RECOVERY

Randomised Evaluation of COVID-19 Therapy

# Statistical Analysis Plan Paediatric multisystem inflammatory syndrome population

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Nuffield Department of
POPULATION HEALTH


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## 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*

Professor Thomas Jaki, co-investigator and SC Member, MRC Biostatistics Unit, University of Cambridge

### *Reviewers*

Professor Edmund Juszczak, non-independent SC Member (University of Nottingham)

Professor Alan Montgomery, SC Member, (University of Nottingham)

Professor Richard Haynes, Clinical Coordinator, NDPH, (University of Oxford)

Professor Saul Faust, SC Member (University of Southampton)

Professor Athimalaipet Ramanan, Member of Paediatric Working Group (University of Bristol)

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.

3. Juszczak E, Altman DG, Hopewell S, Schulz KF. Reporting of multi-arm parallel-group randomized trials: extension of the CONSORT 2010 statement. JAMA 2019;321(16):1610-1620.

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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| Steering Committee Statistician | Name: Professor Thomas Jaki | |
| | Signature: | Date: |

# 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 |