Protocol

This trial protocol has been provided by the authors to give readers additional information about their work.

Protocol for: McArdle AJ, Vito O, Patel H, et al. Treatment of multisystem inflammatory syndrome in children. N Engl J Med. DOI: 10.1056/NEJMoa2102968

This supplement contains the following items:

1. Original protocol for the entire study as submitted for UK ethics and ISRCTN (pp 2-12)
2. Participant-focused protocol as shared with consortium members and including the case report form (pp 13-27)
3. Summary of differences between documents (p28)
4. Initial statistical analysis plan (pp 29-36)
5. Final statistical analysis plan (pp 37-43)
6. Summary of changes in statistical analysis plan (p44)

Imperial College London

Imperial College Healthcare NHS Trust

BATS

Best available treatment study for inflammatory syndromes associated with SARS-CoV-2

Clinical Protocol
Version 1 22/05/20

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Protocol authorised by:

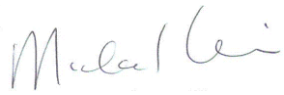
Name & Role	Date	Signature
Michael Levin **Professor of international Child Health** **Imperial College London** **Principal Investigator**	**July1 2020**	

Table of Contents

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General study Information and Documents: bestavailabletreatmentstudy.co.uk/

Sponsor

Imperial College London is the main research Sponsor for this study. For further information regarding the sponsorship conditions, please contact the Head of Regulatory Compliance at:

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Funder

Unfunded

This protocol describes the **Best available treatment study for inflammatory syndromes associated with SARS-CoV-2** study and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study. Problems relating to this study should be referred, in the first instance, to the Chief Investigator.
This study will adhere to the principles outlined in the UK Policy Framework for Health and Social Care Research. It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

Glossary of Abbreviations

CAA	Coronary artery aneurysm
ECHO	echocardiogram
IVIG	Intravenous Immunoglobulin
KD	Kawasaki disease
KD-TS	Kawasaki disease temporally associated with SARS-CoV-2 infection
PIMS-TS	Paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 infection
RCT	Randomised controlled trial
USA	United States of America

Keywords

COVID-19, infectious diseases, inflammatory diseases, paediatrics, SARS-CoV-2

Study summary

TITLE Best available treatment for inflammatory syndromes associated with SARS-CoV-2

DESIGN Multi-centre, international study collecting non-identifiable routinely collected clinical information from clinical records of patients with emerging inflammatory syndromes associated with SARS-CoV-2.

AIMS Collection of longitudinal clinical retrospective data on patients with a spectrum of inflammatory syndromes associated with SARS-CoV-2 from hospitals across the UK and globally in order to:

1) Provide a description of clinical phenotypes, disease progression and the best available treatments offered by institutes in different countries around the world
2) Identify clinical and biological markers of disease progression and poor outcomes
3) Categorize the wide spectrum of the inflammatory syndromes into distinct clinical phenotypes (mild/moderate/severe) using clinical and biological makers
4) Evaluate the clinical progression and management with the available therapeutic modalities to help inform clinical management

OUTCOME MEASURES

Primary
Comparative effectiveness of different anti-inflammatory and immunomodulatory drugs in treating the inflammatory syndrome, as measured by fall in inflammatory markers, and in prevention of cardiac dysfunction, coronary artery aneurysms and other long-term complications.

Secondary
Proportion dying
Proportion requiring ICU/HDU care
Total duration of fever
Risk of long-term complications (excluding CAA)
Proportion receiving any immunomodulator therapy
Proportion receiving individual immunomodulator classes
Total number of immunomodulators received per patient
Proportion with each organ system involved

POPULATION Any patient fulfilling the inclusion criteria (internationally)

DURATION 2 years

1. Introduction

1.1 Background

Since the first reports of a paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 infection (PIM-TS) and establishment of a case definition in the UK (RCPCH 1 May 2020), paediatricians across the world have reported a rapidly increasing number of cases of this disorder. In addition to the critically ill children in the first reports, a wider spectrum of childhood inflammatory syndromes has emerged. These syndromes appear to be an unusual immune response to SARS-CoV-2 infection with features overlapping with Kawasaki disease, however the underlying biology is yet to be understood.

1.2 Rationale for current study

Current management is based on paediatricians providing the treatment they judge to be best for their patient with the resources available in their setting, which include intravenous immunoglobulin (IVIG), anti-inflammatory and immunomodulatory medications. However, we do not know which treatments are beneficial or harmful in these new inflammatory syndromes. Furthermore, anti-inflammatory and immunomodulatory treatments are in short supply due to their use in the ongoing COVID-19 pandemic. It is likely that with the increase in cases with Kawasaki-like syndromes, supplies of IVIG may also become scarce. An evidence-base is urgently needed to help guide clinical management of this condition and ensure the treatment given is appropriate, effective and safe.

The optimal method for determining the effectiveness of the different treatments available would be randomised controlled trials (RCTs). However, RCTs take time to set up and require well phenotyped conditions and funding, it seems unlikely, except where existing trials are in place, that formal RCTs can be set up in time to be offered to the rapidly increasing number of children with these inflammatory syndromes. We propose a study to assist in the dual goals of understanding the range of phenotypes and their natural history and gaining insight into treatment efficacy. We are inviting paediatricians across the world to join our “Best Available Treatment Study”. This study aims to collate and evaluate longitudinal clinical data for all suspected cases of these emerging inflammatory syndromes to provide answers regarding which patients may benefit from treatment and the effectiveness and risk of available treatments.

2. Study Objectives

Primary objectives include:

1) Provide a description of clinical phenotypes, disease progression, long-term complications (primarily coronary artery aneurysms) and the best available treatments offered by institutes in different countries around the world
2) Identify clinical and biological markers of disease progression and poor outcomes
3) Categorize the wide spectrum of the inflammatory syndromes into distinct clinical phenotypes (mild/moderate/severe) using clinical and biological makers
4) Evaluate the clinical progression and management with the available therapeutic modalities to help inform clinical management.

Secondary objectives include:

1) Determine the risk of coronary artery aneurysms (CAA), cardiac dysfunction and any other long-term complication in each group of distinct clinical phenotypes (based on severity).

2) Compare the relationship (e.g. epidemiological, clinical, biological and ECHO findings) between the group of children with PIMS-TS meeting the Kawasaki Disease criteria with children of Kawasaki disease prior to the COVID-19 pandemic, recorded in existing databases (at Imperial College London, Paediatric Infectious disease research group and collaborators in Europe and USA).

3. Study Design

Observational study:
We will collect non-identifiable, routinely collected clinical data from patients presenting to hospitals world-wide with clearly defined clinical phenotypes.

Study size:
We anticipate recruitment of at least 1800 (150 cases from the UK and around 1650 cases from around the globe). In the last month, since the establishment of a case definition in the UK (RCPCH 1 May 2020), over 100 cases have been reported across the UK and numbers are continuing to rise.

Collection of clinical data:
Data will be collected systematically on any patients meeting the study criteria using an online case report form. Patients will be anonymised and identified only by the clinician reporting the case. The severity of each patient's clinical findings, inflammatory markers and organ dysfunction will be recorded on a daily basis before and after initiation of immunomodulating agents, or during observation (if no specific treatment given). Outcomes including time in intensive care units, duration of organ support, development of coronary artery aneurysms, death and any other long-term complications will be recorded. The data will enable the following questions to be addressed, in addition to the primary and secondary objectives listed above

1) Do patients progress from the less severe to more serious categories?
2) Should observation alone or treatment be given to the large number of children with the less severe inflammatory syndrome, and if so what levels of inflammation define need for treatment?
3) Does treatment of children in less severe categories prevent progression to the more severe syndrome?
4) Which treatment strategies (anti-inflammatory and immuno-modulating treatment such as immunoglobulin, steroids, anti-TNF, anti-IL1, anti-IL6 or T cell inhibition, or anticoagulation or anti-platelet agents) are effective in improving clinical outcomes and reducing risk of long-term complications, primarily, coronary artery aneurysms. This will be done by comparing the rate of change in inflammatory markers, organ failure or need for interventions between no intervention group, and each of the individual immunomodulating agents or combinations, using machine learning and other mathematical approaches
5) What are the risk and benefits of administering immunomodulatory agents to large numbers of children who may have persistent SARS-CoV-2 or may have self-resolving inflammatory conditions?

We aim to start data collection as soon as possible and will keep the database open for enrolment of patients for 24 months. We plan to perform interim analysis at 6 months to review the effectiveness and safety of the therapies used in the management of these new syndromes. The final analyses and report will be prepared within 12 months of closing the database.

Design considerations:
The design of the study and clinical database has been led and reviewed by senior investigators and collaborators in the UK, Europe and USA to ensure that the database is user-friendly, the

questions asked are worded clearly and that the data gathered is sufficient for addressing our primary and secondary outcomes.

Durations: 2 years

4. Participant Entry

4.1 Pre-registration evaluations

Recruitment process:
Study information including clear guidance on which patients to enrol into the database and how to use the database will be disseminated across UK NHS hospitals and internationally, through existing consortia and collaborations as well as international societies.

If a centre wants to take part in the study, they will nominate a lead for their institution, who will be provided with an individual REDCap account and a user guide for entering data onto the REDCap database. Doctors caring for patients in emergency departments, wards or intensive care units will identify patients meeting the study criteria. The relevant patients can then be enrolled onto the REDCap database and data entered retrospectively.

Individual REDCap accounts will only give access to records entered from that site.

4.2 Inclusion Criteria

- Any suspected case of multisystem inflammatory condition associated with SARS-CoV-2 in all ages
- Data entry will be retrospective

4.3 EXCLUSION CRITERIA

- There are no exclusion criteria for patients with suspected or proven matching syndrome.

4.4 Withdrawal criteria
N/A

5. Adverse events

There is no patient involvement in the study and therefore no adverse event reporting is relevant.

6. Assessment and follow-up

Not applicable

7. Statistics and data analysis

What is the primary outcome measure for the study?
Comparative effectiveness of different anti-inflammatory and immunomodulatory drugs in treating the inflammatory syndrome, as measured by fall in inflammatory markers, and in prevention of cardiac dysfunction, coronary artery aneurysms and other long-term complications.

What are the secondary outcome measures for the study?

Proportion dying
Proportion requiring intensive/high-dependency care
Total duration of fever
Risk of long-term complications (excluding CAA)
Proportion receiving any immunomodulator therapy
Proportion receiving individual immunomodulator classes
Total number of immunomodulators received per patient
Proportion with each organ system involved

What is the sample size for the research?
This is an urgent study of an emerging disease whose incidence is unknown and whose future incidence will likely be linked closely to the evolution of the COVID-19 outbreak. With evidence of over 100 cases in the UK thus far and expected extensive recruitment from sites already closely linked through existing collaborations (e.g. EU funded, multi-centre DIAMONDS project) we anticipate recruitment of around 1800 cases worldwide.

How was the sample size decided upon?
It is based upon our reasonable expectations given early reports of cases and the number of study sites which are planning to submit data.

For the primary outcome, a representative power calculation considers detection of a two-fold difference in CAA incidence between moderate inflammatory syndrome and severe inflammatory syndrome between 10 and 5% respectively. For power of 80% and two-sided significance threshold of 5%, this requires a sample of 868. If these groups together represent 50% of cases, required sample size would approach 1800.

Describe the methods of analysis by which the data will be evaluated to meet the study objectives:

Statistical analyses will be undertaken using R (R Foundation for Statistical Computing).

We will undertake descriptive analysis of the cohort using summary statistics for continuous variables as median and inter-quartile range, unless normally distributed. We will classify children into the three clinical syndromes at presentation and by discharge and report proportions progressing to more severe syndromes. Patients who died will be described in comparison to the rest of the cohort.

We will also present descriptive analysis of treatment, care and progress by ultimate syndrome categorisation at presentation.

We will classify system involvement for each patient, including gastrointestinal, respiratory, neurological, cardiac, hepatic, renal and coagulation. We will present the proportions with system involvement, and the distribution of numbers of systems involved.

We will explore predictors of immunomodulatory therapy and coronary artery aneurysm development usage by multiple linear regression. We will describe the prevalence and types of complications of immunomodulatory treatment.

In-depth analysis of treatment response accounting for baseline and post-baseline confounders will be undertaken with collaboration of the biostatistics and informatics group within the Department of Infectious Disease utilising advanced modelling approaches.

Data and all appropriate documentation will be stored for a minimum of 10 years after the completion of the study, including the follow-up period.

8. Regulatory issues

8.1 Ethics approval

The Study Coordination Centre has obtained approval from UK Research Ethics Committee (REC) 20/HRA/2957 and Health Regulator Authority (HRA). The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

8.2 Consent

N/A as non-identifiable data collection

8.3 Confidentiality

Personal identifiers will not be recorded and individual patients will not be identified. The Chief Investigator will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act.

8.4 Indemnity

Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this study, which apply to this study.

8.5 Sponsor

Imperial College London will act as the main Sponsor for this study. Delegated responsibilities will be assigned to the NHS trusts taking part in this study.

8.6 Funding

This study is unfunded

8.7 Audits

The study may be subject to inspection and audit by Imperial College London under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the UK Policy Frame Work for Health and Social Care Research.

9. Study Management

The day-to-day management of the study will be co-ordinated through the Imperial College BATS Management Team.

10. Publication Policy

Individuals predominantly involved in the particular work will always be included according to the usual authorship requirements:

- Substantial contributions to the conception or design of the work or the acquisition, analysis, or interpretation of data for the work.
- Drafting the work or revising it critically for important intellectual content.
- Final approval of the version to be published.
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
- The listed authors should acknowledge the different components (clinical/analysis/overall project).

- All papers will list the authors as mentioned above and then indicate *"on Behalf of BATS consortium"* and then list all members who have contributed data.

11. References

Guidance: Paediatric multisystem inflammatory syndrome temporally associated with COVID-19. Royal College of Paediatrics and Child Health. Available online: https://www.rcpch.ac.uk/sites/default/files/2020-05/COVID-19-Paediatric-multisystem-%20inflammatory%20syndrome-20200501.pdf

BATS

Best available treatment study for inflammatory syndromes associated with SARS-CoV-2

Study Handbook

Table of Contents

1 Background

Paediatricians in many countries worldwide are seeing rapidly increasing numbers of children with a new spectrum of inflammatory diseases temporarily associated with the COVID-19 pandemic. Since the first reports of a **paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 infection (PIMS-TS)**, and establishment of a case definition in the UK (RCPCH, 1 May 2020), additional definitions for the new, have been proposed by the CDC in the USA, and by WHO. The disorder was called **Multisystem Inflammatory syndrome in children-MIS-C** in the CDC alert. These different definitions and acronyms (PIMS-TS/MIS-C) are largely overlapping. The disorder has been reported from many countries. However, in addition to the critically ill children described in the first reports, a wider spectrum of childhood inflammatory illness associated with SARSCov2 have emerged, which appear to represent a spectrum of inflammatory illness associated with SARS-CoV-2 pandemic.

1.1 Different definitions in use

1.1.1 Paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) Royal College of Paediatrics and Child Health definition:

1. A child presenting with persistent fever, inflammation (neutrophilia, elevated CRP and lymphopenia) and evidence of single or multi-organ dysfunction (shock, cardiac, respiratory, renal, gastrointestinal or neurological disorder) with additional features (see listed in Appendix 1). This may include children meeting full or partial criteria for Kawasaki disease.
2. Exclusion of any other microbial cause, including bacterial sepsis, staphylococcal or streptococcal shock syndromes, infections associated with myocarditis such as enterovirus (waiting for results of these investigations should not delay seeking expert advice).
3. SARS-CoV-2 PCR testing may be positive or negative

1.1.2 Multisystem Inflammatory Syndrome in Children (MIS-C) WHO case definition:

1 Children and adolescents 0–19 years of age with fever > 3 days

2 AND two of the following:

- Rash or bilateral non-purulent conjunctivitis or muco-cutaneous inflammation signs (oral, hands or feet).
- Hypotension or shock.
- Features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including ECHO findings or elevated Troponin/NT-proBNP),
- Evidence of coagulopathy (by PT, PTT, elevated d-Dimers).
- Acute gastrointestinal problems (diarrhoea, vomiting, or abdominal pain).

3 AND Elevated markers of inflammation such as ESR, C-reactive protein, or procalcitonin.

4 AND No other obvious microbial cause of inflammation, including bacterial sepsis, staphylococcal or streptococcal shock syndromes.

5 AND Evidence of COVID-19 (RT-PCR, antigen test or serology positive), or likely contact with patients with COVID-19.

1.1.3 CDC case definition

1 An individual aged <21 years presenting with fever*, laboratory evidence of inflammation**, and evidence of clinically severe illness requiring hospitalization, with multisystem (>2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological).

2 AND No alternative plausible diagnoses;

3 AND Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or COVID-19 exposure within the 4 weeks prior to the onset of symptoms

** Fever >38.0°C for ≥24 hours, or report of subjective fever lasting ≥24 hours*

*** Including, but not limited to, one or more of the following: an elevated C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen, procalcitonin, d-dimer, ferritin, lactic acid dehydrogenase (LDH), or interleukin 6 (IL-6), elevated neutrophils, reduced lymphocytes and low albumin*

Additional comments

Some individuals may fulfil full or partial criteria for Kawasaki disease but should be reported if they meet the case definition for MIS-C

Consider MIS-C in any pediatric death with evidence of SARS-CoV-2 infection

1.2 Spectrum of Emerging Paediatric Inflammatory syndromes temporally associated with SARSCov2 pandemic

In addition to the cases meeting the above definitions, children presenting with fever, elevated inflammatory markers and some features of PIMS-TS/MISC have been reported which appear to be inflammatory syndromes associated with SARS-CoV-2.

1.2.1 Typical Kawasaki disease, temporally associated with SARS-CoV-2 (KD-TS)

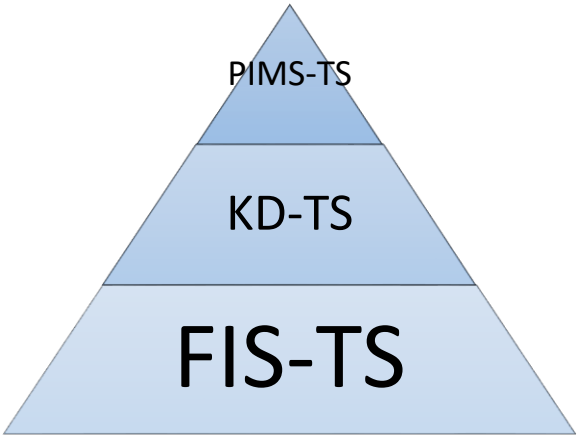
Children meeting the classical criteria for Kawasaki disease (KD), but with evidence of SARS-CoV-2 infection or exposure. It is not clear whether these cases are Kawasaki disease or MIS-C.

1.2.2 Febrile Inflammatory syndrome, temporally associated with SARS Cov2 (FIS-TS)

Febrile children, without features of organ failure or mucocutaneous features of KD, but with inflammatory blood markers (raised CRP, neutrophilia, lymphopenia, elevated D Dimers, ferritin), in whom other infectious or inflammatory causes cannot be identified; SARS-CoV-2 may be positive or negative by PCR and antibody.

1.2.3 Infection complicating inflammatory syndromes

Some children in the preceding PIMS-TS/MIS-C, KD-TS and FIS-TS groups have evidence of invasive bacterial infections or opportunistic infections suggesting that despite the intense inflammation seen in each of the three syndromes, immunity to common pathogens may be impaired.



Spectrum of Emerging Paediatric Inflammatory syndromes temporally associated with SARSCov2 pandemic

These emerging disorders appear to be an unusual response to SARS-Cov-2 infection mediated by the host innate and acquired immune systems.

1.3 Emerging questions on treatment and progression

1. Do patients progress from the less severe to more serious categories?
2. What is the risk of coronary artery aneurysms in each group?
3. What is the relationship between KD-TS and KD prior to the pandemic?
4. Do the same treatments which reduce the risk of coronary artery aneurysms in KD also reduce aneurysm risk in KD-TS?
5. Do anti-inflammatory and immunomodulating treatment such as immunoglobulin, steroids, anti-TNF, anti-IL1, anti-IL-6 or T-cell inhibition, or anticoagulation or anti platelets agents improve the outcome for critically ill children with PIMS-TS including reducing risk of coronary artery aneurysms?
6. Does treatment of children with fever and elevated inflammatory markers (FIS-TS) with any of the available immunomodulating agents prevent progression to the more severe syndromes of Kawasaki disease and PIMS-TS?
7. Should observation alone or treatment be given to the large number of children with FIS-TS, and if so what levels of inflammation define the need for treatment.
8. What are the risks and benefits of administering immunomodulating agents to large numbers of children who may have persistent SARS-CoV-2, or may have self -resolving inflammatory conditions?
9. Are there accurate biomarkers of progression and poor outcome?

1.4 The need for trials

The conventional method for addressing these questions and establishing which of the available treatments are beneficial and which may, in fact, be harmful would be to undertake randomised controlled trials. However, as randomised therapeutic trials take time to set up, require evaluation by national ethics authorities and funding and support, it seems unlikely that formal randomised trials can be set up in time to be offered to the rapidly expanding numbers of children with these inflammatory syndromes, except where existing trials are in progress. Furthermore, many centres will not have biological agents available as there is a world-wide shortage of many agents as a result of their use in COVID-19 patients.

1.4.1 An alternative to randomised trials

In the absence of established randomised controlled treatment trials for the new SARS-CoV-2 associated disorders we invite paediatricians in any country to join a study which we term the "**best available treatment study-BATS**". We believe that the approach outlined below will enable rapid evaluation of the available therapeutic modalities and rapidly provide answers on the questions as to which patients to treat, which treatments work, and which may be harmful.

1.5 The principles of the proposed study

- We do not know which immunomodulating treatments are beneficial or harmful for SARS-CoV-2 associated inflammatory conditions.
- Paediatricians try to provide the best available care to their patients.
- Anti-inflammatory and immuno-modulatory treatments are in short supply as their use in adults with COVID-19 is exhausting supplies of many of the biological agents. The numbers of cases with Kawasaki-like syndromes may also strain supplies of intravenous immunoglobulin.
- Faced with variable availability of treatment options paediatricians will offer their patients their "best guess" of which of the available therapies are likely to be beneficial in their setting.
- We have excellent biological markers of the inflammatory process. Elevation of CRP, ferritin, troponin, BNP, D-dimers, liver function tests and conventional blood markers are indicative of the intensity of the inflammatory process and return to normal as inflammation subsides.
- We have simple clinical markers to evaluate improvement, need for intensive care, need for oxygen, inotropes or other support.
- We have accurate clinical markers of outcome: frequency and severity of coronary artery aneurysms, length of stay in hospital, requirements for inotropes and ventilation, and overall survival.

1.6 Hypothesis

The administration of immunoglobulin, steroids or other immunomodulating agents such as immunoglobulin, anti-TNF, anti-IL-1, or anti-IL-6 therapies, steroids or cyclosporin, will result in more rapid resolution of inflammatory markers, prevent progression from FIS-TS to KD-TS or PIMS-TS, reduce the need for intensive care or organ support and reduce coronary artery aneurysm rate.

2 Study Design

2.1 Study Team

BATS is a truly international collaborative study. All clinicians and institutions enrolling patients into the study will become investigators in the BATS study. The study is being coordinated and the data is being managed by the Paediatric Infectious Disease Research Group at Imperial College London (Chief Investigator, Professor Mike Levin). It has been designed in collaboration and discussion with many researchers and organisations across the world. The Study steering group will include an international advisory board who will work with the Imperial College team to oversee the conduct and reporting of the study.

2.2 Study population

Patients meeting any of the three SARS-CoV-2 associated inflammatory condition (Paediatric Inflammatory Multisystem Syndrome - Temporally associated with SARS-CoV-2 (PIMS-TS/MIS-C),

Kawasaki Disease - Temporally associated with SARS-CoV-2 (KD-TS), and Febrile Inflammatory Syndrome - Temporally associated with SARS-Cov-2 (FIS-TS)) can be enrolled in the study. Patients meeting any of the overlapping definitions of Multisystem Inflammatory Syndrome (MIS-C/PIMS-TS) from RCPCH, CDC or WHO and can also be enrolled.

2.3 Methodology overview

1. Data will be collected systematically on all patients with MIS-C/PIMS-TS, FIS-TS, KD-TS using an online case report form. Patients are anonymised and identified only by the clinician reporting the case, hospital and country, and age of the child in months and years.
2. The severity of each patient's clinical findings, inflammatory markers and organ dysfunction are recorded.
3. Rate of change in inflammatory markers following initiation of immunomodulating agents, or during observation (if no specific treatment given) is recorded.
4. Outcome including presence of coronary artery aneurysms, time in PICU, duration of organ support, or death, and progression from FIS to KD or PIMS-TS is documented.
5. Rate of change in inflammatory markers, organ failure or need for interventions is compared between the no intervention group, and each of the individual immunomodulating agents or combinations.

This approach is likely to be successful because:

- There is genuine equipoise in treatment, as there is no clear evidence on which to base any specific agent or regime.
- Paediatricians in different countries are choosing treatments based on agents that are available, and their personal practice and preferences.
- The different rates of improvement in inflammation and outcome associated with each agent, or combinations of agents, can be detected in a non-randomised study by matching patients for their severity and degree of inflammation, and by studying the rates of improvement of the available markers of inflammation and the outcome variables of coronary artery aneurysms, intensive care and organ support duration and mortality.
- Patients who are included in randomised trials can be included as long as the treatment arm is known
- Propensity matching and other statistical approaches to correct for any severity bias is likely to reveal genuine differences in outcome, as long as the numbers of patients in the trial are large, and matching for severity at the time of initiation of treatment is undertaken.

2.3.1 How to participate - enrolling patients

To enter the trial and provide data: log onto the online study entry site http://bestavailabletreatmentstudy.co.uk/

1. Provide contact details (email, address, country and institution). You will be asked to enter only the date of admission to hospital and the age in years and months of your patient.
2. You will then be asked to provide basic information from a tick box list of the presenting features and enter laboratory findings that document the severity of inflammation on the day of trial entry as well as indicators of the severity of illness.
3. Best available therapy is administered and recorded. If no specific therapy is given this is recorded.
4. Record Daily (if possible) changes in the child's condition and the results of subsequent blood tests, severity markers and follow up echocardiography.

2.3.2 How to participate - inclusion

The entry point to the study is through the paediatrician's recognition of a case of MIS-C/PIMS-TS or FIS-TS, KD-TS. Diagnosis and entry to BATS can be prospective as patients are admitted, or retrospective after the patient has been discharged.

2.3.3 Exclusions

The only exclusions are identification of an alternative diagnosis once all investigations are available. Children with bacteraemia who otherwise fulfil the criteria for MIS-C can be included, unless the entire illness is thought to be explained by the pathogen.

2.4 Analysis

Electronically captured data following treatment with any of the agents will be analysed by the data monitoring group and analysis group at Imperial College. A detailed statistical analysis plan will be approved before analysis commences (see below).

2.4.1 Acknowledgement, participation and ownership of data

All clinicians submitting patients to this study will be listed as a member of the international consortium, have access to the data for their own analyses, and will be included in all subsequent reports as members of the BATS study as an investigator.

3 Instructions for the BATS Database Users

3.1 How to construct and use the Unique patient ID

IMPORTANT: please make sure no person identifiable data is entered in this registry at any point. This includes information on name, date of birth, address, and family members. **You will receive a unique site ID from the BATS team along with your login details** in the form of CCC-TTT-III-DDD, where C=country code; T=city or town code; I=institution code; D=department code; N= local case number. Please use your unique site ID for all your cases (CCC-TTT-III-DDD) and add a unique local 4-digit case number (NNNN).

Your Local patient ID then consist of:
CCC-TTT-III-DDD-NNNN

We suggest your first case has case number 0001; then your second case is number 0002, etc.

Example:

Case nr3 admitted to paediatric intensive care unit at St Marys hospital, London, UK will have the following code:	GBR-LON-SMH-ITU-0003
Case nr7 admitted to the paediatric infectious diseases ward at St Marys hospital, London, UK will have the following code:	GBR-LON-SMH-PID-0007

3.2 Maintaining a local log

We recommend the local clinical team responsible for data entry to maintain a local log of entered cases, to allow for pseudo-anonymisation. This log should contain:

- Name of the responsible, registered user to this registry, with valid secure email address
- the unique patient ID (site code plus local case number),
- the study ID as generated by the data entry system [Record ID]
- name of person entering data
- date of completing data entry
- local hospital patient ID*

*A local hospital patient ID should only be used by members of the clinical team with rights to see patient information. This log should comply with all local information governance requirements (including accessibility of the data, storage of the data, and maintenance of the data).

3.3 How to use the registry

- Once logged in using the username and password sent, the user should select the relevant project under 'My Projects': *Paediatric Inflammatory System – Temporally associated with SARS-CoV-2*
- Each case should only have one entry. Ideally, all data should be entered retrospectively at the time of discharge from hospital. If a patient gets transferred from one ward to another (for example: PICU step down to general paediatric ward), we strongly advise to complete the data entry for that patient using the same unique patient ID and case record.
- The user should click 'add/edit records' in the column on the left-hand side to enter new case.
- The user should enter the unique patient ID (Site ID + local incremental case number see above) and should document the Record ID that is generated by the Redcap platform in their local log. Note that your local case number will NOT equal the automatically generated Record ID.
- The user should complete every page of the form; once a page is completed, please change the scroll down bar at the bottom to the page from 'incomplete' to 'complete'. Redcap has an overview function ('Dashboard') that will allow users to identify pages that are left 'incomplete' which will facilitate data entry completeness.
- Every case should have a new Redcap form (by 'add records'), with a unique Record ID and Local patient ID
- We ask you to complete all pages. Please make sure all items on the pages 'Patient Details', 'Clinical Features at Presentation', 'Covid19 History', 'Severity', 'Vital Signs (first available on day of admission to your hospital)', 'Kawasaki Features', 'Blood Results (first available on day of admission to your hospital)', 'Microbiology and Virology', and 'Clinical Outcome' are completed in full.
- For the pages 'Clinical features at presentation', 'Vital Signs (first available on day of admission to your hospital)', 'Kawasaki Features', 'Blood results (first available on day of admission to your hospital)': these should ideally reflect the first available data when the patient presents to your hospital.
- For 'Blood results (first available on day of admission to your hospital)', please **complete the units of each blood result, even if that specific test has not been done on the day of admission to your hospital** – All the units of measurement will then be the same for the following days without specifying them again.
- For 'Blood results (following day)', 'Cardiac Investigations', and 'Treatment', please complete as much as possible. We understand that not all data are available for all repeat days, and please enter available data for these days.
- For the 'Clinical outcome' page, please select the 'Overall impression of the patient condition' based on the following definitions:

a. Paediatric Inflammatory Multisystem Syndrome- Temporally associated with SARS-CoV-2 (PIMS-TS/MIS-C). Defined by WHO, RCPCH or CDC definitions.
b. Typical Kawasaki disease, Temporally associated with SARS-CoV-2 (KD-TS). Children meeting the classical criteria for Kawasaki disease, with or without evidence of SARS-CoV-2 infection or exposure.

3.3.1 Registered users

- We will allow for one registered user per institution; and for one registered user per department for centres with >5 cases.
- Registered users will receive a unique username and password.
- Users should register with their secure and valid institutional email address as much as possible (for user verification issues).
- In case of multiple registrations from one department and/or institution, we can identify the previously registered user for that particular institution on request. We will only do so if valid and secure email addresses linked to their institution are provided.
- All registered users will be able to add cases; registered users will also be able to review and modify cases that were previously entered, but NOT cases from other institutions.
- Registered users are considered site leads for their department and/or institution; these site leads are responsible for the accurate, timely, and complete entry of the data. In return, all site leads will be named as formal contributor to any scientific output resulting from this data collection. This means any scientific output will be linked to the names of all contributors in PubMed and citations of the paper will be linked to your Scopus/ISI Web profiles.
- All registered users should have a valid certificate of the completion of training in Good Clinical Practice

3.4 Ethical approval

Regulations vary in different countries, and paediatricians enrolling patients should check with their own institution and country guidance. As no patient identifiable data is collected, patient and family consents are not required to utilise routinely collected hospital data. Many international studies using similar non-identified data are in progress and the principle is widely accepted, and some countries would not require ethics approval for this data collection exercise.

In the UK, the study has received National Ethics approval in the UK (IRAS Project ID: 284825; REC reference: 20/HRA/2957). Each site should adhere to local regulations and practice in their country.

3.5 Support

For any questions regarding this registry, and for any technical support, please use the form below https://forms.gle/RzxQxr5ziE7i9y7BA or contact us at bestavailabletreatmentstudy@gmail.com

1.1 PATIENT DETAILS

Has patient been treated in another hospital for this illness? Y ☐ N ☐ Which hospital:

Did the patient receive any treatment(s) in the previous hospital? Y ☐ N ☐ Which treatments and when:

Age: .... Years .... Months	Weight (kg):	Date of Admission:	D D M M Y Y Y Y

Ethnicity (self-reported):		Gender	Male ☐	Female ☐
Number of people in household:				

PMHx: None ☐ Asthma ☐ Severe allergy ☐ 1ary Immunodeficiency ☐ 2ary Immunodeficiency ☐ HIV ☐ Autoimmune disease ☐ JIA ☐ Severe obesity ☐ Chronic lung disease ☐ Congenital heart disease ☐ Chronic kidney disease ☐ Chronic liver disease ☐ Chronic neurological disorder ☐ Previous KD ☐ Malignancy ☐ Sickle cell disease ☐ Indwelling medical device ☐ Other.....

2.1 CLINICAL FEATURES AT PRESENTATION

	Y	N	NK		Y	N	NK		Y	N	NK
Fever (No. of days.....)	☐	☐	☐	Headache	☐	☐	☐	Rash	☐	☐	☐
Sore throat	☐	☐	☐	Seizures	☐	☐	☐	Non-purulent conjunctivitis	☐	☐	☐
Cough	☐	☐	☐	Encephalopathy	☐	☐	☐	Lymphadenopathy	☐	☐	☐
Respiratory distress	☐	☐	☐	Irritability	☐	☐	☐	Mucosal membrane changes	☐	☐	☐
Abdominal pain	☐	☐	☐	Lethargy	☐	☐	☐	BCG reactivation	☐	☐	☐
Diarrhoea	☐	☐	☐	Joint pain	☐	☐	☐	Skin peeling	☐	☐	☐
Vomiting	☐	☐	☐	Oedema	☐	☐	☐				

Other: .....

2.2 COVID-19 History

	Y	N	
Has the patient tested positive for SARS-CoV-2 prior to this illness? (If yes, ask date/test type/site)	☐	☐	Test type: Date and site:
Has the patient had any symptoms compatible with COVID-19 previous of this illness?	☐	☐	
Confirmed/suspected COVID in household contact	☐	☐	

Please complete as fully as possible, based on the information available.
In particular, please complete on day of admission and the day of and 2 days after starting any new immunomodulatory treatment.

	Day of admission	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14		28
3.1 SEVERITY	Options																	
Location of Care	ITU, HDU, Ward, ED																	
Highest resp support	Invasive ventilation, NIV, O2 therapy only, None																	
Inotropes	Y / N																	
Fluid bolus	Y/N																	
Renal replacement therapy	Y/N																	
ECMO	Y/N																	

3.2 VITAL SIGNS (first available on day of admission to your hospital)

Fever > 38 degrees Celsius in the last 24 hrs	
Heart rate (beats per minute)	
Respiratory rate (breaths per minute)	
Systolic blood pressure (mmHg)	
O2 saturations (percentage)	
Was the patient receiving oxygen therapy at the time of oxygen saturation measurement?	Y☐ N☐
Capillary refill time (seconds)	

Level of consciousness – AVPU (Alert, Responsive to voice, Responsive to pain, Unresponsive)		
Level of consciousness – Glasgow Come Score		

3.3 KAWASAKI FEATURES																	
Day of admission	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**		**28**
Fever > 38 degrees Celsius in the last 24 hrs																	
Rash																	
Red lips / Mucosal membrane changes																	
Non purulent conjunctivitis																	
Oedema																	
Skin peeling																	
Lymphadenopathy																	
BCG site reactivation																	

3.4 BLOOD RESULTS	Specify units																
	Day of admission	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**		**28**
Haemoglobin																		
Total white blood cells																		
Neutrophils																		
Lymphocytes																		
Platelets																		
Activated Partial Thromboplastin Time	(seconds)																	
Prothrombin time	(seconds)																	
International Normalised Ratio																		
D-dimer																		
Fibrinogen																		
Sodium																		
Potassium																		
Phosphate																		
Creatinine																		
Lactate																		
Creatinine Kinase																		
Lactate Dehydrogenase																		
C-reactive protein																		
Ferritin																		
Alanine Aminotransferase																		
Albumin																		
BNP																		
Pro-BNP																		
Vitamin D																		
Troponin																		
Procalcitonin																		

3.5 CARDIAC INVESTIGATIONS

Day of admission		0	1	2	3	4	5	6	7	8	9	10	11	12	13	14		28
Did the patient have an echocardiogram today?	Y/N																	
CAAs present?	Y/N																	
Largest CAs location	Left coronary; circumflex; left ant descending; right coronary																	
Largest CAs Z-score	Lopez Z-score																	
Largest CAs int. diam	Mm																	
Number of affected CAs																		
ECHO findings	Endocarditis, Pericarditis, Pericardial effusion, Myocarditis, LV dysfunction, Valve dysfunction																	
Did the patient have an electrocardiogram today?	Y/N																	
ECG Changes	Y/N																	
Which electrocardiogram changes?	Arrhythmia, T wave abnormalities, Other																	

3.6 TREATMENT

Day of admission		0	1	2	3	4	5	6	7	8	9	10	11	12	13	14		28
Was the patient treated for malaria?	Y/N																	
Antibiotics 1; name:	Y/N																	
Antibiotics 2; name:	Y/N																	
Antibiotics 3; name:	Y/N																	
Antibiotics 4; name:	Y/N																	
Antibiotics 5; name:	Y/N																	
Antiviral 1; name:	Y/N																	
Antiviral 2; name:	Y/N																	
Antiviral 3; name:	Y/N																	
Antiviral 4; name:	Y/N																	
Antiviral 5; name:	Y/N																	
Immunoglobulin	Dose (g/kg)																	
Intravenous steroid 1; name:	Dose (mg/kg)																	
Intravenous steroid 2; name:	Dose (mg/kg)																	
Intravenous steroid 3; name:	Dose (mg/kg)																	
Intravenous steroid 4; name:	Dose (mg/kg)																	
Intravenous steroid 5; name:	Dose (mg/kg)																	
Oral steroids 1; name:	Dose (mg/kg)																	
Oral steroids 2; name:	Dose (mg/kg)																	
Oral steroids 3; name:	Dose (mg/kg)																	
Oral steroids 4; name:	Dose (mg/kg)																	
Oral steroids 5; name:	Dose (mg/kg)																	
Aspirin	Dose (mg/kg)																	
Other anti-platelet; name:	Dose																	
Anticoagulant 1; name:	Prophylactic or treatment dose																	

Anticoagulant 2; name:	Prophylactic or treatment dose																	
Anticoagulant 3; name:	Prophylactic or treatment dose																	
Anticoagulant 4; name:	Prophylactic or treatment dose																	
Anticoagulant 5; name:	Prophylactic or treatment dose																	
Anti-TNF 1; name:	Dose (mg/kg)																	
Anti-TNF 2; name:	Dose (mg/kg)																	
Anti-IL1 1; name:	Dose (mg/kg)																	
Anti-IL1 2; name:	Dose (mg/kg)																	
Anti-IL1 3; name:	Dose (mg/kg)																	
Anti-IL1 4; name:	Dose (mg/kg)																	
Anti-IL1 5; name:	Dose (mg/kg)																	
Anti-IL-6 1; name:	Dose (mg/kg)																	
Anti-IL-6 2; name:	Dose (mg/kg)																	
Ciclosporin	Dose (mg/kg)																	
Blinded research study treatment	Study name:																	
Other (incl. non-blinded research study treatment); name:	Dose (mg/kg)																	

3.7 MICROBIOLOGY & VIROLOGY			
Was the patient positive for SARS-CoV-2 PCR test during this admission?	Yes ☐ Date of first positive test: ..... Site of specimen of first positive PCR test:	Tested but negative ☐	Not tested ☐
Was the patient positive for SARS-CoV-2 serology test during this admission?	Yes ☐ Date of first positive test: ..... Antibody type of first positive serology test:	Tested but negative ☐	Not tested ☐
First significant positive blood culture	Date:	Organism(s):	
Second significant positive blood culture	Date:	Organism(s):	
Third significant positive blood culture	Date:	Organism(s):	
Fourth significant positive blood culture	Date:	Organism(s):	
Fifth significant positive blood culture	Date:	Organism(s):	
Other significant pathogens detected	Date: ..... Test performed:	Pathogen(s) detected:	
Other significant pathogens detected	Date: ..... Test performed:	Pathogen(s) detected:	
Other significant pathogens detected	Date: ..... Test performed:	Pathogen(s) detected:	

4.1 CLINICAL OUTCOME							
Overall impression of the patient condition	PIMS-TS ☐ KD-TS ☐ Kawasaki Disease ☐ Inflammatory condition not meeting the above ☐						
Secondary diagnoses/complications	Y ☐	N ☐	If yes specify:				
Did complications arise as a result of drug treatment?	Y ☐	N ☐	Responsible drug:		Which complications:		
Overall Severity (tick all that apply)	O2 only (n days ....)	NIV (n days ....)	Invasive Vent (n days ....)	Inotropes (n days ....)	RRT (n days ....)	ECMO (n days ....)	None
Did the child survive this illness?	Y ☐	N ☐	Did the child develop coronary artery aneurysm?			Y ☐	N ☐

Was the child discharged with any long-term disability not present on admission?	Y ☐	N ☐	Which long-term disability?				Specify:	
Destination on discharge:	Usual place of residence ☐ Another hospital (which hospital: .....) ☐ Died ☐ Other ☐							
Date of death/ discharge:	D	D	M	M	Y	Y	Y	Y
Other notes:								

Summary of changes

BATS protocol

Document 1 (“Clinical Protocol Version 1 22/05/20” as prepared for ethics application) describes the study design at the outset and broad plan for descriptive, prognostic, phenotypic and comparative effectiveness analyses, of which this study represents the latter.

Document 2 (“Study handbook” as shared with consortium) includes detail on procedures for reporting patients.

BATS

Best available treatment study for inflammatory syndromes associated with SARS-CoV-2

Statistical Analysis Plan

Table of Contents

1 Statistical analysis plan – general approach

At the time of launching the BATS study, the rate of enrolment, the completeness of data, the distribution of different treatments, and the effect sizes of each treatment, were all unknown. Therefore, we took a pragmatic approach, and planned a preliminary analysis after the enrolment of 500 patients in order to establish estimates of these parameters to inform further analyses. Due to the urgent need for data to inform treatment of this emerging disease, we plan to publish results of the preliminary analysis, because we believe that they will be useful to clinicians, regardless of whether they demonstrate statistically significant differences between treatment groups. The analysis plan will be updated, with formal power calculations, based on the results of the preliminary analysis. Subsequent analyses are planned as the number of patients increase when 750, 1000 and 1500 cases have been recruited, and thereafter with larger numbers. We recognised that initial analyses of smaller numbers will only allow the major treatment groups to be compared, and that for less common treatments (such as biological agents) much larger sample sizes will be required.

1.0.1 Criteria for inclusion or exclusion in analysis

The analysis recognises that MIS-C is a spectrum of disease, and that the definitions presented in the introduction to this protocol may be too restrictive, particularly as experience of the condition evolves over time; therefore primary analyses will include all patients enrolled in the study, reflecting "**physician diagnosed multisystem inflammatory diseases associated with SARS-CoV-2**"**.** Sensitivity analyses will be performed to examine whether exclusion of those not fully meeting the WHO diagnostic criteria changes the inference from the results.

1.0.2 Timing of Treatments

The day the first immunomodulatory treatment is commenced is considered day 0. All outcomes and additional treatment will then be recorded by day following day 0.

1.0.3 Classification of treatments received

Patients with suspected MIS-C have been treated with a wide range of immunomodulatory and anti-inflammatory agents. Treatments have often been given sequentially if patients fail to respond to the initial treatment. All immunomodulatory treatments will be classified as follows:

1. **Primary treatment**. Where two agents are commenced in the same 24-hour period, this will be considered a **combination treatment** and the effects of the combined agents will be evaluated together. Thus, primary treatment can be either single agent, dual, or triple agent therapy as long as the treatments were commenced in the same 24-hour period.
2. Treatments commenced on the day after the primary treatment will be considered **secondary treatments** and will indicate failure of the primary treatment.
3. Any immunomodulatory treatment administered on the day after secondary treatment will be classified as tertiary treatment and considered to be failure of primary and secondary treatments.
4. As treatments may not have rapid effects, **sensitivity analysis** will be performed, defining primary treatment as treatment given on day 0 and day 1, and treatment failure as administration of treatment on day 2 or beyond.

1.0.4 Clinical severity scale

An ordinal clinical severity scale will be computed on a daily basis, for use in time to event analyses and dichotomous improvement analysis. The patient's severity will be the maximum from:

1. Ventilated (invasive or non-invasive) and on inotropic support
2. Ventilated (invasive or non-invasive)
3. Inotropic support
4. Receiving oxygen
5. No supportive therapy CRP ≥ 50
6. No supportive therapy CRP < 50
7. Discharged

For visualisation of all clinically important events an expanded clinical scale will be used including:

1. Death
2. ECMO
3. Ventilated (invasive or non-invasive) and on inotropic support
4. Ventilated (invasive or non-invasive)
5. Inotropic support
6. Receiving oxygen
7. No supportive therapy CRP ≥ 50
8. No supportive therapy CRP < 50
9. Discharged
10. Transferred

1.1 Outcomes

1.1.1 Primary outcomes

The primary analysis will compare the effect of different treatments on severity and complications of MIS-C.

1. A composite of inotropic support on day 2 or later; ventilator support (invasive or non-invasive) on day 2 or later and death.
2. Improvement of at least one level in the ordinal clinical severity scale between day 0 and day 2

1.1.2 Secondary outcomes

1. **Temporal dynamics of inflammatory markers and markers of organ involvement**
   Immunomodulatory treatments are expected to alter the rate of progression or resolution of abnormal laboratory findings. A number of the laboratory markers are good surrogates for organ damage (such as troponin, liver function tests, and plasma creatinine). For all patients, the rate of change either worsening or improving of the following biomarkers will be compared between treatment groups:
   - Inflammatory
     - CRP
     - Fibrinogen
     - D-dimers
     - Ferritin
     - Albumin
     - Platelet count
     - Lymphocyte count

        - Neutrophil count
    - Organ involvement
        - Haemoglobin
        - Liver enzymes
        - Troponin
        - BNP or proBNP
        - Creatinine
        - LDH

2. **Failure of primary treatment**
   Escalation of immunomodulatory treatment after day 0

3. **Composite time-to-event analyses**
   Time to reach a one-level or greater improvement in ordinal severity scale.

4. **Subgroup time-to-event analyses**
    a. Time to come off ventilator for patients ventilated on day 0
    b. Time to come off inotropes for patients on inotropes on day 0
    c. Time to come off oxygen for patients on oxygen on day 0
    d. Time until CRP < 50 mg/L for all patients
    e. Time to discharge for all patients

5. **Death**

6. **Coronary artery aneurysm persisting at discharge (Z score ≥ 2.5)**

7. **Fever on day 2 or beyond**

8. **Any increase in level of severity (organ support) after day 0**

9. **Distribution of ordinal clinical severity scale on day 3 and 5**

10. **Improvement of at least one level in the ordinal severity scale between day 0 and day 3.**

1.2 Sensitivity analyses

All primary outcomes will undergo sensitivity analysis by estimation with the following subpopulations:

- Meeting full WHO criteria
- Meeting WHO criteria except for presence of bacteremia
- Missing WHO classification by one criterion
- Missing WHO classification by >1 criterion

1.3 Other analyses

1.3.1 Subgroup analyses

Immunomodulators are expected to have the greatest effect on patients with the most severe inflammation, and may differ with severity of illness.

The effect of each treatment regime will be compared within subgroups stratified by different levels of inflammation, and different severity of illness at presentation.

1.3.2 Safety

Immunomodulatory drugs may increase risk of severe infection and be responsible for a range of side-effects. Known side-effects attributable to individual agents (such as hypertension from high dose steroids, and increased infection from individual agents) will be presented for comparison between treatment groups as absolute numbers and proportions.

1.3.3 Secondary diagnoses

Secondary diagnoses (e.g. macrophage activation syndrome) will be reported. It will not be possible to reliably ascertain whether their onset preceded primary treatment, thus any analysis by treatment group will be interpreted with caution.

1.3.4 Accounting for differences in severity at baseline between treatment groups

In order to account for differences in severity or duration of illness prior to initiation of treatment, we will use a propensity score (inverse probability) weighting approach.

1.3.5 Correction for multiple testing

Correction for multiple testing will be undertaken for primary outcomes.

1.3.6 Subsequent analyses

It is expected that larger sample sizes accrued through ongoing enrolment will allow evaluation of the effects of less common treatments (such as biological agents) and second-line treatments. These analyses will follow the principles outlined here, and second-line treatments will require weighting for time-varying confounders. Sample size and power calculations will be performed based on the first preliminary analysis of data, and the statistical analysis plan will be updated.

2 Preliminary analysis plan

2.0.1 Access to data

Prior to preparing the preliminary analysis plan, data was explored for the purpose of data validation and quality control. This included exploration of missingness and data distributions, including numbers receiving primary treatment combinations, and overall outcome progression post-treatment. In this way, appropriate means of analysis could be selected based on factors which could not be determined at the outset of the project. The preliminary analysis plan was prepared with full access to these preliminary extracts of the data from the database, but no exploration of the relationship between pre-treatment variables, treatment and outcomes was undertaken before finalising the analysis plan.

Analysis software

All data analysis will be undertaken in R version 4.0.2 utilising the packages:

- WeightIt for propensity weighting
- Cobalt for covariate balance analysis
- Survey for generalised linear modelling with robust standard errors

2.1 Description of the study cohort

2.1.1 Study enrolment Data

A descriptive analysis will be performed to summarize the number of countries and sites within each country that have enrolled onto the study, along with the number of patients from each country and site. Monthly enrolment numbers will be reviewed to assess uptake and study progress.

2.1.2 Demographic Data

Demographic data will be summarized in a table, including: gender (proportion male/female), age (mean and standard deviation), ethnicity, weight for age (z-scores), proportion with significant comorbidities, and country classification by income level (as defined by the World Bank classification)[1]. In addition to presenting the data for the population as a whole, further stratification will be done by diagnostic groups.

2.1.3 Clinical features and laboratory markers

Salient clinical features during the patient's admission will be summarized and tabulated, including: fever, sore throat, cough, respiratory distress, abdominal pain, diarrhea, vomiting, headache, encephalopathy, irritability, lethargy, and SARS-CoV-2 PCR status. We further present Kawasaki Disease features during admission including the presence of: rash, red lips, mucosal membrane changes, conjunctivitis, oedema, skin peeling, lymphadenopathy, and BCG reactivity.

Laboratory markers are summarized and tabulated showing mean and standard deviation and include: CRP, troponin, lactate dehydrogenase, D-Dimer, ferritin, white cell count, lymphocyte count, neutrophil count, platelets, creatinine, BNP, haemoglobin, prothrombin time, activated partial thromboplastin time, and fibrinogen. These clinical and laboratory marker data will be presented for the entire cohort and further stratified by diagnostic groups.

2.1.4 Missing data and interpolation

The level of care variables, which include ventilation, oxygen, and inotropes will be interpolated for missing days where preceding and following values are identical. Fever will also be similarly interpolated.

Where missing values fall between values of different levels (e.g. feature present and feature absent), variables will be regarded as missing. Where missing level of care data exists after a final value, if the final value indicates the specified treatment is not being received, subsequent daily values will be imputed as the same (e.g. no inotropes will be propagated to the end of the admission if it is the final value reported).

2.1.5 Approach to confounding and baseline differences

Where possible, analyses will be adjusted by propensity score weighting, using the covariate-balancing propensity score as the preferred approach. Multiple methods are available to generate propensity scores and the method selected will be the one producing the best covariate balance, aiming for absolute standardised mean differences of 0.1 and below, and Kolmogorov-Smirnov distances of 0.1 and below. Small subgroup analyses may not be suitable for propensity score weighting, or may require fewer covariates.

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[1] *https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups*

Pre-treatment covariates considered for inclusion in the propensity score model:

1. Transfer vs. admission
2. Treated in referring hospital
3. Age
4. Sex
5. Weight-for-age z-score greater than 2
6. Significant past medical history
7. Days since fever at admission
8. Days of admission at treatment
9. Total number of important clinical features reported up to day 0
10. COVID status: serology and PCR
11. Peak level of care up to day 0
12. Direction of change in level of care at day 0
13. Peak CRP up to day 0
14. Direction of change in CRP at day 0
15. Peak troponin up to day 0
16. Peak BNP up to day 0
17. Peak D-dimer up to day 0
18. Aneurysm status up to day 0

Inclusion of interaction terms and transformed variables will be explored if plausible and necessary to achieve covariate balance.

Where three or more treatment groups are large enough to compare, we will undertake multinomial propensity score weighting if adequate balance can be achieved without excessive weights (e.g. greater than 10). Where IVIG is included, it will be the reference category. Secondary comparisons will compare non-IVIG treatments in a pairwise manner.

If a multinomial approach is not appropriate due to inadequate balance or excessive weights, we will make primary binomial comparisons through separate PS weighting approaches. IVIG will be the reference group if included. Secondary analyses will consider other between-group comparisons.

We will obtain confidence intervals (and p values for primary analyses) using generalised linear models providing sandwich confidence intervals. The propensity matching covariates will be included to achieve double robust confidence intervals.

Statistical Analysis Plan – Analysis 1

Best Available Treatment Study

Introduction

This statistical analysis plan builds upon the general principles and specifics of the preliminary analysis plan in the study handbook.

At the time BATS was initiated, early in the pandemic, the number of potential treatments that would be used for MIS-C was unknown and it was therefore impossible to specify details of the major groups to compare. In addition because the proportion of patients requiring intensive care, inotropic ventilation, ventilatory support or dying was unknown in the first months after recognition of the syndrome our initial plan simply described the intention to use propensity based weightings for the analysis and left open the choice of final primary and secondary outcomes.

Prior to drafting the final analysis plan described below we explored the overall data to identify numbers of patients undergoing different treatments and interventions in order to select primary and secondary endpoints and the groups for comparison. No examination was undertaken of outcomes by treatment group, thus this scoping analysis to design the final analysis plan did not compromise comparison of different treatments in any way.

Data preparation

Data are entered in RedCap version 6.14.2. Included patients will be finalised on 24 February 2021, with subsequent data changes restricted to correction of errors and missing data. Subsequent processing and analysis will be undertaken in R version 4.0.2, using the packages WeightIt, Cobalt and Survey. Validation and correction of admission, discharge and immunomodulatory treatment dates will be undertaken. Data will be processed such that repeated clinical, laboratory and treatment variables are represented in a table with one row per patient-day.

Exclusions

Patients will be excluded from analysis if an admission date is unavailable, data is not entered on the treatment form, there is no daily data and no discharge date or the date of first immunomodulatory treatment was unclear.

Only patients treated from the day of admission or transfer will contribute outcomes for weighted analyses. Death, complications and secondary diagnoses can be reported unadjusted on patients including those treated in the days before transfer.

Missing data and interpolation

Level of care variables, including respiratory support and inotropes, and the clinical variable fever will be interpolated for missing daily data where preceding and following values are identical. Where missing data for respiratory support and inotropes follow a final value, if the final value indicates no support was needed, subsequent daily values will be considered to be the same.

Further, where total number of days of invasive ventilation, non-invasive ventilation, oxygen and inotropic support are available, missing data will be entered assuming no discontinuous periods of treatment (preliminary analysis shows a low frequency of multiple episodes of inotropes, ventilation or oxygen usage in complete data).

Merging consecutive admissions

Where multiple hospitals within one location report patients, we will inspect plots of admissions and ages to identify possible consecutive admissions. More detailed comparison of age, gender, weight, admission periods and laboratory and clinical variables will be used to confirm. Consecutive admissions will be merged into a single record by splicing daily data and taking initial admission baseline data and final admission outcomes.

Laboratory values

Each site will report laboratory variables in units prespecified in the data collection tool, or with alternative units. Conversion to the same units will be undertaken. Manual inspection of result distributions from individual sites will be used to identify and correct incorrect or discrepant units. Extreme outliers will be inspected on a per individual basis and corrected when the value is discrepant with the rest of the biomarker time course. Extreme outliers are those visibly far outside the range of most results.

Clinical severity scale

For each day of admission, clinical severity will be calculated on an ordinal scale:

1. Death
2. Extra-corporeal membrane oxygenation
3. Ventilated (invasive or non-invasive) and on inotropic support
4. Ventilated (invasive or non-invasive)
5. Inotropic support
6. Receiving oxygen
7. No supportive therapy CRP ≥ 50
8. No supportive therapy Unknown
9. No supportive therapy CRP < 50
10. Discharged
11. Transferred

Levels 3-10 will be considered for clinical improvement outcomes. The additional levels will aid in graphical presentation.

Demographics and baseline clinical data

Age is collected in years and additional months. Where additional months are missing they will be assumed to be zero. If age in years is missing and the data cannot be obtained, the child's age will be replaced with the median age in the cohort.

Patients' weight-for-age Z scores will be calculated from the WHO reference data using the RCPCH Growth API. The World Bank lending group classification will be used for country economic status.

Significant past medical history will be regarded as primary or secondary immunodeficiency, HIV, autoimmune disease, chronic lung disease, chronic neurological disorder or malignancy.

Treatment definitions

Patients will be grouped according to first treatments received on the same calendar day. Those receiving IVIG alone, steroids alone or IVIG and steroids in combination, will be selected for comparison in this first analysis as these are accumulating the greatest proportion of patients. IVIG alone will be taken as the reference category.

Primary outcome definitions

Inotropic support, ventilation and death (dichotomous)

Inotropic support and ventilation (invasive or non-invasive) at any time from the second day post-treatment, or death at any time. Inotropic support and ventilation will be regarded as not available if the patient was transferred or died on day one or two, without report of support being received on day 2. If the patient was discharged on day 1 or 2, the outcome will be regarded as negative. Death will be regarded as missing for all transferred patients, and as negative for all patients whose destination was not recorded.

Improvement at day 2 (dichotomous)

Improvement at day 2 will be reported relative to day 0 for:

- Any patient who was discharged on or before day 2
- Patients stepped down from ventilation or inotropic support
- Patients not ventilated or on inotropes who stepped down from oxygen
- Patients not receiving organ support whose CRP fell from above 50 mg/l on or before the day of treatment to below 50 mg/l.

Improvement will be regarded as unknown if a patient was transferred on or before day 2, and negative for a patient who died on or before day 2.

Sensitivity analyses

Two planned sensitivity analyses will be undertaken:

- Patients fully meeting the WHO criteria for MIS-C
- Defining primary treatment as all immunomodulatory treatments administered over two consecutive days (day 0-1)

Additional sensitivity analyses described in the study handbook are preserved for future analyses with larger cohorts.

Subgroup analyses

No subgroup analyses are planned for this analysis, though *post-hoc* exploratory analyses may be undertaken.

Correction for multiple testing

This will be undertaken using the Bonferroni-Holm method for the two primary outcomes

Secondary outcomes definitions

Failure/escalation of primary treatment

Defined as the addition of any immunomodulator from the first day after primary treatment. For patients receiving corticosteroids within primary treatment, an escalation of more than 5 mg/kg prednisolone equivalent in total daily dose will be required for further steroid usage to class as failure. If transferred before the fifth day following primary treatment, failure will be regarded as not available.

Time to improvement in clinical severity

For each patient the time to improvement in clinical severity was calculated as:

- Time to come off ventilator or inotropes for patients receiving both therapies
- Time to come off ventilator for patients ventilated
- Time to come off inotropes for patients receiving inotropes
- Time to come off oxygen for patients receiving oxygen
- Time for CRP to fall below 50 mg/l for patients with final CRP on day of treatment or earlier of greater than or equal to 50 mg/l
- Time until discharge for all patients, where other event did not precede
- Time to come off ventilator

Death

As defined in composite primary outcome.

Fever

Presence of fever at any point from day 2. If no fever reported, but missing data, the outcome will be regarded as not available.

Increase in level of support:

This was based on any commencement of:

- ECMO for patients not on ECMO on day 0
- Ventilation for patients not ventilated on day 0
- Inotropic support for patients not ventilated on day 0
- Oxygen for patients not on oxygen on day 0

Where none of the above led to classification of deterioration, death was regarded as deterioration and transfer was regarded as the outcome being unavailable. Patients discharged home or with unreported discharge destination were regarded as not having increased support.

Persisting coronary artery dilatation

The presence of a coronary artery with Lopez z-score ≥ 2.5 or a report of aneurysm without z-score on the final echocardiogram, undertaken on the second or subsequent days following treatment. Will be regarded as not available if no echocardiogram reported, and negative if echocardiogram reported with no aneurysm or z-score ≥ 2.5. Presence of pre-treatment coronary artery dilatation will be added as a balancing covariate.

Inflammatory markers

Inflammatory markers will be plotted as percentages of the peak value, per patient, throughout the course of their admission. Line plots will be weighted by covariate-balancing propensity scores as described below. Smoothed curves with confidence intervals will be plotted using a generalized additive model (geom_smooth from the ggplot2 package in R).

Complications of drug therapy

Complications deemed by the treating clinician to be the result of immunomodulatory treatment, including but not limited to: allergy/anaphylaxis, cataracts, gastric perforation, gastric ulceration, hip necrosis, hyperglycaemia, hyperlactataemia, opportunistic infection, profound bradycardia, psychosis and steroid-induced hypertension. These will be reported descriptively.

Left ventricular dysfunction

The presence of left ventricular dysfunction on any echocardiogram 24 hours after commencement of primary immunomodulatory treatment. For this analysis, the presence of left ventricular dysfunction prior to starting immunomodulatory treatment will be added as an additional covariate for calculation of propensity scores to control for confounding due to potential differences in pre-treatment prevalence in each of the treatment arms.

Study enrolment Data

A descriptive analysis will be performed to summarize the number of countries and sites within each country that have enrolled onto the study, along with the number of patients from each country and site. Monthly enrolment numbers will be reviewed to show uptake and study progress.

Analysis

Descriptive analyses

Demographic data

Demographic data will be summarized in a table, including: gender (proportion male/female), age (mean and standard deviation), ethnicity, weight for age (z-scores), proportion with significant comorbidities, and country classification by income level (as defined by the World Bank classification). In addition to presenting the data for the population as a whole, further stratification will be done by diagnostic groups. This will include patients not have all the WHO criteria, and patients excluded from WHO criteria due to bactereamia or reported toxic shock syndrome.

Clinical features and laboratory markers

Salient clinical features during the patient's admission will be summarized and tabulated, including: fever, sore throat, cough, respiratory distress, abdominal pain, diarrhea, vomiting, headache, encephalopathy, irritability, lethargy, and SARS-CoV-2 PCR status. We further present Kawasaki Disease features during admission including the presence of: rash, red lips, mucosal membrane changes, conjunctivitis, oedema, skin peeling, lymphadenopathy, and BCG reactivity.

Laboratory markers are summarized and tabulated showing mean and standard deviation and include: CRP, troponin, lactate dehydrogenase, D-Dimer, ferritin, white cell count, lymphocyte count, neutrophil count, platelets, creatinine, BNP, haemoglobin, prothrombin time, activated partial thromboplastin time, and fibrinogen. These clinical and laboratory marker data will be presented for the entire cohort and further stratified by diagnostic groups.

Confounding

All primary outcomes, sensitivity analyses, and secondary outcomes (excluding death, secondary diagnoses and complications) will undergo analysis following weighting by multinomial covariate-balanced propensity scores[1] to control for baseline confounding factors, as implemented by WeightIt version 0.11.0, using the "just-identified" approach. The Average Treatment Effect (ATE) will be estimated, except when comparing inflammatory markers between treated and untreated patients, when the Average Treatment Effect in the Treated (ATT) will be calculated with the untreated group as the reference due to the likely dissimilarity of a smaller untreated group and the need to preserve the full sample.

The following variables will be considered for balancing:

1. Transfer vs. admission (dichotomous)
2. Treated in referring hospital (dichotomous)
3. Age (continuous)
4. Sex (binary)
5. Weight-for-age z-score greater than 2 (binary with missingness indicator)
6. Significant comorbidity (binary)
7. Days since fever at admission (continuous with missingness indicator)
8. Days of admission at treatment (continuous)
9. Total number of important clinical features reported up to day 0 (continuous)
10. COVID status: PCR positive, serology positive (if not PCR positive) or no positive result
11. Peak clinical severity to day of treatment (categorical)
12. Direction of change in clinical severity at day of treatment: increasing, stable, decreasing or unavailable (categorical)
13. Peak CRP up to day of treatment (quartile, or missing)
14. Direction of change in CRP at day of treatment (increasing, decreasing or unavailable)
15. Peak troponin up to day of treatment (quartile, or missing)
16. Peak BNP up to day of treatment (quartile, or missing)
17. Peak D-dimer up to day of treatment (quartile, or missing)
18. Coronary artery status up to day of treatment: last Z score ≥ 2.5, last Z score < 2.5, or not available

This will be reduced based on data availability and clinical priority as determinants of treatment and outcome. Important covariates will be added for certain secondary analyses as described above.

Balancing will be repeated for every analysis on the population providing the outcome. No imputation for missing outcome data will be undertaken.

We will aim for absolute standardised mean differences of 0.1 in continuous variables, and below, and Kolmogorov-Smirnov distances of 0.1 and below. Love plots will be used to examine the extent of imbalance and consider the potential impact. We will tolerate some deviation since covariates are also included in outcome models.

Models

Modelling approaches producing robust sandwich standard errors will be used, with dichotomous outcomes to be analysed using the survey package, adding all covariates used in covariate balancing, to produce doubly-robust estimates. Generalised linear models with a quasibinomial link function will be used to estimate odds ratios and 95% confidence intervals.

Time to event analyses will be undertaken using weighted Cox proportional hazards model[2] estimated average hazard ratios. This allows for violation of the proportional hazards assumption.

Clinical severity over time

Clinical severity over time will be presented as proportional column charts from two days before treatment to 10 days after treatment. Only patients treated after day 1 will contribute severity data for preceding days, since patients treated on day 1 of admission will provide no severity data for pre-treatment days. The charts will be presented both unadjusted and weighted by the covariate-balanced propensity score.

References

1. Imai, K. & Ratkovic, M. Covariate balancing propensity score. *J. R. Stat. Soc. Ser. B Stat. Methodol.* **76**, 243–263 (2014).
2. Schemper, M., Wakounig, S. & Heinze, G. The estimation of average hazard ratios by weighted Cox regression. *Stat. Med.* **28**, 2473–2489 (2009).

Summary of changes

BATS statistical analysis plan

Document 1 (submitted with the original abstract for consideration of rapid review) described the overarching approach for the BATS study through multiple rounds of analysis as the database size grows, and more treatments and treatment patterns are able to be considered ("general approach"). The second section outlined the methods for this first analysis (referred to as preliminary therein).

Document 2 ("Statistical analysis plan – Analysis 1") describes in detail the implementation and specifics of the analysis plan.

Changes comprise:

- Date of data finalisation specified
- Data completeness-based exclusion criteria specified
- Three primary treatment groups specified
- Timing of treatment-based eligibility for propensity-weighted analyses specified
- Missing level-of-care data processes based on total days of supportive therapy
- Process for merging consecutive admissions described
- Process for normalising units of laboratory results and dealing with outliers
- Description of process for dealing with missing age data
- Description of process for calculating weight-for-age z-scores.
- Definition of significant past medical history
- Addition of "No supportive therapy Unknown" CRP level to ordinal scale
- Full definitions of primary and secondary outcomes
- Left ventricular dysfunction added as secondary outcome
- Reduction of planned sensitivity analyses
- Removal of proposed subgroup analyses
- Ordinal scale distribution redefined for graphical presentation only
- Detail on process for reducing covariates for balancing
- Removal of inappropriate criterion for specification of excess weights (absolute value of 10)
- Specification of approach for comparing inflammatory markers between treated and untreated patients