Result *	Upper limit of normal *	Units
yyyy-mm-dd			◉ µmol/L ○ mg/dL

» Other trials

12. Please indicate if the participant participated in any other COVID-19 or influenza trials

Select all that apply

- ☐ PRINCIPLE
- ☐ REMAP-CAP
- ☐ Other treatment trial(s)
- ☐ COVID-19 vaccine trial(s)

Please give name of other treatment trial(s)

Please give name of COVID-19 vaccine trial(s)

» Pregnancy

13. If this woman was pregnant at randomisation (or had recently delivered), please enter UKOSS ID here.

Enter the full UKOSS case ID eg, COR_123

Paediatric follow-up case report form

In addition to the main follow-up form, the following case report form was collected for all children participating in the PIMS-TS comparisons.

Paediatric Follow-up

Demographics

Child's date of birth *

yyyy-mm-dd

1. What is the child's ethnicity? *

- ◯ White
- ◯ Mixed / Multiple ethnic groups
- ◯ Asian / Asian British
- ◯ Black / African / Caribbean / Black British
- ◯ Other ethnic group

2. Has the child had any exposures to another person with confirmed COVID-19? *

◯ Yes ◯ No

Please enter the estimated number of weeks since covid exposure OR estimated exposure date

Estimated number of weeks	Estimated exposure date
	yyyy-mm-dd

3. Number of children in household (including participant) *

◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ >4

Clinical management

5. Did the child require Intensive Care / High Dependency care? *

◯ Yes ◯ No

5.1. Date of admission to ICU/HDU?

yyyy-mm-dd

5.2. Please enter total number of days in ICU/HDU *Please round up to the nearest day ie 4 hours= 1 day, 23 hours=1 day, 24.5 hours = 2 days*	How many of these days was the child in ICU?

6. Did the child require respiratory support? *

◯ Yes ◯ No

6.1. What date did the highest level of respiratory support start?

yyyy-mm-dd

6.2. Select highest level of respiratory support required

- [ ] Invasive ventilation
- [ ] Non-invasive ventilation
- [ ] Supplemental oxygen (including high flow)

How many days did the child receive invasive ventilation?

Please round up to the nearest whole day

How many days did the child receive non-invasive ventilation?

Please round up to the nearest whole day

How many days did the child receive supplemental oxygen (including high flow)?

Please round up to the nearest whole day

7. Did the child receive any of the following:

		Yes	No
Fluid boluses >20mls/kg	*	◯	◯
Inotropes	*	◯	◯

What date did the inotropes start?	How many days did the child receive inotropes?
yyyy-mm-dd	*Please round up to the nearest whole day*

ECMO	*	◯	◯

What date did the ECMO start?	How many days did the child receive ECMO?
yyyy-mm-dd	*Please round up to the nearest whole day*

Renal support	*	◯	◯

How many days did the child receive renal support?

Please round up to the nearest whole day

Investigations

8. Was an ECG performed? *

◯ Yes ◯ No

8.1. Were all ECGs normal? *

◯ Yes ◯ No

8.1.1. Select one or more abnormality found on any ECG:

	Yes	No
Prolonged PR interval?	◯	◯
Prolonged QT interval?	◯	◯
Arrhythmia?	◯	◯
State arrhythmia		
Low voltages?	◯	◯
ST elevation?	◯	◯
Other: please specify		

9. Was an ECHO performed? *

◯ Yes ◯ No

9.1. Were all ECHOs normal?

◯ Yes ◯ No

9.1.1. Select one or more abnormality found on any ECHO (worst abnormality at any point during initial admission):

	Yes	No
Decreased myocardial contractility?	◯	◯
Enter lowest ejection fraction (%)		
Abnormal coronary arteries?	◯	◯
Z score of largest vessel		
Pericardial effusion?	◯	◯
Other: please specify		

Blood results (to be able to interpret decision making)

Date of admission to hospital with current illness

yyyy-mm-dd

Blood results on admission to hospital with current illness

Date yyyy-mm-dd	**Time** *(hh:mm [24 hr])*	**Blood results not available** ◯ Select if not available	
Hb (g/L)	**Neutrophil count (x10⁹/L)**	**Lymphocyte count (x10⁹/L)**	**Platelets (x10⁹/L)**
D-dimer (ng/mL)	**Fibrinogen (g/L)**	**CRP (mg/L)**	**Albumin (g/L)**
ALT (U/L)	**Ferritin (µg/mL)**	**Troponin T (ng/L)**	**NTpro-BNP (pg/ml)**

Other treatments

Did the child receive any of the following treatments before, during or after the trial procedures (tick yes if received as SOC or treatment arm)?

IVIG?

◯ Yes ◯ No

Total daily dose	Date first dose received	Number of doses given
◯ 1 g/kg ◯ 2 g/kg ◯ Other ◯ Unknown	yyyy-mm-dd	

Methylprednisolone?

◯ Yes ◯ No

Total daily dose	Date first dose received	Number of days given
◯ < 10 mg/kg ◯ 10–19 mg/kg ◯ 20–30 mg/kg ◯ Other ◯ Unknown	yyyy-mm-dd	

Prednisolone?

◯ Yes ◯ No

Total daily dose *Select Other if variable*	*Tick if variable*	Date first dose received	Number of days given
◯ 1 mg/kg ◯ 2 mg/kg ◯ Other ◯ Unknown	◯ Tick if variable	yyyy-mm-dd	

Hydrocortisone?

◯ Yes ◯ No

Date first dose received	Number of days given
yyyy-mm-dd	

Anakinra?

◯ Yes ◯ No

Total daily dose	Date first dose received	Number of days given
◯ 2–4 mg/kg ◯ 5–8 mg/kg ◯ Other ◯ Unknown	yyyy-mm-dd	

Azithromycin (other than as part of 1st randomization)?

◯ Yes ◯ No

Infliximab?

◯ Yes ◯ No

Date first dose received	Number of days given
yyyy-mm-dd	

Tocilizumab?

◯ Yes ◯ No

Date first dose received	Number of days given
yyyy-mm-dd	

Aspirin low dose (3–5 mg/kg/day)?

◯ Yes ◯ No ◯ Unknown

Aspirin high dose (30–50 mg/kg/day in 4 divided doses)?

◯ Yes ◯ No ◯ Unknown

Heparin?

◯ Yes ◯ No ◯ Unknown

Low molecular weight heparin?

◯ Yes ◯ No ◯ Unknown

Was low molecular weight heparin given as a prophylactic or treatment?

◯ Prophylactic ◯ Treatment

Additional phone call at 5-8 weeks from discharge. If completed later please answer questions based on time of medical follow up if available.

If phone call made later than 5-7 weeks from discharge to complete dataset please do not complete QoL questionnaire

SARS-CoV2 PCR pos? *

- ◯ Yes
- ◯ No

What date did the child test positive?

yyyy-mm-dd

SARS-CoV2 antibody (IgG) pos at diagnosis or during the first admission?

- ◯ Yes
- ◯ No

SARS-CoV2 antibody (IgG) pos at follow-up?

- ◯ Yes
- ◯ No

Please add date and value of lowest CRP recorded after treatment

What was the lowest CRP recorded after the last treatment?	Date lowest CRP recorded after the last treatment
	yyyy-mm-dd

Treatment and discharge

Date admitted for treatment	Date discharged
yyyy-mm-dd	yyyy-mm-dd

Has the child visited a GP since discharge? *

- ◯ Yes
- ◯ No

Has the child been admitted to hospital since discharge? *

- ◯ Yes
- ◯ No

Was there a recurrence of PIMS?

- ◯ Yes
- ◯ No

Was treatment given?

- Yes
- No

Has the child used antibiotics since discharge (from GP or hospital)? *

- Yes
- No

Was an ECHO performed at follow-up? *

- Yes
- No

What was the result of the ECHO?

- Normal
- Abnormal

Date of ECHO

yyyy-mm-dd

Select one or more abnormality found on the follow-up ECHO:

	Yes	No
Decreased myocardial contractility?		
Enter lowest ejection fraction (%)		
Abnormal coronary arteries?		
Z score of largest vessel		
Pericardial effusion?		
Other: please specify		

Was an ECG repeated at follow-up? *

- Yes
- No

What was the result of the ECG?

- Normal
- Abnormal

Interim analyses: role of the Data Monitoring Committee

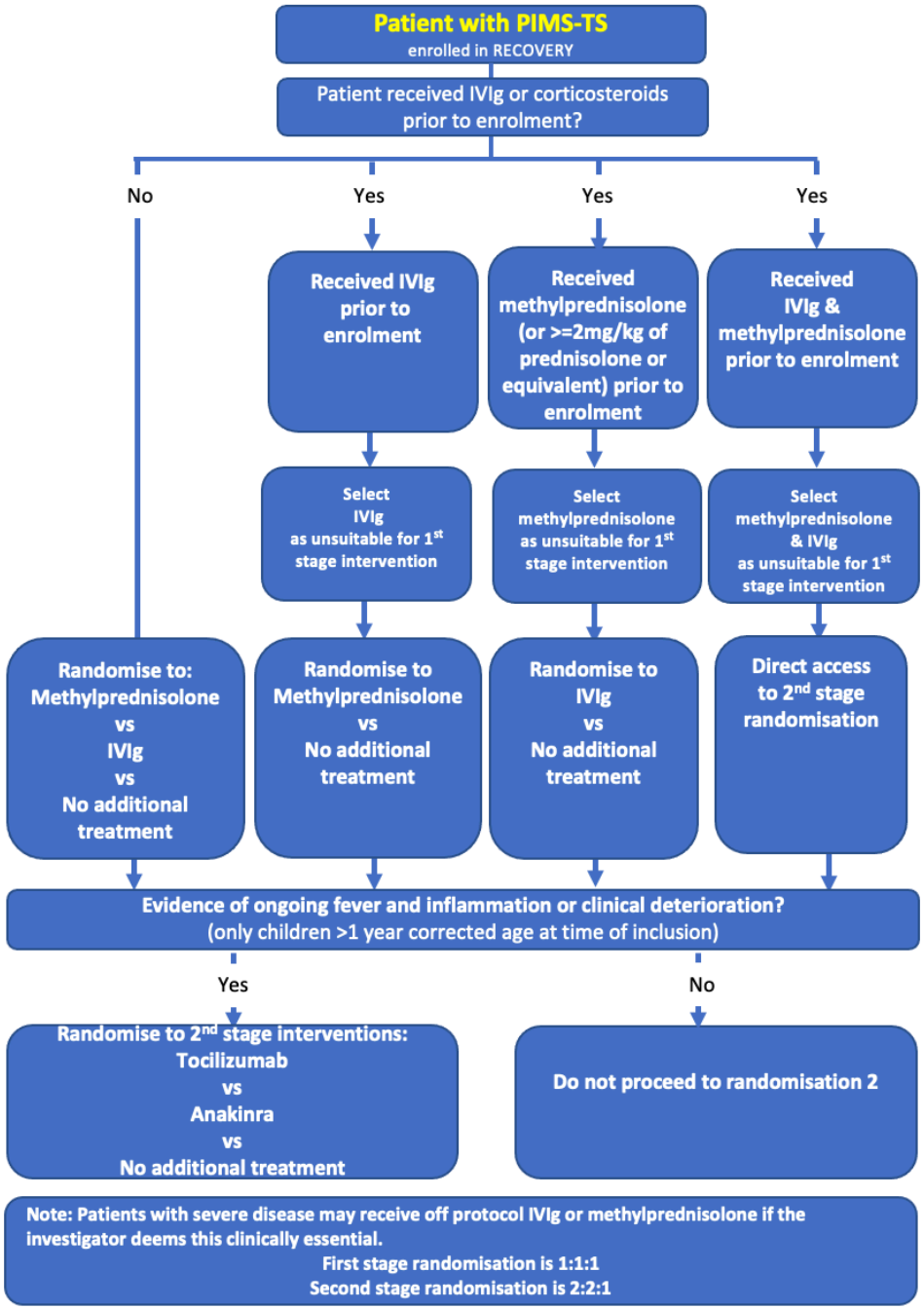
The independent Data Monitoring Committee reviewed unblinded analyses of the study data and any other information considered relevant at intervals of around 2 to 4 weeks. The committee was charged with determining if, in their view, the randomised comparisons in the study provide evidence on mortality that is strong enough (with a range of uncertainty around the results that was narrow enough) to affect national and global treatment strategies. In such a circumstance, the Committee would inform the Steering Committee who would make the results available to the public and amend the trial arms accordingly. Unless that happened, the Steering Committee, investigators, and all others involved in the trial would remain blind to the interim results until 28 days after the last patient had been randomised to a particular intervention arm. Further details about the role and membership of the independent Data Monitoring Committee are provided in the protocol.

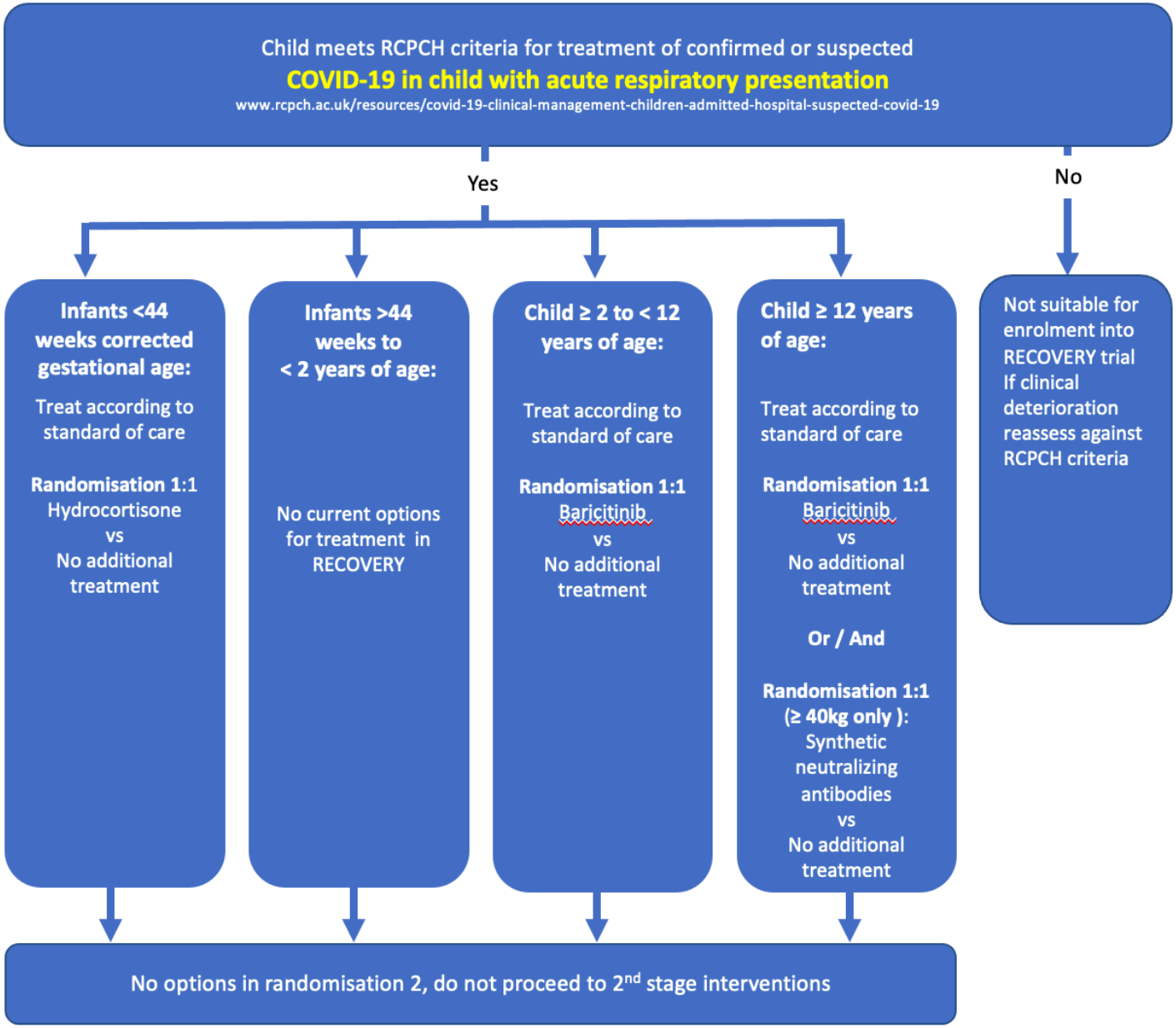
The Data Monitoring Committee determined that to consider recommending stopping a treatment early for benefit would require at least a 3 to 3·5 standard error reduction in mortality. The Committee concluded that examinations of the data at every 10% (or even 5%) of the total data would lead to only a marginal increase in the overall type I error rate.

Information for paediatric patients

The following information was provided to sites to assist with trial conduct.

	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

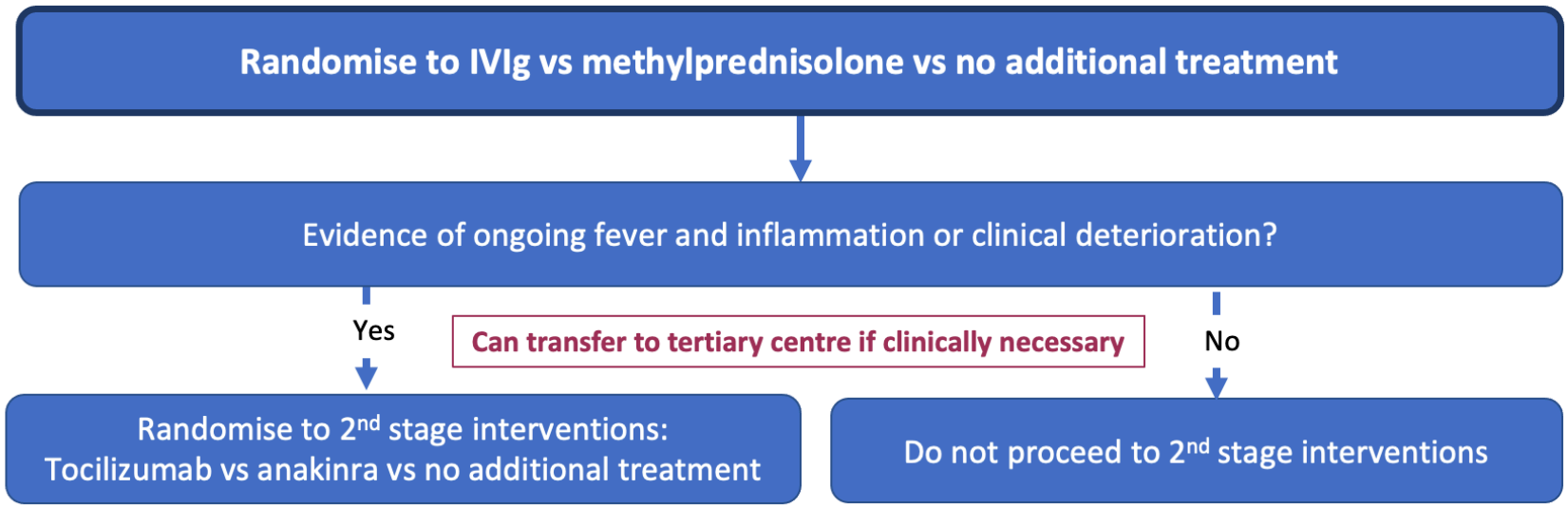
Version	Changes
Version 2 (6th May2020)	Eligibility adaptation for paediatrics – signposting to FAQs New and amended FAQs: Recruitment and randomisation Q1, Q2 and Q3 New FAQ: Clinical management Q1
Version 3 (21st May 2020)	Clarification on hydrocortisone option New FAQs: Recruitment and randomisation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

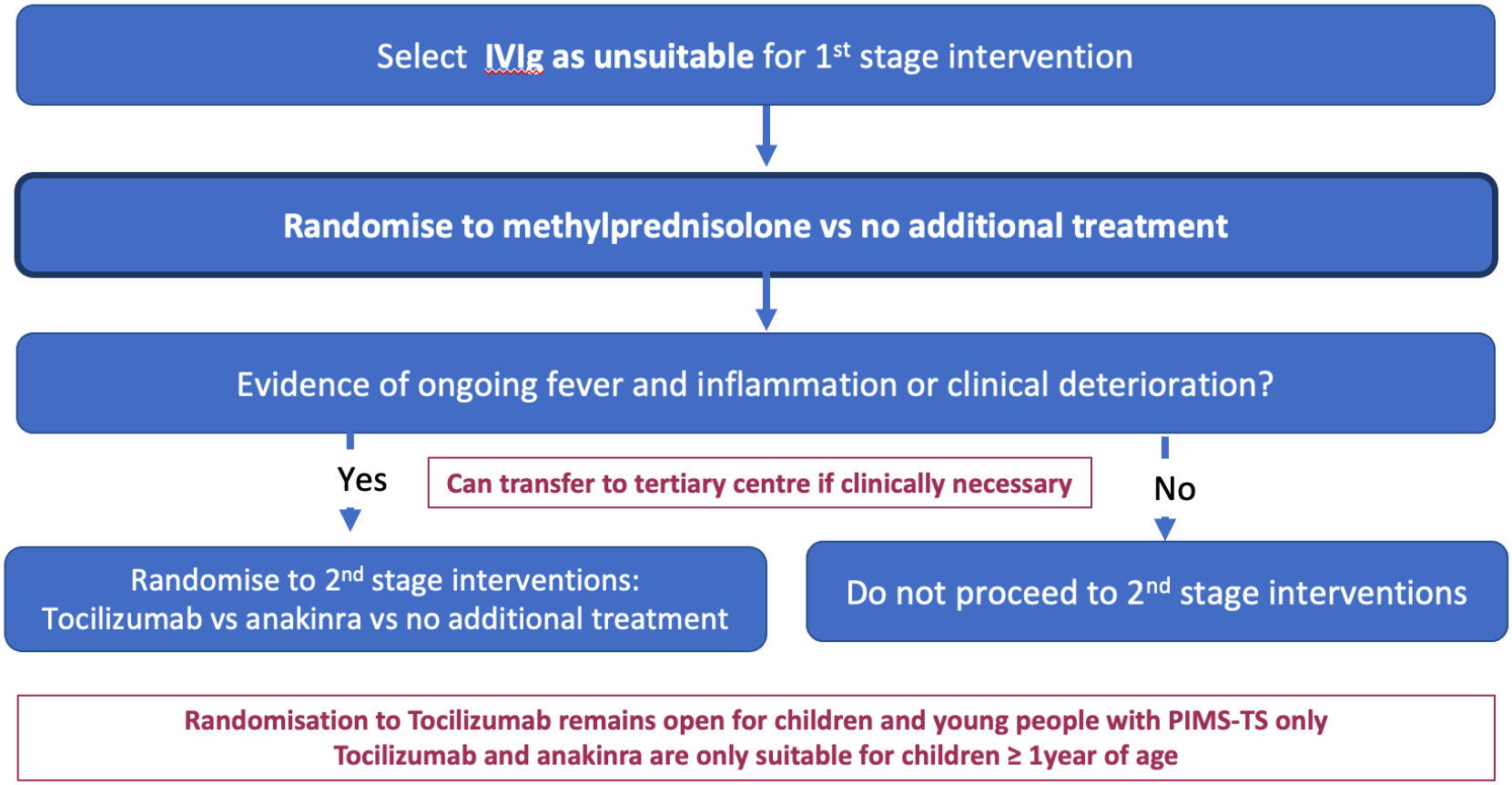
RECOVERY
Randomised Evaluation of COVID-19 Therapy



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

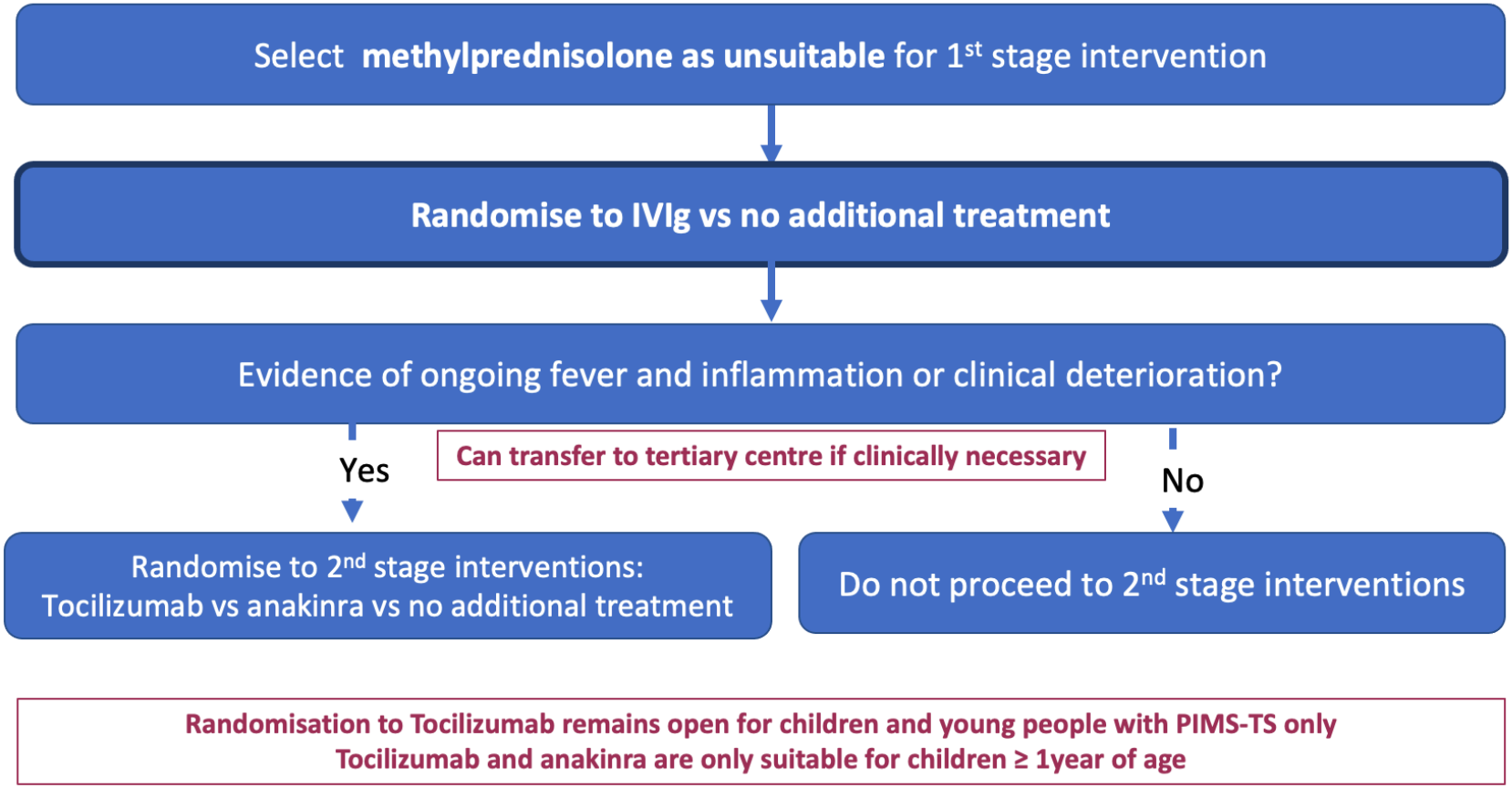
RECOVERY
Randomised Evaluation of COVID-19 Therapy



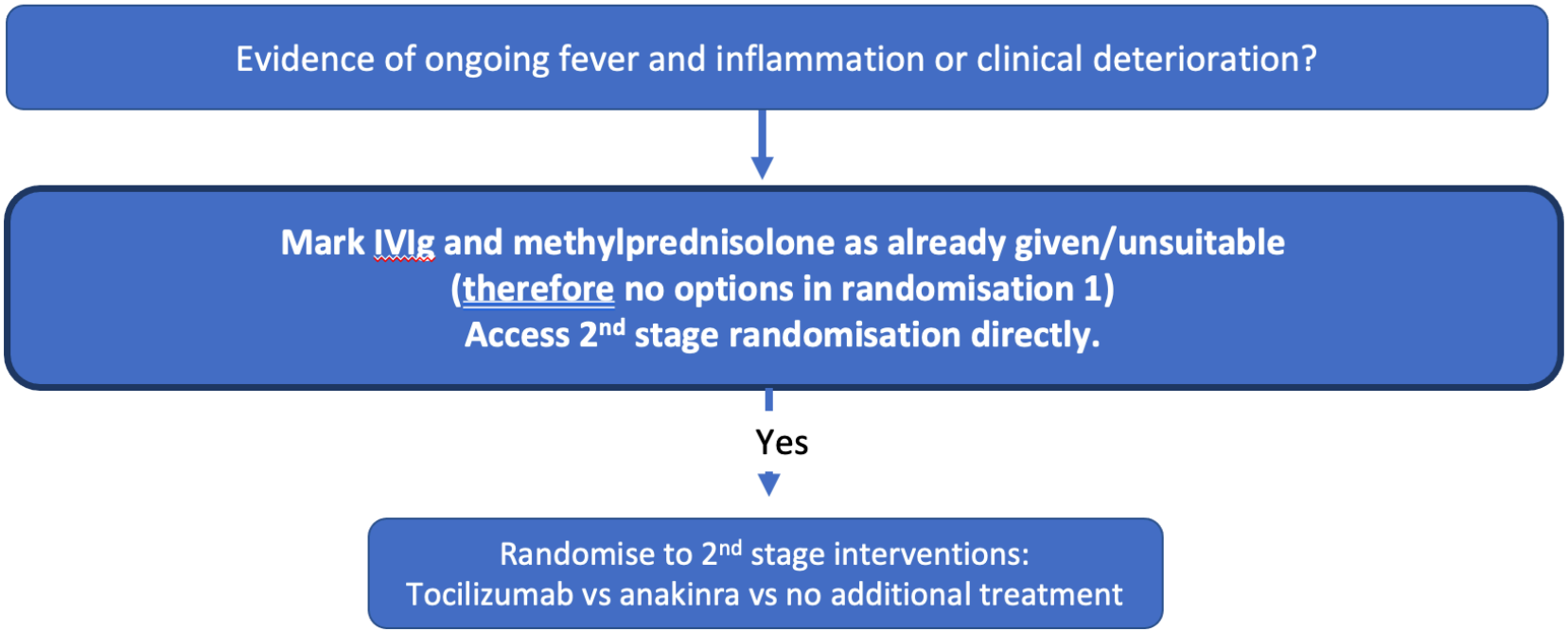
Scenario 3: Patient with PIMS-TS who has already received methylprednisolone* prior to enrolment

*** (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)



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)

Supplementary Tables

Supplementary Table 1: Cardiac arrhythmias, bleeds and thrombotic outcomes, by randomised allocation

	First randomisation				Second randomisation			
	Intravenous immunoglobulin vs usual care		Methylprednisolone vs usual care		Tocilizumab vs usual care		Anakinra vs usual care	
	Intravenous immunoglobulin (n=73)	Usual care (n=55)	Methylprednisolone (n=61)	Usual care (n=66)	Tocilizumab (n=28)	Usual care (n=28)	Anakinra (n=14)	Usual care (n=12)
Number with follow-up form	72	55	61	66	28	28	14	12
Major cardiac arrhythmia								
Atrial flutter or atrial fibrillation	0 (0%)	0 (0%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)	1 (7%)	0 (0%)
Other supraventricular tachycardia	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Subtotal: Supraventricular tachycardia	0 (0%)	0 (0%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)	1 (7%)	0 (0%)
Ventricular tachycardia	0 (0%)	1 (2%)	0 (0%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Ventricular fibrillation	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Subtotal: Ventricular tachycardia or fibrillation	0 (0%)	1 (2%)	0 (0%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Atrioventricular block requiring intervention	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Total: Any major cardiac arrhythmia	0 (0%)	1 (2%)	1 (2%)	1 (2%)	0 (0%)	0 (0%)	1 (7%)	0 (0%)
Thrombotic events								
Pulmonary embolism	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Deep-vein thrombosis	0 (0%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Ischaemic stroke	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Myocardial infarction	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Systemic arterial embolism	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Subtotal: Any thrombotic event	0 (0%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Clinically significant bleeding								
Intra-cranial	0 (0%)	1 (2%)	0 (0%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Gastrointestinal	0 (0%)	1 (2%)	0 (0%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Other/unrecorded site	1 (1%)	1 (2%)	1 (2%)	1 (2%)	1 (4%)	0 (0%)	0 (0%)	0 (0%)
Requiring blood transfusion	1 (1%)	2 (4%)	1 (2%)	1 (2%)	1 (4%)	0 (0%)	0 (0%)	0 (0%)
Requiring surgery	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Requiring endoscopy	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Requiring vasoactive drugs	1 (1%)	1 (2%)	0 (0%)	1 (2%)	1 (4%)	0 (0%)	0 (0%)	0 (0%)
Subtotal: Any clinically significant bleeding	1 (1%)	3 (6%)	1 (2%)	2 (3%)	1 (4%)	0 (0%)	0 (0%)	0 (0%)

Data are n (%).

Supplementary Table 2: Effects of treatments on paediatric outcomes (using separate control groups)

	First randomisation								Second randomisation							
	Intravenous immunoglobulin vs usual care				Methylprednisolone vs usual care				Tocilizumab vs usual care				Anakinra vs usual care			
	Intravenous immunoglobulin (n=73)	Usual care (n=55)	Treatment effect (95% Cr.I)	Post. Pr‖	Methylprednisolone (n=61)	Usual care (n=66)	Treatment effect (95% Cr.I)	Post. Pr‖	Tocilizumab (n=28)	Usual care (n=28)	Treatment effect (95% Cr.I)	Post. Pr‖	Anakinra (n=14)	Usual care (n=12)	Treatment effect (95% Cr.I)	Post. Pr‖
Primary outcome																
28-day mortality	0/73 (0%)	1/55 (2%)			1/61 (2%)	1/66 (2%)			0/28 (0%)	0/28 (0%)			0/14 (0%)	0/12 (0%)		
Discharged from hospital	72/73 (99%)	53/55 (96%)			60/61 (98%)	65/66 (98%)			28/28 (100%)	25/28 (89%)			14/14 (100%)	10/12 (83%)		
Number of days in hospital*	7.4 (0.4)	7.5 (0.5)	-0.1 (-1.4, 1.2)	57%	6.9 (0.5)	7.4 (0.5)	-0.5 (-1.8, 0.7)	81%	6.6 (0.7)	9.9 (0.9)	-3.3 (-5.6, -1.0)	>99%	8.5 (1.2)	11.2 (1.5)	-2.7 (-6.4, 1.1)	92%
Secondary clinical outcomes																
Number of days with inotropes*	0.8 (0.1)	0.9 (0.2)	-0.1 (-0.5, 0.4)	59%	0.9 (0.2)	0.7 (0.1)	0.1 (-0.3, 0.6)	28%	0.6 (0.2)	0.2 (0.1)	0.3 (-0.0, 0.8)	3%	1.1 (0.4)	0.4 (0.2)	0.7 (-0.1, 1.8)	4%
Baseline adjusted ln CRP on day 3†	4.8 (0.1)	4.6 (0.1)	0.2 (-0.1, 0.4)	9%	4.4 (0.1)	4.7 (0.1)	-0.4 (-0.6, -0.1)	>99%	4.2 (0.2)	4.3 (0.2)	-0.1 (-0.6, 0.3)	73%	4.9 (0.2)	4.6 (0.3)	0.3 (-0.4, 1.0)	21%
Subsidiary clinical outcomes																
Need for inotropes$	25/73 (34%)	19/55 (35%)	1.0 (0.6, 1.6)	53%	23/61 (38%)	17/66 (26%)	1.5 (0.9, 2.5)	8%	6/28 (21%)	4/28 (14%)	1.7 (0.5, 4.7)	25%	5/14 (36%)	2/12 (17%)	2.5 (0.6, 7.8)	15%
Need for non-IMV$	6/67 (9%)	2/49 (4%)	2.5 (0.5, 8.7)	18%	2/52 (4%)	5/58 (9%)	0.7 (0.1, 2.0)	82%	2/22 (9%)	2/24 (8%)	1.5 (0.2, 5.8)	46%	3/11 (27%)	0/9 (0%)	31.7 (0.7, 137.3)	7%
Need for IMV$	4/71 (6%)	3/54 (6%)	1.3 (0.3, 3.9)	51%	3/56 (5%)	3/63 (5%)	1.5 (0.3, 4.6)	43%	0/24 (0%)	0/26 (0%)	-	-	2/12 (17%)	0/11 (0%)	-	-
Need for ICU$	44/73 (60%)	31/55 (56%)	1.1 (0.8, 1.5)	33%	36/61 (59%)	36/66 (55%)	1.1 (0.8, 1.5)	31%	23/28 (82%)	19/28 (68%)	1.2 (0.9, 1.7)	11%	10/14 (71%)	8/12 (67%)	1.1 (0.6, 1.9)	40%
Number of days on ICU*	2.0 (0.3)	2.3 (0.4)	-0.3 (-1.2, 0.5)	77%	1.8 (0.3)	2.3 (0.3)	-0.5 (-1.4, 0.4)	87%	2.0 (0.5)	2.5 (0.5)	-0.5 (-1.9, 0.8)	78%	3.5 (1.1)	2.7 (0.8)	0.8 (-1.9, 4.0)	27%
Presence of CAA$	9/73 (12%)	4/55 (7%)	1.9 (0.6, 4.8)	19%	3/61 (5%)	6/66 (9%)	0.7 (0.2, 1.9)	81%	6/28 (21%)	4/28 (14%)	1.7 (0.5, 4.7)	25%	2/14 (14%)	1/12 (8%)	2.4 (0.2, 10.1)	36%
Persistence of CAA$	0/73 (0%)	1/55 (2%)	-	-	0/61 (0%)	2/66 (3%)	-	-	0/28 (0%)	1/28 (4%)	-	-	0/14 (0%)	0/12 (0%)	-	-
Presence of LVD$	14/73 (19%)	11/55 (20%)	1.0 (0.5, 1.9)	56%	8/61 (13%)	13/66 (20%)	0.7 (0.3, 1.5)	83%	9/28 (32%)	6/28 (21%)	1.6 (0.6, 3.6)	19%	5/14 (36%)	3/12 (25%)	1.6 (0.5, 4.5)	30%
Persistence of LVD$	0/73 (0%)	0/55 (0%)	-	-	0/61 (0%)	0/66 (0%)	-	-	0/28 (0%)	0/28 (0%)	-	-	0/14 (0%)	0/12 (0%)	-	-
Readmission to hospital$	11/73 (15%)	12/55 (22%)	0.7 (0.3, 1.4)	84%	13/61 (21%)	13/66 (20%)	1.2 (0.6, 2.2)	40%	7/28 (25%)	5/28 (18%)	1.5 (0.5, 3.7)	28%	2/14 (14%)	2/12 (17%)	1.3 (0.2, 4.4)	56%
Additional antibiotics$	2/73 (3%)	1/55 (2%)	2.3 (0.2, 10.7)	44%	4/61 (7%)	4/66 (6%)	1.3 (0.3, 3.7)	45%	0/28 (0%)	0/28 (0%)	-	-	0/14 (0%)	0/12 (0%)	-	-
Escalation of immunosuppressive treatment‡	38/73 (52%)	35/55 (64%)	0.7 (0.4, 1.1)	96%	13/61 (21%)	43/66 (65%)	0.2 (0.1, 0.4)	>99%	15/28 (54%)	17/28 (61%)	1.0 (0.5, 1.9)	60%	9/14 (64%)	5/12 (42%)	2.1 (0.6, 5.9)	15%

IMV=invasive mechanical ventilation. ICU=intensive care unit. CAA=coronary artery aneurysm. LVD=left ventricular dysfunction.
Data are events/total (%) or mean (SE).
*An age-adjusted model was used which allowed the joint estimation of the two treatment effects vs usual care (ie, mean difference and 95% credible interval (Cr.I)) while preserving the principle of randomisation.
$Treatment effect was presented as a risk ratio (RR) with 95% Cr.I.
†A linear regression model was used (adjusted for age and baseline ln CRP) which allowed the joint estimation of the two treatment effects vs usual care (ie, mean difference and 95% Cr.I) while preserving the principle of randomisation. Missing data were estimated using multiple imputations for ln CRP values (prior to day 4) adjusted for age and sex, and stratified by treatment allocation.
‡A Bayesian Cox proportional hazards model was used and the rate ratio (RR) and 95% Cr.I were presented.
‖Posterior probability of benefit.

Appendices

Appendix 1: RECOVERY Trial Protocol V16.1

RANDOMISED EVALUATION OF COVID-19 THERAPY (RECOVERY)

Background: In early 2020, as this protocol was being developed, there were no approved treatments for COVID-19, a disease induced by the novel coronavirus SARS-CoV-2 that emerged in China in late 2019. The UK New and Emerging Respiratory Virus Threats Advisory Group (NERVTAG) advised that several possible treatments should be evaluated, including Lopinavir-Ritonavir, low-dose corticosteroids, and Hydroxychloroquine (which has now been done). A World Health Organization (WHO) expert group issued broadly similar advice. These groups also advised that other treatments will soon emerge that require evaluation.

Eligibility and randomisation: This protocol describes a randomised trial among patients hospitalised for COVID-19. All eligible patients are randomly allocated between several treatment arms, each to be given in addition to the usual standard of care in the participating hospital. The study is subdivided into several parts, according to whether participants are children or adults, and by geographic area. The study is dynamic, and treatments are added and removed as results and suitable treatments become available. The parts in this version of the protocol (which should be checked and confirmed as the current latest version) are as follows:
Part A (Children only): No additional treatment *vs* corticosteroids *vs* intravenous immunoglobulin. See below for possible second randomisation in the children with PIMS-TS).
Part A (UK adults ≥18 years old only): Early phase assessment - Dimethyl fumarate *vs* no additional treatment, and additional information on efficacy and safety collected.
Part B: discontinued in version 16.0.
Part C: discontinued in V15.0.
Part D (UK [age ≥2 years] and India [age ≥18 years] only): In a factorial design, baricitinib *vs* no additional treatment.
Part E (non-UK countries; adults ≥18 years old with hypoxia only: In a factorial design, high-dose corticosteroids *vs* no additional treatment
Part F (adults ≥18 years): In a factorial design, empagliflozin *vs* no additional treatment
The study allows a subsequent randomisation for children with PIMS-TS (hyper-inflammatory state associated with COVID-19): No additional treatment *vs* tocilizumab *vs* anakinra. For patients for whom not all the trial arms are appropriate or at locations where not all are available, randomisation will be between fewer arms.

RECOVERY will also assess interventions for which additional information is required to determine whether they are considered for large-scale assessment as their potential to improve outcomes in COVID-19 is uncertain. Hence, for some patients the main randomisation part A will include an Early Phase Assessment arm in which patients may be randomised to receive dimethyl fumarate and additional information on efficacy and safety collected.

Adaptive design: The interim trial results will be monitored by an independent Data Monitoring Committee (DMC). The most important task for the DMC will be to assess whether the randomised comparisons in the study have provided evidence on mortality that is strong enough (with a range of uncertainty around the results that is narrow enough) to affect national and global treatment strategies. In such a circumstance, the DMC will inform

the Trial Steering Committee who will make the results available to the public and amend the trial arms accordingly. Regardless, follow-up will continue for all randomised participants, including those previously assigned to trial arms that are modified or ceased. New trial arms can be added as evidence emerges that other candidate therapeutics should be evaluated.

Outcomes: The main outcomes will be death, discharge, need for ventilation and need for renal replacement therapy. For the main analyses, follow-up will be censored at 28 days after randomisation. Additional information on longer term outcomes may be collected through review of medical records or linkage to medical databases where available (such as those managed by NHS Digital and equivalent organisations in the devolved nations).

Simplicity of procedures: To facilitate collaboration, even in hospitals that suddenly become overloaded, patient enrolment (via the internet) and all other trial procedures are greatly streamlined. Informed consent is simple and data entry is minimal. Randomisation via the internet is simple and quick, at the end of which the allocated treatment is displayed on the screen and can be printed or downloaded. Key follow-up information is recorded at a single timepoint and may be ascertained by contacting participants in person, by phone or electronically, or by review of medical records and databases.

Data to be recorded: At randomisation, information will be collected on the identity of the randomising clinician and of the patient, age, sex, major co-morbidity, pregnancy, COVID-19 onset date and severity, and any contraindications to the study treatments. The main outcomes will be death (with date and probable cause), discharge (with date), need for ventilation (with number of days recorded) and need for renal replacement therapy. Reminders will be sent if outcome data have not been recorded by 28 days after randomisation. Suspected Unexpected Serious Adverse Reactions (SUSARs) to one of the study medications (e.g., Stevens-Johnson syndrome, anaphylaxis, aplastic anaemia) will be collected and reported in an expedited fashion. Other adverse events will not be recorded but may be available through linkage to medical databases.

Numbers to be randomised: The larger the number randomised the more accurate the results will be, but the numbers that can be randomised will depend critically on how large the epidemic becomes. If substantial numbers are hospitalised in the participating centres then it may be possible to randomise several thousand with mild disease and a few thousand with severe disease, but realistic, appropriate sample sizes could not be estimated at the start of the trial.

Heterogeneity between populations: If sufficient numbers are studied, it may be possible to generate reliable evidence in certain patient groups (e.g. those with major co-morbidity or who are older). To this end, data from this study may be combined with data from other trials of treatments for COVID-19, such as those being planned by the WHO.

Add-on studies: Particular countries or groups of hospitals, may well want to collaborate in adding further measurements or observations, such as serial virology, serial blood gases or chemistry, serial lung imaging, or serial documentation of other aspects of disease status. While well-organised additional research studies of the natural history of the disease or of the effects of the trial treatments could well be valuable (although the lack of placebo control may bias the assessment of subjective side-effects, such as gastro-intestinal problems), they are not core requirements.

To enquire about the trial, contact the RECOVERY Central Coordinating Office
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Tel: 0800 1385451 | E-mail: recoverytrial@ndph.ox.ac.uk | Website: www.recoverytrial.net
To enquire about the trial outside of the UK, contact the relevant Clinical Trial Units
To RANDOMISE a patient, visit: www.recoverytrial.net

1 BACKGROUND AND RATIONALE

1.1 Setting

In 2019 a novel coronavirus-disease (COVID-19) emerged in Wuhan, China. A month later the Chinese Center for Disease Control and Prevention identified a new beta-coronavirus (SARS coronavirus 2, or SARS-CoV-2) as the aetiological agent.[1] The clinical manifestations of COVID-19 range from asymptomatic infection or mild, transient symptoms to severe viral pneumonia with respiratory failure. As many patients do not progress to severe disease the overall case fatality rate per infected individual is low, but hospitals in areas with significant community transmission have experienced a major increase in the number of hospitalised pneumonia patients, and the frequency of severe disease in hospitalised patients can be as high as 30%.[2-4] The progression from prodrome (usually fever, fatigue and cough) to severe pneumonia requiring oxygen support or mechanical ventilation often takes one to two weeks after the onset of symptoms.[2] The kinetics of viral replication in the respiratory tract are not well characterized, but this relatively slow progression provides a potential time window in which antiviral therapies could influence the course of disease. In May 2020 a new COVID-associated inflammatory syndrome in children was identified, Paediatric Inflammatory Multisystem Syndrome - Temporally associated with SARS-CoV-2 (PIMS-TS).[5] A rapid NHS England-led consensus process identified the need to evaluate corticosteroids and intravenous immunoglobulin (IVIg) as initial therapies in PIMS-TS, and confirmed tocilizumab as one of the biological anti-inflammatory agents to be evaluated as a second line therapy.

1.2 Treatment Options

1.2.1 Main randomisation

This protocol allows reliable assessment of the effects of multiple different treatments (including re-purposed and novel drugs) on major outcomes in COVID-19. All patients will receive usual care for the participating hospital.

Randomisation part A: Eligible patients may be randomly allocated between the following treatment arms:

- **No additional treatment**
- **Dimethyl fumarate (UK adults ≥18 years old only; early phase assessment)**
- **Corticosteroids (children ≤44 weeks gestational age with COVID-19 pneumonia, or >44 weeks gestational age with PIMS-TS only)**
- **Intravenous immunoglobulin (children >44 weeks gestational age with PIMS-TS only)**

Randomisation part D (UK and India only)[a]: Simultaneously, eligible patients will be randomly allocated between the following treatment arms:

- **No additional treatment**
- **Baricitinib (adults, and children ≥2 years old with COVID-19 pneumonia [UK and India only])**

Randomisation part E (adults ≥18 years old with hypoxia only [non-UK countries only]):
Simultaneously, eligible patients will be randomly allocated between the following treatment arms:

- **No additional treatment**[b]
- **High-dose dexamethasone**

Randomisation part F (adults ≥18 years old):
Simultaneously, eligible patients will be randomly allocated between the following treatment arms:

- **No additional treatment**
- **Empagliflozin**

1.2.2 Second randomisation for children with PIMS-TS

Severe COVID-19 is associated with release of pro-inflammatory cytokines, such as IL-1, IL-6 and TNFα, and other markers of systemic inflammation including ferritin and C-reactive protein.[6-8]

Children (at least 1 year old) with PIMS-TS (as evidenced by an exaggerated inflammatory state) may undergo an optional second randomisation between the following treatment arms:

- **No additional treatment**
- **Tocilizumab (children ≥1 <18 years old only)**
- **Anakinra (children ≥1 <18 years old only)**

1.2.3 Modifications to the number of treatment arms

Other arms can be added to the first or second randomisation if evidence emerges that there are suitable candidate therapeutics. Conversely, in some patient populations, not all trial

[a] Main randomisation part B was discontinued in V16.0 and part C in V15.0 of the protocol respectively.
[b] Usual care in hypoxic patients is expected to include low dose (6mg daily) dexamethasone

arms are appropriate (e.g. due to contraindications based on co-morbid conditions or concomitant medication); in some hospitals or countries, not all treatment arms will be available (e.g. due to manufacturing and supply shortages); and at some times, not all treatment arms will be active (e.g. due to lack of relevant approvals and contractual agreements). The Trial Steering Committee may elect to pause one or more of the arms in order to increase trial efficiency during a fluctuating epidemic. In any of these situations, randomisation will be between fewer arms. Depending on the availability and suitability of treatments, it may be allowed for participants to be randomised in only one or two parts (A, D or F [UK], D, E or F [ex-UK]) of the main randomisation.

1.3 Design Considerations

The RECOVERY Protocol describes an overarching trial design to provide reliable evidence on the efficacy of candidate therapies for suspected or confirmed COVID-19 infection in hospitalised patients receiving usual standard of care.

In early 2020, when the trial first started, there were no known treatments for COVID-19. The anticipated scale of the epidemic is such that hospitals, and particularly intensive care facilities, may be massively overstretched at some points in time, with around 10% requiring hospitalisation. In this situation, even treatments with only a moderate impact on survival or on hospital resources could be worthwhile. Therefore, the focus of RECOVERY is the impact of candidate treatments on mortality and on the need for hospitalisation or ventilation.

Critically, the trial is designed to minimise the burden on front-line hospital staff working within an overstretched care system during a major epidemic. Eligibility criteria are therefore simple and trial processes (including paperwork) are minimised.

The protocol is deliberately flexible so that it is suitable for a wide range of settings, allowing:

- a broad range of patients to be enrolled in large numbers;
- randomisation between only those treatment arms that are *both* available at the hospital *and* not believed by the enrolling doctor to be contraindicated (e.g. by particular co-morbid conditions or concomitant medications);
- treatment arms to be added or removed according to the emerging evidence; and
- additional substudies may be added to provide more detailed information on side effects or sub-categorisation of patient types but these are not the primary objective and are not required for participation.

In a cohort of 191 hospitalised COVID-19 patients with a completed outcome, the median time from illness onset to discharge was 22·0 days (IQR 18·0–25·0) and the median time to death was 18·5 days (15·0–22·0). Thirty-two patients (17%) required invasive mechanical ventilation and the median time from onset to mechanical ventilation was 14.5 days. Therefore, early endpoint assessment, such as 28 days after randomisation, is likely to provide largely complete outcome data and will permit early assessment of treatment efficacy and safety.[9]

1.4 Potential for effective treatments to become available

In early 2020, when the trial first started, there were no known treatments for COVID-19. However, over time, effective treatments may become available, typically as the result of

reliable information from randomised trials (including from this study). For example, in June 2020, results from the RECOVERY trial showed that dexamethasone reduces the mortality in COVID-19 patients requiring mechanical ventilation or oxygen. In response, many clinical guidelines now recommend the use of dexamethasone as standard of care for these types of patients.

The RECOVERY trial randomises eligible participant to usual standard of care for the local hospital alone vs usual standard of care plus one or more additional study treatments. Over time, it is expected that usual standard of care alone will evolve. Thus randomisation will always be relevant to the current clinical situation and the incremental effects of the study treatments will be appropriately assessed.

1.5 Early phase assessments

In the UK, the COVID-19 Therapeutics Advisory Panel (CTAP [c]) may propose that RECOVERY assesses interventions for which additional information is required before they are considered for large-scale assessment of the impact on mortality. Such assessments will be tailored to the uncertainty specific to the intervention and typically be conducted at a subset of sites among a smaller group of participants before the results are reviewed and a decision made whether to include them in the main trial.

2 DESIGN AND PROCEDURES

2.1 Eligibility

Patients are eligible for the study if all of the following are true:

(i) Hospitalised

(ii) SARS-CoV-2 infection associated disease (clinically suspected or laboratory confirmed)

In general, SARS-CoV-2 disease should be suspected when a patient presents with:

a) typical symptoms (e.g. influenza-like illness with fever and muscle pain, or respiratory illness with cough and shortness of breath); and
b) compatible chest X-ray findings (consolidation or ground-glass shadowing); and
c) alternative causes have been considered unlikely or excluded (e.g. heart failure, influenza).

However, the diagnosis remains a clinical one based on the opinion of the managing doctor.

[c] https://www.gov.uk/government/publications/covid-19-treatments-making-a-proposal-for-clinical-trials/guidance-making-a-proposal-for-covid-19-therapeutics-clinical-trials#uk-covid-19-therapeutics-advisory-panel-uk-ctap

A small number of children (aged <18 years) present with atypical features, including a hyperinflammatory state and evidence of single or multi-organ dysfunction (called Paediatric Multisystem Inflammatory Syndrome temporally associated with COVID-19 [PIMS-TS]). Some do not have significant lung involvement.[d]

(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 the trial

In addition, if the attending clinician believes that there is a specific contra-indication to one of the active drug treatment arms (see Appendix 2; section 8.2 and Appendix 3; section 8.3 for children) or that the patient should definitely be receiving one of the active drug treatment arms then that arm will not be available for randomisation for that patient. For patients who lack capacity, an advanced directive or behaviour that clearly indicates that they would not wish to participate in the trial would be considered sufficient reason to exclude them from the trial.

In some locations, children (aged <18 years) will not be recruited, to comply with local and national regulatory approvals (see Section 8.3).

2.2 Consent

Informed consent should be obtained from each patient 16 years and over before enrolment into the study. However, if the patient lacks capacity to give consent due to the severity of their medical condition (e.g. acute respiratory failure or need for immediate ventilation) or prior disease, then consent may be obtained from a relative acting as the patient's legally designated representative or – if a suitable relative is not available after reasonable efforts to locate one – an independent doctor. Further consent will then be sought with the patient if they recover sufficiently. For children aged <16 years old consent will be sought from their parents or legal guardian. Where possible, children aged between 10-15 years old will also be asked for assent. Children aged ≥16 years old will asked for consent as for adults. Witnessed consent may be obtained over the telephone or web video link if hospital visiting rules or parental infection mean a parent/guardian cannot be physically present.

Due to the poor outcomes in COVID-19 patients who require ventilation (>90% mortality in one cohort[9]), patients who lack capacity to consent due to severe disease (e.g. needs ventilation), and for whom a relative to act as the legally designated representative is not available, randomisation and consequent treatment will proceed with consent provided by a treating clinician (independent of the clinician seeking to enrol the patient) who will act as the legally designated representative (if allowed by local regulations). Consent will then be obtained from the patient's personal legally designated representative (or directly from the patient if they recover promptly) at the earliest opportunity.

In the UK, participants' GPs will be informed of their participation using routine clinical communications (e.g. discharge summaries). If any other relevant information arises during the trial, this may also be sent to GPs.

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[d] https://www.rcpch.ac.uk/sites/default/files/2020-05/COVID-19-Paediatric-multisystem-%20inflammatory%20syndrome-20200501.pdf

2.3 Baseline information

The following information will be recorded on the web-based form by the attending clinician or delegate:

- Patient details (e.g. name or initials [depending on privacy requirements], NHS/CHI number [UK only] or medical records number, date of birth, sex)
- Clinician details (e.g. name)
- COVID-19 symptom onset date
- COVID-19 severity as assessed by need for supplemental oxygen, non-invasive ventilation or invasive mechanical ventilation/extracorporeal membrane oxygenation (ECMO)
- Oxygen saturations on air (if available), and S/F_{94} ratio (if participating in early phase assessment; see Section 2.7.1)
- Latest routine measurement of creatinine, C-reactive protein, and D-dimer (if available)
- SARS-CoV-2 PCR test result (if available)
- Major co-morbidity (e.g. heart disease, diabetes, chronic lung disease) and pregnancy (including pregnancy test result in all women of child-bearing potential[e])
- Use of relevant medications (corticosteroids, remdesivir, antiplatelet and anticoagulant therapy)
- Date of hospitalisation
- Contraindication to the study treatment regimens (in the opinion of the attending clinician)
- Name of person completing the form

The person completing the form will then be asked to confirm that they wish to randomise the patient and will then be required to enter their name and e-mail address.

2.4 Main randomisation

In addition to receiving usual care, eligible patients will be allocated using a central web-based randomisation service (without stratification or minimisation). From version 6.0 of the protocol, a factorial design will be used such that eligible patients may be randomised to one or more of the treatment arms in Randomisations A, D, E and F (depending on location). From version 12.1 of the protocol, children may be recruited into the trial even if there are no main randomisation treatments which are both available and suitable provided they meet the criteria for inclusion in the second randomisation, per section 2.5. They will not be allocated to a main randomisation group, but will be potentially eligible for the second randomisation between tocilizumab, anakinra and control.

[e] A woman of childbearing potential is defined as a post-menarchal pre-menopausal female capable of becoming pregnant. This includes women on oral, injectable, or mechanical contraception; women who are single; women whose male partners have been vasectomized or whose male partners have received or are utilizing mechanical contraceptive devices.

2.4.1 Main randomisation part A:

Eligible patients may be randomised to one of the arms listed below. The doses in this section are for adults. Please see Appendix 3 for paediatric dosing. Study treatments do not need to be continued after discharge from hospital.

- **No additional treatment**

- **Dimethyl fumarate: 120 mg every 12 hours for 4 doses followed by 240 mg every 12 hours** by mouth for 8 days (10 days in total).[f] (Adults ≥18 years old only, excluding those on ECMO.) If 240 mg every 12 hours cannot be tolerated, the dose may be reduced.

- **Corticosteroid (in children ≤44 weeks gestational age, or >44 weeks gestational age with PIMS-TS only)**: see Appendix 3.

- **Intravenous immunoglobulin (in children >44 weeks gestational age with PIMS-TS only)**: see Appendices 2 and 3 for dose, contraindications and monitoring information.

For randomisation part A, the randomisation program will allocate patients in a ratio of 1:1 between the no additional treatment arm and each of the other arms available. 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. If no treatments are both available and suitable, then it may be possible to only be randomised in part B (UK only) and/or part D (UK only) and/or part E (ex-UK only) and/or part F.

2.4.2 Main randomisation part D [adults (UK and India only), and children with COVID-19 pneumonia aged ≥2 years only (UK only)]:

Eligible patients may be randomised to one of the arms listed below.

- **No additional treatment**

- **Baricitinib 4 mg once daily** by mouth or nasogastric tube for 10 days in total.[f]

The randomisation program will allocate patients in a ratio of 1:1 between the arms being evaluated in part D of the main randomisation.

2.4.3 Main randomisation part E [adults with hypoxia; non-UK countries only]:

Adult patients enrolled in the RECOVERY trial and with clinical evidence of hypoxia (i.e. receiving oxygen or with oxygen saturations <92% on room air) may be randomised to one of the arms listed below.

- No additional treatment[b]

[f] Treatment should be discontinued at 10 days or on discharge from hospital if sooner

• High-dose corticosteroids: **dexamethasone 20 mg (base) once daily** by mouth, nasogastric tube or intravenous infusion for 5 days follow by **dexamethasone 10 mg (base) once daily** by mouth, nasogastric tube or intravenous infusion for 5 days.[g]

The randomisation program will allocate patients in a ratio of 1:1 between the arms being evaluated in part E of the main randomisation.

2.4.4 Main randomisation part F [adults ≥18 years old only]:

Adult patients enrolled in the RECOVERY trial may be randomised to one of the arms listed below.

• No additional treatment

• **Empagliflozin 10 mg once daily** by mouth for 28 days (or until discharge, if earlier).

The randomisation program will allocate patients in a ratio of 1:1 between the arms being evaluated in part F of the main randomisation.

2.5 Second randomisation for children with progressive PIMS-TS

Children (≥1 year old) enrolled in the RECOVERY trial and with clinical evidence of a hyper-inflammatory state may be considered for a second randomisation if they meet the following criteria:

(i) Recruited into the RECOVERY trial no more than 21 days ago[h]
(ii) Clinical evidence of PIMS-TS:
    a. significant systemic disease with persistent pyrexia, with or without evidence of respiratory involvement)[i]; 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. (Note: Pregnancy and breastfeeding are not specific exclusion criteria.)

Note: Participants may undergo this second randomisation at any point after being first randomised, provided they meet the above criteria, and thus may receive up to two study treatments (one from Main randomisation part A plus one from the second randomisation). For some participants the second randomisation may be immediately after the first but for others it may occur a few hours or days later, if and when they deteriorate.

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[g] Pregnant women should receive either prednisolone (130 mg) orally or hydrocortisone (540 mg in four divided doses) intravenously or methylprednisolone (100 mg) intravenously for five days, followed by either prednisolone (65 mg) orally or hydrocortisone (270 mg in four divided doses) intravenously or methylprednisolone (50 mg) intravenously for five days.
[h] Children recruited into RECOVERY for whom no main randomisation treatment are both available and suitable (see section 2.4) should undergo this second randomisation as soon as possible after recruitment.
[i] 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)

The following information will be recorded (on the web-based form) by the attending clinician or delegate:

- Patient details (e.g. name or initials, NHS/CHI number [UK only] or medical records number, date of birth, sex)
- Clinician details (e.g. name)
- COVID-19 severity as assessed by need for supplemental oxygen or ventilation/ECMO
- Markers of progressive COVID-19 (including oxygen saturation, C-reactive protein)
- Contraindication to the study drug treatments (in the opinion of the attending clinician)
- Name of person completing the form

The person completing the form will then be asked to confirm that they wish to randomise the patient and will then be required to enter their own name and e-mail address.

Eligible participants may be randomised between the following treatment arms (see Appendix 3 for dose information):

- **Tocilizumab** by intravenous infusion
  Tocilizumab should be given as a single intravenous infusion over 60 minutes in 100ml sodium chloride 0.9%. A second dose may be given ≥12 and <24 hours later if, in the opinion of the attending clinician, the patient's condition has not improved.

- **Anakinra** subcutaneously or intravenously once daily for 7 days or discharge (if sooner).
  NB Anakinra will be excluded from the randomisation of children <10 kg in weight.

- **No additional treatment**

The randomisation program will allocate patients in a ratio of 2:2:1 (tocilizumab:anakinra:no additional treatment) between the arms being evaluated in the second randomisation. Participants should receive standard management (including blood tests such as liver function tests and full blood count) according to their clinical need.

2.6 Administration of allocated treatment

The details of the allocated study treatments will be displayed on the screen and can be printed or downloaded. The hospital clinicians are responsible for prescription and administration of the allocated treatments. The patient's own doctors are free to modify or stop study treatments if they feel it is in the best interests of the patient without the need for the patient to withdraw from the study (see section 2.9). This study is being conducted within hospitals. Therefore use of medication will be subject to standard medication reviews (typically within 48 hours of enrolment) which will guide modifications to both the study treatment and use of concomitant medication (e.g. in the case of potential drug interactions).

2.7 Collecting follow-up information

The following information will be ascertained at the time of death or discharge or at 28 days after first 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)

- SARS-CoV-2 test result
- Use of ventilation (with days of use and type, if appropriate)
- Use of renal dialysis or haemofiltration
- Documented new major cardiac arrhythmia (including atrial and ventricular arrhythmias)
- Major bleeding (defined as intracranial bleeding or bleeding requiring transfusion, endoscopy, surgery, or vasoactive drugs)
- Thrombotic event, defined as either (i) acute pulmonary embolism; (ii) deep vein thrombosis; (iii) ischaemic stroke; (iv) myocardial infarction; or (v) systemic arterial embolism.
- Non-coronavirus infection, categorised by site and putative organism (virus, bacteria, fungus, other)
- Use of any medications included in the RECOVERY trial protocol (including drugs in the same class) or other purported COVID-19 treatments (e.g. remdesivir)
- Participation in other randomised trials of interventions (vaccines or treatments) for COVID-19.
- Metabolic complications: Ketoacidosis; hyperglycaemic hyperosmolar state; hyperglycaemia requiring new use of insulin; severe hypoglycaemia (defined as hypoglycaemia causing reduced conscious level requiring another person to help recover)
- Laboratory results: highest creatinine recorded during admission

- Additional information including results of routine tests (including full blood count, coagulation and inflammatory markers, cardiac biomarkers, electro- and echo-cardiograms), other treatments given, length of stay in paediatric high-dependency/intensive care and a paediatric-appropriate frailty score will be collected for children in the UK. This information will be obtained and entered into the web-based IT system by a member of the hospital clinical or research staff. Some of this information may be collected at about 6 weeks after randomisation (at the time of a routine hospital follow-up appointment in-person or by telephone) ideally by someone unaware of treatment allocation.

- At some locations, electrocardiograms done as part of routine care of adult participants will also be collected.

Follow-up information is to be collected on all study participants, irrespective of whether or not they complete the scheduled course of allocated study treatment. Study staff will seek follow-up information through various means including medical staff, reviewing information from medical notes, routine healthcare systems, and registries.

For all randomised participants, vital status (alive / dead, with date and presumed cause of death, if appropriate) is to be ascertained at 28 days after first randomisation. This may be achieved through linkage to routine death registration data (e.g. in the UK) or through direct contact with the participant, their relatives, or medical staff and completion of an additional follow-up form.

2.7.1 Additional procedures for participants in early phase assessments

2.7.1.1 Dimethyl fumarate vs. Usual Care

In addition, the following information will be collected for participants in the early phase assessment of dimethyl fumarate (see Appendix 5 for further details), including participants allocated usual care in this comparison:

- S/F_{94} ratio on days 3, 5 and 10 (unless discharged sooner)
- WHO Ordinal Score[10] each day after randomisation until day 10 (or discharge if sooner)
- Blood C-reactive protein, creatinine and alanine (or aspartate) transaminase on days 3, 5 and 10 (unless discharged sooner)
- Incidence and severity of flushing and gastrointestinal symptoms
- Reasons for stopping dimethyl fumarate

2.8 Duration of follow-up

All randomised participants are to be followed up until death, discharge from hospital or 28 days after randomisation (whichever is sooner). It is recognised that in the setting of this trial, there may be some variability in exactly how many days after randomisation, information on disease status is collected. This is acceptable and will be taken account of in the analyses and interpretation of results, the principle being that some information about post-randomisation disease status is better than none.

In the UK, longer term (up to 10 years) follow-up will be sought through linkage to electronic healthcare records and medical databases including those held by NHS Digital, Public Health England and equivalent bodies, and to relevant research databases (e.g. UK Biobank, Genomics England). Outside the UK, due to the absence of electronic health data linkage, additional follow-up will be conducted at 3 and 6 months after first randomisation by telephone or in person (at a clinic) in order to collect information on mortality (including date and cause) and re-admission to hospital (including date[s] and primary reason[s]). This information will be captured on a web-based case report form.

2.9 Withdrawal of consent

A decision by a participant (or their parent/guardian) that they no longer wish to continue receiving study treatment should **not** be considered to be a withdrawal of consent for follow-up. However, participants (or their parent/guardian) are free to withdraw consent for some or all aspects of the study at any time if they wish to do so. In accordance with regulatory guidance, de-identified data that have already been collected and incorporated in the study database will continue to be used (and any identifiable data will be destroyed).

For participants who lack capacity, if their legal representative withdraws consent for treatment or methods of follow-up then these activities would cease.

3 STATISTICAL ANALYSIS

All analyses for reports, presentations and publications will be prepared by the coordinating centre at the Nuffield Department of Population Health, University of Oxford. A more detailed statistical analysis plan will be developed by the investigators and published on the study website whilst still blind to any analyses of aggregated data on study outcomes by treatment allocation.

3.1 Outcomes

For each pairwise comparison with the 'no additional treatment' arm, the **primary objective** is to provide reliable estimates of the effect of study treatments on all-cause mortality at 28 days after randomisation (with subsidiary analyses of cause of death and of death at various timepoints following discharge).

The **secondary objectives** are to assess the effects of study treatments on duration of hospital stay; and, among patients not on invasive mechanical ventilation at baseline, the composite endpoint of death or need for invasive mechanical ventilation or ECMO.

Other objectives include the assessment of the effects of study treatments on the need for any ventilation (and duration of invasive mechanical ventilation), acute kidney injury and renal replacement therapy, and thrombotic events. Safety outcomes include bleeding, new major cardiac arrhythmias, metabolic complications (ketoacidosis, hyperglycaemic hyperosmolar state, hyperglycaemia requiring new use of insulin, severe hypoglycaemia) and (assessed at 72 hours after randomization among participants in main randomization part B only) sudden worsening in respiratory status, severe allergic reaction, significant fever, sudden hypotension and clinical haemolysis (which were collected until 15 January 2021 when the DMC recommended they were no longer required).

Study outcomes will be assessed based on data recorded up to 28 days and up to 6 months after randomisation.

Where available, data from routine healthcare records (including linkage to medical databases held by organisations such as NHS Digital in the UK) and from relevant research studies (such as UK Biobank, Genomics England, ISARIC-4C and PHOSP-COVID) will allow subsidiary analyses of the effect of the study treatments on particular non-fatal events (e.g. ascertained through linkage to Hospital Episode Statistics), the influence of pre-existing major co-morbidity (e.g. diabetes, heart disease, lung disease, hepatic insufficiency, severe depression, severe kidney impairment, immunosuppression), and longer-term outcomes as well as in particular sub-categories of patient (e.g. by genotype, pregnancy).

3.2 Methods of analysis

For all outcomes, comparisons will be made between all participants randomised to the different treatment arms, irrespective of whether they received their allocated treatment ("intention-to-treat" analyses).

For time-to-event analyses, each treatment group will be compared with the no additional treatment group using the log-rank test. Kaplan-Meier estimates for the time to event will also be plotted (with associated log-rank p-values). The log-rank 'observed minus expected' statistic (and its variance) will also be used to estimate the average event rate ratio (and its

confidence interval) for those allocated to each treatment group versus the no additional treatment group. For binary outcomes where the timing is unknown, the risk ratio and absolute risk difference will be calculated with confidence intervals and p-value reported. For the primary outcome (death within 28 days of randomisation), discharge alive before 28 days will assume safety from the event (unless there is additional data confirming otherwise).

Pairwise comparisons within each randomisation will be made between each treatment arm and the no additional treatment arm (reference group) in that particular randomisation (main randomisation part A, B, C, D, E or F and second randomisation). However, since not all treatments may be available or suitable for all patients, those in the no additional treatment arm will only be included in a given comparison if, at the point of their randomisation, they *could* alternatively have been randomised to the active treatment of interest. Allowance for multiple treatment comparisons due to the multi-arm design will be made. All p-values will be 2-sided.

Pre-specified subgroup analysis (e.g., level of respiratory support, time since onset of symptoms; sex; age group; ethnicity; use of corticosteroids) will be conducted for the primary outcome using the statistical test for interaction (or test for trend where appropriate). Sensitivity analyses will be conducted among those patients with laboratory confirmed SARS-CoV-2. Further details will be fully described in the Statistical Analysis Plan.

3.3 Children

The primary outcome for children will be the number of days in hospital. This will be analysed using a negative binomial model utilizing a Bayesian framework with treatment indicators for tocilizumab and anakinra as well as site and age. Non-informative prior distributions will be used for the treatment effects and mildly informative priors for the covariates. Further details will be described in a children-specific statistical analysis plan which will be agreed prior to unblinding any results to the Steering Committee.

3.4 Early phase assessments

The primary objective for the early phase assessment of dimethyl fumarate is to assess the effect of dimethyl fumarate on the S/F_{94} ratio. The primary comparison will involve an “intention to treat” analysis among all participants randomised between dimethyl fumarate and its control of the effect of dimethyl fumarate on SpO_2:FiO_2 ratio at day 5. Secondary objectives include assessment of the effect of dimethyl fumarate on: time to improvement by at least one category from the WHO ordinal scale at baseline; time to discharge; odds of improvement in clinical status at day 10; average WHO ordinal scale on days 3, 7 and 10; and study average blood C-reactive protein. These data (along with information on tolerability and safety) would be reviewed to determine whether the balance of information favours assessing dimethyl fumarate in a larger comparison or not. Full details will be described in a statistical analysis plan which will be agreed prior to unblinding any results to the Steering Committee.

Based on unpublished data from 8500 patients with COVID-19, assuming a mean (standard deviation) S/F_{94} ratio of 3.3 (1.7) at day 5, and a correlation between an individual’s baseline and day 5 S/F_{94} ratio of 0.5, randomisation of 400 participants will provide 90% power (at 2p=0.05) to detect a difference in S/F_{94} ratio of 0.5 (the chosen minimum clinically

meaningful difference [which is similar to the difference in 1 point on the WHO ordinal scale]), even if 10% of participants discontinue study treatment before day 5.

4 DATA AND SAFETY MONITORING

4.1 Recording Suspected Serious Adverse Reactions

The focus is on those events that, based on a single case, are highly likely to be related to the study medication. Examples include anaphylaxis, Stevens Johnson Syndrome, or bone marrow failure, where there is no other plausible explanation.

Any Serious Adverse Event[j] that is believed with a reasonable probability to be due to one of the study treatments will be considered a Suspected Serious Adverse Reaction (SSAR). In making this assessment, there should be consideration of the probability of an alternative cause (for example, COVID-19 itself or some other condition preceding randomisation), the timing of the event with respect to study treatment, the response to withdrawal of the study treatment, and (where appropriate) the response to subsequent re-challenge.

All SSARs should be reported by telephone to the Central Coordinating Office and recorded on the study IT system immediately.

4.2 Central assessment and onward reporting of SUSARs

Clinicians at the Central Coordinating Office are responsible for expedited review of reports of SSARs received. Additional information (including the reason for considering it both serious and related, and relevant medical and medication history) will be sought.

The focus of Suspected Unexpected Serious Adverse Reaction (SUSAR) reporting will be on those events that, based on a single case, are highly likely to be related to the study medication. To this end, anticipated events that are either efficacy endpoints, consequences of the underlying disease, or common in the study population will be exempted from expedited reporting. Thus the following events will be exempted from expedited reporting:

(i) Events which are the consequence of COVID-19; and
(ii) Common events which are the consequence of conditions preceding randomisation.

Any SSARs that are not exempt will be reviewed by a Central Coordinating Office clinician and an assessment made of whether the event is “expected” or not (assessed against the relevant Summary of Product Characteristics or Investigator Brochure). Any SSARs that are not expected would be considered a Suspected Unexpected Serious Adverse Reaction (SUSAR).

[j] Serious Adverse Events are defined as those adverse events that result in death; are life-threatening; require in-patient hospitalisation or prolongation of existing hospitalisation; result in persistent or significant disability or incapacity; result in congenital anomaly or birth defect; or are important medical events in the opinion of the responsible investigator (that is, not life-threatening or resulting in hospitalisation, but may jeopardise the participant or require intervention to prevent one or other of the outcomes listed above).

All confirmed SUSARs will be reported to the Chair of the DMC and to relevant regulatory authorities, ethics committees, and investigators in an expedited manner in accordance with regulatory requirements.

4.3 Recording other Adverse Events

In addition to recording Suspected Serious Adverse Reactions (see section 4.1), information will be collected on all deaths and efforts will be made to ascertain the underlying cause. Other serious or non-serious adverse events will not be recorded unless specified in section 2.7. [k] It is anticipated that for some substudies, more detailed information on adverse events (e.g. through linkage to medical databases) or on other effects of the treatment (e.g. laboratory or radiological features) will be recorded and analysed but this is not a requirement of the core protocol.

4.4 Role of the Data Monitoring Committee (DMC)

During the study, interim analyses of all study data will be supplied in strict confidence to the independent DMC. The DMC will request such analyses at a frequency relevant to the emerging data from this and other studies.

The DMC will independently evaluate these analyses and any other information considered relevant. The DMC will determine if, in their view, the randomised comparisons in the study have provided evidence on mortality that is strong enough (with a range of uncertainty around the results that is narrow enough) to affect national and global treatment strategies. In such a circumstance, the DMC will inform the Trial Steering Committee who will make the results available to the public and amend the trial arms accordingly. Unless this happens, the Trial Steering Committee, Chief Investigator, study staff, investigators, study participants, funders and other partners will remain blind to the interim results until 28 days after the last patient has been randomised for a particular intervention arm (at which point analyses may be conducted comparing that arm with the no additional treatment arm).

The DMC will review the safety and efficacy analyses among children (age <18 years) both separately and combined with the adult data.

4.5 Blinding

This is an open-label study. However, while the study is in progress, access to tabular results of study outcomes by allocated treatment allocation will not be available to the research team, patients, or members of the Trial Steering Committee (unless the DMC advises otherwise).

[k] Outside the UK, additional serious adverse event information (event description, date of onset, outcome, relatedness to study treatment) will be collected if required by national regulations. This will be collected on a web-based case report form and any forms required by local regulations.

5 QUALITY MANAGEMENT

5.1 Quality By Design Principles

In accordance with the principles of Good Clinical Practice and the recommendations and guidelines issued by regulatory agencies, the design, conduct and analysis of this trial is focussed on issues that might have a material impact on the wellbeing and safety of study participants (hospitalised patients with suspected or confirmed SARS-CoV-2 infection) and the reliability of the results that would inform the care for future patients.

The critical factors that influence the ability to deliver these quality objectives are:

- to minimise the burden on busy clinicians working in an overstretched hospital during a major epidemic
- to ensure that suitable patients have access to the trial medication without impacting or delaying other aspects of their emergency care
- to provide information on the study to patients and clinicians in a timely and readily digestible fashion but without impacting adversely on other aspects of the trial or the patient's care
- to allow individual clinicians to use their judgement about whether any of the treatment arms are not suitable for the patient
- to collect comprehensive information on the mortality and disease status

In assessing any risks to patient safety and well-being, a key principle is that of proportionality. Risks associated with participation in the trial must be considered in the context of usual care. At present, there are no proven treatments for COVID-19, basic hospital care (staffing, beds, ventilatory support) may well be overstretched, and mortality for hospitalised patients may be around 10% (or more in those who are older or have significant co-morbidity).

5.2 Training and monitoring

The focus will be on those factors that are critical to quality (i.e. the safety of the participants and the reliability of the trial results). Remedial actions would focus on issues with the potential to have a substantial impact on the safety of the study participants or the reliability of the results.

The study will be conducted in accordance with the principles of International Conference on Harmonisation Guidelines for Good Clinical Research Practice (ICH-GCP) and relevant local, national and international regulations. Any serious breach of GCP in the conduct of the clinical trial will be handled in accordance with regulatory requirements. Prior to initiation of the study at each Local Clinical Centre (LCC), the Central Coordinating Office (CCO) or relevant Regional Coordinating Centre (RCC) will confirm that the LCC has adequate facilities and resources to carry out the study. LCC lead investigators and study staff will be provided with training materials.

In the context of this epidemic, visits to hospital sites is generally not appropriate as they could increase the risks of spreading infection, and in the context of this trial they generally would not influence the reliability of the trial results or the well-being of the participants. In exceptional circumstances, the CCO or RCC may arrange monitoring visits to LCCs as considered appropriate based on perceived training needs and the results of central

statistical monitoring of study data.[11,12] The purpose of such visits will be to ensure that the study is being conducted in accordance with the protocol, to help LCC staff to resolve any local problems, and to provide extra training focussed on specific needs. No routine source data verification will take place.

5.3 Data management

LCC clinic staff will use the bespoke study web-based applications for study management and to record participant data (including case report forms) in accordance with the protocol. Data will be held in central databases located at the CCO or on secure cloud servers. In some circumstances (e.g. where there is difficulty accessing the internet or necessary IT equipment), paper case report forms may be required with subsequent data entry by either LCC or CCO staff. Although data entry should be mindful of the desire to maintain integrity and audit trails, in the circumstances of this epidemic, the priority is on the timely entry of data that is sufficient to support reliable analysis and interpretation about treatment effects. CCO staff will be responsible for provision of the relevant web-based applications and for generation of data extracts for analyses.

All data access will be controlled by usernames and passwords, and any changes to data will require the user to enter their username and password. Staff will have access restricted to the functionality and data that are appropriate for their role in the study.

5.4 Source documents and archiving

Source documents for the study constitute the records held in the study main database. These will be retained for at least 25 years from the completion of the study. Identifiable data will be retained only for so long as it is required to maintain linkage with routine data sources (see section 2.8), with the exception of children for whom such data must be stored until they reach 21 years old (due to the statute of limitations). The sponsor and regulatory agencies will have the right to conduct confidential audits of such records in the CCO and LCCs (but should mindful of the workload facing participating hospitals and the infection control requirements during this epidemic).

6 OPERATIONAL AND ADMINISTRATIVE DETAILS

6.1 Sponsor and coordination

The University of Oxford will act as the trial Sponsor. The trial will be coordinated by a Central Coordinating Office (CCO) within the Nuffield Department of Population Health staffed by members of the two registered clinical trials units – the Clinical Trial Service Unit and the National Perinatal Epidemiology Unit Clinical Trials Unit. The CCO will oversee Regional Coordinating Centres which will assist with selection of Local Clinical Centres (LCCs) within their region and for the administrative support and monitoring of those LCCs. The data will be collected, analysed and published independently of the source of funding.

6.2 Funding

This study is supported by grants to the University of Oxford from UK Research and Innovation/National Institute for Health Research (NIHR) and the Wellcome Trust, and by core funding provided by NIHR Oxford Biomedical Research Centre, the Wellcome Trust,

the Bill and Melinda Gates Foundation, Department for International Development, Health Data Research UK, NIHR Health Protection Unit in Emerging and Zoonotic Infections and the Medical Research Council Population Health Research Unit, and NIHR Clinical Trials Unit Support Funding.

6.3 Indemnity

The University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London). In the UK, NHS indemnity operates in respect of the clinical treatment that is provided.

6.4 Local Clinical Centres

The study will be conducted at multiple hospitals (LCCs) within each region. At each LCC, a lead investigator will be responsible for trial activities but much of the work will be carried out by medical staff attending patients with COVID-19 within the hospital and by hospital research nurses, medical students and other staff with appropriate education, training, and experience. Where LCCs plan to recruit children the principal investigator will co-opt support from a local paediatrician and/or neonatologists to oversee the management of children and infants in the trial.

6.5 Supply of study treatments

For licensed treatments (e.g. corticosteroids, baricitinib) all aspects of treatment supply, storage, and management will be in accordance with standard local policy and practice for prescription medications. Treatments issued to randomised participants will be by prescription. Such study treatments will not be labelled other than as required for routine clinical use. They will be stored alongside other routine medications with no additional monitoring. No accountability records will be kept beyond those used for routine prescriptions.

For unlicensed treatments, manufacture, packaging, labelling and delivery will be the responsibility of the pharmaceutical company and, in the UK, the Department of Health and Social Care. Each LCC will maintain an accountability log and will be responsible for the storage and issue of study treatment. If treatments require storage at a specific temperature, LCCs can use existing temperature-controlled facilities and associated monitoring. Treatment issue to randomised participants will be in accordance with local practice (and may be in line with the processes required for routine prescriptions or compassionate use).

Treatment will be issued to randomised participants by prescription.

6.6 End of trial

The end of the scheduled treatment phase is defined as the date of the last follow-up visit of the last participant. In the UK, it is intended to extend follow-up for a year or more beyond the final study visit through linkage to routine medical records and central medical databases. The end of the study is the date of the final data extraction from NHS Digital (anticipated to be 10 years after the last patient is enrolled).

6.7 Publications and reports

The Trial Steering Committee will be responsible for drafting the main reports from the study and for review of any other reports. In general, papers initiated by the Trial Steering

Committee (including the primary manuscript) will be written in the name of the RECOVERY Collaborative Group, with individual investigators named personally at the end of the report (or, to comply with journal requirements, in web-based material posted with the report).

The Trial Steering Committee will also establish a process by which proposals for additional publications (including from independent external researchers) are considered by the Trial Steering Committee. The Trial Steering Committee will facilitate the use of the study data and approval will not be unreasonably withheld. However, the Trial Steering Committee will need to be satisfied that any proposed publication is of high quality, honours the commitments made to the study participants in the consent documentation and ethical approvals, and is compliant with relevant legal and regulatory requirements (e.g. relating to data protection and privacy). The Trial Steering Committee will have the right to review and comment on any draft manuscripts prior to publication.

6.8 Substudies

Proposals for substudies must be approved by the Trial Steering Committee and by the relevant ethics committee and competent authorities (where required) as a substantial amendment or separate study before they begin. In considering such proposals, the Trial Steering Committee will need to be satisfied that the proposed substudy is worthwhile and will not compromise the main study in any way (e.g. by impairing recruitment or the ability of the participating hospitals to provide care to all patients under their care).

7 VERSION HISTORY

Version number	Date	Brief Description of Changes
1.0	13-Mar-2020	Initial version
2.0	21-Mar-2020	Addition of hydroxychloroquine. Administrative changes and other clarifications.
3.0	07-Apr-2020	Extension of eligibility to those with suspected COVID-19 Addition of azithromycin arm. Addition of inclusion of adults who lack permanently lack capacity. Change to primary outcome from in-hospital death to death within 28 days of randomisation.
4.0	14-Apr-2020	Addition of second randomisation to tocilizumab vs. standard of care among patients with progressive COVID-19.
5.0	24-Apr-2020	Addition of children to study population.
6.0	14-May-2020	Addition of convalescent plasma
7.0	18-Jun-2020	Allowance of randomisation in part B of main randomisation without part A. Removal of hydroxychloroquine and dexamethasone treatment arms.
8.0	03-Jul-2020	Removal of lopinavir-ritonavir Addition of intravenous immunoglobulin arm for children Changes to corticosteroid dosing for children. Addition of baseline serum sample in convalescent plasma randomisation
9.0	10-Sep-2020	Addition of synthetic neutralizing antibodies Additional baseline data collection Addition of countries outside UK
9.1	18-Sep-2020	Addition of information about vaccination of children of pregnant mothers receiving REGN10933+REGN10987
9.2 [not submitted in UK]	15-Oct-2020	Additional information for countries outside UK
10.0	26-Oct-2020	Addition of main randomisation part C General updates to avoid duplication and improve clarity
10.1	01-Nov-2020	Additional information for pregnant women
11.0	19-Nov-2020	Addition of colchicine to main randomisation part A Removal of azithromycin from main randomisation part A Change in randomisation ratio in main randomisation part A from 2:1 to 1:1
11.1	21-Nov-2020	Clarification of colchicine age thresholds
11.2 [not submitted in UK]	01-Dec-2020	Addition of modified aspirin dose if 150mg not available
12.0	10-Dec-2020	Allow second randomisation of children without first randomisation
12.1	16-Dec-2020	Clarification of change in V12.0
13.0	26-Jan-2021	Addition of baricitinib and anakinra (and change to allocation ratio in second randomization for children); addition of pregnancy test for women of child-bearing potential (and change to colchicine eligibility); removal of tocilizumab for adults; removal of convalescent plasma and additional assessment of antibody-based therapy; addition of dexamethasone as substitute if methylprednisolone unavailable
14.0	15-Feb-2021	Addition of Early Phase Assessments; the inclusion of dimethyl fumarate for initial early phase assessment; restriction of main randomisation part B to children with COVID-19 pneumonia; modification of barictinib and tocilizumab co-administration guidance
15.0	12-Apr-2021	Removal of aspirin and colchicine; addition of infliximab and high-dose corticosteroids (ex-UK only)

15.1 [not submitted in UK]	18-May-2021	Addition of South Africa
16.0	05-Jul-2021	Removal of REGN-COV2 and main randomisation part B Removal of infliximab from main randomisation part E (and associated endemic infection monitoring section) Addition of empagliflozin as main randomisation part F and metabolic outcomes Addition of India, Sri Lanka and Pakistan

8 APPENDICES

8.1 Appendix 1: Information about the treatment arms

All patients will receive usual care in the participating hospital.

Corticosteroids: RECOVERY is assessing corticosteroids in the following contexts:

i. Moderate dose *vs* usual care in neonates with COVID-19 pneumonia (UK only)
ii. High dose *vs* usual care in children with PIMS-TS (UK only)
iii. High dose *vs* usual care in adults with COVID-19 and hypoxia (ex-UK only)

Favourable modulation of the immune response is considered one of the possible mechanisms by which corticosteroids might be beneficial in the treatment of severe acute respiratory coronavirus infections, including COVID-19, SARS and MERS. Common to severe cases of these infections is the presence of hypercytokinemia and the development of acute lung injury or acute respiratory distress syndrome (ARDS).[13-16] Pathologically, diffuse alveolar damage is found in patients who die from these infections.[17] RECOVERY and other randomised trials have now demonstrated the benefit of corticosteroids in hypoxic COVID-19 patients.[18,19]

RECOVERY showed that a dose of 6mg dexamethasone once daily for ten days or until discharge (which ever happens earliest) provided a significant reduction in mortality. Combining the IL-6 inhibitor tocilizumab with low dose dexamethasone resulted in a further reduction in mortality. This raises the question whether simply increasing the dose of corticosteroid could confer a similar clinical benefit to that of adding tocilizumab, but at substantially lower cost. Of note, even with dexamethasone 6mg and tocilizumab, mortality remained high at 29%. Although other randomised clinical trials in critically ill COVID-19 patients have used higher doses of dexamethasone (20mg once daily for five days followed by 10mg once daily for a further five days) and reported clinical benefit, these doses have not been compared with the lower dose used in RECOVERY. There is, therefore, uncertainty regarding the optimal dose of corticosteroids in moderate to severe COVID-19.Uncertainty remains about whether higher doses of corticosteroids may provide additional benefit in adults with hypoxia hospitalised with COVID-19.

Unlike lower doses, higher doses (>15mg dexamethasone) would completely saturate cytosolic glucocorticoid receptors and have enhanced non-genomic effects.[20] In conditions where rapid control of inflammatory processes are required, short-term, high to very high doses of corticosteroids are used e.g.

- Sepsis 7.5 - 15mg dexamethasone equivalent daily[21]
- ARDS: 20mg dexamethasone for five days followed by 10mg for five days[22]
- Bacterial meningitis: 40mg dexamethasone daily for four days[23]
- Tuberculous Meningitis 0.4mg/k/day dexamethasone for 7 days then reducing over 8 weeks.[24]
- Rheumatoid arthritis flare: 120mg dexamethasone pulse therapy.[25]
- Community acquired pneumonia: 0.6mg/day dexamethasone for 2 days and methyl prednisolone 200m g /day then 80m g /day for 10 days.[26]

PIMS-TS is associated with a hyper-inflammatory state with elevated ESR, C-reactive protein, D-dimers, lactate dehydrogenase, ferritin, and increased levels of pro-inflammatory cytokines including as IL-1 and IL-6. While there is a pharmacological basis for using high dose methylprednisolone, the Delphi consensus process conducted by NHS England identified equipoise for its use in the treatment of PIMS-TS.

[UK only] Dimethyl fumarate: Dimethyl fumarate (DMF) is thought to prevent NLRP3 inflammasome activation and the process of pyroptosis (inflammatory cell death) through its action on the protein gasdermin D.[27] SARS-CoV-2 induces inflammasome activation and the degree of activation is thought to correlate with disease severity.[28] DMF has demonstrated anti-viral and anti-inflammatory effects against SARS-CoV-2 *in vitro.*[29] Other inflammasome-modulating drugs, such as colchicine, have demonstrated provisionally promising results in small randomised trials.[30,31] DMF is licensed to treat relapsing remitting multiple sclerosis and plaque psoriasis as a long-term immunomodulatory agent and is generally well-tolerated with no major safety concerns.[32,33] The UK COVID-19 Therapeutics Advisory Panel has recommended that RECOVERY investigate the safety and efficacy of DMF in an early phase assessment among patients hospitalised with COVID-19.

[UK only] Baricitinib: Baricitinib is a JAK (Janus kinase) 1/2 inhibitor licensed for the treatment of rheumatoid arthritis and atopic dermatitis. JAK 1/2 inhibition prevents downstream phosphorylation (and hence activation) of STAT (signal transducers and activators of transcription). The JAK-STAT pathway mediates the effect of several interleukins (including IL-6), so JAK inhibitors reduce the cascade of inflammatory mediators that derive from IL-6 activation of its receptor. Baricitinib also binds tyrosine kinase 2, preventing its activation.[34] Recent genetic data support a causal link between high tyrosine kinase expression (hence activity) and severe COVID-19.[35] Baricitinib was tested in the Adaptive Covid-19 Treatment Trial-2 and was shown to improve time to recovery (rate ratio for recovery 1.16, 95% CI 1.01-1.32). 28-day mortality was 5.1% among participants allocated baricitinib compared to 7.8% allocated placebo (HR 0.65, 95% CI 0.39-1.09).[36] Serious adverse events were less frequent among participants allocated baricitinib (16.0% vs. 21.0%; p=0.03).

[UK only] Intravenous immunoglobulin (IVIg): IVIg is human normal immunoglobulin, available in a number of different preparations in routine NHS practice. The NHS England consensus process has established intravenous immunoglobulin as the interim first line treatment in non-shocked COVID-associated PIMS-TS and also that there is need for evaluation of intravenous immunoglobulin and corticosteroid in the initial management of PIMS-TS. In the similar but different disease process known as Kawasaki Diseases, randomised controlled trials and meta-analyses have demonstrated that early recognition and treatment of KD with IVIg (and aspirin) reduces the occurrence of coronary artery aneurysms. Current published guidelines recommend a dose of 2 g/kg IVIg given as a single infusion, as this has been shown to reduce the coronary artery aneurysm rate compared to a lower divided dose regimen.[37]

IVIg is licensed for immunomodulation in adults, children and adolescents (0-18 years) in a number of clinical conditions including but not limited to primary immune thrombocytopenia, Guillain Barré syndrome, Kawasaki disease (in association with aspirin), chronic inflammatory demyelinating polyradiculoneuropathy and multifocal motor neuropathy.

[UK only] Tocilizumab is a monoclonal antibody that binds to the receptor for IL-6, blocking IL-6 signalling and reduces inflammation. Tocilizumab is licensed for use in patients with rheumatoid arthritis and for use in people aged at least 2 years with chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome.

Severe COVID-19 is associated with a hyper-inflammatory state with elevated ESR, C-reactive protein, D-dimers, lactate dehydrogenase, ferritin, and increased levels of pro-inflammatory cytokines including as IL-1 and IL-6.[4,9,38] There have been published and unpublished (pre-print) case series reports of the successful treatment of COVID-19 patients with IL-6 inhibitors.[38,39] IL-6 inhibitors have not been evaluated for the treatment of COVID-19 in randomised controlled trials.

[UK only] Anakinra: Anakinra is an antagonist of the interleukin-1 receptor licensed for the treatment of rheumatoid arthritis, periodic fever syndromes and Still's disease. Anakinra is widely used in several paediatric conditions with hyperinflammation including macrophage activation syndrome, systemic JIA and autoinflammatory disorders.[40] The hyperinflammatory syndrome associated with COVID-19 in children (PIMS-TS) is characterised by high inflammatory markers and wide range of elevated cytokines. Immunomodulatory therapy with IL-1 inhibition using anakinra has been used in the management of the children with PIMS-TS,[41] but controlled trials are lacking. Anakinra has been shown to be safe in sepsis and has a short half-life which may be advantageous for use in very ill children with PIMS-TS.

Empagliflozin: Sodium glucose co-transporter 2 inhibitors (SGLT-2i) decrease glucose and insulin levels, and shift energy metabolism to an increased reliance on lipid oxidation, with a reduced reliance on glucose, and inhibition of glycolysis.[42] This mechanism may be particularly important in COVID-19, as SARS-CoV-2 may depend on the glycolytic pathway for its replication, stimulating lipogenesis, which appears to be one of the key drivers of cellular damage.[43,44] SGLT-2i rapidly improve endothelial function, possibly because of reduced oxidative stress.[45] SGLT-2i have significant anti-inflammatory effects, reducing levels of C-reactive protein and interleukin-6.[46] Experimental studies have also shown reduced activation of the NLRP3 inflammasome.[47] SGLT-2i increase erythropoiesis resulting in increased haematocrit,[48,49] and together with improved endothelial function[45] may improve oxygen delivery to tissues. Moreover, SGLT-2i result in reduced extracellular volume in patients with fluid overload,[50,51] and appear to reduce pulmonary artery pressure in patients with heart failure rapidly,[52] leading to haemodynamic decongestion. Thus, SGLT-2i may favourably affect multiple processes, including but not limited to energy metabolism, endothelial function, oxidative stress, inflammation and autophagy, which are dysregulated during a major acute illness such as COVID-19. The DARE-19 trial compared dapagliflozin 10 mg with placebo for 30 days among 1250 patients admitted to hospital with COVID-19 who had mild hypoxia (SpO_2 ≥94% on ≤5 L/min oxygen) and at least one risk factor (hypertension, type 2 diabetes mellitus, atherosclerotic cardiovascular disease, heart failure or chronic kidney disease).[53] The treatment was well tolerated (11% discontinued prematurely with similar proportion in treatment and placebo group). The hazard ratio for the co-primary outcome of organ failure (non-invasive or invasive ventilation, requirement for cardiovascular support or new/worsened heart failure, doubling of creatinine or dialysis) or death was 0.80 (95% CI 0.58-1.10; 70 *vs* 86 events).[54] Although this trial lacked statistical sensitivity, it supports the rationale for a larger trial.

8.2 Appendix 2: Drug specific contraindications and cautions

Corticosteroid
Contraindications:
- Known contra-indication to short-term corticosteroid.

Endemic infections may be screened for as required by local practice.

Dimethyl fumarate
Contraindications:
- Pregnancy
- Breast-feeding
- Known hypersensitivity to excipients in any oral therapy

If symptoms develop which the participant or their doctor attributes to dimethyl fumarate (e.g. flushing, gastrointestinal disturbance), its dose may be reduced e.g. from 240 mg twice daily to 120 mg twice daily or 120 mg once daily (or it may be discontinued if considered necessary by the managing clinician or participant).

Baricitinib
Contraindications:
- eGFR <15 mL/min/1.73m^2 (including participants on dialysis/haemofiltration)
- Neutrophil count <0.5 x 10^9/L
- Evidence of active TB infection
- Pregnancy

Cautions:
- Dose should be reduced in presence of renal impairment
  - eGFR ≥30 <60 mL/min/1.73m^2: 2 mg once daily
  - eGFR ≥15 <30 mL/min/1.73m^2: 2 mg on alternate days
- Dose should be halved in patients also taking probenecid
- Baricitinib and tocilizumab may be co-administered, but the managing clinician should consider the risk of infection and gastrointestinal perforation (which may present atypically due to suppressed C-reactive protein production and concomitant corticosteroids)

Intravenous Immunoglobulin (children only)
- Hypersensitivity to the active substance (human immunoglobulins) or to any of the excipients
- Patients with selective IgA deficiency who developed antibodies to IgA, as administering an IgA-containing product can result in anaphylaxis
- Hyperprolinaemia type I or II.

Potential complications can often be avoided by ensuring that participants:
i. are carefully monitored for any symptoms throughout the infusion period;
ii. have urine output and serum creatinine levels monitored; and
iii. avoid concomitant use of loop diuretics.

Such monitoring should occur regularly during the admission, at a frequency appropriate to the illness of the child.

Tocilizumab

- Known hypersensitivity to tocilizumab.
- Evidence of active TB infection[l]
- Clear evidence of active bacterial, fungal, viral, or other infection (besides COVID-19)

(Note: Pregnancy and breastfeeding are not exclusion criteria.)

Anakinra

- Known hypersensitivity to anakinra
- Neutrophil count <1.5 x10^9 cells/L
- Pregnancy

Empagliflozin

Contraindications:

- Type 1 diabetes mellitus
- Pregnancy and breast-feeding

Cautions:

- Clinicians should consider temporarily discontinuing empagliflozin in participants with type 2 diabetes mellitus who cannot maintain oral calorific intake (until nutrition is restored)
- Clinicians should be aware of “euglycaemic ketoacidosis” which occurs with empagliflozin and should check ketones (ideally blood) if this is suspected (e.g. unexplained metabolic acidosis)
- Empagliflozin does not cause hypoglycaemia alone, but may do so in combination with insulin or insulin secretagogues (e.g. sulphonylureas). Doses of these other medications may need to be temporarily modified while the participant is taking empagliflozin
- Empagliflozin causes an osmotic diuresis so careful fluid balance assessment is required
- Empagliflozin increases the risk of mycotic genital infections (e.g. candidiasis) which are usually easily treated with topical therapy. It is unclear whether it causes Fournier’s gangrene (a very rare genital infection), but clinicians should be aware.

[l] Note: The risk of reactivation of latent tuberculosis with tocilizumab is considered to be extremely small.

8.3 Appendix 3: Paediatric dosing information

Children (aged <18 years old) will be recruited in the UK only.

Main Randomisation Part A

Arm	Route	Weight/Age [#]	Dose
No additional treatment	-	-	-
Corticosteroid - Solution for injection* - Powder for solution for injection* - *various strengths available	Intravenous	Neonates/infants with a corrected gestational age of ≤44 weeks with COVID-19 pneumonia	**Hydrocortisone** (IV): 0.5 mg/kg every 12 hours for 7 days and then 0.5mg/kg once daily for 3 days
	Intravenous	>44 weeks with PIMS-TS	**Methylprednisolone sodium succinate[†]** 10 mg/kg (as base) once daily for 3 days (max 1 gram) 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	>44 weeks with PIMS-TS	2 g/kg as a single dose. (Dose should be based on ideal body weight in line with NHS England guidance.)
Baricitinib - 2 and 4 mg tablets	Oral/ other enteral routes	≥ 2 years with COVID-19 pneumonia	Once daily for 10 days or until discharge, whichever is sooner eGFR (mL/min/1.73 m^2) / 2 to < 9 yr / ≥ 9 yr ≥60 / 2mg / 4mg ≥30 to <60 / 2mg alt die / 2mg ≥15 to <30 / Excluded / 2mg alt die Those on renal replacement therapy are excluded

[#] Weight to be rounded to the nearest kg unless dosage expressed as mg/kg or mL/kg.
[†] If methylprednisolone is unavailable, intravenous dexamethasone may be substituted (0.3 mg/kg as base; max 19.8 mg) once daily for 3 days.

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.
Anakinra	Subcutaneous (Intravenous route if clinically required)	Infants < 1 year or <10 kg excluded	
		≥ 10 kg	2 mg/kg daily for 7 days or discharge whichever is sooner

8.4 Appendix 4: Use of IMPs in pregnant and breastfeeding women

All trial drugs (except baricitinib and empagliflozin) have been used in pregnant women with pre-existing medical disorders where benefits outweigh the risks to fetus or woman, including in the first trimester. The existing data related to each drug is summarized below.

Dimethyl fumarate

Dimethyl fumarate is contraindicated in pregnant or breastfeeding women. Dimethyl fumarate will only be included in the randomisation of women of child-bearing potential if they have had a negative pregnancy test since admission.

Corticosteroids

Prednisolone or, in women unable to take oral medicine, hydrocortisone or methylprednisolone are recommended instead of dexamethasone treatment in light of accumulating evidence that repeated doses of dexamethasone have deleterious effects on long-term neurodevelopment of the fetus.[56-58] While 90% dexamethasone is transferred transplacentally to the fetus, both hydrocortisone and prednisolone are converted by 11β-hydroxysteroid dehydrogenase to inactive glucocorticoids and considerably less drug is transferred to the fetus. Glucocorticoids can worsen maternal glycaemic control, so blood glucose should be checked and managed appropriately. Otherwise there is no convincing evidence that prednisolone use is associated with increased rates of adverse pregnancy outcomes when taken in the first trimester or later pregnancy.[59] Very low concentrations of prednisolone enter breastmilk. There is a paucity of data about pharmacological use of hydrocortisone, but it is likely that this is also safe when breastfeeding,[59] as also reviewed in the Lactmed database (www.ncbi.nlm.nih.gov/books/NBK501076/). Prednisolone (or hydrocortisone) should be used in breastfeeding women, in preference to dexamethasone.

Tocilizumab

Two pharmaceutical global safety registry database studies have reported on tocilizumab use in pregnancy, including outcomes from 288 pregnancies [60] and 61 pregnancies,[61] typically for rheumatoid or other arthritides, and with the majority having received the drug in the first trimester. These data suggest that the rates of congenital abnormality, spontaneous pregnancy loss and other adverse outcomes were not higher than in the general population.[61] Small studies have shown that tocilizumab is transferred to the fetus with serum concentrations approximately 7-fold lower than those observed in maternal serum at the time of birth.[62] Very low concentrations of tocilizumab are identified in breast milk and no drug is transferred into the serum of breast fed infants.[62,63] Women should be advised that if treated after 20 weeks' gestation, their infant should not be immunised with live vaccines (rotavirus and BCG) for the first 6 months of life. All non-live vaccinations are safe and should be undertaken.[64]

Baricitinib

Baricitinib is contraindicated in pregnant or breastfeeding women. Baricitinib will only be included in the randomisation of women of child-bearing potential if they have had a negative pregnancy test since admission.

Anakinra

Data on the use of anakinra in pregnancy data are currently limited. Although renal agenesis and oligohydramnios have been described in exposed infants, controlled studies are lacking.

Anakinra will only be included in the randomisation of women of child-bearing potential if they have had a negative pregnancy test since admission.

Empagliflozin
Empagliflozin is not recommended for use in pregnant or breastfeeding women.

8.5 Appendix 5: Early phase assessment details

S/F_{94} ratio:
The SpO_2:FiO_2 ratio is a simple correction for the measured oxygen saturation (SpO_2) to account for how much oxygen the patient is receiving (FiO_2). If the measured SpO_2 is >94% the ratio is less accurate (because it cannot rise much further regardless of FiO_2). Therefore the SpO_2:FiO_2 ratio will be measured when the patient's SpO_2 is <94% (called the S/F_{94}).

The participant should be resting in bed with the head of the bed at 30º for at least 10 minutes. If they are receiving oxygen via simple nasal prongs or face mask, this will be switched to a Venturi mask (which controls FiO_2 more precisely). The FiO_2 will then be reduced gradually until SpO_2 <94% (or the participant is receiving room air, ie FiO_2 =0.21).

Short periods of hypoxia (e.g. SpO_2 of 80%) are not considered harmful. The participant should be monitored throughout and if they become breathless or distressed after a reduction in FiO_2 it will be immediately increased. Once SpO_2 <94% (or the participant is breathing room air) the details of oxygen delivery mode, SpO_2, FiO_2 and respiratory rate will be recorded. The participant's oxygen will then be returned to baseline. Further details will be provided in a Standard Operating Procedure.

WHO Ordinal Scale
The World Health Organization have endorsed the use of an ordinal scale as an outcome measure in clinical trials in order to capture the trajectory of patients' clinical progression and of healthcare resource use.[10]

Score	Descriptor
1	Discharged (alive)
2	Hospital admission, not requiring supplemental oxygen, no longer requiring medical care (hospitalisation extended for infection control or other nonmedical reasons e.g. social care. Sometimes documented as "medically fit for discharge" or "medically stable for discharge")
3	Hospital admission, not requiring supplemental oxygen, but requiring ongoing medical care
4	Hospital admission, requiring supplemental oxygen (by face mask or nasal prongs)
5	Hospital admission, requiring high flow nasal oxygen, continuous positive airways pressure or non-invasive ventilation
6	Hospital admission, requiring invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO)
7	Death

8.6 Appendix 6: Organisational Structure and Responsibilities

Chief Investigator
The Chief Investigator has overall responsibility for:

(i) Design and conduct of the Study in collaboration with the Trial Steering Committee;
(ii) Preparation of the Protocol and subsequent revisions;

Trial Steering Committee
The Trial Steering Committee (see Section 0 for list of members) is responsible for:

(i) Agreement of the final Protocol and the Data Analysis Plans;
(ii) Reviewing progress of the study and, if necessary, deciding on Protocol changes;
(iii) Review and approval of study publications and substudy proposals;
(iv) Reviewing new studies that may be of relevance.

International Steering Committee
The internationalSteering Committee (see below for list of members) is responsible for:

(i) Reviewing progress of the study in sites outside the UK;
(ii) Review of study publications and substudy proposals;
(iii) Considering potential new therapies to be included in sites outside the UK;
(iv) Assisting RCC in selection of LCCs
(v) Reviewing new studies that may be of relevance.

Data Monitoring Committee
The independent Data Monitoring Committee is responsible for:

(i) Reviewing unblinded interim analyses according to the Protocol;
(ii) Advising the Steering Committee if, in their view, the randomised data provide evidence that may warrant a change in the protocol (e.g. modification or cessation of one or more of the treatment arms).

Central Coordinating Office (CCO)
The CCO is responsible for the overall coordination of the Study, including:

(i) Study planning and organisation of Steering Committee meetings;
(ii) Ensuring necessary regulatory and ethics committee approvals;
(iii) Development of Standard Operating Procedures and computer systems
(iv) Monitoring overall progress of the study;
(v) Provision of study materials to RCCs/LCCs;
(vi) Monitoring and reporting safety information in line with the protocol and regulatory requirements;
(vii) Dealing with technical, medical and administrative queries from LCCs.

Regional Coordinating Centre (RCC)
The RCCs are responsible for:

(i) Ensuring necessary regulatory and ethics committee approvals;
(ii) Provision of study materials to LCCs;
(iii) Dealing with technical, medical and administrative queries from LCCs.

Local Clinical Centres (LCC)
The LCC lead investigator and LCC clinic staff are responsible for:

(i) Obtaining all relevant local permissions (assisted by the CCO)
(ii) All trial activities at the LCC, including appropriate training and supervision for clinical staff
(iii) Conducting trial procedures at the LCC in line with all relevant local policies and procedures;
(iv) Dealing with enquiries from participants and others.

Organisational Details

STEERING COMMITTEE
(Major organisational and policy decisions, and scientific advice; blinded to treatment allocation)

Chief Investigator	Peter Horby
Deputy Chief Investigator	Martin Landray
Clinical Trial Unit Lead	Richard Haynes
Co-investigators	Kenneth Baillie (Scotland Lead), Maya Buch, Lucy Chappell, Saul Faust, Thomas Jaki, Katie Jeffery, Edmund Juszczak, Wei Shen Lim, Marion Mafham, Alan Montgomery, Andrew Mumford, Kathy Rowan, Guy Thwaites, Jeremy Day (South East Asia Leads)

International Steering Committee

Chair	Do Van Dung
Regional Lead Investigators	Guy Thwaites, Jeremy Day
Independent members:	Vietnam : Nguyen Ngo Quang, Prof. Binh Indonesia: Erlina Burhan, Bachti Alisjahbana Nepal: Janak Koirala, Sudha Basnet
Other members:	Evelyne Kestelyn, Buddha Basnyat, Pradip Gyanwali, Raph Hamers, John Amuasi, Peter Horby

DATA MONITORING COMMITTEE
(Interim analyses and response to specific concerns)

Chair	Peter Sandercock
Members	Janet Darbyshire, David DeMets, Robert Fowler, David Lalloo, Mohammed Munavvar, Adilia Warris, Janet Wittes
Statisticians (non-voting)	Jonathan Emberson, Natalie Staplin

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To RANDOMISE a patient, visit:

Website: www.recoverytrial.net

Appendix 2: RECOVERY Trial PaediatricStatistical Analysis Plan V1.1

RECOVERY
Randomised Evaluation of COVID-19 Therapy

Statistical Analysis Plan Paediatric multisystem inflammatory syndrome population

Version 1.1

Date: 31 August 2021

Protocol version: 16.1, 08 July 2021

IRAS no: 281712
REC ref: EE/20/0101
ISRCTN: 50189673
EudraCT: 2020-001113-21

Nuffield Department of
POPULATION HEALTH

Table of Contents

Abbreviations

ADaM	Analysis Data Model
AE	Adverse event
CDISC	The Clinical Data Interchange Standards Consortium
CI	Confidence interval
CoV	Coronavirus
COVID	coronavirus-induced disease
CPAP	Continuous Positive Airway Pressure
CRP	C-reactive protein
CTU	Clinical trials unit
CTSU	Clinical Trials Service Unit
DMC	Data Monitoring Committee
ECMO	Extra Corporeal Membrane Oxygenation
eCRF	Electronic case report form
FiO_2	Fraction of inspired oxygen
ICD	International Classification of Diseases
IFN	Interferon
ICNARC	Intensive Care National Audit and Research Centre
IQR	Interquartile range
ITT	Intention to treat
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle East Respiratory Syndrome
NPEU	National Perinatal Epidemiology Unit
OPCS-4	NHS Classification of Interventions and Procedures
PaO_2	Partial pressure of oxygen
PIMS-TS	Paediatric Multisystem Inflammatory Syndrome temporally associated with COVID-19
RR	Risk ratio
SAE	Serious adverse event
SARS	Severe acute respiratory syndrome
SARS-CoV-2	Virus causing COVID-19
SSAR	Suspected serious adverse reaction
SUSAR	Suspected unexpected serious adverse reaction
SD	Standard deviation
SC	Steering Committee

List of authors and reviewers

Authors

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Dr Christine Jones, Member of Paediatric Working Group (University of Southampton)

Dr Elizabeth Whittaker, Member of Paediatric Working Group (Imperial College London)

Roles and responsibilities

Trial Statisticians

Enti Spata (NDPH, University of Oxford)

Role: To develop the statistical analysis plan and conduct the final comparative analyses in the paediatric population. Blinded to trial allocation.

Data Monitoring Committee (DMC) Statisticians

Professor Jonathan Emberson and Dr Natalie Staplin (NDPH, University of Oxford)

Role: To conduct regular interim analyses for the DMC. Contribution restricted up until unblinded to trial allocation.

Statisticians on the Trial Steering Committee (TSC)

Professor Thomas Jaki (University of Cambridge, co-investigator)

Role: To develop the statistical analysis plan. Major organisational and policy decisions, and scientific advice; blinded to treatment allocation

Professor Alan Montgomery (University of Nottingham, independent)

Role: Major organisational and policy decisions, and scientific advice; blinded to treatment allocation

Other Non-independent Statisticians

Professor Edmund Juszczak (NDPH, University of Oxford until 06/07/2020; University of Nottingham thereafter)

Role: Oversight, statistical support/scientific advice; blinded to treatment allocation.

Trial IT systems & Programmers

Andy King, David Murray, Richard Welsh (NDPH, University of Oxford)

Role: To generate and prepare reports monitoring the randomisation schedule. To supply data snapshots for interim and final analysis. Responsibility for randomisation system, clinical databases and related activities.

Bob Goodenough (NDPH, University of Oxford)

Role: Validation of IT systems

Dr Will Stevens, Karl Wallendszuz (NDPH, University of Oxford)

Role: To produce analysis-ready datasets according to CDISC standards.

1 INTRODUCTION

This document details the proposed presentation and analysis for the main paper(s) reporting results from the **paediatric investigations of treatments for PIMS-TS** within the multicentre randomised controlled trial RECOVERY (ISRCTN50189673) trial. Assessments of treatments for COVID-19 pneumonia conducted among paediatric participants are included in the adult comparisons so the details are provided in the main Statistical Analysis Plan (SAP), along with all other evaluations. This document should be read in conjunction with the current protocol and main SAP available at www.recoverytrial.net.

The results reported in papers concerning the paediatric investigations will follow the strategy set out here, which adheres to the guidelines for the content of a statistical analysis plan (SAP).[1] Any subsequent analyses of an exploratory nature will not be bound by this strategy.

Suggestions for subsequent analyses by oversight committees, journal editors or referees, will be considered carefully in line with the principles of this analysis plan.

Any deviations from the statistical analysis plan will be described and justified in the final report to the funder. The analysis will be carried out by an identified, appropriately qualified and experienced statisticians, who will ensure the integrity of the data during their processing e.g. by parallel programming.

This SAP is based on multiple versions of the protocol. All regulatory documents can be found in the RECOVERY trial directory: https://www.recoverytrial.net/for-site-staff/site-set-up-1/regulatory-documents.

2 BACKGROUND INFORMATION

2.1 Rationale

In early 2020, as the protocol was first being developed, there were no approved treatments for COVID-19. The aim of the trial is to provide reliable evidence on the efficacy of candidate therapies (including re-purposed and novel drugs) for suspected or confirmed COVID-19 infection on major outcomes in hospitalised adult patients receiving standard care.

Subsequently additional investigations into children with COVID-19 pneumonia and Paediatric Inflammatory Multisystem Syndrome - Temporally associated with SARS-CoV-2 (PIMS-TS) were included in the study. The aim of these additional investigations is to provide reliable evidence on the efficacy of candidate therapies for these conditions.

The remainder of this document focuses on the aspects relating to the paediatric investigations of this study, specifically the analysis of children with PIMS-TS. Children with COVID pneumonia will be included in the adult evaluations. Additionally, descriptive analyses for neonates with COVID pneumonia will be undertaken.

2.2 Objectives of the paediatric investigations

2.2.1 Primary objective PIMS-TS

To provide reliable estimates of the effect of study treatments on the number of days in hospital.

2.2.2 Secondary objectives PIMS-TS

To investigate the effect of study treatments on the need for

- Inotropes; and
- Respiratory support (non-invasive or invasive ventilation).

2.3 Trial design

See current protocol and main SAP available at www.recoverytrial.net.

2.4 Eligibility

See current protocol and main SAP available at www.recoverytrial.net.

2.5 Treatments: PIMS-TS

All children will receive standard management for the participating hospital. The main randomisation will be between the following treatment arms.

2.5.1 Main randomisation for children with PIMS-TS

- **No additional treatment**
- **Methylprednisolone**
- **Intravenous immunoglobulin**

2.5.2 Second randomisation for children with PIMS-TS

Children (at least 1 year old) with PIMS-TS (as evidenced by an exaggerated inflammatory state) may undergo an optional second randomisation between the following treatment arms:

- **No additional treatment**
- **Tocilizumab**
- **Anakinra**

2.6 Definitions of primary and secondary outcomes PIMS-TS

Outcomes will be assessed at 28 days.

2.6.1 Primary outcome PIMS-TS

- Number of days in hospital

2.6.2 Secondary clinical outcomes PIMS-TS

- Number of days on inotropes
- Baseline adjusted CRP on day 3

2.6.3 Subsidiary clinical outcomes PIMS-TS

- Need for inotropes after recruitment
- Number of days on invasive mechanical ventilator
- Number of days on non invasive respiratory support
- Presence of coronary artery aneurysm (CAA) at 6 weeks
- Presence of left ventricular dysfunction (LVD)
- Number of days in a paediatric intensive care unit
- Readmission to hospital within 8 weeks of discharge
- Use of additional antibiotics post discharge
- Time to addition of 'next' escalation of immunosuppressive treatment
- Area under the curve of CRP between day 1 and day 8

2.6.4 Detailed derivation of outcomes

The detailed derivation of outcomes included in statistical analysis will be described separately in a data derivation document and included in the Study Data Reviewer's Guide.

2.7 Hypothesis framework

For each of the primary, secondary and subsidiary outcomes, the null hypothesis will be that there is no true difference in effect between any of the treatment arms.

A Bayesian framework is used to assess the null hypothesis and the posterior distribution of the difference between the outcome on an active treatment and the outcome on standard of care will use used to assess efficacy of the intervention. If the probability that the active group has a better outcome then the usual care arm (i.e. the difference in outcome is negative) is 95% or larger this will signify a very strong signal of benefit. A probability between 80% and 95% is interpreted as strong signal while a probability of 70%-80% constitutes a moderate positive signal. Similarly, a probability of 30% or less will be taken as a signal for harm.

2.8 Sample size

The larger the number randomised, the more accurate the results will be, but the numbers that can be randomised will depend critically on how large the epidemic becomes. If substantial numbers are hospitalised in the participating centres then it may be possible to randomise several hundred with moderate disease and fewer with severe disease. Sample size and recruitment will be monitored by the Steering Committee (SC) throughout the trial.

2.9 Randomisation

Eligible patients will be randomised using a 24/7 secure central web-based randomisation system, developed and hosted within NDPH, University of Oxford. Users of the system will have no insight into the next allocation, given that simple randomisation is being used. If a patient is randomised inadvertently more than once during the same hospital admission, the first allocation will be used.

The implementation of the randomisation procedure will be monitored by the Senior Trials Programmer, and the SC notified if an error in the randomisation process is identified.

2.9.1 Main randomisation

Simple randomisation will be used with a 1:1:1 allocation ratio between the following arms.

- No additional treatment
- Methylprednisolone
- Intravenous immunoglobulin

2.9.2 Second randomisation

Eligible participants were initially randomised with a 1:1 allocation ratio between no additional treatment and tocilizumab. After protocol V13.0 was implemented, eligible participants are randomised using simple randomisation with an allocation ratio 1:2:2 (no additional treatment:Tocilizumab:Anakinra) between the following arms:

- No additional treatment
- Tocilizumab
- Anakinra

2.10 Blinding

This is an open-label study. However, while the study is in progress, access to tabular results of study outcomes by treatment allocation will not be available to the research team, CIs, trial statisticians, clinical teams, or members of the SC (unless the DMC advises otherwise). The DMC and DMC statisticians will be unblinded.

2.11 Data collection schedule

Baseline and outcome information will be collected on trial-specific electronic case report forms (eCRFs) and entered into a web-based IT system by a member of the hospital or research staff. In addition to the standard follow-up CRF collected for all participants (including adults), a further eCRF will be collected for children to collect additional details of their care including results of investigations (laboratory, electrocardiogram, echocardiogram and the Strength and Difficulty Questionnaire) and treatment (circulatory support and other treatments). Follow-up information will be collected on all study participants, irrespective of whether they complete the scheduled course of allocated study treatment. Study staff will seek follow-up information through various means, including routine healthcare systems and registries.

All randomised participants will be followed up until death or 6 months post-randomisation (whichever is sooner). NHS Digital and equivalent organisations in the devolved nations will supply data fields relevant to trial baseline and outcome measures to NDPH, University of Oxford on a regular basis, for participants enrolled into the trial. This will be combined with the trial-specific data collected via the web-based IT system and adjudicated internally.

Longer term (up to 10 years) follow-up will be sought through linkage to electronic healthcare records and medical databases including those held by NHS Digital, Public Health England and equivalent bodies, and to relevant research databases (e.g. UK Biobank, Genomics England).

2.12 Data monitoring

During the study all study data will be supplied in strict confidence to the independent DMC for independent assessment and evaluation. The DMC will request such analyses at a frequency relevant to the emerging data from this and other studies.

The DMC has been requested to determine if, in their view, the randomised comparisons in the study have provided evidence on the primary outcome is strong enough (with a range of uncertainty around the results that is narrow enough) to affect national and global treatment strategies. Hence, multiple reviews by the Data Monitoring Committee have no material impact on the final analysis. In such a circumstance, the DMC will inform the SC who will make the results available to the public and amend the trial arms accordingly.

2.13 Trial reporting

The paediatric investigations in this trial will be reported according to the principles of the CONSORT statements.[2, 3] The exact composition of the trial publication(s) depends on the size of the epidemic, the availability of drugs, and the findings from the various pairwise comparative analyses.

3 ANALYSIS POPULATIONS

3.1 Population definitions

The intention to treat (ITT) population will be all participants randomised only to the relevant randomisation (ie, main or second randomisation), irrespective of treatment received. This ITT population will be used for analysis of efficacy and safety data.

4 DESCRIPTIVE ANALYSES

4.1 Participant throughput

The flow of participants through the trial will be summarised for each separate pairwise comparison using a CONSORT diagram, for the main and second randomisations separately. The flow diagrams will describe the numbers of participants randomly allocated, who received allocation, withdrew consent, and included in the ITT analysis population. The flow diagrams for arms in the main randomisation will also report the number of participants who underwent the second randomisation.

4.2 Baseline comparability of randomised groups

The following characteristics will be described separately for patients randomised to each main comparison and separately for the main and second randomisation.

4.2.1 Main randomisation

- Age at randomisation
- Sex
- Ethnicity
- Time since hospitalisation
- Latest biochemical results

- Type of ventilation support currently required (none, non-invasive ventilation, mechanical ventilation or ECMO)
- SARS-Cov-2 PCR result
- SARS-CoV Antibody result as recorded on the case record form
- If female, known to be pregnant
- Drugs used prior to randomisation (corticosteroids, intravenous immunoglobulin, remdesivir)

4.2.2 Second randomisation

In addition to the above:

- Allocation in main randomisation
- Interval between main and second randomisation

The number and percentage will be presented for binary and categorical variables. The mean and standard deviation or the median and the interquartile range will be presented for continuous variables, or the range if appropriate.

4.3 Completeness of follow-up

All reasonable efforts will be taken to minimise loss to follow-up, which is expected to be minimal as data collection for primary and secondary outcomes using trial-specific eCRFs is combined with linkage to routine clinical data on study outcomes from NHS Digital, ICNARC, and similar organisations in the devolved nations.

The number and percentage of participants with follow-up information at day 28 and at 8 weeks post discharge will be reported. Data will be shown for each of the following: all-cause mortality, hospital discharge status, ventilation status, and will be shown for each randomised group for the main and second randomisation separately.

4.4 Adherence to treatment

The number and proportion of patients who did not receive the treatment they were allocated to will be reported. If any other trial treatment options were known to be received, instead of or in addition to, the allocated treatment during the 28-day follow-up period after the first randomisation, these will be collected and reported. Details on the number of days (or doses) of treatment received will be reported for all trial treatments received where available.

5 COMPARATIVE ANALYSES

For all outcomes, the primary analysis will be performed on the intention to treat (ITT) population at 28 days after the main randomisation.

Pairwise comparisons will be made between each treatment arm and the no additional treatment arm (reference group) in that particular randomisation (main randomisation and second randomisation) for the primary analysis. Since not all treatments may be available or suitable for all patients, those in the no additional treatment arm will only be included in a

given comparison if, at the point of their randomisation, they *could* alternatively have been randomised to the active treatment of interest (i.e. the active treatment was available at the time and it was not contra-indicated). The same applies to treatment arms added at a later stage; they will only be compared to those patients recruited concurrently.

5.1 Main randomisation

5.1.1 Primary outcome PIMS-TS

The number of days in hospital, *y*, will be summarised with frequency tables by randomised comparison group. The following Bayesian negative binomial regression model:

$$y|\beta_0, \beta_1, \dots, \beta_{I+2}, r \sim NB(\mu, r)$$
$$\mu = \beta_0 + \sum_{i=1}^{I} \beta_i * trt_i + \beta_{I+1} * age$$
$$\beta_0 \sim t_3(location = \log(8), scale = 2.5)$$
$$\beta_i \sim N(0, 10^2)\ i = 1, \dots, I+2$$
$$r \sim Gamma(0.1, 0.1)$$

will be fit. The shape parameter of the negative binomial distribution is denoted *r* and t_3 denotes a t-distribution with 3 degrees of freedom. The treatment indicator is denoted by trt_i and *I* is the total number of active treatments in this comparison. The prior distributions for treatment and age are non-informative, while the prior for the location is informed by the UK national surveillance data[4].

The posterior distribution of the treatment effect reported and interpreted as described in section 2.7. Posterior mean estimates of the treatment effects and 95% credibility intervals will be reported.

5.1.2 Secondary outcomes

5.1.2.1 Number of days on inotropes

The same negative binomial model as for the primary endpoint is used with the following prior on the intercept

$$\beta_0 \sim t_3(location = \log(3), scale = 2.5).$$

5.1.2.2 Baseline adjusted CRP between on day 3

This outcome will be analysed using the following Bayesian linear regression model:

$$\log(y_3)|\beta_0, \beta_1, \dots, \beta_{I+3}, \tau \sim N(\mu, \tau^{-1})$$
$$\mu = \beta_0 + \sum_{i=1}^{I} \beta_i * trt_i + \beta_{I+1} * \log(y_1) + \beta_{I+2} * age$$
$$\beta_i \sim N(0, 10^2)\ i = 0, \dots, I+3$$
$$\tau \sim Gamma(0.1, 0.1)$$

were y_1 is CRP on day 1 and y_3 is CRP on day 3.

5.1.3 Subsidiary clinical outcomes

5.1.3.1 Need for inotropes after recruitment

A beta-binomial model with Beta(1,1) prior distribution is used. Posterior mean estimates of the treatment effects and 95% credibility intervals will be reported.

5.1.3.2 Number of days on ventilator

The same negative binomial model as for the primary endpoint is used with the following prior on the intercept

$$\beta_0 \sim t_3(location = \log(4), scale = 2.5).$$

5.1.3.3 Number of days on non invasive respiratory support

The same negative binomial model as for the primary endpoint is used with the following prior on the intercept

$$\beta_0 \sim t_3(location = \log(7), scale = 2.5).$$

5.1.3.4 Presence of CAA

A beta-binomial model with Beta(1,1) prior distribution is used. Posterior mean estimates of the treatment effects and 95% credibility intervals will be reported.

5.1.3.5 Persistence of CAA at 6 weeks

A beta-binomial model with Beta(1,1) prior distribution is used. Posterior mean estimates of the treatment effects and 95% credibility intervals will be reported.

5.1.3.6 Presence of LVD

A beta-binomial model with Beta(1,1) prior distribution is used. Posterior mean estimates of the treatment effects and 95% credibility intervals will be reported.

5.1.3.7 Persistence of LVD at 6 weeks

A beta-binomial model with Beta(1,1) prior distribution is used. Posterior mean estimates of the treatment effects and 95% credibility intervals will be reported.

5.1.3.8 Number of days in a paediatric intensive care unit

The same negative binomial model as for the primary endpoint is used with the following prior on the intercept

$$\beta_0 \sim t_3(location = \log(3), scale = 2.5).$$

5.1.3.9 Readmission to hospital within 8 weeks of discharge

A beta-binomial model with Beta(1,1) prior distribution is used. Posterior mean estimates of the treatment effects and 95% credibility intervals will be reported.

5.1.3.10 Use of additional antibiotics post discharge

A beta-binomial model with Beta(1,1) prior distribution is used. Posterior mean estimates of the treatment effects and 95% credibility intervals will be reported.

5.1.3.11 Time to addition of 'next' escalation of immunosuppressive treatment

A Bayesian Cox proportional hazards model with normal prior, N(0, 10^5), for the regression coefficients and gamma prior, *Gamma(0.1,0.1)*, for the baseline hazard.

5.1.3.12 Area under the curve of CRP between day 1 and day 8

The following Bayesian linear regression model:

$$y|\beta_0, \ldots, \beta_I, \tau \sim N(\mu, \tau^{-1})$$
$$\mu = \beta_0 + \sum_{i=1}^{I} \beta_i * trt_i$$
$$\beta_i \sim N(0, 10^2)\ i = 0, \ldots, I$$
$$\tau \sim Gamma(0.1, 0.1).$$

will be used.

5.2 Second randomisation

Evaluation of treatment effects in the main randomisation and the second randomisation will be conducted independently, as described in 5.1.

5.3 Pre-specified subgroup analyses

No pre-specified subgroup analyses are planned.

5.4 Adjustment for baseline characteristics

The main analyses described above will be adjusted for age . If there are any other important imbalances between the randomised groups emphasis will be placed on analyses that are adjusted for the relevant baseline characteristic(s).

5.5 Statistical software employed

The statistical software SAS version 9.4, R Studio 3.6.2 and Stata/SE version 15 (or later) for Windows will be used for the interim and final analyses.

5.6 Data standards and coding terminology

Datasets for analysis will be prepared using CDISC standards for SDTM and ADaM. Wherever possible, clinical outcomes (which may be obtained in a variety of standards, including ICD10 and OPCS-4) will be coded using MedDRA version 20.1.

6 SAFETY DATA

Suspected serious adverse reactions (SSARs) and suspected unexpected serious adverse reactions (SUSARs) will be listed by trial allocation.

Additional safety data will be collected in a subset of patients randomised to part B.

7 ADDITIONAL EXPLORATORY ANALYSIS

Any post-hoc analysis requested by the oversight committees, a journal editor or referees will be labelled explicitly as such. Any further future analyses not specified in the analysis protocol will be exploratory in nature and will be documented in a separate statistical analysis plan.

8 REFERENCES

8.1 Trial documents

Dummy tables and the data derivation document can be found in the RECOVERY trial directory and will be published with this SAP on the trial website (www.recoverytrial.net).

8.2 Other references

1. Gamble C, Krishan A, Stocken D, Lewis S, Juszczak E, Doré C, Williamson PR, Altman DG, Montgomery A, Lim P, Berlin J, Senn S, Day S, Barbachano Y, Loder E. Guidelines for the Content of Statistical Analysis Plans in Clinical Trials. JAMA 2017;318(23):2337-2343.

2. Schulz KF, Altman DG, Moher D for the CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. BMJ 2010;340:698-702.

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4. Flood J, Shingleton J, Bennett E, Walker B, Amin-Chowdhury Z, Oligbu G, Avis J, Lynn RM, Davis P, Bharucha T, Pain CE. Paediatric multisystem inflammatory syndrome temporally associated with SARS-CoV-2 (PIMS-TS): Prospective, national surveillance, United Kingdom and Ireland, 2020. The Lancet Regional Health-Europe. 2021 Apr 1;3:100075.

Approval

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9 DOCUMENT HISTORY

Version	Date	Edited by	Comments/Justification	Timing in relation to unblinded interim monitoring	Timing in relation to unblinding of Trial Statisticians
0.1	21/03/21	TJ	First draft.	Prior	Prior
0.2	20/4/21	TJ	Updated in light of paediatric committee comments	Prior	Prior
0.3	07/05/21	TJ	Incorporation of additional comments by paediatric committee and cross checking with ECRF	Prior	Prior
0.4	14/05/21	TJ	Removal of analysis sections for COVID pneumonia as included in adult evaluation	Prior	Prior
0.5	29/5/21	TJ	Changed secondary endpoint for CRP	Prior	Prior
1.0	23/07/21	TJ	Remove tracked changes and prepared for signature	Prior	Prior
1.1	31/08/21	TJ	Reviewed by statisticians based on blinded data after cross checking with paediatric committee	Prior	Prior

Appendix 3: Definition and Derivation of Baseline Characteristics and Outcomes

Definition and Derivation of Baseline Characteristics and Outcomes

Contents

1 Version

Date	Version	Comments
06-Jun-2020	0.1	Initial version
08-Jun-2020	0.2	Minor updates
09-Jun-2020	1.0	First released version
11-Dec-2020	2.0	Update to sections 6.4 (use of assisted ventilation) and 6.6 (use of renal replacement therapy)
06-Jan-2020	3.0	Update to clarify the derivation of outcomes and baseline data for the second randomisation and define complete follow-up
14-April-2022	4.0	Updates to frequency of dataset transfers and additional datasets. Addition of section 8relating to 6-month outcomes. Addition of appendix 4 to provide detail on discharge outcome

2 Scope

This document describes the definition and derivation of the primary, secondary and other outcomes of the RECOVERY trial for the published trial analyses. It should be read alongside the study protocol which defines the study outcomes briefly, and the Statistical Analysis Plan (SAP) which describes the statistical methods used to analyse these outcomes. The SAP

refers to this document (see Section 2.6.4 Detailed derivation of outcomes) which provides detail on how the outcomes are defined, captured and derived.

Most outcomes have more than one potential source which improves completeness of capture but also will inevitably identify discrepancies between different sources. This document describes the principles for how such discrepancies are resolved; the rules for this were developed blind to results. Further details of the methods are described in the RECOVERY trial internal operating procedure for identifying data discrepancies.

3 Abbreviations

ADDE	Annual District Death Extract
CCDS	Critical Care Dataset
CHESS	COVID-19 Hospitalisation in England Surveillance System
CPAP	Continuous Positive Airway Pressure
CRP	C-reactive protein
ECMO	Extra-corporeal membrane oxygenation
eCRF	Electronic Case Report Form
FCE	Finished Consultant Episode
FU	Follow-up
HESAPC	Hospital Episode Statistics Admitted Patient Care
HFNO	High-flow nasal oxygen
ICD-10	International Classification of Diseases 10th edition
ICNARC	Intensive Care National Audit and Research Centre
IMV	Invasive mechanical ventilation
NHSCR	NHS Central Register (Scotland)
NIV	Non-invasive ventilation
NRS	National Records of Scotland
ONS	Office for National Statistics (ONS)
OPCS-4	Office of Population Censuses Surveys Classification of Surgical Operations and Procedures 4th revision
PDS	Patient Demographic Service
PEDW	Patient Episode Database for Wales
RRT	Renal replacement therapy
PHE	Public Health England
SAP	Statistical Analysis Plan
SICSAG	Scottish Intensive Care Society Audit Group
SMR	Scottish Morbidity Record
SUSAPC	Secondary Use Service Admitted Patient Care
UKRR	UK Renal Registry
WDSD	Welsh Demographic Service
WRRS	Welsh Results Reporting Service

4 Data sources

4.1 Electronic case report forms

4.1.1 Main randomisation

The Randomisation eCRF is completed by hospital staff after patients (or a legal representative) have given consent to participate in the trial. It collects the following participant information:

- Identifiers
    - First name, family name

  - NHS number
  - Date of birth
  - Sex (male/female/unknown)
- Inclusion criteria
  - COVID-19 symptom onset date
  - Date of hospitalisation
- Details of acute illness
  - Requirement for oxygen[1]
  - Requirement for ventilatory support (none, continuous positive airway pressure, non-invasive ventilation, high-flow nasal oxygen, invasive mechanical ventilation (IMV) or extra-corporeal membrane oxygenation) (ECMO)
  - Latest oxygen saturation
  - Latest C-reactive protein, creatinine and D-dimer measurement (if available)
- Comorbidities
  - Diabetes
  - Heart disease
  - Chronic lung disease
  - Tuberculosis
  - HIV
  - Severe chronic liver disease
  - Severe kidney impairment (eGFR <30 mL/min/1.73m^2 or on dialysis)
  - Long QT syndrome
  - Pregnancy
- Current treatment
  - Macrolide antibiotics
  - Aspirin or other antiplatelet therapy
  - Warfarin or direct oral anticoagulant
  - Venous thromboembolism prophylaxis (standard or increased dose due to COVID-19)
  - Remdesivir
  - Systemic corticosteroids
- Other
  - Weight (children only)

4.1.2 Second randomisation

The Second Randomisation eCRF is completed by hospital staff when they wish to randomise participants between tocilizumab or standard care alone if they fulfil the protocol-defined oxygenation and inflammation criteria. It collects the following participant information:

[1] NHS England advice published on 9 April 2020 stated that the usual oxygen target saturation for prescribed oxygen should change from 94-98% to 92-96% in the first instance. Hospitals may further reduce this to 90-94% if clinically appropriate according to prevailing oxygen demands. https://www.england.nhs.uk/coronavirus/wp-content/uploads/sites/52/2020/04/C0256-specialty-guide-oxygen-therapy-and-coronavirus-9-april-2020.pdf. Guidance on admission to hospital was similar in Scotland. https://www.nhsggc.org.uk/media/259232/covid-19_gps_national_supporting_guidance_for_scottish_general_practice.pdf although hospital guidelines in Scotland did not specify a target oxygen saturation.

- Inclusion criteria
    - Requirement for oxygen
    - Current level of ventilation support (none/CPAP/NIV/HFNO/IMV/ECMO)
    - Latest CRP
- Other information
    - Latest ferritin and creatinine

4.1.3 Convalescent plasma safety eCRF

This eCRF is completed by hospital staff as soon as possible after 72 hours post-main randomisation for participants who entered the convalescent plasma comparison. It collects the following information:

- Adherence to convalescent plasma allocation (number of units received, whether any were stopped early)
- Adverse events
    - Sudden worsening of respiratory status
    - Severe allergic reaction
    - Temperature ≥39C (or rise ≥2C above baseline)
    - Sudden hypotension
    - Clinical haemolysis
    - Thrombotic event

4.1.4 Follow-up

The FU eCRF is completed by hospital staff at the earliest of (i) discharge from acute care (see Section 6.3 below), (ii) death, or (iii) 28 days after the main randomisation. It collects the following information from date of randomisation onwards:

- Adherence to randomised allocation, and receipt of other study treatments or relevant therapies (and number of days of treatment)
- Vital status and underlying cause of death (COVID, other infection, cardiovascular, other; if other, a free text description is collected)
- Date of discharge
- Requirement for assisted ventilation (CPAP, NIV, HFNO, IMV, ECMO) and number of days of assisted ventilation and IMV/ECMO separately
- Occurrence of major cardiac arrhythmia (atrial flutter/fibrillation, supraventricular tachycardia, ventricular tachycardia [including torsades de pointes], ventricular fibrillation or bradycardia requiring intervention) (from 12 May 2020)
- Occurrence of thrombotic event (pulmonary embolism; deep-vein thrombosis; ischaemic stroke; myocardial infarction; systemic arterial embolism; other) (from 6 November 2020)
- Occurrence of clinically-significant bleeding i.e. intracranial or requiring intervention (blood transfusion; surgery; endoscopy; vasoactive drug or blood transfusion), by site (intra-cranial; gastrointestinal; other) (from 6 November 2020)
- Requirement for renal replacement therapy and peak creatinine after randomisation
- Other infections after randomisation (by site and by organism type)
- Metabolic complications (ketoacidosis, hyperglycaemia, hypoglycaemia)

4.1.5 Non-UK sites

Whereas in the UK participants will be followed by linkage with routinely collected data (see Section 4.2) for up to 10 years after randomisation, in other countries this is not possible. Sites will be asked to complete an additional case report form for participants discharged

alive from hospital at 28 days after randomisation to confirm vital status (and date and cause of death if relevant).

4.2 Registries and NHS datasets

4.2.1 Hospital admissions datasets

4.2.1.1 Secondary Use Service Admitted Patient Care

The SUSAPC dataset is a repository of data hosted by NHS Digital that relates to in-patient care provided in England, which aims to enable reporting and analyses to support the NHS in the delivery of healthcare services. These data are submitted on a regular basis by NHS hospital trusts and at pre-arranged dates during the year. Submissions are consolidated, validated and cleaned and then incorporated into the HESAPC dataset. Data may be incomplete in places and is not quality assured to the same extent as HES, but is available more rapidly.

In the SUSAPC dataset, each record contains data relating to a continuous period of care under one consultant known as a Finished Consultant Episode (FCE). FCEs can be grouped together to form 'Spells'. Each spell is a continuous periods of inpatient care within one hospital. Each FCE contains data about the patient (e.g. sex, ethnicity), the specialty providing the care (e.g. cardiology), ICD-10 diagnostic and OPCS-4 procedure codes, along with dates for each procedure and details about the admission and discharge and other data.

For the main RECOVERY analyses the following data are used;

- Admission method (which indicates whether the admission was emergency or elective and whether it involved a transfer from another healthcare provider)
- Admission source (used to identify transfers between hospitals)
- Ethnicity
- Sex
- Date of admission and discharge
- Start and end date of the FCE
- Discharge method and destination (which may indicate death of participant)
- Diagnoses recorded during FCE (ICD-10 coded)
- Procedures performed during FCE (OPCS-4 coded) and corresponding dates

Linked SUSAPC data are imported to the RECOVERY trial database approximately monthly.

4.2.1.2 Hospital Episode Statistics Admitted Patient Care

HESAPC contains data relating to admissions to NHS hospitals in England and is produced from the SUSAPC following a number of cleaning and validation steps. For participants in England, HESAPC is available for the 5 year period prior to enrolment in the study. For the main RECOVERY analyses these data are used to identify prior medical conditions on the basis of recorded ICD-10 and OPCS-4 codes (excluding the admission during which the patient was randomised). For the analysis of 6-month outcomes, these data are used to identify the Hospital Recorded Diagnoses (see section 8). Linked HESAPC data are imported to the RECOVERY trial database quarterly.

4.2.1.3 NHS Central Register Scottish Morbidity Record One

The NHSCR SMR01 data set holds episode level data on hospital inpatient and day case discharges from acute specialities from hospitals in Scotland. The data fields used in the RECOVERY trial are equivalent to those used in SUSAPC and HESAPC. Linked NHSCR-SMR01 data are imported approximately monthly.

4.2.1.4 Patient Episode Data Wales

4.2.2 PEDW contains data relating to admissions to NHS hospitals in Wales. The data fields used in the RECOVERY trial are equivalent to those used in SUSAPC and HESAPC Mortality datasets

4.2.2.1 Patient Demographic Service

The PDS is the electronic database of NHS patient details such as name, address, date of birth and NHS Number for patients in England. For RECOVERY it is used to provide information on fact and date of death. It provides both 'informal' notifications of death (which occur when a health care provider is informed of their patients death and records the reported date of death in their electronic data systems) and 'formal' notifications of death (which are provided by the Office for National Statistics).

4.2.2.2 Office for National Statistics Mortality data

The ONS mortality data contains information related to a person's death taken from the death certificate for all deaths registered in England and Wales. The following data are provided

- The underlying cause of death
- Contributory causes of death
- Other conditions recorded on the death certificate but not contributing to death
- Whether a post-mortem took place

Clinical data are recorded using ICD-10 codes. Linked ONS mortality data are imported into the RECOVERY trial via a quarterly extract from NHS Digital.

4.2.2.3 Welsh Demographic Service

WDS data are the electronic database of NHS patient details for patients in Wales and are similar to PDS (4.2.2), providing fact and date of death (including formal or informal notifications). Linked data for RECOVERY participants recruited via sites in Wales will be available for future analysis.

4.2.2.4 National Records of Scotland Mortality Data

The NRS mortality data contain information related to a person's death taken from the death certificate for all deaths registered in Scotland. The data provided includes the date of death and the underlying and contributory causes of death coded in ICD-10. Linked data are imported into the RECOVERY trial database approximately monthly.

4.2.3 COVID specific datasets

4.2.3.1 Public Health England Second Generation Surveillance data

The SGSS is an application that captures, stores and manages routine laboratory surveillance data on infectious diseases and antimicrobial resistance from laboratories across England. Once the reports have been loaded into SGSS, each record is subject to a number of validation processes, and local LIMS codes are translated to SGSS codes to standardise the data for analysis. The data is stored in a central database within PHE and details of tests indicating SAR-CoV-2 have been made available to NHS Digital for dissemination for a limited time period. For each test, the following data are available

- Date the sample was collected
- Date the result was reported
- Organism identified (only SARS-CoV-2)

Linked PHE SGSS data are imported into the RECOVERY trial approximately monthly.

4.2.3.2 Public Health Scotland COVID-19 laboratory antigen test positive list

The Electronic Communication of Surveillance in Scotland (ECOSS) collects routine laboratory surveillance data on infectious diseases from laboratories in Scotland. The data provided to RECOVERY is limited to SARS-CoV-2 results along with the date of the sample and result.

4.2.3.3 Welsh Results Reporting Service Pathology Data

The WRRS contains all Pathology Test Results for Wales in a single database. Tests indicating a positive SAR-CoV-2 antigen linked to the trial participants are obtained.

4.2.3.4 COVID-19 Hospitalisation in England Surveillance System

PHE has established the COVID-19 Hospitalisation in England Surveillance System (CHESS), which collects epidemiological data (demographics, risk factors, clinical information on severity, and outcome) on COVID-19 infection in patients requiring hospitalisation and ICU/HDU level care. This dataset has been made available to NHS Digital for dissemination for a limited time period. For RECOVERY the following information is used;

- Date of ICU/HDU admission and discharge
- Use of respiratory support during the admission (including oxygen via cannulae or mask, high flow nasal oxygen, non-invasive ventilation, invasive mechanical ventilation and ECMO)
- Complications during the admission (including viral pneumonia, secondary bacterial pneumonia, ARDS, unknown, and other co-infections)

The CHESS dataset is imported into the RECOVERY trial approximately monthly.

4.2.3.5 GPES Data for Pandemic Planning and Research (COVID-19) (GDPPR)

GDPPR data is available for RECOVERY participants in England. Data includes patient demographic information and coded medical information (mainly in SNOMED codes).

4.2.4 Intensive Care Datasets

4.2.4.1 Intensive Care National Audit and Research Centre

The ICNARC Case Mix Programme is the national clinical audit covering all NHS adult, general intensive care and combined intensive care/high dependency units in England, Wales and Northern Ireland, plus some additional specialist and non-NHS critical care units. Data are collected about the first 24 hours in ICU/HDU and at discharge from the ICU/HDU with a further data collection point after discharge from hospital. For RECOVERY, the following data recorded at discharge from ICU/HDU are used:

- Date of admission to and discharge from ICU/HDU
- Use of Advanced Respiratory Support (ARS), Basic Respiratory Support (BRS) or Renal Support during the admission
- The number of days of ARS, BRS or Renal Support during the admission
- Date of death (if relevant)

Linked ICNARC data is requested for hospitals recruiting to RECOVRY and are imported approximately monthly.

4.2.4.2 Scottish Intensive Care Society Audit Group

SICSAG collects data from all general adult Intensive Care Units, Combined Units and the majority of High Dependency Units in Scotland using the WardWatcher system. The following data are used in the RECOVERY trial:

- Date of admission and discharge from ICU/HDU

- Used of mechanical ventilation via endotracheal tube or tracheostomy and use of haemofiltration for each day of during admission

Linked SICSAG data are imported into the RECOVERY trial approximately monthly.

4.2.4.3 Critical Care dataset

In England and Wales much of the key data collected by ICNARC is also available in the CCDS from NHS Digital or the SAIL datalink Wales. However, both the ICNARC and CCDS data can be subject to different delays during collection, consolidation and dissemination and therefore either source may be incomplete at any one time-point. Both sources are therefore combined to provide information about ICU/HDU care for participants in England and Wales.

4.2.5 Disease specific registries

4.2.5.1 UK Renal Registry

The UK Renal Registry collates data from renal units and hospital laboratories in all four nations in the UK. Linked data relating to laboratory tests for patients who trigger a hospital laboratory "acute kidney injury alert" are available for a subset of patients. Data relating to the provision of care for end stage kidney disease discuss is provided to RECOVERY on an annual basis.

5 Baseline characteristics

Baseline characteristics for the trial cohort are obtained from the first randomisation eCRF for the main randomisation comparisons. For the second randomisation comparisons, the baseline data are obtained either from the second randomisation form directly (e.g. baseline use of respiratory support) or from a calculation based on the first randomisation form data and the number of days between the first and second randomisation forms (e.g. days since symptom onset).

Where fields are missing, they may be supplemented by data from the linked health care data. Generally corrections to the randomisation eCRF data are not made. Exceptions to this would include key participant identifiers (Date of birth, NHS or CHI number) or cases where information is missing. For example, if a site later report that the date of birth was entered incorrectly, this would be confirmed with the site (recorded in the trial data query system) and updated (with appropriate audit trail).

5.1.1 Baseline corticosteroid use

Baseline steroid use is determined as follows:

- Baseline steroid use = yes if allocated dexamethasone in main randomisation OR responded 'yes' to baseline steroid question on main randomisation form (OR [for tocilizumab comparison only] responded 'yes' to baseline steroid question on second randomisation form
- Otherwise, Baseline steroid use = no if answered 'no' to steroid question on main OR [for tocilizumab comparison only] second randomisation forms
- Otherwise, Baseline steroid use = not asked if recruited prior to June 18th[2]
- Otherwise, Baseline steroid use = unknown

[2] From 18th June onwards a question on baseline systemic corticosteroid use was added to the main randomisation form following the release of the dexamethasone comparison results.

For the purposes of analysis, baseline steroid use = no and not asked will be combined for subgroup analyses. Participants with baseline steroid use = unknown will be exluded from subgroup analysis, but the number in this subgroup provided in a footnote.

5.2 Additional baseline characteristics

Some baseline characteristics that are not collected on the randomisation eCRF may be extracted from registry data or other sources. These include:

- Ethnicity by Office for National Statistics 2001 census categories (White, BAME [Mixed, Asian or Asian British, Black or Black British, Other Ethnic Groups], Unknown) from linked health care records. Ethnic groups characterised using SNOMED codes within the GDPPR data are mapped to these categories. Where ethnicity records are discrepant between individual episodes in HES/SMR01/PEDW, the most frequently recorded code is used. Within the GDPPR dataset ethnicity is recorded in two places, the ethnic field in the patient table and the presence of a relevant SNOMED code in the journals table. The most recent code in the journals table is used, where available, otherwise the code from the patient table is used. Where there is discrepancy between the best estimate from GDPPR and HES/SMR01/PEDW existsthe GDPPR code is used. Where neither are available the most frequent fode in the SUS data is used. Individual SNOMED codes are categorised as defined with the SNOMED hierarchy and ethnicity categoriese according to the UK department of health categories.[3]
- Confirmed SARS-CoV-2 diagnostic test from linked health care records. A positive SARS-CoV-2 with a test date within 28 days of the date of first randomisation is considered as confirmed SARS-CoV-2. In the absence of such data for a participant, the data from the randomisation eCRF may be used.
- Comorbidity score: It is possible to calculate comorbidity and frailty scores (e.g. Charlston Comorbidity Score) from prior linked hospital admissions data and this will be done for future exploratory analyses (not specified in the trial SAP).
- Prior End Stage Kidney Disease (see section 6.6)
- Risk: The risk of death by 28 days can be modelled using available baseline characteristics (in the overall trial population) and a risk score derived. Participants will be divided into thirds based on this score (such that each third has approximately the same number of deaths), with the tertiles rounded to clinically-relevant values. For the main trial analyses the groups will defined as risk of death by 28 days of <30%; ≥30 ≤45%; and >45%.

6 Outcomes

6.1 All-cause mortality

The primary outcome is all-cause mortality at 28 days after randomisation. All-cause mortality will also be assessed at 6 months and other later time points.

6.1.1 Sources

Information on death may come from the following sources:

- FU eCRF (for deaths within first 28 days after randomisation)
- PDS (for participants in England)
- PDS Wales ((or participants in Wales)
- SUSAPC (for participants in England)

[3] https://www.ethnicity-facts-figures.service.gov.uk/style-guide/ethnic-groups

- SMR01 (for participants in Scotland)
- PEDW (for participants in Wales)
- ONS mortality data (for participants in England and Wales)
- NRS mortality data (for participants in Scotland)

In general, the primary source will be considered ONS (which includes formal death notification within PDS) and NRS mortality data as these are the official national death registries.

6.1.2 Discrepancies

6.1.2.1 Fact of death

The ONS and NRS mortality data will be considered the defining source for fact of death. In order to allow rapid analysis of results, other sources (e.g. informal death notification via PDS, report of death on the FU eCRF, report of death from SUSAPC) are used for DMC and interim analyses. Cases where these reports are not later substantiated by ONS or NRS are individually reviewed and are not considered as deaths, unless a suitable explanation exists.

6.1.2.2 Date of death

The ONS and NRS data will be considered the defining source for date of death. In order to allow rapid analysis of data, other sources may be used. Where data sources are discrepant the following hierarchy is applied;

- ONS/NRS (most reliable for date of death), then
- Linked hospital admissions data, then
- FU eCRF , then
- PDS informal death notification (least reliable for date of death)

6.2 Cause-specific mortality

The cause of death for the 28 day analysis will be the underlying cause of death as provided by ONS. The causes of death will be categorised as follows:

- Non-vascular death
    - Death from infection
        - Death from COVID-19
        - Death from other infection
    - Death from cancer
    - Death from other medical causes
    - External deaths
- Vascular death
    - Cardiac death
    - Stroke death
    - Other vascular death
- Unknown death

The ICD-10 codes contributing to these categories are available to download from the RECOVERY website.

6.3 Time to discharge

Time to discharge (which is a more accurate term for duration of admission because only the period from randomisation onwards is relevant) is defined as the number of days a participant remained in hospital for acute care after randomisation. Discharge excludes transfer to

another acute hospital, but might include transfer to community hospital for rehabilitation or a hospice for end-of-life care.

6.3.1 Sources

Information on date of discharge may come from the following sources:

- FU eCRF
- SUSAPC (for participants in England)
- PEDW (for participants in Wales)
- SMR01 (for participants in Scotland)

The participant is considered to have been discharged from hospital if there is a discharge date recorded with a discharge method and destination which do not indicate that the participant died or was transferred (see appendix 4). In addition there must be no other admission with an admission date up to 4 days before or 1 day after the discharge date where either the method or source of the admission recorded suggest transfer from another hospital (see appendix 4). The first date of discharge which fulfils these criteria after first or second randomisation is used to determine time to discharge.

6.3.2 Discrepancies

Linked hospital admissions data will be used if date of discharge is discrepant with FU eCRF data. If no linked hospital admissions data are available and the FU eCRF indicates discharge without a date, the date of completion for the FU eCRF will be used.

6.4 Use and duration of ventilation

Assisted ventilation can be broadly divided into

i. Invasive mechanical ventilation (IMV) which includes ECMO (a secondary outcome in combination with all-cause mortality)
ii. Non-invasive ventilation which includes CPAP, NIV and HFNO (which are included in the subsidiary outcomes)

Information on non-invasive ventilation was collected because at the time the trial was designed there were concerns that the availability of mechanical ventilators would be insufficient to meet demand, so some patients would be treated with non-invasive ventilation when in other circumstances they would have received invasive mechanical ventilation. In reality this situation did not occur, so the emphasis of the analyses (and efforts to resolve discrepancies) is on invasive mechanical ventilation.

6.4.1 Sources

Information on ventilation may come from the following sources:

- FU eCRF
- SUSAPC/SMR01/PEDW
- ICNARC
- SICSAG
- CHESS
- CCDS

However, the coding of ventilation is different in each source.

6.4.2 Fact of assisted ventilation

A participant is considered to have received IMV/ECMO if use of these treatments was recorded on the FU eCRF; if a relevant procedure code was recorded in

SUSAPC/SMR01/PEDW within 28 days of randomisation (Appendix 1); if days of advanced respiratory support (ARS) in the ICNARC/CCDS data were considered to fall between randomisation and 28 days (see section 6.4.3) or if the daily SICSAG record indicated that the participant was receiving respiratory support via an endotracheal tube or tracheostomy.

A participant is considered to have received non-invasive ventilation if the site recorded 'yes' to the question 'did the participant receive assisted ventilation' or 'yes' to any of the individual types of non-invasive ventilation (CPAP, BIPAP, HFNO) on the FU eCRF; if a relevant procedure code was recorded in SUSAPC/SMR01/PEDW within 28 days of randomisation (Appendix 2) or if use of HFNO or NIV was recorded in CHESS when the admission and discharge date were both between randomisation and 28 days.

6.4.3 Duration of invasive mechanical ventilation

The data from the critical care datasets (ICNARC, CCDS and SICSAG) are considered the primary source of the duration of IMV. Within ICNARC/CCDS, ARS is considered to be equivalent to IMV, however only the dates of admission and discharge from ICU/HDU and the number of days of ARS are provided. The days of ARS within each critical care episode are assumed to be continuous. The days of ARS were assumed to include randomisation if the participant was recorded as receiving IMV at baseline on the first or second randomisation eCRF as appropriate. Otherwise, the days of ARS are assumed to start from admission to critical care, occur at the mid-point of the critical care admission or end on discharge from critical care depending on the level of care recorded on admission and discharge and, in some cases, the destination on discharge (Appendix 2). Using these assumptions, the information from both ICNARC and the CCDS were used to identify whether IMV was received on each of the 28 days following randomisation. The SICSAG daily record indicated use of IMV on each day.

If no relevant information on IMV is received from ICNARC/CCDS/SICSAG, then the duration of IMV was obtained from the FU eCRF. Cessation of mechanical ventilation is deemed successful if it occurs within (and the participant survives until) 28 days after randomisation.

6.5 Major cardiac arrhythmia

Major cardiac arrhythmias are defined as either:

i. Atrial flutter or fibrillation
ii. Supraventricular tachycardia
iii. Ventricular tachycardia (including torsades de pointes)
iv. Ventricular fibrillation
v. Significant bradycardia (requiring intervention)

6.5.1 Sources

Information on cardiac arrhythmias is collected on the FU eCRF (but only for those eCRFs completed from 12 May 2020 onwards when these outcomes were added).

6.6 Renal replacement therapy

Renal replacement therapy (RRT) includes haemodialysis, haemofiltration (and their combination) and peritoneal dialysis. (Kidney transplantation is not relevant in this case.) Individuals receiving RRT at baseline are identified as follows;

- Patients already receiving renal replacement for End Stage Kidney Disease at baseline are identified using linked hospitalisation data (appendix 3).

- From the ICNARC/CCDS data, the combination of the number of Renal Support Days and the start and end date of a critical episode may imply that they must have been receiving renal support at randomisation.
- The SICSAG daily record indicates that Renal Support was received on the day of, or on the day before randomisation.
- A procedure code in SUS/SMR01/PEDW indicating dialysis or haemofiltration with a date within the 3 days prior to first or second randomisation as appropriate (appendix 1).
- (When available) A record of prior RRT (without documented recovery) from the UK Renal Registry

6.6.1 Sources

- FU eCRF
- Linked hospitalisation data (SUSAPC, HES, PEDW, SMR01)
- ICNARC
- SICSAG
- UKRR

6.6.2 Discrepancies

Use of RRT is collected on the FU eCRF. Use of RRT is also identified within the linked hospitalisation data from relevant OPCS-4 codes (Appendix 1). Use of RRT in the ICNARC/CCDS is identified from the recording of Renal Support days where the both the date of admission to and discharge from critical care fall between randomisation and 28 days. The SICSAG daily record indicates RRT if Renal Support is recorded on any day between randomisation and 28 days.

Further information on renal outcomes may become available from the UK Renal Registry data.

7 Competeness of Follow-up

For the 28 day analysis, follow-up information is considered to be complete if a FU eCRF has been completed, or data has been received from a hospital admissions dataset (SUSAPC, PEDW or SMR01) which includes data from the admission during which the participant was randomised.

8 Analysis of outcomes at 6-months

8.1 Collection of outcomes at 6-months in the UK

In the UK, outcome collection after the initial 28-day follow-up is undertaken by linkage to the routine healthcare datasets, with no further eCRF completion by the site staff. Unless indicated below, the outcomes analysed at 6-months are derived in the same way as for the main trial analyses described in section 6.

8.1.1 Use of ventilation

For the analysis of outcomes at 6-months, use of ventilation is defined in the same way as described in section 6.4. However, periods of ventilation during an elective (i.e. planned) admission following the index admission are excluded, since such procedures are likely to be related to elective surgery rather than complications of COVID-19. Dates of subsequent admissions are obtained from HESAPC and categorised into elective admission or non-

elective admission (including emergency admissions and transfers) on the basis of recorded the admission method (see Appendix 4).

8.1.2 Hospital recorded diagnosis

Diagnoses recorded as the primary reason for a period of in-hospital care are extracted from HESAPC, SMR01 and PEDW. Diagnostic codes are restricted to the first diagnostic position and ICD-10 codes in other positions are not considered. ICD-10 codes within the same block (e.g. I25.1 and I25.2) are considered to relate to the same hospital recorded diagnosis. For each hospital spell the first ICD-10 code recorded within the relevant block is extracted along with a start and end date. The start date is defined as the start of the first episode in which an ICD-10 code in the relevant block is recorded within that spell. The end date is defined as the end of the episode in which an ICD-10 code in the relevant block is recorded within that spell. Examples showing how the dates are extracted are shown in Appendix 5.

Diagnoses for which the first record in that spell is in an episode which started after randomisation are considered to be post-randomisation. Only post-randomisation diagnoses are to be used for the analyses.

Caution should be applied when considering absolute event rates derived from the hospital recorded diagnosis. As can be seen from example 1 and 3 in Appendix 5, more than one hospital recorded diagnoses could be derived from one clinical event, where ICD-10 codes from different blocks are used to record the same clinical event in subsequent episodes. While this is unlikely to result in bias when assessing the proportional effects of treatment, the absolute number of hospital recorded diagnoses should not be interpreted as the absolute number of serious adverse events.

8.1.3 Total duration of critical and hospital in-patient care

Total duration of hospital in-patient care during the 6-months after randomisation is derived from HESAPC based on admission and discharge dates. This is categorised separately by elective vs non-elective (including transfers) as defined in Appendix 4. The total duration of critical care during the 6-months after randomisation is derived from the dates of admission to and discharge from critical care in ICNARC, SUSCCDS, PEDWCCDS and SICSAG. If a period of critical care exists in any of these datasets it will contribute days to this outcome.

8.2 Collection of 6-month outcomes outside the UK

Sites will complete a case report form at 6 months after randomisation to capture information on vital status, use of ventilation and any admissions to hospital.

9 Appendix 1: OPCS-4 and ICD-10 codes used to identify assisted ventilation and other outcomes in the linked hospitalisation data

Outcome	code	Code type	Description
Use of CPAP	E85.6	OPCS	Continuous positive airway pressure
Use of NIV	E85.2	OPCS	Non-invasive ventilation NEC
Use IMV	E85.1	OPCS	Invasive ventilation
Use of ECMO	X58.1	OPCS	Extracorporeal membrane oxygenation
Use of RRT	X40.1	OPCS	Renal dialysis
	X40.3	OPCS	Haemodialysis NEC
	X40.4	OPCS	Haemofiltration

(OPCS and ICD-10 codes used to identify serious arrhythmia and other non-fatal outcomes to be added at a later date.)

10 Appendix: 2: Rules for determining start/end of advanced respiratory support days in the critical care datasets

Information is available in ICNARC/CCDS on

- The start and end date of the critical care episode
- The level of care at admission to the unit
- The level of care at discharge from the unit
- The reason for discharge from the unit
- The number of days of Advance Respiratory Support (ARS) received during the episode

The table below defines the rules for deciding whether the days on ARS in an ICNARC/CCDS episode should count from admission onwards (A), before discharge (D) or at the midpoint between admission and discharge (M)

		Level of care at admission to the unit				
		0	1	2	3	blank
Level of care at discharge from the unit	0	M	M	M	A	A
	1	M	M	M	A	A
	2	M	M	M	A	A
	3	D	D	D	A	D
	blank	*	*	*	A	A

* If the reason for discharge from the unit is ‘comparable critical care’ or ‘more-specialist critical care’ then D, otherwise M.

The following definitions are taken from the ICNARC data collection manual Version 3.1 (29 June 2009).

Level 3 – indicated by one or more of the following:

- admissions receiving advanced respiratory monitoring and support due to an acute illness
- admissions receiving monitoring and support for two or more organ system dysfunctions (excluding gastrointestinal support) due to an acute illness
- admissions solely receiving basic respiratory monitoring and support and basic cardiovascular monitoring and support due to an acute illness only meet Level 2

Level 2 – indicated by one or more of the following:

- admissions receiving monitoring and support for one organ system dysfunction (excluding gastrointestinal support) due to an acute illness
- admissions solely receiving advanced respiratory monitoring and support due to an acute illness meet Level 3
- admissions solely receiving basic respiratory and basic cardiovascular monitoring and support due to an acute illness meet Level 2
- admissions receiving pre-surgical optimisation including invasive monitoring and treatment to improve organ system function
- admissions receiving extended post-surgical care either because of the procedure and/or the condition of the admission
- admissions stepping down to Level 2 from Level 3 care

Level 1 – indicated by one or more of the following:

- admission recently discharged from a higher level of care
- admissions receiving a greater degree of observation, monitoring, intervention(s), clinical input or advice than Level 0 care
- admissions receiving critical care outreach service support fulfilling the medium-score group, or higher, as defined by NICE Guidelines 50

Level 0 – indicated by the following:

- admissions in hospital and receiving normal ward care

11 Appendix 3: Definition of prior RRT for End Stage Renal Disease

A previously validated algorithm was adapted to identify people requiring dialysis for ESRD from the prior HES/SMR01/PEDW.

Individuals who met the criteria for Rules 2-4 during a hospital admission prior to the admission during which they were randomised were considered to have prior ESRD provided they did not meet the criteria for Rule 1 after meeting the other criteria.

Rule 1: Kidney Transplantation

Occurrence of any incident kidney transplant code (with no removal within 90 days), or a prevalent kidney transplant code with no removal having occurred prior to the record.

Rule 2: Peritoneal maintenance dialysis

Occurrence of any admission with a peritoneal dialysis code (without diagnosis of acute kidney injury).

Rule 3: Definite maintenance dialysis

Occurrence of a dialysis code in a patient who has had:

(a) a diagnostic code for ESRD any time prior to, or within 365 days; or

(b) the insertion of an AV fistula or graft any time prior to, or within 365 days.

Rule 4: Probable maintenance dialysis

The occurrence of at least two episodes containing a dialysis code, with at least 90 days between the start of the first recorded dialysis, and the start of any subsequent dialysis (without agnosis of acute kidney injury).

Relevant ICD-10 and OPCS-4 codes for Rules 1-4 above

Group	Category	ICD-10	OPCS-4	Description
Diagnosis	Acute kidney injury	N17		Acute renal failure
Diagnosis	End-stage renal disease	N18.0		End-stage renal disease
Diagnosis	End-stage renal disease	N18.5		Chronic kidney disease, stage 5
Diagnosis	End-stage renal disease	Q60.1		Renal agenesis, bilateral
Dialysis	Dialysis	E85.3		Secondary systemic amyloidosis (dialysis related)
Dialysis	Dialysis	Y60.2		Unintentional cut, puncture, perforation or haemorrhage during surgical and medical care; during kidney dialysis…..
Dialysis	Dialysis	Y61.2		Foreign object accidentally left in body during surgical and medical care; during kidney dialysis or other perfusion
Dialysis	Dialysis	Y62.2		Failure of sterile precautions during surgical and medical care; during kidney dialysis or other perfusion
Dialysis	Dialysis	Y84.1		Other medical procedures as the cause of abnormal reaction of the patient, or of later complication; kidney dialysis
Dialysis	Dialysis	Z99.2		Dependence on enabling machines and devices, not elsewhere classified; dependence on renal dialysis
Dialysis	Dialysis		X40.1	Renal dialysis
Dialysis	Haemodialysis	T82.4		Mechanical complication of vascular dialysis catheter
Dialysis	Haemodialysis	Z49.1		Care involving dialysis; extracorporeal dialysis
Dialysis	Haemodialysis		X40.3	Haemodialysis NEC
Dialysis	Haemodialysis		X40.4	Haemofiltration
Dialysis	Insertion of AVF or graft		L74.1	Insertion of arteriovenous prosthesis
Dialysis	Insertion of AVF or graft		L74.2	Creation of arteriovenous fistula NEC
Dialysis	Insertion of AVF or graft		L74.6	Creation of graft fistula for dialysis
Dialysis	Insertion of AVF or graft		L74.8	Other specified arteriovenous shunt
Dialysis	Insertion of AVF or graft		L74.9	Unspecified arteriovenous shunt
Dialysis	Insertion of PD catheter		X41.1	Insertion of ambulatory peritoneal dialysis catheter
Dialysis	Peritoneal dialysis	Z49.2		Care involving dialysis; other dialysis
Dialysis	Peritoneal dialysis		X40.2	Peritoneal dialysis NEC
Dialysis	Peritoneal dialysis		X40.5	Automated peritoneal dialysis
Dialysis	Peritoneal dialysis		X40.6	Continuous ambulatory peritoneal dialysis
Dialysis	Tunnelled line insertion		L91.5	Insertion of tunnelled venous catheter
Transplantation	Incident kidney transplant		M01.2	Allotransplantation of kidney from live donor
Transplantation	Incident kidney transplant		M01.3	Allotransplantation of kidney from cadaver NEC
Transplantation	Incident kidney transplant		M01.4	Allotransplantation of kidney from cadaver heart beating
Transplantation	Incident kidney transplant		M01.5	Allotransplantation of kidney from cadaver heart non-beating
Transplantation	Incident kidney transplant		M01.8	Other specified transplantation of kidne
Transplantation	Incident kidney transplant		M01.9	Unspecified transplantation of kidney
Transplantation	Prevalent kidney transplant	N16.5		Renal tubulo-interstitial disorders in transplant rejection
Transplantation	Prevalent kidney transplant	T86.1		Kidney transplant failure and rejection
Transplantation	Prevalent kidney transplant	Z94.0		Kidney transplant status
Transplantation	Prevalent kidney transplant		M08.4	Exploration of transplanted kidney
Transplantation	Prevalent kidney transplant		M17.4	Post-transplantation of kidney examination - recipient
Transplantation	Prevalent kidney transplant		M17.8	Other specified interventions associated with transplantation of kidney
Transplantation	Prevalent kidney transplant		M17.9	Unspecified interventions associated with transplantation of kidney
Transplantation	Removal of kidney transplant		M02.6	Excision of rejected transplanted kidney

12 Appendix 4: Definitions of discharge and of elective/planned admissions

Definition of discharge used for the time to discharge outcome (see section 6.3)

Dataset	Criteria	Definition
PEDW	Discharge method not died or tranfer	Discharge method not 4 or 8, and Discharge destination not 49, 51, 52, 53, 55, 56, 57, 79, 87, 98
	No other admission up to 4 days before or 1 day after discharge which suggests transfer	Admission source 51 or 87, or Admission method 2B, 81 or 28
HES/SUS	Discharge not died or tranfer	Discharge method not 4 or 8, and Discharge destination not 49, 50, 51, 52, 53, 79, 87 or 98
	No other admission up to 4 days before or 1 day after discharge which suggests transfer	Admission source 51 or 87, or Admission method 2B, 81 or 28
SMR01	Discharge not died or tranfer	Discharge type not 40-43, and Discharge type is 10, 11, 18, 19, 70, 20-23, 28, 29
	No other admission up to 4 days before or 1 day after discharge which suggests transfer	Admission type 18, 30, 36, 38, 39, 40

Definition of planned / elective admissions used for the 6-months outcomes (see section 8.1.1)

Dataset	Admission type	Definitions
PEDW	Planned	If admission method NOT (21 or 22 or 23 or 24 or 25 or 27 or 28 or 81)
HES/SUS	Planned	IF admission method NOT (21 or 22 or 23 or 24 or 25 or 28 or 81 or 2A or 2B or 2C or 2D)
SMR01	Planned	IF admission type NOT (18 or 20 or 21 or 22 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 38 or 39)

13 Appendix 5: Example hospital recorded diagnoses showing extraction of start and end dates

Table: Four example HESAPC spells each containing three episodes

	Example 1	**Example 2**	**Example 3**	**Example 4**
Episode 1 Episode start date 01/02/2021 Episode end date 02/02/2021	R07.4 Chest pain unspecified	I219 Acute myocardial infarction, unspecified	J18.0 Bronchopneumonia unspecified	N17.9 Acute renal failure unspecified
Episode 2 Episode start date 02/02/2021 Episode end date 05/02/2021	I21.4 Acute subendocardial myocardial infarction	I210 Acute transmural myocardial infarction of anterior wall	J15.9 Bacterial pneumonia unspecified	I26.0 Pulmonary embolism with mention of acute cor pulmonale
Episode 3 Episode start date 05/02/2021 Episode end date 08/02/2021	A04.7 Enterocolitis due to Clostridium difficile	I210 Acute transmural myocardial infarction of anterior wall	J15.2 Pneumonia due to staphylococcus	N17.9 Acute renal failure unspecified

The hospital recorded diagnoses and relevant dates which would be extracted from these examples are as follows:

Example 1:

- R07.4 Start date 01/02/2021 End date 02/02/2021
- I21.4 Start date 02/02/2021 End date 05/02/2021
- A04.7 Start date 05/02/2021 End date 08/02/2021

Example 2:

- I219 Start date 01/02/2021 End date 08/02/2021

Example 3:

- J18.0 Start date 01/02/2021 End date 02/02/2021
- J15.9 Start date 02/02/2021 End date 08/02/2021

Example 4:

- N17.9 Start date 01/02/2021 End date 08/02/2021
- I26.0 Start date 02/02/2021 End date 05/02/2021