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# Swissped-RECOVERY – An Approach for the Interpretation of Non-randomised Treatment in an Open-label Randomised Controlled Trial in Paediatric Inflammatory Multisystem Syndrome Temporally Associated with SARS-CoV-2 (PIMS-TS)



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**Original Article**

# Swissped-RECOVERY – An Approach for the Interpretation of Non-randomised Treatment in an Open-label Randomised Controlled Trial in Paediatric Inflammatory Multisystem Syndrome Temporally Associated with SARS-CoV-2 (PIMS-TS)

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## Abstract

**Objectives:** In trials of acute severe infections or inflammations frequent administration of non-randomised treatment (i.e., intercurrent event, ICE) in response to clinical events is expected. These events may affect the interpretation of trial findings. Swissped-RECOVERY was set-up as one of the first open-label randomised controlled trials (RCT) worldwide, investigating the comparative effectiveness of anti-inflammatory treatment with intravenous methylprednisolone or intravenous immunoglobulins in children and adolescents with Paediatric Inflammatory Multisystem Syndrome Temporally Associated with SARS-CoV-2 (PIMS-TS). We present one approach towards improving interpretation of non-randomised treatment in an RCT.

**Design:** Pre-planned ancillary analysis of the Swissped-RECOVERY trial an investigator-initiated randomised multicentre open-label two-arm trial (intravenous methylprednisolone versus intravenous immunoglobulins) in children hospitalised with PIMS-TS at ten Swiss paediatric hospitals

**Interventions:** All patient-first ICEs, if applicable, were presented to an independent adjudication committee consisting of four international paediatric COVID-19 experts to provide independent clinical adjudication to a set of standardised questions relating to whether additional non-randomised treatments were clinically indicated and disease classification at the time of the ICE.

**Results:** Of 41 treatments in 75 participants (24/41 (59%) and 17/41 (41%) in the intravenous methylprednisolone and immunoglobulin arms of the trial, respectively), two-thirds were considered indicated. The most common treatment (oral glucocorticoids, 14/41, 35%) was mostly considered not indicated (11/14, 79%), although in line with local guidelines. ICEs among patients with Shock-like PIMS-TS at baseline were mostly considered indicated. A significant proportion of patients with undifferentiated PIMS-TS at

baseline were not attributed to the same group at the time of the ICE (6/12 unchanged, 4/12 KD-like at time of ICE, 2/12 Shock-like).

**Conclusion:** The masked adjudication of ICEs contributes to the interpretation of results in open-label trials and should be consistently incorporated in the future.

**Trial registration:** Swiss National Clinical Trials Portal (SNCTP000004720) and clinicaltrial.gov (NCT 04826588)

## Strengths and Limitations of this study

- This is one of the first prospective randomised controlled trials in patients with PIMS-TS worldwide.
- These anxillary analyses were pre-planned and the non-randomised events of interest were defined a priori for further evaluation. Which results in an improvement of the interpretation of the trial findings.
- Four international PIMS-TS experts reviewed the charts in a masked process. Their reviews proved valuable to provide independent assessment on whether non-randomised anti-inflammatory treatment was likely given as treatment for persistent or progressive PIMS-TS.
- The small sample size and the fact that only patient-first ICEs, excluding subsequent ICEs and excluding patients not experiencing ICEs, were adjudicated by the committee is a limitation of the study.

**Funding and Declaration of interests:**

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## Introduction

In trials of acute severe infections or inflammatory syndromes, frequent administration of non-randomised treatment in response to clinical events is expected. In the terminology of the ICH E9(R1) Addendum on Estimands and Sensitivity Analyses in Clinical Trials, these are defined as *Intercurrent Events* (ICEs) [1]. ICEs take place after randomisation and may affect the interpretation of trial findings. They can be a source of bias if knowledge of allocated treatment differentially affects post-randomisation patient management. The ICH Addendum outlines the importance of explicit pre-planned identification and handling of ICEs to enable all clinical questions addressed by a trial to be answered fully and robustly.

Here, we present one approach applied in a recent pragmatic open-label randomised trial (Swissped-RECOVERY) investigating the comparative effectiveness of first anti-inflammatory treatment with intravenous methylprednisolone (IVMP) or intravenous immunoglobulins (IVIG) in children and adolescents with Paediatric Inflammatory Multisystem Syndrome Temporally Associated with SARS-CoV-2 (PIMS-TS) [2,3]. Patients with PIMS-TS exhibit clinical and laboratory signs of inflammation together with single or multiple organ-dysfunction, in presence of confirmed or suspected previous exposure to or infection with SARS-CoV-2 [3]. In Swissped-RECOVERY we expected non-randomised anti-inflammatory treatments to be common and were interested in differentiating between patients experiencing these because of on-going or progressive inflammation (considered clinically indicated and potentially related to effectiveness of randomised treatments), and those in whom a clear clinical reason for additional non-randomised anti-inflammatory treatment was lacking. We put in place an independent adjudication committee (IAC) to evaluate these ICEs, masked to randomised and received non-randomised treatment. Here, we describe and interpret the adjudication results, including indicated and non-indicated ICEs and a comparison between randomisation arms.

## Methods

*Study design*

This is a pre-planned ancillary analysis of the Swissped-RECOVERY trial (Swiss National Clinical Trials Portal (SNCTP000004720) and clinicaltrial.gov (NCT 04826588)), an investigator-initiated randomised multicentre open-label two-arm trial (IVIG vs IVMP) in children hospitalised with PIMS-TS at ten Swiss paediatric hospitals (Aarau, Basel, Bellinzona, Bern, Fribourg, Geneva, Lausanne, Lucerne, St. Gallen, and Zurich) [2]. The study was approved by the lead ethics committee (Ethics Committee Northwest and Central Switzerland; and other responsible ethics committees in Switzerland. Informed consent has been obtained. We aimed to determine clinical indication of ICEs according to masked IAC consensus as the gold standard.

*Patient and Public Involvement*

Given the expedited process of setting up this trial due to the developments of the pandemic it was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of our research.

*Definition of Intercurrent Events*

ICEs of interest were defined *a priori* in a dedicated IAC charter (Supplement) as non-randomised anti-inflammatory treatments including additional or fewer doses of the randomised treatment, IVMP in the IVIG group and vice versa, biological treatment and any oral tapering of glucocorticoids. Patients experiencing at least one of these were presented to the IAC.

*Masked independent adjudication committee*

The IAC consisted of four international PIMS-TS experts who met virtually in five sessions between June 6, 2022, and August 9, 2022. The work of the IAC was governed by a dedicated charter (Supplement), and in line with this, at least two members had to be present at each meeting. All chronologically first ICEs per patient were assessed, meaning if one patient experienced multiple ICEs, clinical indication was adjudicated only for the first non-randomised anti-inflammatory treatment. Masked narratives were prepared and presented by a non-independent facilitator (TW), who did not contribute to the discussions about clinical indication but provided further information upon IAC request. IAC consensus decisions were required and recorded directly into a designated form on the electronic data capture system REDCap™.

*Configuration of ICE narratives*

The case narratives presented to the IAC included baseline *general information* (patient demographics, known exposure to a SARS-CoV-2 case, estimated number of weeks since SARS-CoV-2 exposure and underlying comorbidities), *clinical characteristics* (organ involvement, vital signs, need for inotropes, respiratory support or fluid resuscitation), *cardiological examinations* (electrocardiogram, echocardiogram), *laboratory parameters* (SARS-CoV-2 PCR and serology, haematology, coagulation and biochemical markers), and follow-up information for these variables until the ICE. All narratives were carefully masked regarding randomised treatment and non-randomised treatment received. The time point of the ICE was shown as 'during trial treatment + x hours' to avoid unmasking resulting from differential duration of IVIG (one dose) and IVMP (one daily dose for three consecutive days).

*Adjudication details*

The IAC adjudicated ICEs starting with disease classification at the time of the ICE, defined as in the Best Practice Recommendations for the Diagnosis and Management of PIMS-TS in Switzerland [4]: i) Shock-like PIMS-TS, ii) KD-like PIMS-TS, iii) undifferentiated PIMS-TS, and iv) other disease; in case of iv), no further adjudication was required. The IAC was aware of the site investigator's allocation at baseline but not at the time of the ICE. For i-iii) the first question was followed by the likelihood that the ICE was clinically indicated: i) definitely >80%, ii) probably 51-80%, iii) unlikely 21-50%, iv) not <21%, v) too little information. ICEs classified as v) were re-presented to the IAC upon receipt of additional narrative information. ICEs considered to be in category i) or ii) were classified as "clinically indicated".

*Statistical analysis*

Exploratory description of baseline patient characteristics was summarised using the number (percentage) for categorical variables and the median (inter-quartile range [IQR]) for continuous variables. Between group differences were investigated using the chi-square test for categorical variables and the Wilcoxon rank sum test for continuous variables.

A statistical significance level of 5% was considered statistically significant throughout. All analyses were performed in R (version 4.2.2) [5].

## Results

Between May 21, 2021, and April 15, 2022, a total of 76 patients were enrolled. Of these, 75 patients were included for the primary analysis (37 were allocated to IVMP, 38 to IVIG). Detailed information on the cohort, including baseline characteristics, is presented in the original publication [6].

*Non-randomised anti-inflammatory treatment*

In total, 41 ICEs were adjudicated. In the IVMP arm, 24/37 (65%) patients experienced at least one ICE, compared to 17/38 (45%) in the IVIG arm (p=0.13).

The most common first ICE was oral glucocorticoids, with or without tapering, accounting for 14/41 (34%) ICEs (11/24 (46%) in the IVMP and 3/17 (18%) in the IVIG arm). Further first ICEs occurred because of addition of non-randomised treatment, including IVMP >3 days or >10 mg/kg; IVMP in case of IVIG randomisation or vice versa, IVIG >2 g/kg or >1 dose and intravenous or subcutaneous anakinra administration. Figure 1

*Independent adjudication committee findings*

Non-randomised anti-inflammatory treatment was considered clinically indicated by the IAC for 27/41 (66%) patients (13/24 (54%) in the IVMP arm, 14/17 (82%) in the IVIG arm). Overall, there was a trend towards a greater proportion of clinically indicated ICEs among patients in the IVIG arm (p=0.061). Non-indicated ICEs in the IVMP arm were dominated by receipt of oral glucocorticoids (10/11; 91%). Non-indicated ICEs were rare in the IVIG arm (3/17; 18%) and comprised in two cases of switch to IVMP and in one case of addition of oral glucocorticoids. Figure 1

A different pattern of ICEs and their clinical indication was observed among patients with the three phenotypes of PIMS-TS (Table 1). ICEs among patients with Shock-like PIMS-TS at baseline were mostly considered indicated. For patients with KD-like PIMS-TS at baseline, 7/8 ICEs among patients randomised to IVIG were considered indicated, in contrast to only 2/6 among patients randomised to IVMP. ICEs were more common among patients with undifferentiated PIMS-TS at baseline and allocated to IVMP (10/12) compared to IVIG (2/12). Of note, while patients considered to show a Shock- or KD-like clinical phenotype at baseline most displayed the same phenotype at the time of receipt of non-randomised anti-

inflammatory treatment (12/15 Shock-like patients, 11/14 KD-like patients), this was not the case for the undifferentiated PIMS-TS group (6/12 unchanged, 4/12 KD-like at time of ICE, 2/12 Shock-like). Figure 2

*Clinical and laboratory characteristics of patients with ICEs*

Whereas there was a difference in baseline characteristics for patients with and without ICEs in lymphocytopaenia, thrombocytopaenia, ferritin, D-Dimers and need for inotropic support, no such difference was observed when comparing baseline characteristics of patients with a clinically indicated vs non-indicated ICE, apart from a longer fever duration in patients with a clinically indicated ICE. Table S1

## Discussion

Swissped-RECOVERY was the first research group publishing data from an RCT on medical interventions in patients with PIMS-TS. As expected, in such a pragmatic, open-label trial that was set-up in an expedited process, non-randomised anti-inflammatory treatment was common, and presented challenges for the interpretation of the trial results. Masked end-point review committees have been used in open-label trials to mitigate against bias in endpoint assessment [7,8]. Analogously, we involved an IAC to provide independent adjudication on the necessity/indication for non-randomised treatments. This information can then be incorporated in to pre-specified analyses of the main trial results.

The IAC considered two out of three ICEs observed in the trial clinically indicated, mostly in children presenting with Shock-like PIMS-TS patients and in those with KD-like PIMS-TS when allocated to IVIG. However, the IAC also identified one in three ICEs as not clinically indicated. Those ICEs predominantly comprised of added oral glucocorticoids and were most likely based on local guidelines rather than clinical necessity. We identified rapid reporting of primary and secondary endpoints from an interventional RCT in PIMS-TS, an emerging

disease with a potentially high global impact, as an utmost priority. Therefore, we decided to report additional findings from the IAC on ICEs separately from the main trial publication.

ICEs that were identified as nonindicated may reflect variability in regional practice and evolution of local, national and international guidelines during the trial. For example, administration of tapering oral corticosteroids was commonly reported and usually considered to be unnecessary by the IAC but has been included in guidelines [4] (predominately related to existing recommendations for treatment of KD [9]).

Disease classification and severity also seem to be associated with clinical decision-making, leading to non-randomised treatment usually being considered indicated among patients with Shock-like PIMS-TS. PIMS-TS is difficult to distinguish from KD. IVIG is standard treatment for KD [10] and so may have been added to the allocated treatment in a proportion of patients randomised to IVMP, due to investigator concern about under-treating possible KD. Such non-randomised treatment was usually considered non-indicated.

IAC interpretation of ICEs in Swissped-RECOVERY had several limitations. First, narratives had to be presented in a way that prevented inferences on allocated treatment and unmasking of the exact nature of the ICE. This limited information available to the IAC, potentially impacting their adjudication. Second, IAC reviews rely on clinical expertise of independent members. Since PIMS-TS was an emerging disease at the time of the trial, the IAC members had limited evidence available to inform management, potentially leading to more permissive adjudication relying on experience and expertise alone. Furthermore, IAC reviews occur in a somewhat artificial setting where experts adjudicate ICEs in a virtual meeting in contrast to clinicians making bedside decisions. Fourth, only patients' first ICEs were reviewed. A review of all ICEs may have provided further insight into management of PIMS-TS patients

in the trial but would have substantially increased the complexity of the review process. Fifth, the IAC was not asked to adjudicate the management of patients not experiencing ICEs. This may theoretically have identified patients who should have, in the view of the IAC, received additional anti-inflammatory treatment, adding to the interpretation of trial findings. Lastly, the analyses considering phenotype classification rely on the classification at baseline. However, especially for undifferentiated PIMS-TS, there is a substantial proportion of cases being re-classified by the IAC, which might further impact the interpretation of the results.

The previously published trial results showed no difference in the primary outcome of length of hospital stay between IVMP and IVIG [6]. A posthoc analysis of the data including ICEs, incorporating the IAC assessment, also indicated no differences (Atkinson A and Bielicki JA, submitted). With 54.7 % of patients receiving non-randomised anti-inflammatory treatment, there is a risk of many patients converging on a single treatment or being exposed to both treatments, reducing the informativeness of the trial. Alternative or complementary strategies are the utilisation of sequential randomisation as well as attempts to minimise clinically unwarranted non-randomised anti-inflammatory treatments, for example through rigorous training and increased documentation requirements for ICEs. Neither of these strategies would have been compatible with the pragmatic nature of the trial.

Overall, IAC reviews proved valuable to provide independent assessment on whether non-randomised anti-inflammatory treatment was likely given as treatment for persistent or progressive PIMS-TS. Such assessments should be considered in the context of the Estimand Framework in future trials, and will help to improve interpretation of trial findings.

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**Contributors:**

JB, TW and CS planned and implemented the masked review of intercurrent events. JB and NS contributed to the first draft, approved the final version, and take responsibility for the accuracy of reported findings. AB, KW, AT, PR, TW, LS, AA and CS contributed to the draft and approved the final version. CS performed the analysis and is the data manager for Swissped-RECOVERY.

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## Data Presentation

This data has been submitted as an abstract and accepted as a poster at the Annual Meeting of the European Society of Paediatric Infectious Diseases (ESPID) in Lisbon 2023.

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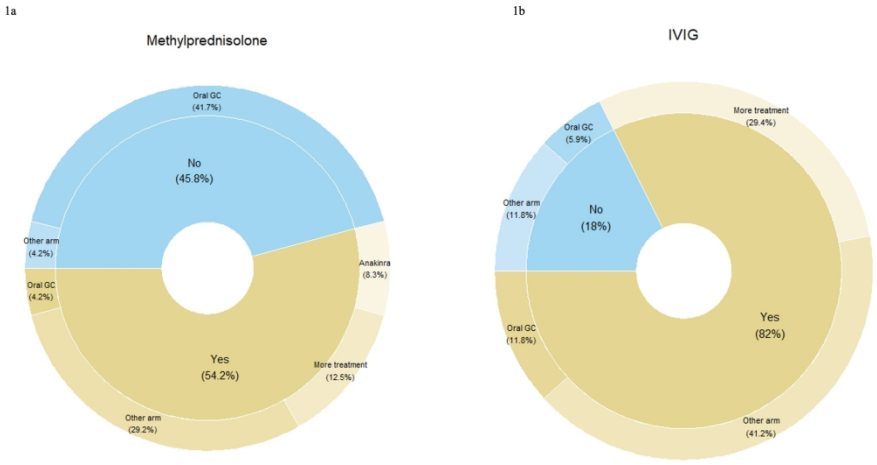


Figures 1a and 1b: Independent adjudication committee findings for intercurrent events of additional anti-inflammatory treatment in patients allocated to the intravenous methylprednisolone arm (IVMP, 1a) or to the intravenous immunoglobulin arm (IVIG, 1b).
1a: A total of 24 intercurrent events reported; considered clinically indicated 13/24, with administration of IVIG in 7/13 clinically indicated ICEs; considered non-indicated 11/24, with administration of oral glucocorticoids in 10/11 non-indicated ICEs.
1b: A total of 17 intercurrent events reported; considered clinically indicated 14/17 with administration of IVMP in 7/14 clinically indicated ICEs; considered non-indicated 3/17.
ICE: intercurrent event, IVIG: intravenous immunoglobulins, IVMP: intravenous methylprednisolone, GC: glucocorticoids.

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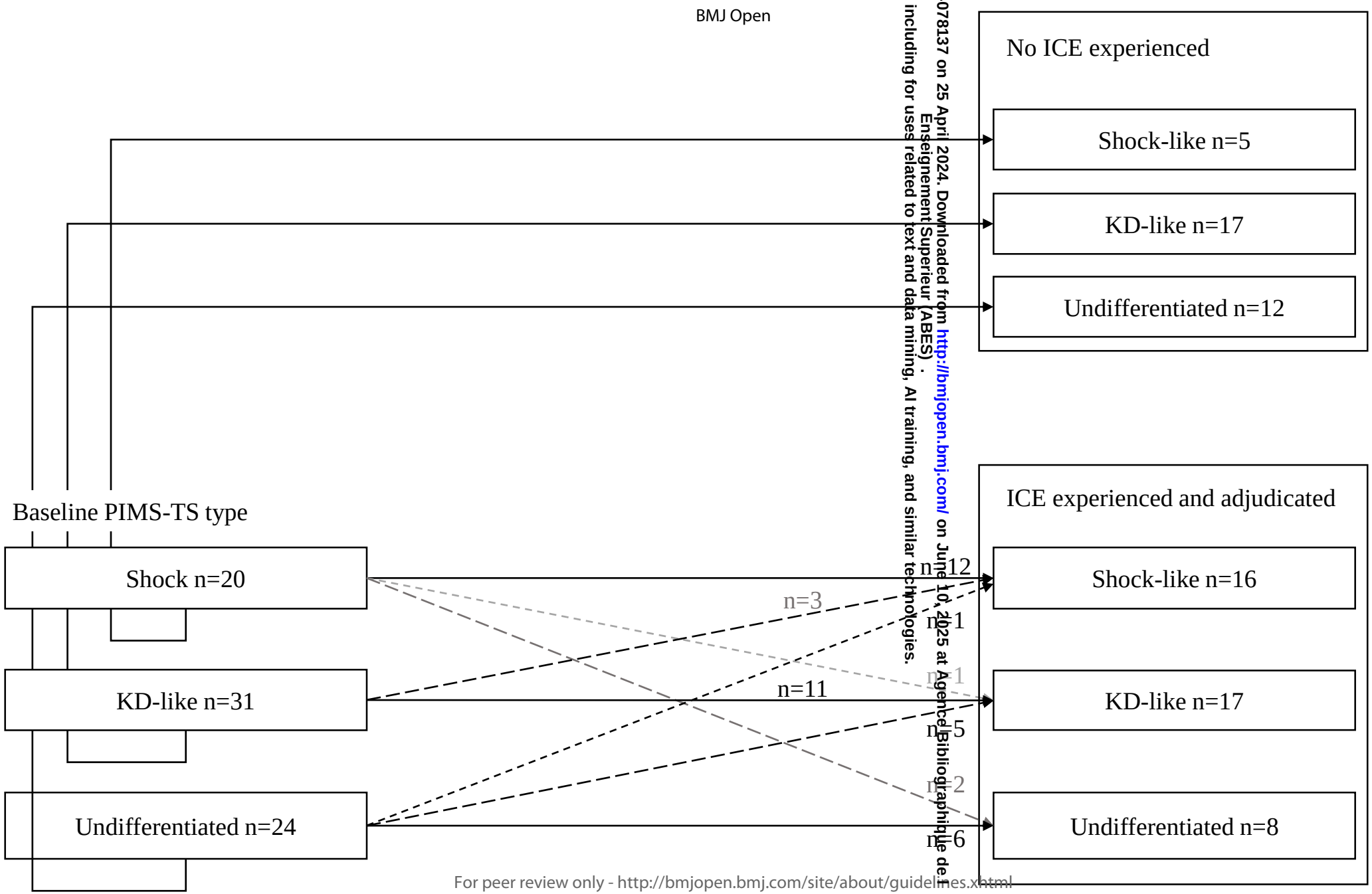


| | | | IVMP | IVIG |
|---|---|---|---|---|
| Entire trial cohort, | | | n=37 | n=38 |
| n = 75 | ICE | None | 13 (35%) | 21 (55%) |
| | | Indicated | 13 (35%) | 14 (37%) |
| | | Not indicated | 11 (30%) | 3 (8%) |
| Shock-like, | | | n=10 | n=10 |
| n = 20 | ICE | None | 2 (20%) | 3 (30%) |
| | | Indicated | 6 (60%) | 6 (60%) |
| | | Not indicated | 2 (20%) | 1 (10%) |
| KD-like, | | | n=15 | n=16 |
| n = 31 | ICE | None | 9 (60%) | 8 (50%) |
| | | Indicated | 2 (13%) | 7 (44%) |
| | | Not indicated | 4 (27%) | 1 (6%) |
| Undifferentiated, | | | n=12 | n=12 |
| n = 24 | ICE | None | 2 (16%) | 10 (84%) |
| | | Indicated | 5 (42%) | 1 (8%) |
| | | Not indicated | 5 (42%) | 1 (8%) |

**Tables S1a and S1b: Baseline characteristics stratified by presence or absence of an ICE (S1a) and stratified by the IAC consensus (S1b)**

1a

| N (%) for categorical variables, median [IQR] for continuous | **ICE** N=41 | **No ICE** N=34 | **p-value** |
|---|---|---|---|
| Age, years | 9.8 [6.6, 12.1] | 9.0 [6.2, 12.9] | 0.87 |
| Weight, kilogram | 32.0 [22.6, 40.5] | 28.0 [19.1, 38.1] | 0.65 |
| Fever duration, days | 3.0 [1.0, 4.0] | 2.5 [1.0, 4.0] | 0.53 |
| Any inotropes | 19 (46.3) | 6 (17.6) | 0.02 |
| Lymphocytes, G/l | 0.66 [0.47, 1.03] | 1.00 [0.64, 1.42] | 0.04 |
| Platelets, G/l | 127.00 [100.25, 166.00] | 179.50 [142.25, 260.75] | 0.004 |
| D-Dimers, ug/l | 4249.50 [1868.00, 6355.75] | 1840.00 [1233.50, 3491.25] | 0.01 |
| Ferritin, ug/l | 679.00 [447.25, 1095.75] | 247.00 [194.00, 488.00] | <0.001 |
| C-reactive Protein, mg/l | 169.50 [115.30, 230.65] | 140.50 [90.12, 199.00] | 0.13 |
| Troponin, ng/l | 11.00 [6.00, 25.80] | 24.00 [16.00, 55.10] | 0.05 |
| NTproBNP, pg/ml | 2418.50 [807.75, 7281.00] | 3330.00 [924.50, 7130.50] | 0.77 |

1b

| N (%) for categorical variables, median [IQR] for continuous | **ICE indicated** N=27 | **ICE non-indicated** N=14 | **p-value** |
|---|---|---|---|
| Age, years | 9.4 [8.1, 11.3] | 10.7 [6.2, 12.1] | 0.98 |
| Weight, kilogram | 32.2 [23.9, 37.8] | 32.0 [22.8, 41.8] | 0.99 |
| Fever duration, days | 1.0 [1.0, 2.0] | 3.0 [2.0, 5.0] | 0.02 |
| Any inotropes | 5 (35.7) | 14 (51.9) | 0.51 |
| Lymphocytes, G/l | 0.80 [0.70, 1.41] | 0.62 [0.45, 0.79] | 0.11 |
| Platelets, G/l | 116.50 [99.75, 133.25] | 137.00 [101.50, 177.00] | 0.31 |
| D-Dimers, ug/l | 2440.00 [1834.50, 5310.25] | 4458.50 [2306.75, 6747.25] | 0.27 |
| Ferritin, ug/l | 549.00 [444.00, 588.00] | 816.00 [552.00, 1297.00] | 0.08 |
| C-reactive Protein, mg/l | 137.00 [111.50, 230.30] | 182.30 [117.20, 235.50] | 0.66 |
| Troponin, ng/l | 13.00 [8.00, 34.00] | 10.50 [5.25, 25.00] | 0.69 |
| NTproBNP, pg/ml | 3212.50 [1360.75, 7683.50] | 1628.00 [697.00, 7199.50] | 0.51 |

2a: Difference in baseline characteristics for patients with and without ICEs in lymphocytopaenia, thrombocytopaenia, ferritin, D-Dimers and need for inotropic support.

2b: Difference in baseline characteristics for patients with a clinically indicated versus non-indicated ICE in longer fever duration.

ICE = intercurrent event, IAC = independent adjudication committee

# Swiss Pediatric Randomised Evaluation of COVID-19 Therapy (Swissped RECOVERY)

NCT: 04826588

## Blinded Review Committee Charter

Version 1.2, Date 18 July 2022

**Authorised by:**

| | | | |
|---|---|---|---|
| Name: | PD Dr. med. Julia Bielicki | Role: | Sponsor-Investigator |
| Signature: |  | Date: | 20.07.2022 |

**Prepared by**

| | | | |
|---|---|---|---|
| Name: | Dr. med. Tatjana Welzel | Role: | Trial Physician |
| Signature: |  | Date: | 18.07.2022 |

| CONTENT | DETAILS OF BRC |
|---|---|
| **1. Introduction** | |
| Name (& Sponsor's ID) of trial | Swissped RECOVERY |
| Objectives of trial, including interventions being investigated | Swissped-RECOVERY will compare the effectiveness of intravenous methylprednisolone 10 mg/kg/dose over three days versus intravenous immunoglobulins (IVIG) 2 g/kg as single dose in children and adolescents hospitalized with paediatric inflammatory multisystem syndrome-temporally associated with SARS-CoV-2 (PIMS-TS).<br><br>**Interventions**<br><br>Children and adolescents will be randomised to:<br><br>Randomisation 1: Methylprednisolone 10 mg/kg/dose (maximum dose 1000 mg per day) for three days once daily<br><br>Randomisation 2: IVIG 2 g/kg/dose (maximum dose 100 g) as a single dose given as a slow infusion<br><br>**Objectives**<br><br>*Primary objective:*<br>The primary objective is to compare the effect of study treatments on the duration of hospital stay after randomization.<br><br>*Secondary objectives*<br>Secondary objectives are to assess the effects of study treatments on<br>• all-cause mortality at 28 days or discharge from hospital (whichever occurs first).<br>• among patients *not* on invasive mechanical ventilation at baseline, the composite endpoint of all-cause death or need for invasive mechanical ventilation or ECMO.<br>• the need for ventilation support (excluding O2 supplementation).<br>• duration of invasive mechanical ventilation.<br>• among patients not on inotropes at baseline, the endpoint of need for any inotropic support.<br>• the need for renal replacement therapy.<br>• cardiac outcomes.<br><br>*Other objectives*<br>• To measure the rate of major bleeding and thrombotic events in the cohort and by study treatment.<br>• To explore the use and duration of rescue treatment in the cohort and by study treatment; as well as the use and duration of indicated rescue treatment as adjudicated by a blinded review committee.<br>• To explore changes in markers of inflammation (fever, C-reactive protein) in the cohort and by study treatment.<br>• To assess health status and functional outcome as measured by the SDQ 6 months post randomisation.<br>• To explore SARS-CoV-2 vaccination patterns and attitudes |

| CONTENT | DETAILS OF BRC |
|---|---|
| | towards SARS-CoV-2 vaccination prior and after enrolment in the trial. |
| Outline of scope of Charter | The purpose of this document is to describe the membership, terms of reference, roles, responsibilities, authority, decision-making and relationships of the Blinded Review Committee (BRC) for this trial, including the timing of meetings, methods of providing information to and from the BRC, frequency and format of meetings and relationships with other trial committees. |
| Facilitation | The Swissped-RECOVERY Trial Physician at the Paediatric Research center University Children`s Hospital of Basel (PRC UKBB) will be the Facilitator for the trial. The Facilitator will be responsible for the organisation of meetings and should be copied into all communications with and between the BRC. |
| **2. Roles and responsibilities** | |
| A broad statement of the aims of the BRC | To perform independent assessment of all administered immunomodulatory treatments other anti-inflammatory than randomized trial medication that might influence the trial primary endpoints. |
| Terms of reference | The primary endpoint for the Swissped-RECOVERY study is to compare the effect of study treatments on the duration of hospital stay after randomization.<br>Reason and clinical indication for any systemic anti-inflammatory treatment other than trial medication will be adjudicated by a Blinded Review Committee (BRC) to randomised allocations.<br>The role of the Swissped-RECOVERY BRC is to adjudicate if the non-trial systemic anti-inflammatory treatment was clinically indicated. |
| Specific roles of BRC | • Provide assessment of clinical events that might influence trial endpoints, as follows:<br>- adjudicate based on the clinical case vignettes<br>○ Disease classification<br>○ Likelihood that non-trial systemic anti-inflammatory treatment was indicated<br>○ if anti-inflammatory treatment is indicated<br>▪ Reason why<br>• Maintain confidentiality of all trial information that is not already in the public domain<br>• Review and approve the BRC form<br>• Review the BRC charter |
| **Trial specific BRC issues** | |
| Any issues specific to the disease under study | • The trial is open-label, however, the BRC will be blinded to the treatment allocation.<br>• Lack of information – for some events, a limited amount of clinical information may influence the BRC decision. If more detailed information not presented in the case vignettes is needed for the BRC assessment, this can be requested from the trial physician. In this case, the assessment must be delayed until the information is available<br>• Event date is the date of the non-trial systemic anti-inflammatory treatment administration. |

| CONTENT | DETAILS OF BRC |
|---|---|
| **3. Composition** | |
| Membership and size of the BRC | All members of the Swissped-RECOVERY BRC must be blinded to study treatment allocation. The BRC consists of independent members. The BRC Chair will be independent [1] of the trial (see section 5).<br>The members of the BRC for this trial are:<br>(1) Alasdair Bamford - BRC Chair (Independent)<br>(2) Adriana Tremoulet – Independent member<br>(3) Pablo Rojo Conejo – Independent member<br>(4) Kate Webb – Independent member<br>The membership of the BRC will be reviewed in situations where members can no longer fulfil their responsibilities or where a potential conflict of interest arises. |
| The Chair, how they are chosen and the Chair's role. | The Chair should be a medical practitioner and have previous experience of serving on review committees, experience of chairing meetings, and should be able to facilitate and summarise discussions; knowledge of the disease area (PIMS-TS) would be beneficial. |
| The responsibilities of the Facilitator | The Facilitator will be a member of staff at the PRC UKBB. The Facilitator will be responsible for arranging meetings of the BRC, producing and circulating agendas, minutes and action points. The facilitator will work with the data manager to produce a case summary for each event to be adjudicated before the meeting of the BRC. The Facilitator will be the central point for all communications between the BRC and other bodies, will be copied into all correspondence between BRC members and will be kept aware of BRC issues as they arise. |
| Whether members of the BRC will have a contract | BRC members will not be asked to formally sign a contract but should formally register their agreement to join the group by confirming (1) that they agree to be a member of the BRC and (2) that they agree with the contents of this Charter. Any potential competing interests should be declared at the same time. Members should complete and return the form in Annexe 1. Any observers (attendees who are not members and not part of the PRC UKBB) will sign a confidentiality agreement on the first occasion they attend a meeting (Annexe 2). |
| **4. Relationships** | |
| Advisory and executive bodies | The BRC is an oversight body and is delegated the roles in Section 2. |
| The need for BRC members to disclose information about any real or potential competing interests | Any competing interests, both real or potential, should be disclosed. These are not restricted to financial matters – involvement in other trials or intellectual investment could be relevant. Although members may well be able to act objectively despite such connections, complete disclosure enhances credibility (see Annex 1).<br>BRC members should not use any trial data to inform trading in pharmaceutical shares, and careful consideration should be given to trading in stock of companies with competing products. Changes in declarations of real or potential competing interests should be minuted at the start of each meeting. |

[1] Independence is defined in Table 1 of Annexe 1

| CONTENT | DETAILS OF BRC |
|---|---|
| **5. Organisation of meetings** | |
| Expected frequency of BRC meetings | The regularity of BRC meetings will depend upon the number of accumulated clinical events to be adjudicated and will be organised on an Ad Hoc basis, depending upon the availability of members. |
| Attendance of BRC members at meetings | Minimum attendance at BRC meetings in order to make adjudication decisions should ideally include the BRC chair together with at least one other member. If the chair is not available, the meeting can go ahead with another independent member of the BRC acting as a chair for the meeting. All meetings are planned as telephone conference.<br>The PRC UKBB Facilitator will work to identify meeting dates that enable maximum attendance of BRC members. |
| How BRC meetings will be organised including who will be present in each session | All meetings are planned as telephone conference. Presence will be usually limited to the BRC members, observers from participating sites in the trial and the Facilitator. Other attendees may be invited as observers by the BRC, too. Observers are not members of the BRC but may be invited to provide input. |
| Can BRC members who cannot attend the meeting input | All decisions will be made through discussion during the BRC meeting. However, BRC members who are unable to attend may provide their input ahead of the meeting by sending comments to the facilitator. |
| What happens to independent members who do not attend meetings | If an independent member does not attend a meeting or provide comments when requested between meetings, it should be ensured that the independent member is available for the next meeting. If an independent member does not attend the next meeting or provide comments when requested, they should be asked if they wish to remain part of the BRC. If an independent member does not attend a third meeting, strong consideration should be given to replacing this member. |
| **6. BRC documentation and procedures to ensure confidentiality and proper communication** | |
| Intended content of material to be considered during meetings | A case summary will be prepared by the data manager and facilitator for each event to be adjudicated. The case summary will contain the following:<br>• Blinded trial data relevant to adjudication of the event. This data will be downloaded from the trial database by the data manager<br>• Additional clinical narrative from PI, GP records or hospital notes, if available |
| Whether documentation will be available before the meeting or only at/during the meeting | Case summaries and reference documents (see annex 5) will be circulated in advance to all BRC members attending the meeting. |
| To whom the BRC will communicate the decisions made | (See Section 8) |
| What will happen to the papers after the meeting | BRC members are expected to delete, destroy or store securely copies of the provided case summaries, any reports or communications to and from the BRC and agenda and minutes. All documentation should be considered confidential. The PRC UKBB Facilitator will keep a central record of all minutes, reports and correspondence by the BRC. |

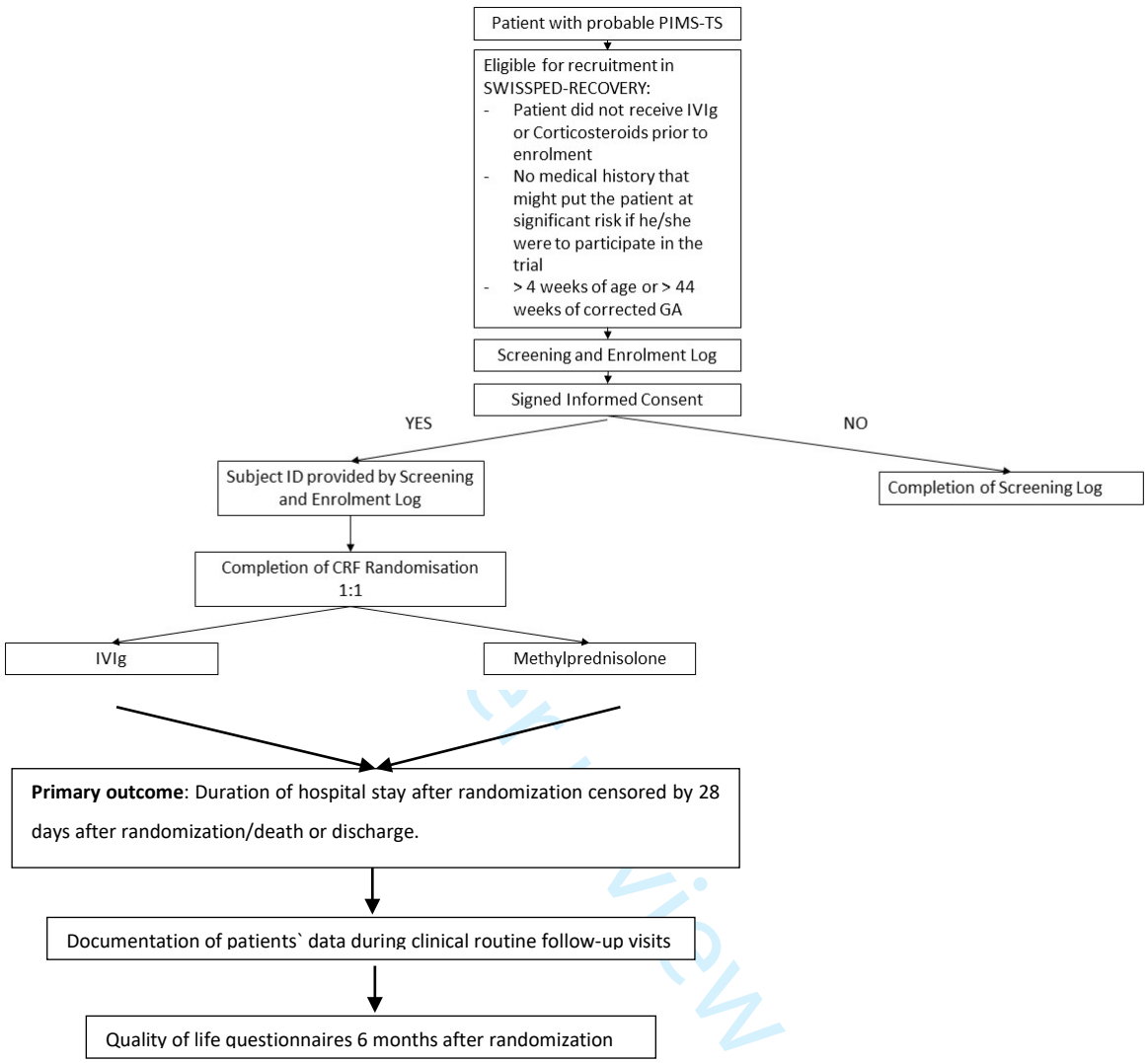
| CONTENT | DETAILS OF BRC |
|---|---|
| **7. Decision making** | |
| What is reviewed by the trial physician in advance of BRC meetings? | All events of non-trial systemic anti-inflammatory treatment reported by Swissped-RECOVERY trial sites. |
| What decisions are open to the trial physician in advance of BRC meetings | The information available for all events of non-trial systemic anti-inflammatory treatment will be screened by the trial physician in advance of a meeting of the BRC. Where the trial physician feels there is sufficient clinical information for a decision to be made by the BRC, the event will be referred to the BRC for review. Where it is felt there is insufficient clinical information for a decision, the event will be referred back to the reporting site for additional narrative and clinical information.<br>No adjudications on the endpoint will be made by the trial physician during this screening process. |
| What is reviewed at meetings of the BRC | All events of non-trial systemic anti-inflammatory treatment, referred by the trial physician following initial screening. |
| What decisions will be open to the BRC | Based on discussions within meetings of the BRC, for each event the following decisions should be made and recorded on the BRC form:<br>• Provide assessment of clinical events that might influence trial endpoints, as follows:<br>- adjudicate based on the clinical case vignettes<br>○ Disease classification<br>○ Likelihood that non-trial systemic anti-inflammatory treatment was indicated<br>○ if anti-inflammatory treatment is indicated<br>▪ Reason why<br>Guidelines for completion of the BRC form are provided in annex 4. |
| How decisions or recommendations will be reached within the BRC | The final decision will be made by members of the BRC present at the meeting. Every effort should be made to achieve consensus. The role of the Chair is to summarise discussions and encourage consensus; therefore, it is usually best for the Chair to give their own opinion last. |
| When the BRC is quorate for decision-making | (see section 5) |
| Any specific issues relating to the trial design that might influence the proceedings | (See Section 2) |
| **8. Reporting** | |
| To whom will the BRC report their recommendations/decisions, and in what form | The BRC will report their decisions using the approved BRC form (see annex 4 for guidelines on completion of the BRC form). A paper example of the BRC form will be sent with the meeting agenda via facilitator for illustrative purposes. The BRC form is programmed in Redcap and will be filled in electronically supported by the facilitator during the meeting.. A central log of all BRC adjudications and the decisions made will also be stored securely by the facilitator.<br>Following a meeting of the BRC, all completed BRC forms will be reviewed by the facilitator and/or data manager. Any resulting queries will be raised with the BRC for resolution at a subsequent |

| CONTENT | DETAILS OF BRC |
|---|---|
| | meeting. |
| **9. After the trial** | |
| The information about the BRC that will be included in published trial reports | BRC members will be named and their affiliations listed in the main report, unless they explicitly request otherwise. |
| Any constraints on BRC members divulging information about their deliberations after the trial has been published | The BRC members should not discuss issues relating to their involvement in the trial until 12 months after the primary trial results have been published. |

**Abbreviations and glossary**

| | |
|---|---|
| AE | Adverse event |
| AR | Adverse reaction |
| CF | Consent form |
| BRC | Blinded Review Commitee |
| CI | Chief Investigator |
| CRF | Case Report Form |
| CTA | Clinical Trials Authorisation |
| DMC | Data Monitoring Committee |
| HE | Health Economics |
| IB | Investigator's Brochure |
| IDMC | Independent Data Monitoring Committee |
| ISRCTN | International standard randomised controlled trial number |
| MHRA | Medicines and Healthcare products Regulatory Authority |
| MRC | Medical Research Council |
| NHS | National Health Service |
| PI | Principal Investigator |
| PIS | Patient information Sheet |
| PIMS-TS | Paediatric inflammatory multisystem syndrome-temporally associated with SARS-CoV-2 |
| QL | Quality of life |
| SAE | Serious adverse event |
| SAR | Serious adverse reaction |
| SOP | Standard operating procedures |
| SPC | Summary of product characteristics |
| SSA | Site specific assessment |
| SUSAR | Suspected unexpected serious adverse reaction |
| TMG | Trial Management Group |
| TSC | Trial Steering Committee |
| UAR | Unexpected adverse reaction |

**Figure 1: Diagram summarizing trial**



# Annexe 1: Agreement and competing interests form for independent members

**<u>Swissped-RECOVERY Blinded Review Committee</u>: Agreement to join the Blinded Review Committee as an independent member and disclosure of potential competing interests**

Please complete the following document and return to the BRC Facilitator.

(please initial box to agree)

| | |
|---|---|
| | I have read and understood the BRC Charter version V1.2, dated 18 July 2022 |
| | I agree to join the Blinded Review Committee for this trial as an independent member |
| | I agree to treat all sensitive trial data and discussions confidentially |

The avoidance of any perception that independent members of an BRC may be biased in some fashion is important for the credibility of the decisions made by the BRC and for the integrity of the trial.

Potential competing interests should be disclosed. In many cases simple disclosure up front should be sufficient. Otherwise, the (potential) independent BRC member should remove the conflict or stop participating in the BRC. **Table 1** lists potential competing interests.

| | |
|---|---|
| | **No,** I have no potential competing interests to declare |
| | **Yes,** I have potential competing interests to declare (please detail below) |

Please provide details of any potential competing interests:

_____

_____

_____

Name: _____

Signed: _____ Date: _____

**Table 1: Potential competing interests for independent members**

- Stock ownership in any commercial company manufacturing amoxicillin
- Stock transaction in any commercial company involved (if previously holding stock)
- Consulting arrangements with the Sponsor/Funder
- Ongoing advisory role to a company manufacturing amoxicillin
- Career tied up in a product or technique assessed by trial
- Hands-on participation in the trial
- Involvement in the running of the trial
- Emotional involvement in the trial
- Intellectual conflict e.g. strong prior belief in the trial's experimental arm
- Involvement in regulatory issues relevant to the trial procedures
- Investment (financial or intellectual) or career tied up in competing products
- Involvement in the writing up of the main trial results in the form of authorship

# Annexe 2: Agreement and confidentiality agreement for observers

**<u>Swissped-RECOVERY Blinded Review Committee</u>: Agreement to attend the Blinded Review Committee and treat all information confidentially**

Please complete the following document and return to the Facilitator.

(please initial box to agree)

| | |
|---|---|
| | I have received a copy of the BRC Charter version V1.2, dated 18 July 2022 |
| | I agree to attend the Endpoint Review Committee meeting on ____/_____/_____ |
| | I agree to treat as confidential any sensitive information gained during this meeting unless explicitly permitted |

Name: _____

Signed: _____ Date: _____

# Annexe 3: Summarise changes from previous version

**Version 1.0**

This is version 1.0 of the BRC charter for this trial. There are no changes to be reported.

**Version 1.1**

This is version 1.1 of the BRC charter for this trial. Names for the BRC members have been added and BRC form has been updated

**Version 1.2**

This is version 1.2 of the BRC charter for this trial. BRC charter has been updated in line with the shared decisions, which have been made during the first BRC meeting that : 1) reporting: the facilitator will capture BRC decisions in RedCap, no release of the BRC chair is required, 2) Decision: if non-randomized systemic anti-inflammatory treatment is indicated the BRC don`t have to find consensus which anti-inflammatory treatment is indicated, 3) deviation time will be reported as treatment initiation + XX hours, 4) critically ill is defined as involvement of two organ systems.

# Annex 4: BRC Form Completion Guidelines

## Blinded Review Form

**Meeting details section will be completed by the BRC facilitator during the BRC meeting.**

Question 1 – Event number

- A unique number allocated to the event being adjudicated by the Swissped-RECOVERY BRC is noted.

Question 2 – date of BRC review

- The date of review will be noted.

**Form details section will be completed by the BRC facilitator during the BRC meeting.**

Question 3 – Type of Review

- Initial will be selected for events being reviewed by the BRC for the first time. Where an event has previously been reviewed by the BRC and referred back to the site for more information, follow-up will be selected when the event is reviewed again with the additional information supplied by site. The follow-up number will be recorded as 1 for the first time an event is reviewed after being referred back to site for additional information, 2 for the second time etc.

**BRC Adjudication section**

The BRC is blinded to the randomized anti-inflammatory trial treatment. The question 4 to 6 will be discussed by the independent members of the BRC. There is only one possible answer for each question. The selected answer will be communicated to the facilitator. The facilitator will document the selected answer in the database during the meeting.

Question 4 – Classification of disease at time of event

Based on provided clinical and laboratory information the BRC should adjudge type of PIMS-TS

A) Shocked PIMS-TS

B) KD-like PIMS-TS

C) Undifferentiated PIMS-TS

D) Other disease (no further action needed)

Question 5 – Likelihood that non-trial systemic anti-inflammatory treatment was clinically indicated.

Based on provided clinical and laboratory data and additional examinations (echo, ECG) the BRC should determine whether non-trial systemic anti-inflammatory treatment was clinically indicated.

A) Definitely

B) Probably/Possibly

C) Unlikely (no further action needed)

D) No (no further action needed)

E) Too little info (no further action needed)

(Definition: Definitely >80% likely, Possibly >50 -80% likely, Unlikely >20-50% likely, No < 20% likely)

Question 6 – Primary reason for non-trial systemic ant-inflammatory treatment

The BRC should adjudicate why non-trial systemic anti-inflammatory treatment is indicated:

A) Evidence of ongoing PIMS-TS inflammation even if patients is in a stable condition
B) Evidence of ongoing PIMS-TS inflammation and worsening of the general condition
C) Evidence of ongoing PIMS-TS inflammation and critically ill patient
D Intolerance to the IMP/Adverse event
E) Other:_____

**BRC Outcome section will be completed by the facilitator during the BRC meeting**

Question 7 and 8 – Can a decision be reached today?

- If the BRC has reached a decision based on the information available in questions 4 – 6, this should be answered as "Yes".
- If the BRC has not been able to reach a decision based on the information available in questions 4 – 6, this should be answered in question 8 as "No, further information needed". The BRC facilitator will follow-up with the relevant site and requests additional information. When the additional information has been provided by the site, the case will be reviewed again by the BRC.

**Attendance section will be completed by the facilitator during the BRC meeting**

Question 9 –Attendance

The facilitator will document the attendance of the BRC members at each meeting.

**Final approval section will be completed during or up to one week after the BRC meeting by the BRC chair**

Question 10 – Final approval

- Facilitator will indicate at the e CRF that form is completed

## Annex 5: BRC Reference Documents

1) Current version of the Swissped-RECOVERY protocol (Version 1.3, 18.01.2022);
2) Current version of the BRC Forms

BMJ Open

# Swissped-RECOVERY – An Approach for the Interpretation of Non-randomised Treatment in an Open-label Randomised Controlled Trial in Paediatric Inflammatory Multisystem Syndrome Temporally Associated with SARS-CoV-2 (PIMS-TS) Involving Ten Secondary and Tertiary Paediatric Hospitals in Switzerland



| | |
|---|---|
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| Complete List of Authors: | Schöbi, Nina; Inselspital University Hospital Bern Children's Clinic,<br>Sanchez, Carlos; University of Basel<br>Welzel, Tatjana; University of Basel; University of Basel, Pediatric Rheumatology<br>Bamford, Alasdair; Great Ormond Street Hospital, Paediatric infectious diseases and immunology; UCL<br>Webb, Kate; University of Cape Town<br>Rojo, Pablo; University Hospital October 12<br>Tremoulet, Adriana; Rady Children's Hospital San Diego, Department of Paediatrics<br>Atkinson, Andrew; University of Basel; Washington University in St Louis School of Medicine<br>Schlapbach, Luregn; University Children's Hospital Zürich, Department of Intensive Care and Neonatology; The University of Queensland, Child Health Research Centre<br>Bielicki , Julia ; University of Basel; St George's University |
| Primary Subject Heading: | Paediatrics |
| Secondary Subject Heading: | Infectious diseases, Research methods |
| Keywords: | Paediatric intensive & critical care < INTENSIVE & CRITICAL CARE, Paediatric infectious disease & immunisation < PAEDIATRICS, Post-Infectious Disorders, Randomized Controlled Trial, SARS-CoV-2 Infection |
| | |

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**Original Article**

# Swissped-RECOVERY – An Approach for the Interpretation of Non-randomised Treatment in an Open-label Randomised Controlled Trial in Paediatric Inflammatory Multisystem Syndrome Temporally Associated with SARS-CoV-2 (PIMS-TS) Involving Ten Secondary and Tertiary Paediatric Hospitals in Switzerland

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## Abstract

**Objectives:** In trials of acute severe infections or inflammations frequent administration of non-randomised treatment (i.e., intercurrent event) in response to clinical events is expected. These events may affect the interpretation of trial findings. Swissped-RECOVERY was set up as one of the first randomised controlled trials worldwide, investigating the comparative effectiveness of anti-inflammatory treatment with intravenous methylprednisolone or intravenous immunoglobulins in children and adolescents with Paediatric Inflammatory Multisystem Syndrome Temporally Associated with SARS-CoV-2 (PIMS-TS). We present one approach towards improving the interpretation of non-randomised treatment in a randomised controlled trial.

**Design:** This is a pre-planned ancillary analysis of the Swissped-RECOVERY trial, a randomised multicentre open-label two-arm trial.

**Setting:** Ten Swiss paediatric hospitals (secondary and tertiary care) participated.

**Participants**: Paediatric patients hospitalised with PIMS-TS.

**Interventions:** All patient-first intercurrent events, if applicable, were presented to an independent adjudication committee consisting of four international paediatric COVID-19 experts to provide independent clinical adjudication to a set of standardised questions relating to whether additional non-randomised treatments were clinically indicated and disease classification at the time of the intercurrent event.

**Results:** Of 41 treatments in 75 participants (24/41 (59%) and 17/41 (41%) in the intravenous methylprednisolone and immunoglobulin arms of the trial, respectively), two-thirds were considered indicated. The most common treatment (oral glucocorticoids, 14/41, 35%) was mostly considered not indicated (11/14, 79%), although in line with local guidelines. Intercurrent events among patients with Shock-like PIMS-TS at baseline were mostly considered indicated. A significant proportion of patients with undifferentiated PIMS-

TS at baseline were not attributed to the same group at the time of the intercurrent event (6/12 unchanged, 4/12 Kawasaki Disease-like, 2/12 Shock-like).

**Conclusion:** The masked adjudication of intercurrent events contributes to the interpretation of results in open-label trials and should be incorporated in the future.

**Trial registration:** Swiss National Clinical Trials Portal (SNCTP000004720) and clinicaltrial.gov (NCT 04826588)

## Strengths and Limitations of this study

- These anxillary analyses were pre-planned and the non-randomised events of interest were defined a priori for further evaluation. Which results in an improvement of the interpretation of the trial findings.
- All case narratives were carefully masked not only regarding randomised but also non-randomised treatment. Additionally, the time point of the intercurrent event was reported as during trial treatment + x hours to avoid unmasking resulting from different duration of treatment administration.
- The small sample size and the fact that only patient-first ICEs, excluding subsequent ICEs and excluding patients not experiencing ICEs, were adjudicated by the committee is a limitation of the study.
- The independent adjudication committee's reviews occurred in an artificial setting in a virtual meeting and in hindsight which contrasts the clinical bedside decisions-making.

**Funding statement:**

This work was supported by grants from the NOMIS Foundation, the Vontobel Foundation, and the Gaydoul Foundation (LJS). Swiss PedNet (https://www.swisspednet.ch/) provides infrastructure support for study coordination, GCP, and monitoring.

**Conflict of interest statement:**

JB received grant support paid to the institution from the European and Developing Countries Clinical Trials Partnership (PediCaP, RIA2017MC-2023), Horizon 2020 (NeoIPC, grant 965328), the Swiss National Science Foundation (KIDS-STEP, grant 173532), National Institute for Health Research (CAP-IT, project 13/88/11), Innosuisse (SPEARHEAD flagship grant), the Swiss Personalised Health Network (Secretariat for Education Research and Innovation) (SwissPedHealth, award NDS-2021-911), in the past 36 months; consulting fees paid to the institution from Shionogi, Sandoz, Basilea, and GSK; payments to the institution for presentations, lectures, speakers bureaus, manuscript writing or educational events in the past 36 months from Pfizer, Sandoz, and Bayer; participated at independent data monitoring committee boards of Avenir trial (member, expenses), Lakana trial (member, unfunded), CURLY trial (Chair, unfunded) in the past 36 months; is the vice president of the SwissPedNet (unpaid) and leadership of Severe Bacterial Infection and Antimicrobial Resistance working group of the Penta Foundation (unpaid). TW gave presentations for Novartis (payment to the institution) in the past 36 months. AB had received fixed term consultancy fees from Gilead. KW is supported by the Crick African Network (CAN). The CAN receives its funding from the UK's Global Challenges Research Fund (MR/P028071/1), and by the Francis Crick Institute which receives its core funding from Cancer Research UK (FC1001647), the UK Medical Research Council (FC1001647), and the Wellcome Trust (FC1001647). KW is also supported by the South African Medical Research Council with funds received from National Treasury. The content and findings reported/ illustrated are the sole deduction, view and responsibility of the researchers and do not reflect the official position and sentiments of the SAMRC or SA National Treasury. PJ received grant support from ViiV and consulting fees from MSD. AT received grant support paid to the institution/UCSD from the National Institute of Health and consulted Janssen

Pharmaceuticals and Kiniksa with no payment received. All other authors declared no conflicts of interest.

**Data sharing statement:**

Deidentified participant data will be shared upon reasonable request unless the request is conflicting with ongoing or planned analyses. Requests need to be addressed to the corresponding author and will require approval by the Swissped-RECOVERY steering group, and with a signed data access agreement. Researchers with a proposed use, approved by appropriate institutional review boards and the Swissped-RECOVERY Steering Committee, can access the data.

**Ethical approval statement**

The study was approved by the lead ethics committee (Ethics Committee Northwest and Central Switzerland, EKNZ, Project ID: 2021-00362); and other responsible ethics committees in Switzerland. Informed consent has been obtained by the participants and or the parents/legal guardians.

**Abbreviation list**

| | |
|---|---|
| COVID-19 | Coronavirus disease 2019 |
| IAC | independent adjudication committee |
| ICE | Intercurrent Event |
| IQR | interquartile range |
| IVIG | intravenous immunoglobulins |
| IVMP | intravenous methylprednisolone |
| PIMS-TS | Paediatric Inflammatory Multisystem Syndrome Temporally Associated with SARS-CoV-2 |

| | |
|---|---|
| REDCap | Research Electronic Data Capture |

## Introduction

In trials of acute severe infections or inflammatory syndromes, frequent administration of non-randomised treatment in response to clinical events is expected. In the terminology of the ICH E9(R1) Addendum on Estimands and Sensitivity Analyses in Clinical Trials, these are defined as *Intercurrent Events* (ICEs) (1). ICEs take place after randomisation and may affect the interpretation of trial findings. They can be a source of bias if knowledge of allocated treatment differentially affects post-randomisation patient management. The ICH Addendum outlines the importance of explicit pre-planned identification and handling of ICEs to enable all clinical questions addressed by a trial to be answered fully and robustly.

Here, we present one approach applied in a recent pragmatic open-label randomised trial (Swissped-RECOVERY) investigating the comparative effectiveness of first anti-inflammatory treatment with intravenous methylprednisolone (IVMP) or intravenous immunoglobulins (IVIG) in children and adolescents with Paediatric Inflammatory Multisystem Syndrome Temporally Associated with SARS-CoV-2 (PIMS-TS) (2,3). Patients with PIMS-TS exhibit clinical and laboratory signs of inflammation together with single or multiple organ-dysfunction, in presence of confirmed or suspected previous exposure to or infection with SARS-CoV-2 (3). Overall, the disease presentation was severe in a substantial proportion of children, and even more at the beginning of the pandemic. Therefore, treatment was warranted. However, given that at the time there was no evidence available regarding the best treatment, recommendations were based on expert opinion and consensus guidelines mostly. Corticosteroids and intravenous immunoglobulins became the mainstay of treatment informed by the resemblance of PIMS-TS cases and Kawasaki Disease. Phenotype classification, i.e., Shock-like PIMS-TS, Kawasaki Disease-like PIMS-TS, and undifferentiated PIMS-TS, emphasising different presentations and severities were routinely considered in the management of PIMS-TS in Switzerland, and therefore, included in our analyses (4). In Swissped-RECOVERY we expected non-randomised anti-inflammatory

treatments to be common and were interested in differentiating between patients experiencing these because of on-going or progressive inflammation (considered clinically indicated and potentially related to effectiveness of randomised treatments), and those in whom a clear clinical reason for additional non-randomised anti-inflammatory treatment was lacking. We put in place an independent adjudication committee (IAC) to evaluate these ICEs, masked to randomised and received non-randomised treatment. Here, we describe and interpret the adjudication results, including indicated and non-indicated ICEs and a comparison between randomisation arms.

## Methods

### *Study design*

This is a pre-planned ancillary analysis of the Swissped-RECOVERY trial (Swiss National Clinical Trials Portal (SNCTP000004720) and clinicaltrial.gov (NCT 04826588)), an investigator-initiated randomised multicentre open-label two-arm trial (IVIG vs IVMP) in children hospitalised with PIMS-TS at ten Swiss paediatric hospitals (Aarau, Basel, Bellinzona, Bern, Fribourg, Geneva, Lausanne, Lucerne, St. Gallen, and Zurich) (2). The study was approved by the lead ethics committee (Ethics Committee Northwest and Central Switzerland, EKNZ, Project ID: 2021-00362) and other responsible ethics committees in Switzerland. Informed consent has been obtained. We aimed to determine clinical indication of ICEs according to masked IAC consensus as the gold standard.

### *Patient and Public Involvement*

Given the expedited process of setting up this trial due to the developments of the pandemic it was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of our research.

*Definition of Intercurrent Events*

ICEs of interest were defined *a priori* in a dedicated IAC charter (Supplement) as non-randomised anti-inflammatory treatments including additional or fewer doses of the randomised treatment, IVMP in the IVIG group and vice versa, biological treatment and any oral tapering of glucocorticoids. Patients experiencing at least one of these were presented to the IAC.

*Masked independent adjudication committee*

The IAC consisted of four international PIMS-TS experts who met virtually in five sessions between June 6, 2022, and August 9, 2022. The work of the IAC was governed by a dedicated charter (Supplement), and in line with this, at least two members had to be present at each meeting. All chronologically first ICEs per patient were assessed, meaning if one patient experienced multiple ICEs, clinical indication was adjudicated only for the first non-randomised anti-inflammatory treatment. Masked narratives were prepared and presented by a non-independent facilitator (TW), who did not contribute to the discussions about clinical indication but provided further information upon IAC request. IAC consensus decisions were required by agreement of all present experts and was recorded directly into a designated form on the electronic data capture system REDCap™.

*Configuration of ICE narratives*

The case narratives presented to the IAC included baseline *general information* (patient demographics, known exposure to a SARS-CoV-2 case, estimated number of weeks since SARS-CoV-2 exposure and underlying comorbidities), *clinical characteristics* (organ involvement, vital signs, need for inotropes, respiratory support or fluid resuscitation), *cardiological examinations* (electrocardiogram, echocardiogram), *laboratory parameters* (SARS-CoV-2 PCR and serology, haematology, coagulation and biochemical markers), and

follow-up information for these variables until the ICE. All narratives were carefully masked regarding randomised treatment and non-randomised treatment received. The time point of the ICE was shown as 'during trial treatment + x hours' to avoid unmasking resulting from differential duration of IVIG (one dose) and IVMP (one daily dose for three consecutive days).

*Adjudication details*

The IAC adjudicated ICEs starting with disease classification at the time of the ICE, defined as in the Best Practice Recommendations for the Diagnosis and Management of PIMS-TS in Switzerland (4): i) Shock-like PIMS-TS, ii) Kawasaki Disease-like PIMS-TS, iii) undifferentiated PIMS-TS, and iv) other disease; in case of iv), no further adjudication was required. The IAC was aware of the site investigator's allocation at baseline but not at the time of the ICE. For i-iii) the first question was followed by the likelihood that the ICE was clinically indicated: i) definitely >80%, ii) probably 51-80%, iii) unlikely 21-50%, iv) not <21%, v) too little information. ICEs classified as v) were re-presented to the IAC upon receipt of additional narrative information. ICEs considered to be in category i) or ii) were classified as "clinically indicated".

*Statistical analysis*

Exploratory description of baseline patient characteristics was summarised using the number (percentage) for categorical variables and the median (interquartile range [IQR]) for continuous variables. Between group differences were investigated using the chi-square test for categorical variables and the Wilcoxon rank sum test for continuous variables. Due to the small number of patients and skewed data parametric testing was not appropriate.

A statistical significance level of 5% was considered statistically significant throughout. All analyses were performed in R (version 4.2.2) (5).

## Results

Between May 21, 2021, and April 15, 2022, a total of 76 patients were enrolled. Of these, 75 patients were included for the primary analysis (37 were allocated to IVMP, 38 to IVIG). Detailed information on the cohort, including baseline characteristics, is presented in the original publication (6).

### *Non-randomised anti-inflammatory treatment*

In total, 41 ICEs were adjudicated. In the IVMP arm, 24/37 (65%) patients experienced at least one ICE, compared to 17/38 (45%) in the IVIG arm (p=0.13).

The most common first ICE was oral glucocorticoids, with or without tapering, accounting for 14/41 (34%) ICEs (11/24 (46%) in the IVMP and 3/17 (18%) in the IVIG arm). Further first ICEs occurred because of addition of non-randomised treatment, including IVMP >3 days or >10 mg/kg; IVMP in case of IVIG randomisation or vice versa, IVIG >2 g/kg or >1 dose and intravenous or subcutaneous anakinra administration. Figure 1

### *Independent adjudication committee findings*

Non-randomised anti-inflammatory treatment was considered clinically indicated by the IAC for 27/41 (66%) patients (13/24 (54%) in the IVMP arm, 14/17 (82%) in the IVIG arm). Overall, there was a trend towards a greater proportion of clinically indicated ICEs among patients in the IVIG arm (p=0.061). Non-indicated ICEs in the IVMP arm were dominated by receipt of oral glucocorticoids (10/11; 91%). Non-indicated ICEs were rare in the IVIG arm (3/17; 18%) and comprised in two cases of switch to IVMP and in one case of addition of oral glucocorticoids. Figure 1

A different pattern of ICEs and their clinical indication was observed among patients with the three phenotypes of PIMS-TS (Table 1). ICEs among patients with Shock-like PIMS-TS at baseline were mostly considered indicated. For patients with Kawasaki Disease-like PIMS-TS at baseline, 7/8 ICEs among patients randomised to IVIG were considered indicated, in contrast to only 2/6 among patients randomised to IVMP. ICEs were more common among patients with undifferentiated PIMS-TS at baseline and allocated to IVMP (10/12) compared to IVIG (2/12). Of note, while patients considered to show a Shock- or Kawasaki Disease-like clinical phenotype at baseline most displayed the same phenotype at the time of receipt of non-randomised anti-inflammatory treatment (12/15 Shock-like patients, 11/14 Kawasaki Disease-like patients), this was not the case for the undifferentiated PIMS-TS group (6/12 unchanged, 4/12 Kawasaki Disease-like at time of ICE, 2/12 Shock-like). Figure 2

*Clinical and laboratory characteristics of patients with ICEs*

Whereas there was a difference in baseline characteristics for patients with and without ICEs in lymphocytopaenia, thrombocytopaenia, ferritin, D-Dimers and need for inotropic support, no such difference was observed when comparing baseline characteristics of patients with a clinically indicated vs non-indicated ICE, apart from a longer fever duration in patients with a clinically indicated ICE. Table 2

## Discussion

Swissped-RECOVERY was the first research group publishing data from a randomised controlled trial on medical interventions in patients with PIMS-TS. As expected, in such a pragmatic, open-label trial that was set-up in an expedited process, non-randomised anti-inflammatory treatment was common, and presented challenges for the interpretation of the trial results investigating treatment response to just one immunomodulatory treatment (IVMP

compared to IVIG). Masked end-point review committees have been used in open-label trials to mitigate against bias in endpoint assessment (7,8). Analogously, we involved an IAC to provide independent adjudication on the necessity/indication for non-randomised treatments. This information can then be incorporated in to pre-specified analyses of the main trial results. Our findings support the results provided by the original publication that initial monotherapy with either IVMP or IVIG is sufficient and safe, but may need to be expanded in critically unwell patients not responding to treatment after a period of observation. Our findings highlight that, e.g. the addition of a tapering regime of oral corticosteroids, even though part of many international guidelines, seems to be largely unnecessary.

The IAC considered two out of three ICEs observed in the trial clinically indicated, mostly in children presenting with Shock-like PIMS-TS patients and in those with Kawasaki Disease-like PIMS-TS when allocated to IVIG. However, the IAC also identified one in three ICEs as not clinically indicated. Those ICEs predominantly comprised of added oral glucocorticoids.

ICEs that were identified as non-indicated may reflect variability in regional practice and evolution of local, national and international guidelines during the trial. For example, administration of tapering oral corticosteroids was commonly reported and usually considered to be unnecessary by the IAC but has been included in guidelines (4) (predominately related to existing recommendations for treatment of Kawasaki Disease (9)).

Disease classification and severity also seem to be associated with clinical decision-making, leading to non-randomised treatment usually being considered indicated among patients with Shock-like PIMS-TS. PIMS-TS is difficult to distinguish from Kawasaki Disease. IVIG is standard treatment for Kawasaki Disease (10) and so may have been added to the allocated treatment in a proportion of patients randomised to IVMP, due to investigator concern about

under-treating possible Kawasaki Disease. Such non-randomised treatment was usually considered non-indicated.

IAC interpretation of ICEs in Swissped-RECOVERY had several limitations. First, narratives had to be presented in a way that prevented inferences on allocated treatment and unmasking of the exact nature of the ICE. This limited information available to the IAC, potentially impacting their adjudication. Second, IAC reviews rely on clinical expertise of independent members. Since PIMS-TS was an emerging disease at the time of the trial, the IAC members had limited evidence available to inform management, potentially leading to more permissive adjudication relying on experience and expertise alone. Furthermore, IAC reviews occur in a somewhat artificial setting where experts adjudicate ICEs in a virtual meeting in contrast to clinicians making bedside decisions. Fourth, only patients' first ICEs were reviewed. A review of all ICEs may have provided further insight into management of PIMS-TS patients in the trial but would have substantially increased the complexity of the review process. Fifth, the IAC was not asked to adjudicate the management of patients not experiencing ICEs. This may theoretically have identified patients who should have, in the view of the IAC, received additional anti-inflammatory treatment, adding to the interpretation of trial findings. Lastly, the analyses considering phenotype classification rely on the classification at baseline. However, especially for undifferentiated PIMS-TS, there is a substantial proportion of cases being re-classified by the IAC, which might further impact the interpretation of the results.

We considered rapid reporting of primary and secondary endpoints from an interventional randomised controlled trial in PIMS-TS, an emerging disease with a potentially high global impact, as an utmost priority. Therefore, we decided to report additional findings from the IAC on ICEs separately from the main trial publication.

The previously published trial results showed no difference in the primary outcome of length of hospital stay between IVMP and IVIG (6). A posthoc analysis of the data including ICEs, incorporating the IAC assessment, also indicated no differences (Atkinson A and Bielicki JA, submitted). With 54.7 % of patients receiving non-randomised anti-inflammatory treatment, there is a risk of many patients converging on a single treatment or being exposed to both treatments, reducing the informativeness of the trial. Alternative or complementary strategies are the utilisation of sequential randomisation as well as attempts to minimise clinically unwarranted non-randomised anti-inflammatory treatments, for example through rigorous training and increased documentation requirements for ICEs. Neither of these strategies would have been compatible with the pragmatic nature of the trial.

Overall, IAC reviews proved valuable to provide independent assessment on whether non-randomised anti-inflammatory treatment was likely given as treatment for persistent or progressive PIMS-TS. Such assessments should be considered in the context of the Estimand Framework in future trials, and will help to improve interpretation of trial findings.

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**Contributors:**

JB, TW and CS planned and implemented the masked review of intercurrent events. JB and NS contributed to the first draft, approved the final version, and take responsibility for the accuracy of reported findings. AB, KW, AT, PR, TW, LS, AA and CS contributed to the draft and approved the final version. CS performed the analysis and is the data manager for Swissped-RECOVERY.

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## Data Presentation

This data has been submitted as an abstract and accepted as a poster at the Annual Meeting of the European Society of Paediatric Infectious Diseases (ESPID) in Lisbon 2023.

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## Tables

*Table 1: Independent masked adjudication of intercurrent events of additional anti-inflammatory treatment according to three clinical phenotypes of Paediatric Inflammatory Multisystem Syndrome Temporally Associated with SARS-CoV-2 (PIMS-TS)*

| | | | IVMP | IVIG | p-value |
|---|---|---|---|---|---|
| Entire trial cohort, n = 75 | | | n=37 | n=38 | 0.04 |
| | ICE | None | 13 (35%) | 21 (55%) | |
| | | Indicated | 13 (35%) | 14 (37%) | |
| | | Non-indicated | 11 (30%) | 3 (8%) | |
| Shock-like, n = 20 | | | n=10 | n=10 | 0.77 |
| | ICE | None | 2 (20%) | 3 (30%) | |
| | | Indicated | 6 (60%) | 6 (60%) | |
| | | Non-indicated | 2 (20%) | 1 (10%) | |
| Kawasaki Disease-like, n = 31 | | | n=15 | n=16 | 0.10 |
| | ICE | None | 9 (60%) | 8 (50%) | |
| | | Indicated | 2 (13%) | 7 (44%) | |
| | | Non-indicated | 4 (27%) | 1 (6%) | |
| Undifferentiated, n = 24 | | | n=12 | n=12 | 0.004 |
| | ICE | None | 2 (16%) | 10 (84%) | |
| | | Indicated | 5 (42%) | 1 (8%) | |
| | | Non-indicated | 5 (42%) | 1 (8%) | |

Considering the non-indicated ICEs among patients classified as having Kawasaki Disease-like and undifferentiated PIMS-TS at baseline, all were considered to be Kawasaki Disease-like at the time of ICE; among patients with undifferentiated PIMS-TS at baseline and non-indicated ICEs, three episodes were reclassified as Kawasaki Disease-like PIMS-TS at the

time of the ICE, one was considered to be Shock-like PIMS-TS with improvement and one was considered undifferentiated PIMS-TS.

ICE = intercurrent event, IVMP = intravenous methylprednisolone, IVIG = intravenous immunoglobulins

*Table 2a and 2b: Baseline characteristics stratified by presence or absence of an ICE (2a) and stratified by the IAC consensus (2b)*

*2a*

| N (%) for categorical variables, median [IQR] for continuous | **ICE** N=41 | **No ICE** N=34 | **p-value** |
|---|---|---|---|
| Age, years | 9.8 [6.6, 12.1] | 9.0 [6.2, 12.9] | 0.87 |
| Weight, kilogram | 32.0 [22.6, 40.5] | 28.0 [19.1, 38.1] | 0.65 |
| Fever duration, days | 3.0 [1.0, 4.0] | 2.5 [1.0, 4.0] | 0.53 |
| Any inotropes | 19 (46.3) | 6 (17.6) | 0.02 |
| Lymphocytes, G/l | 0.66 [0.47, 1.03] | 1.00 [0.64, 1.42] | 0.04 |
| Platelets, G/l | 127.00 [100.25, 166.00] | 179.50 [142.25, 260.75] | 0.004 |
| D-Dimers, ug/l | 4249.50 [1868.00, 6355.75] | 1840.00 [1233.50, 3491.25] | 0.01 |
| Ferritin, ug/l | 679.00 [447.25, 1095.75] | 247.00 [194.00, 488.00] | <0.001 |
| C-reactive Protein, mg/l | 169.50 [115.30, 230.65] | 140.50 [90.12, 199.00] | 0.13 |

| | | | |
|---|---|---|---|
| Troponin, ng/l | 11.00 [6.00, 25.80] | 24.00 [16.00, 55.10] | 0.05 |
| NTproBNP, pg/ml | 2418.50 [807.75, 7281.00] | 3330.00 [924.50, 7130.50] | 0.77 |

*2b*

| N (%) for categorical variables, median [IQR] for continuous | **ICE indicated** N=27 | **ICE non-indicated** N=14 | **p-value** |
|---|---|---|---|
| Age, years | 9.4 [8.1, 11.3] | 10.7 [6.2, 12.1] | 0.98 |
| Weight, kilogram | 32.2 [23.9, 37.8] | 32.0 [22.8, 41.8] | 0.99 |
| Fever duration, days | 1.0 [1.0, 2.0] | 3.0 [2.0, 5.0] | 0.02 |
| Any inotropes | 5 (35.7) | 14 (51.9) | 0.51 |
| Lymphocytes, G/l | 0.80 [0.70, 1.41] | 0.62 [0.45, 0.79] | 0.11 |
| Platelets, G/l | 116.50 [99.75, 133.25] | 137.00 [101.50, 177.00] | 0.31 |
| D-Dimers, ug/l | 2440.00 [1834.50, 5310.25] | 4458.50 [2306.75, 6747.25] | 0.27 |
| Ferritin, ug/l | 549.00 [444.00, 588.00] | 816.00 [552.00, 1297.00] | 0.08 |
| C-reactive Protein, mg/l | 137.00 [111.50, 230.30] | 182.30 [117.20, 235.50] | 0.66 |
| Troponin, ng/l | 13.00 [8.00, 34.00] | 10.50 [5.25, 25.00] | 0.69 |
| NTproBNP, pg/ml | 3212.50 [1360.75, 7683.50] | 1628.00 [697.00, 7199.50] | 0.51 |

2a: Difference in baseline characteristics for patients with and without ICEs in lymphocytopaenia, thrombocytopaenia, ferritin, D-Dimers and need for inotropic support.

2b: Difference in baseline characteristics for patients with a clinically indicated versus non-indicated ICE in longer fever duration.

ICE = intercurrent event, IAC = independent adjudication committee

**Legend figures**

*Figure 1*

1a: A total of 24 ICEs reported; considered clinically indicated 13/24, with administration of IVIG in 7/13 clinically indicated ICEs; considered non-indicated 11/24, with administration of oral glucocorticoids in 10/11 non-indicated ICEs.

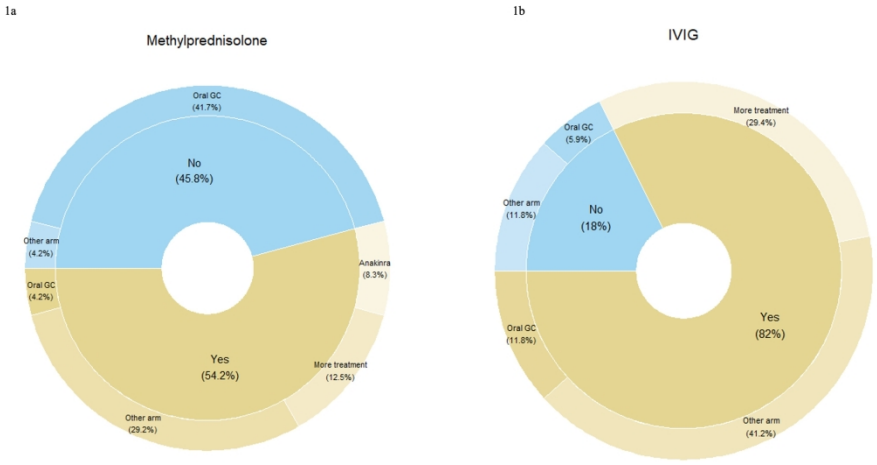
1b: A total of 17 ICEs reported; considered clinically indicated 14/17 with administration of IVMP in 7/14 clinically indicated ICEs; considered non-indicated 3/17.

ICE: intercurrent event, IVIG: intravenous immunoglobulins, IVMP: intravenous methylprednisolone, GC: glucocorticoids

*Figure 2*

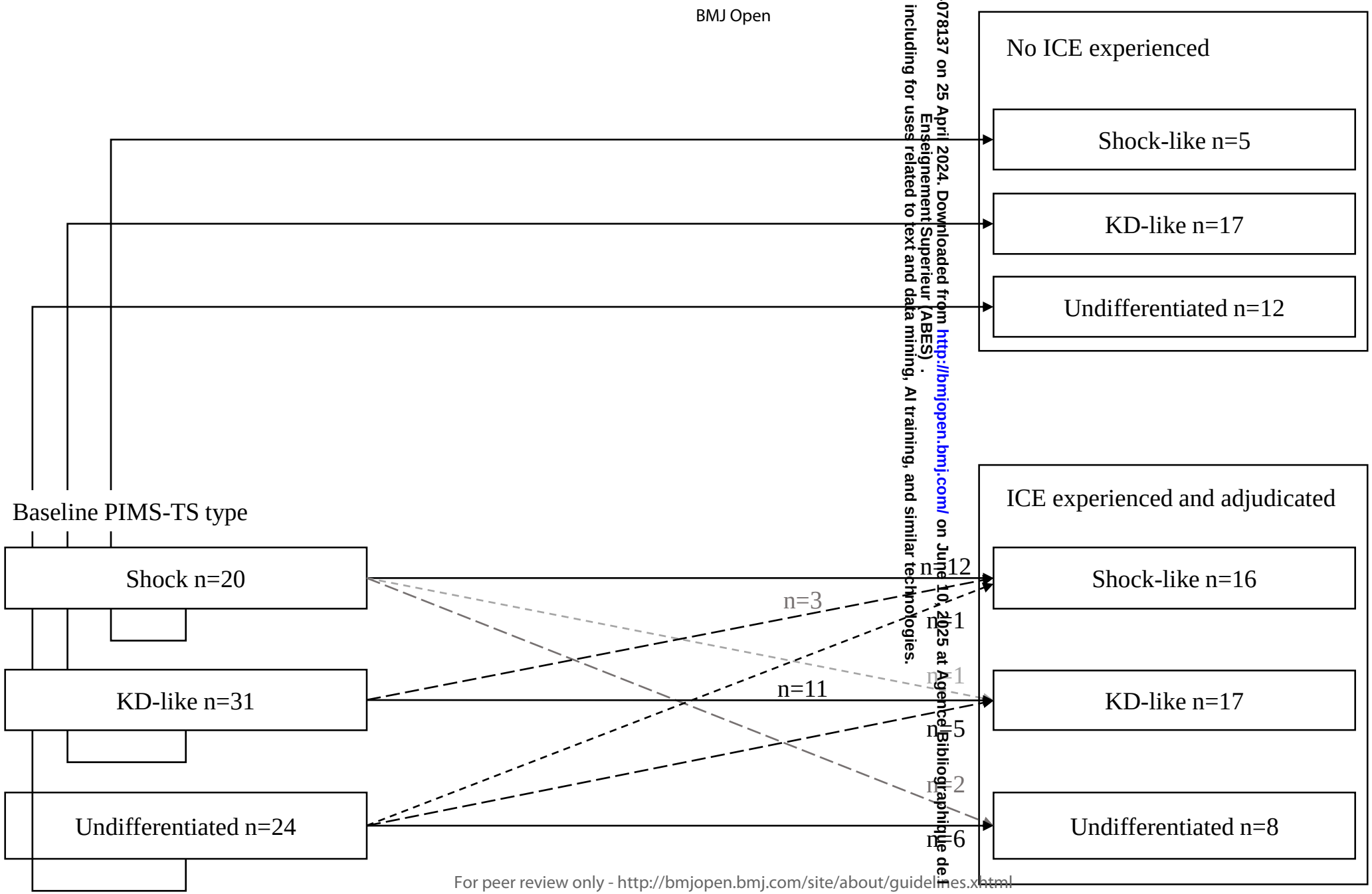
Patients considered to show a Shock- or Kawasaki Disease-like clinical phenotype of PIMS-TS at baseline most displayed the same phenotype at the time of receipt of non-randomised anti-inflammatory treatment (12/15 Shock-like PIMS-TS, 11/14 Kawasaki Disease-like PIMS-TS patients), this was not the case for the undifferentiated PIMS-TS group (6/12 unchanged, 4/12 Kawasaki Disease-like, 2/12 Shock-like at time of ICE).

PIMS-TS = Paediatric Inflammatory Multisystem Syndrome Temporally Associated with SARS-CoV-2, ICE = intercurrent event




Figures 1a and 1b: Independent adjudication committee findings for intercurrent events of additional anti-inflammatory treatment in patients allocated to the intravenous methylprednisolone arm (IVMP, 1a) or to the intravenous immunoglobulin arm (IVIG, 1b)

338x190mm (300 x 300 DPI)



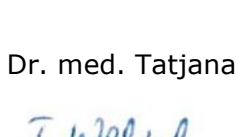
# Swiss Pediatric Randomised Evaluation of COVID-19 Therapy (Swissped RECOVERY)

NCT: 04826588

## Blinded Review Committee Charter

Version 1.2, Date 18 July 2022

**Authorised by:**

| | | | |
|---|---|---|---|
| Name: | PD Dr. med. Julia Bielicki | Role: | Sponsor-Investigator |
| Signature: |  | Date: | 20.07.2022 |

**Prepared by**

| | | | |
|---|---|---|---|
| Name: | Dr. med. Tatjana Welzel | Role: | Trial Physician |
| Signature: |  | Date: | 18.07.2022 |

| CONTENT | DETAILS OF BRC |
|---|---|
| **1. Introduction** | |
| Name (& Sponsor's ID) of trial | Swissped RECOVERY |
| Objectives of trial, including interventions being investigated | Swissped-RECOVERY will compare the effectiveness of intravenous methylprednisolone 10 mg/kg/dose over three days versus intravenous immunoglobulins (IVIG) 2 g/kg as single dose in children and adolescents hospitalized with paediatric inflammatory multisystem syndrome-temporally associated with SARS-CoV-2 (PIMS-TS).<br><br>**Interventions**<br><br>Children and adolescents will be randomised to:<br><br>Randomisation 1: Methylprednisolone 10 mg/kg/dose (maximum dose 1000 mg per day) for three days once daily<br><br>Randomisation 2: IVIG 2 g/kg/dose (maximum dose 100 g) as a single dose given as a slow infusion<br><br>**Objectives**<br><br>*Primary objective:*<br>The primary objective is to compare the effect of study treatments on the duration of hospital stay after randomization.<br><br>*Secondary objectives*<br>Secondary objectives are to assess the effects of study treatments on<br>• all-cause mortality at 28 days or discharge from hospital (whichever occurs first).<br>• among patients *not* on invasive mechanical ventilation at baseline, the composite endpoint of all-cause death or need for invasive mechanical ventilation or ECMO.<br>• the need for ventilation support (excluding O2 supplementation).<br>• duration of invasive mechanical ventilation.<br>• among patients not on inotropes at baseline, the endpoint of need for any inotropic support.<br>• the need for renal replacement therapy.<br>• cardiac outcomes.<br><br>*Other objectives*<br>• To measure the rate of major bleeding and thrombotic events in the cohort and by study treatment.<br>• To explore the use and duration of rescue treatment in the cohort and by study treatment; as well as the use and duration of indicated rescue treatment as adjudicated by a blinded review committee.<br>• To explore changes in markers of inflammation (fever, C-reactive protein) in the cohort and by study treatment.<br>• To assess health status and functional outcome as measured by the SDQ 6 months post randomisation.<br>• To explore SARS-CoV-2 vaccination patterns and attitudes |

| CONTENT | DETAILS OF BRC |
|---|---|
| | towards SARS-CoV-2 vaccination prior and after enrolment in the trial. |
| Outline of scope of Charter | The purpose of this document is to describe the membership, terms of reference, roles, responsibilities, authority, decision-making and relationships of the Blinded Review Committee (BRC) for this trial, including the timing of meetings, methods of providing information to and from the BRC, frequency and format of meetings and relationships with other trial committees. |
| Facilitation | The Swissped-RECOVERY Trial Physician at the Paediatric Research center University Children`s Hospital of Basel (PRC UKBB) will be the Facilitator for the trial. The Facilitator will be responsible for the organisation of meetings and should be copied into all communications with and between the BRC. |
| **2. Roles and responsibilities** | |
| A broad statement of the aims of the BRC | To perform independent assessment of all administered immunomodulatory treatments other anti-inflammatory than randomized trial medication that might influence the trial primary endpoints. |
| Terms of reference | The primary endpoint for the Swissped-RECOVERY study is to compare the effect of study treatments on the duration of hospital stay after randomization.<br>Reason and clinical indication for any systemic anti-inflammatory treatment other than trial medication will be adjudicated by a Blinded Review Committee (BRC) to randomised allocations.<br>The role of the Swissped-RECOVERY BRC is to adjudicate if the non-trial systemic anti-inflammatory treatment was clinically indicated. |
| Specific roles of BRC | • Provide assessment of clinical events that might influence trial endpoints, as follows:<br>- adjudicate based on the clinical case vignettes<br>○ Disease classification<br>○ Likelihood that non-trial systemic anti-inflammatory treatment was indicated<br>○ if anti-inflammatory treatment is indicated<br>▪ Reason why<br>• Maintain confidentiality of all trial information that is not already in the public domain<br>• Review and approve the BRC form<br>• Review the BRC charter |
| **Trial specific BRC issues** | |
| Any issues specific to the disease under study | • The trial is open-label, however, the BRC will be blinded to the treatment allocation.<br>• Lack of information – for some events, a limited amount of clinical information may influence the BRC decision. If more detailed information not presented in the case vignettes is needed for the BRC assessment, this can be requested from the trial physician. In this case, the assessment must be delayed until the information is available<br>• Event date is the date of the non-trial systemic anti-inflammatory treatment administration. |

| CONTENT | DETAILS OF BRC |
|---|---|
| **3. Composition** | |
| Membership and size of the BRC | All members of the Swissped-RECOVERY BRC must be blinded to study treatment allocation. The BRC consists of independent members. The BRC Chair will be independent [1] of the trial (see section 5).<br>The members of the BRC for this trial are:<br>(1) Alasdair Bamford - BRC Chair (Independent)<br>(2) Adriana Tremoulet – Independent member<br>(3) Pablo Rojo Conejo – Independent member<br>(4) Kate Webb – Independent member<br>The membership of the BRC will be reviewed in situations where members can no longer fulfil their responsibilities or where a potential conflict of interest arises. |
| The Chair, how they are chosen and the Chair's role. | The Chair should be a medical practitioner and have previous experience of serving on review committees, experience of chairing meetings, and should be able to facilitate and summarise discussions; knowledge of the disease area (PIMS-TS) would be beneficial. |
| The responsibilities of the Facilitator | The Facilitator will be a member of staff at the PRC UKBB. The Facilitator will be responsible for arranging meetings of the BRC, producing and circulating agendas, minutes and action points. The facilitator will work with the data manager to produce a case summary for each event to be adjudicated before the meeting of the BRC. The Facilitator will be the central point for all communications between the BRC and other bodies, will be copied into all correspondence between BRC members and will be kept aware of BRC issues as they arise. |
| Whether members of the BRC will have a contract | BRC members will not be asked to formally sign a contract but should formally register their agreement to join the group by confirming (1) that they agree to be a member of the BRC and (2) that they agree with the contents of this Charter. Any potential competing interests should be declared at the same time. Members should complete and return the form in Annexe 1. Any observers (attendees who are not members and not part of the PRC UKBB) will sign a confidentiality agreement on the first occasion they attend a meeting (Annexe 2). |
| **4. Relationships** | |
| Advisory and executive bodies | The BRC is an oversight body and is delegated the roles in Section 2. |
| The need for BRC members to disclose information about any real or potential competing interests | Any competing interests, both real or potential, should be disclosed. These are not restricted to financial matters – involvement in other trials or intellectual investment could be relevant. Although members may well be able to act objectively despite such connections, complete disclosure enhances credibility (see Annex 1).<br>BRC members should not use any trial data to inform trading in pharmaceutical shares, and careful consideration should be given to trading in stock of companies with competing products. Changes in declarations of real or potential competing interests should be minuted at the start of each meeting. |

[1] Independence is defined in Table 1 of Annexe 1

| CONTENT | DETAILS OF BRC |
|---|---|
| **5. Organisation of meetings** | |
| Expected frequency of BRC meetings | The regularity of BRC meetings will depend upon the number of accumulated clinical events to be adjudicated and will be organised on an Ad Hoc basis, depending upon the availability of members. |
| Attendance of BRC members at meetings | Minimum attendance at BRC meetings in order to make adjudication decisions should ideally include the BRC chair together with at least one other member. If the chair is not available, the meeting can go ahead with another independent member of the BRC acting as a chair for the meeting. All meetings are planned as telephone conference.<br>The PRC UKBB Facilitator will work to identify meeting dates that enable maximum attendance of BRC members. |
| How BRC meetings will be organised including who will be present in each session | All meetings are planned as telephone conference. Presence will be usually limited to the BRC members, observers from participating sites in the trial and the Facilitator. Other attendees may be invited as observers by the BRC, too. Observers are not members of the BRC but may be invited to provide input. |
| Can BRC members who cannot attend the meeting input | All decisions will be made through discussion during the BRC meeting. However, BRC members who are unable to attend may provide their input ahead of the meeting by sending comments to the facilitator. |
| What happens to independent members who do not attend meetings | If an independent member does not attend a meeting or provide comments when requested between meetings, it should be ensured that the independent member is available for the next meeting. If an independent member does not attend the next meeting or provide comments when requested, they should be asked if they wish to remain part of the BRC. If an independent member does not attend a third meeting, strong consideration should be given to replacing this member. |
| **6. BRC documentation and procedures to ensure confidentiality and proper communication** | |
| Intended content of material to be considered during meetings | A case summary will be prepared by the data manager and facilitator for each event to be adjudicated. The case summary will contain the following:<br>• Blinded trial data relevant to adjudication of the event. This data will be downloaded from the trial database by the data manager<br>• Additional clinical narrative from PI, GP records or hospital notes, if available |
| Whether documentation will be available before the meeting or only at/during the meeting | Case summaries and reference documents (see annex 5) will be circulated in advance to all BRC members attending the meeting. |
| To whom the BRC will communicate the decisions made | (See Section 8) |
| What will happen to the papers after the meeting | BRC members are expected to delete, destroy or store securely copies of the provided case summaries, any reports or communications to and from the BRC and agenda and minutes. All documentation should be considered confidential. The PRC UKBB Facilitator will keep a central record of all minutes, reports and correspondence by the BRC. |

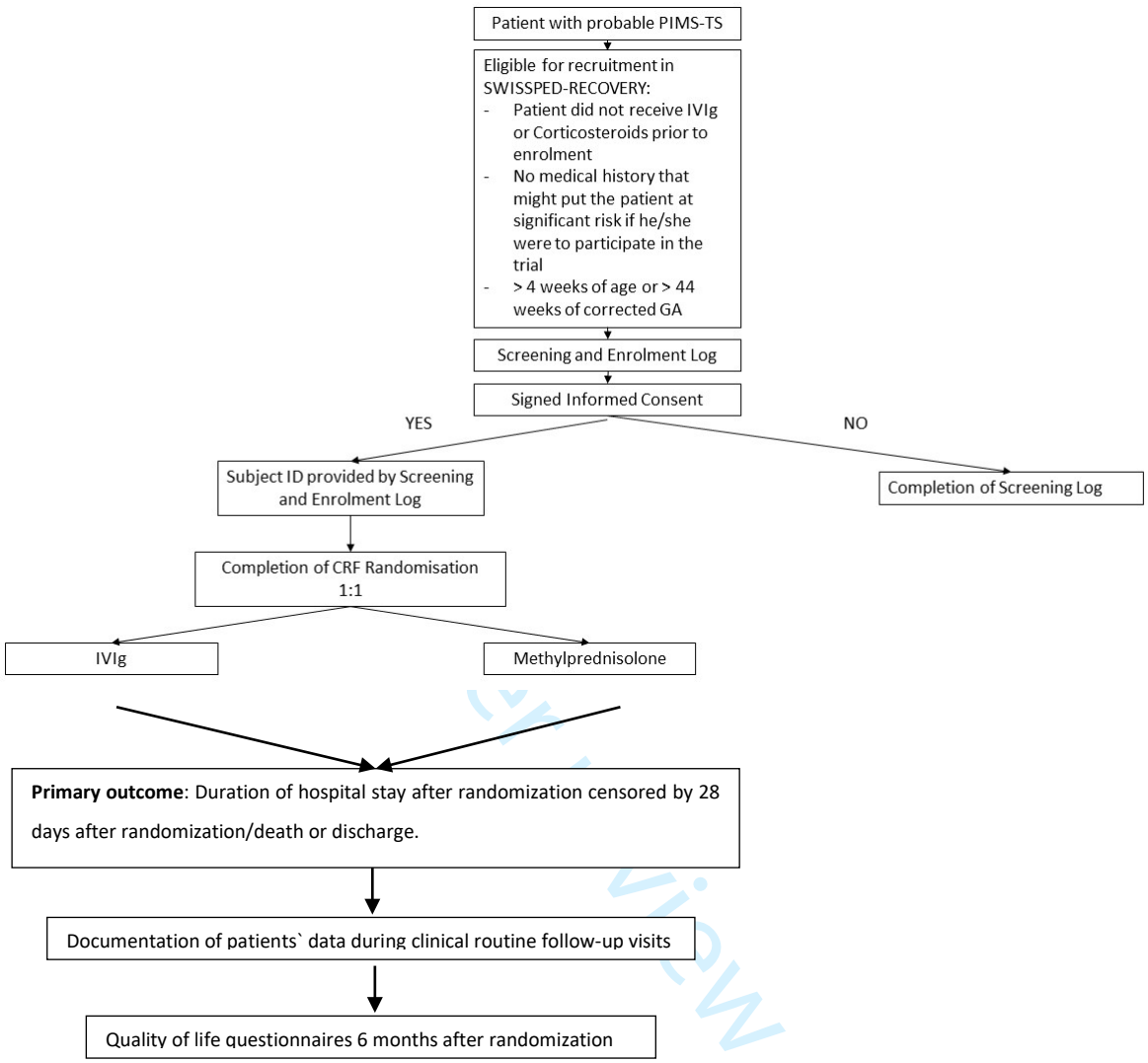
| CONTENT | DETAILS OF BRC |
|---|---|
| **7. Decision making** | |
| What is reviewed by the trial physician in advance of BRC meetings? | All events of non-trial systemic anti-inflammatory treatment reported by Swissped-RECOVERY trial sites. |
| What decisions are open to the trial physician in advance of BRC meetings | The information available for all events of non-trial systemic anti-inflammatory treatment will be screened by the trial physician in advance of a meeting of the BRC. Where the trial physician feels there is sufficient clinical information for a decision to be made by the BRC, the event will be referred to the BRC for review. Where it is felt there is insufficient clinical information for a decision, the event will be referred back to the reporting site for additional narrative and clinical information.<br>No adjudications on the endpoint will be made by the trial physician during this screening process. |
| What is reviewed at meetings of the BRC | All events of non-trial systemic anti-inflammatory treatment, referred by the trial physician following initial screening. |
| What decisions will be open to the BRC | Based on discussions within meetings of the BRC, for each event the following decisions should be made and recorded on the BRC form:<br>• Provide assessment of clinical events that might influence trial endpoints, as follows:<br>- adjudicate based on the clinical case vignettes<br>○ Disease classification<br>○ Likelihood that non-trial systemic anti-inflammatory treatment was indicated<br>○ if anti-inflammatory treatment is indicated<br>▪ Reason why<br>Guidelines for completion of the BRC form are provided in annex 4. |
| How decisions or recommendations will be reached within the BRC | The final decision will be made by members of the BRC present at the meeting. Every effort should be made to achieve consensus. The role of the Chair is to summarise discussions and encourage consensus; therefore, it is usually best for the Chair to give their own opinion last. |
| When the BRC is quorate for decision-making | (see section 5) |
| Any specific issues relating to the trial design that might influence the proceedings | (See Section 2) |
| **8. Reporting** | |
| To whom will the BRC report their recommendations/decisions, and in what form | The BRC will report their decisions using the approved BRC form (see annex 4 for guidelines on completion of the BRC form). A paper example of the BRC form will be sent with the meeting agenda via facilitator for illustrative purposes. The BRC form is programmed in Redcap and will be filled in electronically supported by the facilitator during the meeting.. A central log of all BRC adjudications and the decisions made will also be stored securely by the facilitator.<br>Following a meeting of the BRC, all completed BRC forms will be reviewed by the facilitator and/or data manager. Any resulting queries will be raised with the BRC for resolution at a subsequent |

| CONTENT | DETAILS OF BRC |
|---|---|
| | meeting. |
| **9. After the trial** | |
| The information about the BRC that will be included in published trial reports | BRC members will be named and their affiliations listed in the main report, unless they explicitly request otherwise. |
| Any constraints on BRC members divulging information about their deliberations after the trial has been published | The BRC members should not discuss issues relating to their involvement in the trial until 12 months after the primary trial results have been published. |

**Abbreviations and glossary**

| | |
|---|---|
| AE | Adverse event |
| AR | Adverse reaction |
| CF | Consent form |
| BRC | Blinded Review Commitee |
| CI | Chief Investigator |
| CRF | Case Report Form |
| CTA | Clinical Trials Authorisation |
| DMC | Data Monitoring Committee |
| HE | Health Economics |
| IB | Investigator's Brochure |
| IDMC | Independent Data Monitoring Committee |
| ISRCTN | International standard randomised controlled trial number |
| MHRA | Medicines and Healthcare products Regulatory Authority |
| MRC | Medical Research Council |
| NHS | National Health Service |
| PI | Principal Investigator |
| PIS | Patient information Sheet |
| PIMS-TS | Paediatric inflammatory multisystem syndrome-temporally associated with SARS-CoV-2 |
| QL | Quality of life |
| SAE | Serious adverse event |
| SAR | Serious adverse reaction |
| SOP | Standard operating procedures |
| SPC | Summary of product characteristics |
| SSA | Site specific assessment |
| SUSAR | Suspected unexpected serious adverse reaction |
| TMG | Trial Management Group |
| TSC | Trial Steering Committee |
| UAR | Unexpected adverse reaction |

**Figure 1: Diagram summarizing trial**



# Annexe 1: Agreement and competing interests form for independent members

**<u>Swissped-RECOVERY Blinded Review Committee</u>: Agreement to join the Blinded Review Committee as an independent member and disclosure of potential competing interests**

Please complete the following document and return to the BRC Facilitator.

(please initial box to agree)

| | |
|---|---|
| | I have read and understood the BRC Charter version V1.2, dated 18 July 2022 |
| | I agree to join the Blinded Review Committee for this trial as an independent member |
| | I agree to treat all sensitive trial data and discussions confidentially |

The avoidance of any perception that independent members of an BRC may be biased in some fashion is important for the credibility of the decisions made by the BRC and for the integrity of the trial.

Potential competing interests should be disclosed. In many cases simple disclosure up front should be sufficient. Otherwise, the (potential) independent BRC member should remove the conflict or stop participating in the BRC. **Table 1** lists potential competing interests.

| | |
|---|---|
| | **No,** I have no potential competing interests to declare |
| | **Yes,** I have potential competing interests to declare (please detail below) |

Please provide details of any potential competing interests:

_____

_____

_____

Name: _____

Signed: _____ Date: _____

**Table 1: Potential competing interests for independent members**

- Stock ownership in any commercial company manufacturing amoxicillin
- Stock transaction in any commercial company involved (if previously holding stock)
- Consulting arrangements with the Sponsor/Funder
- Ongoing advisory role to a company manufacturing amoxicillin
- Career tied up in a product or technique assessed by trial
- Hands-on participation in the trial
- Involvement in the running of the trial
- Emotional involvement in the trial
- Intellectual conflict e.g. strong prior belief in the trial's experimental arm
- Involvement in regulatory issues relevant to the trial procedures
- Investment (financial or intellectual) or career tied up in competing products
- Involvement in the writing up of the main trial results in the form of authorship

# Annexe 2: Agreement and confidentiality agreement for observers

**<u>Swissped-RECOVERY Blinded Review Committee</u>: Agreement to attend the Blinded Review Committee and treat all information confidentially**

Please complete the following document and return to the Facilitator.

(please initial box to agree)

| | |
|---|---|
| | I have received a copy of the BRC Charter version V1.2, dated 18 July 2022 |
| | I agree to attend the Endpoint Review Committee meeting on ____/_____/_____ |
| | I agree to treat as confidential any sensitive information gained during this meeting unless explicitly permitted |

Name: _____

Signed: _____ Date: _____

# Annexe 3: Summarise changes from previous version

**Version 1.0**

This is version 1.0 of the BRC charter for this trial. There are no changes to be reported.

**Version 1.1**

This is version 1.1 of the BRC charter for this trial. Names for the BRC members have been added and BRC form has been updated

**Version 1.2**

This is version 1.2 of the BRC charter for this trial. BRC charter has been updated in line with the shared decisions, which have been made during the first BRC meeting that : 1) reporting: the facilitator will capture BRC decisions in RedCap, no release of the BRC chair is required, 2) Decision: if non-randomized systemic anti-inflammatory treatment is indicated the BRC don`t have to find consensus which anti-inflammatory treatment is indicated, 3) deviation time will be reported as treatment initiation + XX hours, 4) critically ill is defined as involvement of two organ systems.

# Annex 4: BRC Form Completion Guidelines

## Blinded Review Form

**Meeting details section will be completed by the BRC facilitator during the BRC meeting.**

Question 1 – Event number

- A unique number allocated to the event being adjudicated by the Swissped-RECOVERY BRC is noted.

Question 2 – date of BRC review

- The date of review will be noted.

**Form details section will be completed by the BRC facilitator during the BRC meeting.**

Question 3 – Type of Review

- Initial will be selected for events being reviewed by the BRC for the first time. Where an event has previously been reviewed by the BRC and referred back to the site for more information, follow-up will be selected when the event is reviewed again with the additional information supplied by site. The follow-up number will be recorded as 1 for the first time an event is reviewed after being referred back to site for additional information, 2 for the second time etc.

**BRC Adjudication section**

The BRC is blinded to the randomized anti-inflammatory trial treatment. The question 4 to 6 will be discussed by the independent members of the BRC. There is only one possible answer for each question. The selected answer will be communicated to the facilitator. The facilitator will document the selected answer in the database during the meeting.

Question 4 – Classification of disease at time of event

Based on provided clinical and laboratory information the BRC should adjudge type of PIMS-TS

A) Shocked PIMS-TS

B) KD-like PIMS-TS

C) Undifferentiated PIMS-TS

D) Other disease (no further action needed)

Question 5 – Likelihood that non-trial systemic anti-inflammatory treatment was clinically indicated.

Based on provided clinical and laboratory data and additional examinations (echo, ECG) the BRC should determine whether non-trial systemic anti-inflammatory treatment was clinically indicated.

A) Definitely

B) Probably/Possibly

C) Unlikely (no further action needed)

D) No (no further action needed)

E) Too little info (no further action needed)

(Definition: Definitely >80% likely, Possibly >50 -80% likely, Unlikely >20-50% likely, No < 20% likely)

Question 6 – Primary reason for non-trial systemic ant-inflammatory treatment

The BRC should adjudicate why non-trial systemic anti-inflammatory treatment is indicated:

A) Evidence of ongoing PIMS-TS inflammation even if patients is in a stable condition
B) Evidence of ongoing PIMS-TS inflammation and worsening of the general condition
C) Evidence of ongoing PIMS-TS inflammation and critically ill patient
D Intolerance to the IMP/Adverse event
E) Other:_____

**BRC Outcome section will be completed by the facilitator during the BRC meeting**

Question 7 and 8 – Can a decision be reached today?

- If the BRC has reached a decision based on the information available in questions 4 – 6, this should be answered as "Yes".
- If the BRC has not been able to reach a decision based on the information available in questions 4 – 6, this should be answered in question 8 as "No, further information needed". The BRC facilitator will follow-up with the relevant site and requests additional information. When the additional information has been provided by the site, the case will be reviewed again by the BRC.

**Attendance section will be completed by the facilitator during the BRC meeting**

Question 9 –Attendance

The facilitator will document the attendance of the BRC members at each meeting.

**Final approval section will be completed during or up to one week after the BRC meeting by the BRC chair**

Question 10 – Final approval

- Facilitator will indicate at the e CRF that form is completed

## Annex 5: BRC Reference Documents

1) Current version of the Swissped-RECOVERY protocol (Version 1.3, 18.01.2022);
2) Current version of the BRC Forms

BMJ Open

# Swissped-RECOVERY – Masked Independent Adjudication for the Interpretation of Non-randomised Treatment in a Two-arm Open-label Randomised Controlled Trial (Methylprednisolone vs Immunoglobulins) in Paediatric Inflammatory Multisystem Syndrome Temporally Associated with SARS-CoV-2 (PIMS-TS) Involving Ten Secondary and Tertiary Paediatric Hospitals in Switzerland

| | |
|---|---|
| Journal: | *BMJ Open* |
| Manuscript ID | bmjopen-2023-078137.R2 |
| Article Type: | Original research |
| Date Submitted by the Author: | 30-Jan-2024 |
| Complete List of Authors: | Schöbi, Nina; Inselspital University Hospital Bern Children's Clinic,<br>Sanchez, Carlos; University of Basel<br>Welzel, Tatjana; University of Basel; University of Basel, Pediatric Rheumatology<br>Bamford, Alasdair; Great Ormond Street Hospital, Paediatric infectious diseases and immunology; UCL<br>Webb, Kate; University of Cape Town<br>Rojo, Pablo; University Hospital October 12<br>Tremoulet, Adriana; Rady Children's Hospital San Diego, Department of Paediatrics<br>Atkinson, Andrew; University of Basel; Washington University in St Louis School of Medicine<br>Schlapbach, Luregn; University Children's Hospital Zürich, Department of Intensive Care and Neonatalogy; The University of Queensland, Child Health Research Centre<br>Bielicki , Julia ; University of Basel; St George's University |
| Primary Subject Heading: | Paediatrics |
| Secondary Subject Heading: | Infectious diseases, Research methods |
| Keywords: | Paediatric intensive & critical care < INTENSIVE & CRITICAL CARE, Paediatric infectious disease & immunisation < PAEDIATRICS, Post-Infectious Disorders, Randomized Controlled Trial, SARS-CoV-2 Infection |
| | |

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**Original Article**

# Swissped-RECOVERY – Masked Independent Adjudication for the Interpretation of Non-randomised Treatment in a Two-arm Open-label Randomised Controlled Trial (Methylprednisolone vs Immunoglobulins) in Paediatric Inflammatory Multisystem Syndrome Temporally Associated with SARS-CoV-2 (PIMS-TS) Involving Ten Secondary and Tertiary Paediatric Hospitals in Switzerland

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## Abstract

**Objectives:** In trials of acute severe infections or inflammations frequent administration of non-randomised treatment (i.e., intercurrent event) in response to clinical events is expected. These events may affect the interpretation of trial findings. Swissped-RECOVERY was set up as one of the first randomised controlled trials worldwide, investigating the comparative effectiveness of anti-inflammatory treatment with intravenous methylprednisolone or intravenous immunoglobulins in children and adolescents with Paediatric Inflammatory Multisystem Syndrome Temporally Associated with SARS-CoV-2 (PIMS-TS). We present one approach towards improving the interpretation of non-randomised treatment in a randomised controlled trial.

**Design:** This is a pre-planned ancillary analysis of the Swissped-RECOVERY trial, a randomised multicentre open-label two-arm trial.

**Setting:** Ten Swiss paediatric hospitals (secondary and tertiary care) participated.

**Participants**: Paediatric patients hospitalised with PIMS-TS.

**Interventions:** All patient-first intercurrent events, if applicable, were presented to an independent adjudication committee consisting of four international paediatric COVID-19 experts to provide independent clinical adjudication to a set of standardised questions relating to whether additional non-randomised treatments were clinically indicated and disease classification at the time of the intercurrent event.

**Results:** Of 41 treatments in 75 participants (24/41 (59%) and 17/41 (41%) in the intravenous methylprednisolone and immunoglobulin arms of the trial, respectively), two-thirds were considered indicated. The most common treatment (oral glucocorticoids, 14/41, 35%) was mostly considered not indicated (11/14, 79%), although in line with local guidelines. Intercurrent events among patients with Shock-like PIMS-TS at baseline were mostly considered indicated. A significant proportion of patients with undifferentiated PIMS-

TS at baseline were not attributed to the same group at the time of the intercurrent event (6/12 unchanged, 4/12 Kawasaki Disease-like, 2/12 Shock-like).

**Conclusion:** The masked adjudication of intercurrent events contributes to the interpretation of results in open-label trials and should be incorporated in the future.

**Trial registration:** Swiss National Clinical Trials Portal (SNCTP000004720) and clinicaltrial.gov (NCT 04826588)

## Strengths and Limitations of this study

- These ancillary analyses were pre-planned and the non-randomised events of interest were defined a priori for further evaluation which results in an improvement of the interpretation of the trial findings.
- All case narratives were carefully masked not only regarding randomised but also non-randomised anti-inflammatory treatment. Additionally, the time point of the intercurrent event was reported as during trial treatment + x hours to avoid unmasking resulting from different durations of treatment administration.
- The small sample size and the fact that only patient-first ICEs, excluding subsequent ICEs and patients not experiencing ICEs, were adjudicated by the committee is a limitation of the study.
- The independent adjudication committee's reviews occurred in an artificial setting in a virtual meeting and in hindsight which contrasts the clinical bedside decision-making.

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**Conflict of interest statement:**

JB received grant support paid to the institution from the European and Developing Countries Clinical Trials Partnership (PediCaP, RIA2017MC-2023), Horizon 2020 (NeoIPC, grant 965328), the Swiss National Science Foundation (KIDS-STEP, grant 173532), National Institute for Health Research (CAP-IT, project 13/88/11), Innosuisse (SPEARHEAD flagship grant), the Swiss Personalised Health Network (Secretariat for Education Research and Innovation) (SwissPedHealth, award NDS-2021-911), in the past 36 months; consulting fees paid to the institution from Shionogi, Sandoz, Basilea, and GSK; payments to the institution for presentations, lectures, speakers bureaus, manuscript writing or educational events in the past 36 months from Pfizer, Sandoz, and Bayer; participated at independent data monitoring committee boards of Avenir trial (member, expenses), Lakana trial (member, unfunded), CURLY trial (Chair, unfunded) in the past 36 months; is the vice president of the SwissPedNet (unpaid) and leadership of Severe Bacterial Infection and Antimicrobial Resistance working group of the Penta Foundation (unpaid). TW gave presentations for Novartis (payment to the institution) in the past 36 months. AB had received fixed-term consultancy fees from Gilead. KW is supported by the Crick African Network (CAN). The CAN receives its funding from the UK's Global Challenges Research Fund (MR/P028071/1), the Francis Crick Institute which receives its core funding from Cancer Research UK (FC1001647), the UK Medical Research Council (FC1001647), and the Wellcome Trust (FC1001647). KW is also supported by the South African Medical Research Council with funds received from the National Treasury. The content and findings reported/ illustrated are the sole deduction, view, and responsibility of the researchers and do not reflect the official position and sentiments of the SAMRC or SA National Treasury. PJ received grant support from ViiV and consulting fees from MSD. AT received grant support paid to the institution/UCSD from the National Institute of Health and consulted Janssen

Pharmaceuticals and Kiniksa with no payment received. All other authors declared no conflicts of interest.

**Data sharing statement:**

Deidentified participant data will be shared upon reasonable request unless the request is conflicting with ongoing or planned analyses. Requests need to be addressed to the corresponding author and will require approval by the Swissped-RECOVERY steering group, and with a signed data access agreement. Researchers with a proposed use, approved by appropriate institutional review boards and the Swissped-RECOVERY Steering Committee, can access the data.

**Ethical approval statement**

The study was approved by the lead ethics committee (Ethics Committee Northwest and Central Switzerland, EKNZ, Project ID: 2021-00362); and other responsible ethics committees in Switzerland (i.e., Bern, Geneva, Eastern Switzerland, Ticino, Vaud, and Zurich). Written informed consent has been obtained by the participants and or the parents/legal guardians.

**Abbreviation list**

| | |
|---|---|
| COVID-19 | Coronavirus disease 2019 |
| IAC | independent adjudication committee |
| ICE | Intercurrent Event |
| IQR | interquartile range |
| IVIG | intravenous immunoglobulins |
| IVMP | intravenous methylprednisolone |

| | |
|---|---|
| PIMS-TS | Paediatric Inflammatory Multisystem Syndrome Temporally Associated with SARS-CoV-2 |
| REDCap | Research Electronic Data Capture |

## Introduction

In trials of acute severe infections or inflammatory syndromes, frequent administration of non-randomised treatment in response to clinical events is expected. In the terminology of the ICH E9(R1) Addendum on Estimands and Sensitivity Analyses in Clinical Trials, these are defined as *Intercurrent Events* (ICEs) (1). ICEs take place after randomisation and may affect the interpretation of trial findings. They can be a source of bias if knowledge of allocated treatment differentially affects post-randomisation patient management. The ICH Addendum outlines the importance of explicit pre-planned identification and handling of ICEs to enable all clinical questions addressed by a trial to be answered fully and robustly.

Here, we present one approach applied in a recent pragmatic open-label randomised trial (Swissped-RECOVERY) investigating the comparative effectiveness of first anti-inflammatory treatment with intravenous methylprednisolone (IVMP) or intravenous immunoglobulins (IVIG) in children and adolescents with Paediatric Inflammatory Multisystem Syndrome Temporally Associated with SARS-CoV-2 (PIMS-TS) (2,3). Patients with PIMS-TS exhibit clinical and laboratory signs of inflammation together with single or multiple organ dysfunction, in the presence of confirmed or suspected previous exposure to or infection with SARS-CoV-2 (3). Overall, the disease presentation was severe in a substantial proportion of children, and even more at the beginning of the pandemic. Therefore, treatment was warranted. However, given that at the time there was no evidence available regarding the best treatment, recommendations were based on expert opinion and consensus guidelines mostly. Corticosteroids and intravenous immunoglobulins became the mainstay of treatment informed by the resemblance of PIMS-TS cases and Kawasaki Disease. Phenotype classification, i.e., Shock-like PIMS-TS, Kawasaki Disease-like PIMS-TS, and undifferentiated PIMS-TS, emphasising different presentations and severities were routinely considered in the management of PIMS-TS in Switzerland, and therefore, included in our analyses (4). In Swissped-RECOVERY we expected non-randomised anti-

inflammatory treatments to be common and were interested in differentiating between patients experiencing these because of ongoing or progressive inflammation (considered clinically indicated and potentially related to the effectiveness of randomised treatments), and those in whom a clear clinical reason for additional non-randomised anti-inflammatory treatment was lacking. We put in place an independent adjudication committee (IAC) to evaluate these ICEs, masked to randomised and received non-randomised treatment. Here, we describe and interpret the adjudication results, including indicated and non-indicated ICEs and a comparison between randomisation arms.

## Methods

### *Study design*

This is a pre-planned ancillary analysis of the Swissped-RECOVERY trial (Swiss National Clinical Trials Portal (SNCTP000004720) and clinicaltrial.gov (NCT 04826588)), an investigator-initiated randomised multicentre open-label two-arm trial (IVIG vs IVMP) in children hospitalised with PIMS-TS at ten Swiss paediatric hospitals (Aarau, Basel, Bellinzona, Bern, Fribourg, Geneva, Lausanne, Lucerne, St. Gallen, and Zurich) (2). The study was approved by the lead ethics committee (Ethics Committee Northwest and Central Switzerland, EKNZ, Project ID: 2021-00362) and other responsible ethics committees in Switzerland (i.e., Bern, Geneva, Eastern Switzerland, Ticino, Vaud, and Zurich). Written informed consent has been obtained. We aimed to determine clinical indication of ICEs according to masked IAC consensus as the gold standard.

### *Patient and Public Involvement*

Given the expedited process of setting up this trial due to the developments of the pandemic, it was not appropriate or possible to involve patients or the public in the design, conduct, reporting, or dissemination plans of our research.

*Definition of Intercurrent Events*

ICEs of interest were defined *a priori* in a dedicated IAC charter (Supplement) as non-randomised anti-inflammatory treatments including additional or fewer doses of the randomised treatment, IVMP in the IVIG group and vice versa, biological treatment, and any oral tapering of glucocorticoids. Patients experiencing at least one of these were presented to the IAC.

*Masked independent adjudication committee*

The IAC consisted of four international PIMS-TS experts who met virtually in five sessions between June 6, 2022, and August 9, 2022. The work of the IAC was governed by a dedicated charter (Supplement), and in line with this, at least two members had to be present at each meeting. All chronologically first ICEs per patient were assessed, meaning if one patient experienced multiple ICEs, the clinical indication was adjudicated only for the first non-randomised anti-inflammatory treatment. Masked narratives were prepared and presented by a non-independent facilitator (TW), who did not contribute to the discussions about clinical indication but provided further information upon IAC request. IAC consensus decisions were required by agreement of all present experts and were recorded directly into a designated form on the electronic data capture system REDCap™.

*Configuration of ICE narratives*

The case narratives presented to the IAC included baseline *general information* (patient demographics, known exposure to a SARS-CoV-2 case, estimated number of weeks since SARS-CoV-2 exposure and underlying comorbidities), *clinical characteristics* (organ involvement, vital signs, need for inotropes, respiratory support or fluid resuscitation), *cardiological examinations* (electrocardiogram, echocardiogram), *laboratory parameters*

(SARS-CoV-2 PCR and serology, haematology, coagulation, and biochemical markers), and follow-up information for these variables until the ICE. All narratives were carefully masked regarding randomised treatment and non-randomised treatment received. The time point of the ICE was shown as 'during trial treatment + x hours' to avoid unmasking resulting from differential duration of IVIG (one dose) and IVMP (one daily dose for three consecutive days).

*Adjudication details*

The IAC adjudicated ICEs starting with disease classification at the time of the ICE, defined as in the Best Practice Recommendations for the Diagnosis and Management of PIMS-TS in Switzerland (4): i) Shock-like PIMS-TS, ii) Kawasaki Disease-like PIMS-TS, iii) undifferentiated PIMS-TS, and iv) other disease; in case of iv), no further adjudication was required. The IAC was aware of the site investigator's allocation at baseline but not at the time of the ICE. For i-iii) the first question was followed by the likelihood that the ICE was clinically indicated: i) definitely >80%, ii) probably 51-80%, iii) unlikely 21-50%, iv) not <21%, v) too little information. ICEs classified as v) were re-presented to the IAC upon receipt of additional narrative information. ICEs considered to be in category i) or ii) were classified as "clinically indicated".

*Statistical analysis*

Exploratory description of baseline patient characteristics was summarised using the number (percentage) for categorical variables and the median (interquartile range [IQR]) for continuous variables. Between group differences were investigated using the chi-square test for categorical variables and the Wilcoxon rank sum test for continuous variables. Due to the small number of patients and skewed data parametric testing was not appropriate.

A statistical significance level of 5% was considered statistically significant throughout. All analyses were performed in R (version 4.2.2) (5).

## Results

Between May 21, 2021, and April 15, 2022, a total of 76 patients were enrolled. Of these, 75 patients were included for the primary analysis (37 were allocated to IVMP, 38 to IVIG). Detailed information on the cohort, including baseline characteristics, is presented in the original publication (6).

### *Non-randomised anti-inflammatory treatment*

In total, 41 ICEs were adjudicated. In the IVMP arm, 24/37 (65%) patients experienced at least one ICE, compared to 17/38 (45%) in the IVIG arm (p=0.13).

The most common first ICE was oral glucocorticoids, with or without tapering, accounting for 14/41 (34%) ICEs (11/24 (46%) in the IVMP and 3/17 (18%) in the IVIG arm). Further first ICEs occurred because of the addition of non-randomised treatment, including IVMP >3 days or >10 mg/kg; IVMP in case of IVIG randomisation or vice versa, IVIG >2 g/kg or >1 dose and intravenous or subcutaneous anakinra administration. Figure 1

### *Independent adjudication committee findings*

Non-randomised anti-inflammatory treatment was considered clinically indicated by the IAC for 27/41 (66%) patients (13/24 (54%) in the IVMP arm, 14/17 (82%) in the IVIG arm). Overall, there was a trend towards a greater proportion of clinically indicated ICEs among patients in the IVIG arm (p=0.061). Non-indicated ICEs in the IVMP arm were dominated by receipt of oral glucocorticoids (10/11; 91%). Non-indicated ICEs were rare in the IVIG arm (3/17; 18%) and comprised in two cases of switch to IVMP and in one case of addition of oral glucocorticoids. Figure 1

A different pattern of ICEs and their clinical indication was observed among patients with the three phenotypes of PIMS-TS (Table 1). ICEs among patients with Shock-like PIMS-TS at baseline were mostly considered indicated. For patients with Kawasaki Disease-like PIMS-TS at baseline, 7/8 ICEs among patients randomised to IVIG were considered indicated, in contrast to only 2/6 among patients randomised to IVMP. ICEs were more common among patients with undifferentiated PIMS-TS at baseline and allocated to IVMP (10/12) compared to IVIG (2/12). Of note, while patients considered to show a Shock- or Kawasaki Disease-like clinical phenotype at baseline most displayed the same phenotype at the time of receipt of non-randomised anti-inflammatory treatment (12/15 Shock-like patients, 11/14 Kawasaki Disease-like patients), this was not the case for the undifferentiated PIMS-TS group (6/12 unchanged, 4/12 Kawasaki Disease-like at time of ICE, 2/12 Shock-like). Figure 2

*Clinical and laboratory characteristics of patients with ICEs*

Whereas there was a difference in baseline characteristics for patients with and without ICEs in lymphocytopaenia, thrombocytopaenia, ferritin, D-Dimers, and need for inotropic support, no such difference was observed when comparing baseline characteristics of patients with a clinically indicated vs non-indicated ICE, apart from a longer fever duration in patients with a clinically indicated ICE. Table 2

## Discussion

Swissped-RECOVERY was the first research group to publish data from a randomised controlled trial on medical interventions in patients with PIMS-TS investigating treatment response to just one immunomodulatory treatment (IVMP compared to IVIG). Masked end-point review committees have been used in open-label trials to mitigate against bias in endpoint assessment (7,8). Analogously, we involved an IAC to provide independent

adjudication on the necessity/indication for non-randomised anti-inflammatory treatments, given that their clinically indicated use may reflect limitations in effectiveness of first randomised treatment.

While we did not identify a relevant difference in effectiveness between first treatment with IVMP or IVIG in the main trial analysis taking a standard intention-to-treat approach (6), we noted the high proportion of participants receiving non-randomised anti-inflammatory treatment (41/75, 55%). With 55 % of patients receiving non-randomised anti-inflammatory treatment, there is a risk of many patients converging on a single treatment or being exposed to both treatments, reducing the informativeness of the trial. The IAC considered two out of three of these ICEs clinically indicated, mostly in children presenting with Shock-like PIMS-TS patients and in those with Kawasaki Disease-like PIMS-TS when allocated to IVIG. However, the IAC also identified one in three ICEs as not clinically indicated. Those ICEs predominantly comprised of added oral glucocorticoids. This assessment supports the conclusion that monotherapy with either IVMP or IVIG is sufficient and safe for the majority of the study population (48/75, 64 %; 34 patients with no ICE and 14 patients with a clinically non-indicated ICE) but may need to be expanded in critically unwell patients not responding to treatment after a period of observation. Our findings specifically highlight that the addition of a tapering regime of oral corticosteroids after a course of IVMP (4,9) seems to be largely unnecessary.

Disease classification and severity influence adjudication and clinical-decision making, leading to non-randomised treatment usually being considered indicated among patients with Shock-like PIMS-TS. PIMS-TS is difficult to distinguish from Kawasaki Disease. IVIG is the standard treatment for Kawasaki Disease (10) and so may have been added to the allocated treatment in a proportion of patients randomised to IVMP, due to investigator concern about

under-treating possible Kawasaki Disease. Such non-randomised treatment was usually considered non-indicated. ICEs that were identified as non-indicated may reflect variability in regional practice and evolution of local, national, and international guidelines during the trial, such as tapering of oral corticosteroids (4) (predominately related to existing recommendations for the treatment of Kawasaki Disease (9)).

IAC interpretation of ICEs in Swissped-RECOVERY had several limitations. First, narratives had to be presented in a way that prevented inferences on allocated treatment and unmasking of the exact nature of the ICE. This limited information available to the IAC, potentially impacting their adjudication. Second, IAC reviews rely on the clinical expertise of independent members. Since PIMS-TS was an emerging disease at the time of the trial, the IAC members had limited evidence available to inform management, potentially leading to more permissive adjudication relying on experience and expertise alone. Furthermore, IAC reviews occur in a somewhat artificial setting where experts adjudicate ICEs in a virtual meeting in contrast to clinicians making bedside decisions. Fourth, only patients' first ICEs were reviewed. A review of all ICEs may have provided further insight into the management of PIMS-TS patients in the trial but would have substantially increased the complexity of the review process. Fifth, the IAC was not asked to adjudicate the management of patients not experiencing ICEs. This may theoretically have identified patients who should have, in the view of the IAC, received additional anti-inflammatory treatment, adding to the interpretation of trial findings. Lastly, the analyses considering phenotype classification rely on the classification at baseline. However, especially for undifferentiated PIMS-TS, there is a substantial proportion of cases being re-classified by the IAC, which might further impact the interpretation of the results.

We considered rapid reporting of primary and secondary endpoints from an interventional randomised controlled trial in PIMS-TS, an emerging disease with a potentially high global impact, as an utmost priority. IAC review can be complex and needs to be carefully prepared and supported by the trial team to maintain masking of adjudicating members. We therefore took the decision to present the trial findings within a standard intention-to-treat framework but incorporated the IAC review in our statistical analysis plan as a key secondary analysis to address and robustly interpret expected high frequency of non-randomised anti-inflammatory treatment.

Overall, IAC reviews proved valuable in providing an independent assessment of whether non-randomised anti-inflammatory treatment was likely given as treatment for persistent or progressive PIMS-TS. This was found to have been the case in two out of three ICEs considered. Alternative or complementary strategies to minimise clinically non-indicated deviations from randomised treatment would be the utilisation of sequential randomisation as well as rigorous training and increased documentation requirements for ICEs. Neither of these strategies would have been compatible with the pragmatic nature of the trial. We therefore feel that IAC assessments should be considered in the context of the Estimand Framework in future open-label trials, as the information can be incorporated into pre-specified analyses and will help to improve the interpretation of trial findings.

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**Contributors:**

JB, TW, and CS planned and implemented the masked review of intercurrent events. JB and NS contributed to the first draft, approved the final version, and take responsibility for the accuracy of the reported findings. AB, KW, AT, PR, TW, LS, AA, and CS contributed to the draft and approved the final version. CS performed the analysis and is the data manager for Swissped-RECOVERY.

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## Data Presentation

This data has been submitted as an abstract and accepted as a poster at the Annual Meeting of the European Society of Paediatric Infectious Diseases (ESPID) in Lisbon 2023.

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## Tables

*Table 1: Independent masked adjudication of intercurrent events of additional anti-inflammatory treatment according to three clinical phenotypes of Paediatric Inflammatory Multisystem Syndrome Temporally Associated with SARS-CoV-2 (PIMS-TS)*

| | | | IVMP | IVIG | p-value |
|---|---|---|---|---|---|
| Entire trial cohort, n = 75 | | | n=37 | n=38 | 0.04 |
| | ICE | None | 13 (35%) | 21 (55%) | |
| | | Indicated | 13 (35%) | 14 (37%) | |
| | | Non-indicated | 11 (30%) | 3 (8%) | |
| Shock-like, n = 20 | | | n=10 | n=10 | 0.77 |
| | ICE | None | 2 (20%) | 3 (30%) | |
| | | Indicated | 6 (60%) | 6 (60%) | |
| | | Non-indicated | 2 (20%) | 1 (10%) | |
| Kawasaki Disease-like, n = 31 | | | n=15 | n=16 | 0.10 |
| | ICE | None | 9 (60%) | 8 (50%) | |
| | | Indicated | 2 (13%) | 7 (44%) | |
| | | Non-indicated | 4 (27%) | 1 (6%) | |
| Undifferentiated, n = 24 | | | n=12 | n=12 | 0.004 |
| | ICE | None | 2 (16%) | 10 (84%) | |
| | | Indicated | 5 (42%) | 1 (8%) | |
| | | Non-indicated | 5 (42%) | 1 (8%) | |

Considering the non-indicated ICEs among patients classified as having Kawasaki Disease-like and undifferentiated PIMS-TS at baseline, all were considered to be Kawasaki Disease-like at the time of ICE; among patients with undifferentiated PIMS-TS at baseline and non-indicated ICEs, three episodes were reclassified as Kawasaki Disease-like PIMS-TS at the time of the ICE, one was considered to be Shock-like PIMS-TS with improvement and one was considered undifferentiated PIMS-TS.

ICE = intercurrent event, IVMP = intravenous methylprednisolone, IVIG = intravenous immunoglobulins

*Table 2a and 2b: Baseline characteristics stratified by the presence or absence of an ICE (2a) and stratified by the IAC consensus (2b)*

*2a*

| N (%) for categorical variables, median [IQR] for continuous | **ICE** N=41 | **No ICE** N=34 | **p-value** |
|---|---|---|---|
| Age, years | 9.8 [6.6, 12.1] | 9.0 [6.2, 12.9] | 0.87 |
| Weight, kilogram | 32.0 [22.6, 40.5] | 28.0 [19.1, 38.1] | 0.65 |
| Fever duration, days | 3.0 [1.0, 4.0] | 2.5 [1.0, 4.0] | 0.53 |
| Any inotropes | 19 (46.3) | 6 (17.6) | 0.02 |
| Lymphocytes, G/l | 0.66 [0.47, 1.03] | 1.00 [0.64, 1.42] | 0.04 |
| Platelets, G/l | 127.00 [100.25, 166.00] | 179.50 [142.25, 260.75] | 0.004 |

| | | | |
|---|---|---|---|
| D-Dimers, ug/l | 4249.50 [1868.00, 6355.75] | 1840.00 [1233.50, 3491.25] | 0.01 |
| Ferritin, ug/l | 679.00 [447.25, 1095.75] | 247.00 [194.00, 488.00] | <0.001 |
| C-reactive Protein, mg/l | 169.50 [115.30, 230.65] | 140.50 [90.12, 199.00] | 0.13 |
| Troponin, ng/l | 11.00 [6.00, 25.80] | 24.00 [16.00, 55.10] | 0.05 |
| NTproBNP, pg/ml | 2418.50 [807.75, 7281.00] | 3330.00 [924.50, 7130.50] | 0.77 |

*2b*

| N (%) for categorical variables, median [IQR] for continuous | **ICE indicated** N=27 | **ICE non-indicated** N=14 | **p-value** |
|---|---|---|---|
| Age, years | 9.4 [8.1, 11.3] | 10.7 [6.2, 12.1] | 0.98 |
| Weight, kilogram | 32.2 [23.9, 37.8] | 32.0 [22.8, 41.8] | 0.99 |
| Fever duration, days | 1.0 [1.0, 2.0] | 3.0 [2.0, 5.0] | 0.02 |
| Any inotropes | 5 (35.7) | 14 (51.9) | 0.51 |
| Lymphocytes, G/l | 0.80 [0.70, 1.41] | 0.62 [0.45, 0.79] | 0.11 |
| Platelets, G/l | 116.50 [99.75, 133.25] | 137.00 [101.50, 177.00] | 0.31 |
| D-Dimers, ug/l | 2440.00 [1834.50, 5310.25] | 4458.50 [2306.75, 6747.25] | 0.27 |
| Ferritin, ug/l | 549.00 [444.00, 588.00] | 816.00 [552.00, 1297.00] | 0.08 |

| | | | |
|---|---|---|---|
| C-reactive Protein, mg/l | 137.00 [111.50, 230.30] | 182.30 [117.20, 235.50] | 0.66 |
| Troponin, ng/l | 13.00 [8.00, 34.00] | 10.50 [5.25, 25.00] | 0.69 |
| NTproBNP, pg/ml | 3212.50 [1360.75, 7683.50] | 1628.00 [697.00, 7199.50] | 0.51 |

2a: Difference in baseline characteristics for patients with and without ICEs in lymphocytopaenia, thrombocytopaenia, ferritin, D-Dimers, and need for inotropic support.
2b: Difference in baseline characteristics for patients with a clinically indicated versus non-indicated ICE in longer fever duration.
ICE = intercurrent event, IAC = independent adjudication committee

**Legend figures**

*Figure 1*

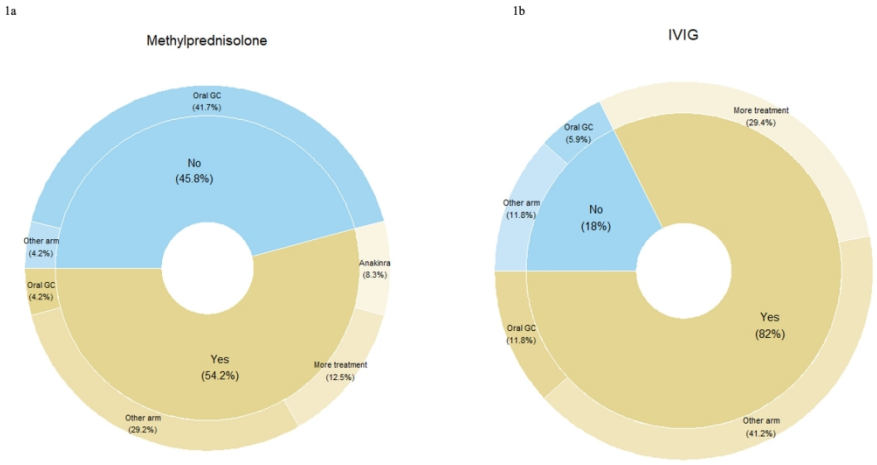
1a: A total of 24 ICEs reported; considered clinically indicated 13/24, with administration of IVIG in 7/13 clinically indicated ICEs; considered non-indicated 11/24, with administration of oral glucocorticoids in 10/11 non-indicated ICEs.
1b: A total of 17 ICEs reported; considered clinically indicated 14/17 with administration of IVMP in 7/14 clinically indicated ICEs; considered non-indicated 3/17.
ICE: intercurrent event, IVIG: intravenous immunoglobulins, IVMP: intravenous methylprednisolone, GC: glucocorticoids

*Figure 2*

Patients considered to show a Shock- or Kawasaki Disease-like clinical phenotype of PIMS-TS at baseline most displayed the same phenotype at the time of receipt of non-randomised

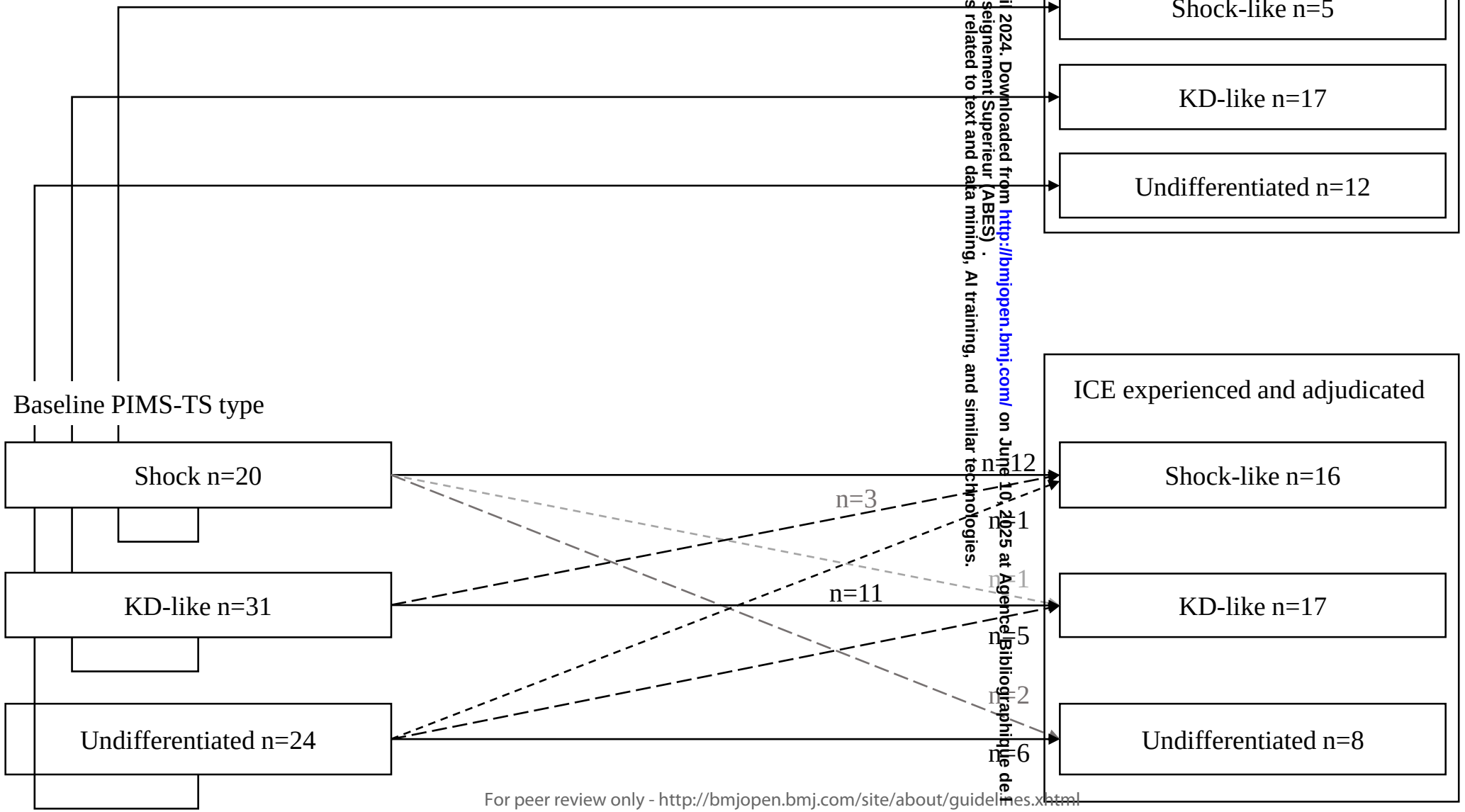
anti-inflammatory treatment (12/15 Shock-like PIMS-TS, 11/14 Kawasaki Disease-like PIMS-TS), this was not the case for the undifferentiated PIMS-TS group (6/12 unchanged, 4/12 Kawasaki Disease-like, 2/12 Shock-like at the time of the ICE).

PIMS-TS = Paediatric Inflammatory Multisystem Syndrome Temporally Associated with SARS-CoV-2, ICE = intercurrent event




Figures 1a and 1b: Independent adjudication committee findings for intercurrent events of additional anti-inflammatory treatment in patients allocated to the intravenous methylprednisolone arm (IVMP, 1a) or to the intravenous immunoglobulin arm (IVIG, 1b)

338x190mm (300 x 300 DPI)



PRC Paediatric Research Centre

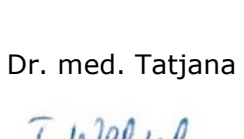
# Swiss Pediatric Randomised Evaluation of COVID-19 Therapy (Swissped RECOVERY)

NCT: 04826588

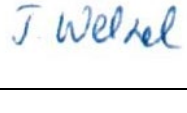
## Blinded Review Committee Charter

Version 1.2, Date 18 July 2022

**Authorised by:**

| | | | |
|---|---|---|---|
| Name: | PD Dr. med. Julia Bielicki | Role: | Sponsor-Investigator |
| Signature: |  | Date: | 20.07.2022 |

**Prepared by**

| | | | |
|---|---|---|---|
| Name: | Dr. med. Tatjana Welzel | Role: | Trial Physician |
| Signature: |  | Date: | 18.07.2022 |

| CONTENT | DETAILS OF BRC |
|---|---|
| **1. Introduction** | |
| Name (& Sponsor's ID) of trial | Swissped RECOVERY |
| Objectives of trial, including interventions being investigated | Swissped-RECOVERY will compare the effectiveness of intravenous methylprednisolone 10 mg/kg/dose over three days versus intravenous immunoglobulins (IVIG) 2 g/kg as single dose in children and adolescents hospitalized with paediatric inflammatory multisystem syndrome-temporally associated with SARS-CoV-2 (PIMS-TS).<br><br>**Interventions**<br><br>Children and adolescents will be randomised to:<br><br>Randomisation 1: Methylprednisolone 10 mg/kg/dose (maximum dose 1000 mg per day) for three days once daily<br><br>Randomisation 2: IVIG 2 g/kg/dose (maximum dose 100 g) as a single dose given as a slow infusion<br><br>**Objectives**<br><br>*Primary objective:*<br>The primary objective is to compare the effect of study treatments on the duration of hospital stay after randomization.<br><br>*Secondary objectives*<br>Secondary objectives are to assess the effects of study treatments on<br>• all-cause mortality at 28 days or discharge from hospital (whichever occurs first).<br>• among patients *not* on invasive mechanical ventilation at baseline, the composite endpoint of all-cause death or need for invasive mechanical ventilation or ECMO.<br>• the need for ventilation support (excluding O2 supplementation).<br>• duration of invasive mechanical ventilation.<br>• among patients not on inotropes at baseline, the endpoint of need for any inotropic support.<br>• the need for renal replacement therapy.<br>• cardiac outcomes.<br><br>*Other objectives*<br>• To measure the rate of major bleeding and thrombotic events in the cohort and by study treatment.<br>• To explore the use and duration of rescue treatment in the cohort and by study treatment; as well as the use and duration of indicated rescue treatment as adjudicated by a blinded review committee.<br>• To explore changes in markers of inflammation (fever, C-reactive protein) in the cohort and by study treatment.<br>• To assess health status and functional outcome as measured by the SDQ 6 months post randomisation.<br>• To explore SARS-CoV-2 vaccination patterns and attitudes |

| CONTENT | DETAILS OF BRC |
|---|---|
| | towards SARS-CoV-2 vaccination prior and after enrolment in the trial. |
| Outline of scope of Charter | The purpose of this document is to describe the membership, terms of reference, roles, responsibilities, authority, decision-making and relationships of the Blinded Review Committee (BRC) for this trial, including the timing of meetings, methods of providing information to and from the BRC, frequency and format of meetings and relationships with other trial committees. |
| Facilitation | The Swissped-RECOVERY Trial Physician at the Paediatric Research center University Children`s Hospital of Basel (PRC UKBB) will be the Facilitator for the trial. The Facilitator will be responsible for the organisation of meetings and should be copied into all communications with and between the BRC. |
| **2. Roles and responsibilities** | |
| A broad statement of the aims of the BRC | To perform independent assessment of all administered immunomodulatory treatments other anti-inflammatory than randomized trial medication that might influence the trial primary endpoints. |
| Terms of reference | The primary endpoint for the Swissped-RECOVERY study is to compare the effect of study treatments on the duration of hospital stay after randomization.<br>Reason and clinical indication for any systemic anti-inflammatory treatment other than trial medication will be adjudicated by a Blinded Review Committee (BRC) to randomised allocations.<br>The role of the Swissped-RECOVERY BRC is to adjudicate if the non-trial systemic anti-inflammatory treatment was clinically indicated. |
| Specific roles of BRC | • Provide assessment of clinical events that might influence trial endpoints, as follows:<br>- adjudicate based on the clinical case vignettes<br>○ Disease classification<br>○ Likelihood that non-trial systemic anti-inflammatory treatment was indicated<br>○ if anti-inflammatory treatment is indicated<br>▪ Reason why<br>• Maintain confidentiality of all trial information that is not already in the public domain<br>• Review and approve the BRC form<br>• Review the BRC charter |
| **Trial specific BRC issues** | |
| Any issues specific to the disease under study | • The trial is open-label, however, the BRC will be blinded to the treatment allocation.<br>• Lack of information – for some events, a limited amount of clinical information may influence the BRC decision. If more detailed information not presented in the case vignettes is needed for the BRC assessment, this can be requested from the trial physician. In this case, the assessment must be delayed until the information is available<br>• Event date is the date of the non-trial systemic anti-inflammatory treatment administration. |

| CONTENT | DETAILS OF BRC |
|---|---|
| **3. Composition** | |
| Membership and size of the BRC | All members of the Swissped-RECOVERY BRC must be blinded to study treatment allocation. The BRC consists of independent members. The BRC Chair will be independent [1] of the trial (see section 5).<br>The members of the BRC for this trial are:<br>(1) Alasdair Bamford - BRC Chair (Independent)<br>(2) Adriana Tremoulet – Independent member<br>(3) Pablo Rojo Conejo – Independent member<br>(4) Kate Webb – Independent member<br>The membership of the BRC will be reviewed in situations where members can no longer fulfil their responsibilities or where a potential conflict of interest arises. |
| The Chair, how they are chosen and the Chair's role. | The Chair should be a medical practitioner and have previous experience of serving on review committees, experience of chairing meetings, and should be able to facilitate and summarise discussions; knowledge of the disease area (PIMS-TS) would be beneficial. |
| The responsibilities of the Facilitator | The Facilitator will be a member of staff at the PRC UKBB. The Facilitator will be responsible for arranging meetings of the BRC, producing and circulating agendas, minutes and action points. The facilitator will work with the data manager to produce a case summary for each event to be adjudicated before the meeting of the BRC. The Facilitator will be the central point for all communications between the BRC and other bodies, will be copied into all correspondence between BRC members and will be kept aware of BRC issues as they arise. |
| Whether members of the BRC will have a contract | BRC members will not be asked to formally sign a contract but should formally register their agreement to join the group by confirming (1) that they agree to be a member of the BRC and (2) that they agree with the contents of this Charter. Any potential competing interests should be declared at the same time. Members should complete and return the form in Annexe 1. Any observers (attendees who are not members and not part of the PRC UKBB) will sign a confidentiality agreement on the first occasion they attend a meeting (Annexe 2). |
| **4. Relationships** | |
| Advisory and executive bodies | The BRC is an oversight body and is delegated the roles in Section 2. |
| The need for BRC members to disclose information about any real or potential competing interests | Any competing interests, both real or potential, should be disclosed. These are not restricted to financial matters – involvement in other trials or intellectual investment could be relevant. Although members may well be able to act objectively despite such connections, complete disclosure enhances credibility (see Annex 1).<br>BRC members should not use any trial data to inform trading in pharmaceutical shares, and careful consideration should be given to trading in stock of companies with competing products. Changes in declarations of real or potential competing interests should be minuted at the start of each meeting. |

[1] Independence is defined in Table 1 of Annexe 1

| CONTENT | DETAILS OF BRC |
|---|---|
| **5. Organisation of meetings** | |
| Expected frequency of BRC meetings | The regularity of BRC meetings will depend upon the number of accumulated clinical events to be adjudicated and will be organised on an Ad Hoc basis, depending upon the availability of members. |
| Attendance of BRC members at meetings | Minimum attendance at BRC meetings in order to make adjudication decisions should ideally include the BRC chair together with at least one other member. If the chair is not available, the meeting can go ahead with another independent member of the BRC acting as a chair for the meeting. All meetings are planned as telephone conference.<br>The PRC UKBB Facilitator will work to identify meeting dates that enable maximum attendance of BRC members. |
| How BRC meetings will be organised including who will be present in each session | All meetings are planned as telephone conference. Presence will be usually limited to the BRC members, observers from participating sites in the trial and the Facilitator. Other attendees may be invited as observers by the BRC, too. Observers are not members of the BRC but may be invited to provide input. |
| Can BRC members who cannot attend the meeting input | All decisions will be made through discussion during the BRC meeting. However, BRC members who are unable to attend may provide their input ahead of the meeting by sending comments to the facilitator. |
| What happens to independent members who do not attend meetings | If an independent member does not attend a meeting or provide comments when requested between meetings, it should be ensured that the independent member is available for the next meeting. If an independent member does not attend the next meeting or provide comments when requested, they should be asked if they wish to remain part of the BRC. If an independent member does not attend a third meeting, strong consideration should be given to replacing this member. |
| **6. BRC documentation and procedures to ensure confidentiality and proper communication** | |
| Intended content of material to be considered during meetings | A case summary will be prepared by the data manager and facilitator for each event to be adjudicated. The case summary will contain the following:<br>• Blinded trial data relevant to adjudication of the event. This data will be downloaded from the trial database by the data manager<br>• Additional clinical narrative from PI, GP records or hospital notes, if available |
| Whether documentation will be available before the meeting or only at/during the meeting | Case summaries and reference documents (see annex 5) will be circulated in advance to all BRC members attending the meeting. |
| To whom the BRC will communicate the decisions made | (See Section 8) |
| What will happen to the papers after the meeting | BRC members are expected to delete, destroy or store securely copies of the provided case summaries, any reports or communications to and from the BRC and agenda and minutes. All documentation should be considered confidential. The PRC UKBB Facilitator will keep a central record of all minutes, reports and correspondence by the BRC. |

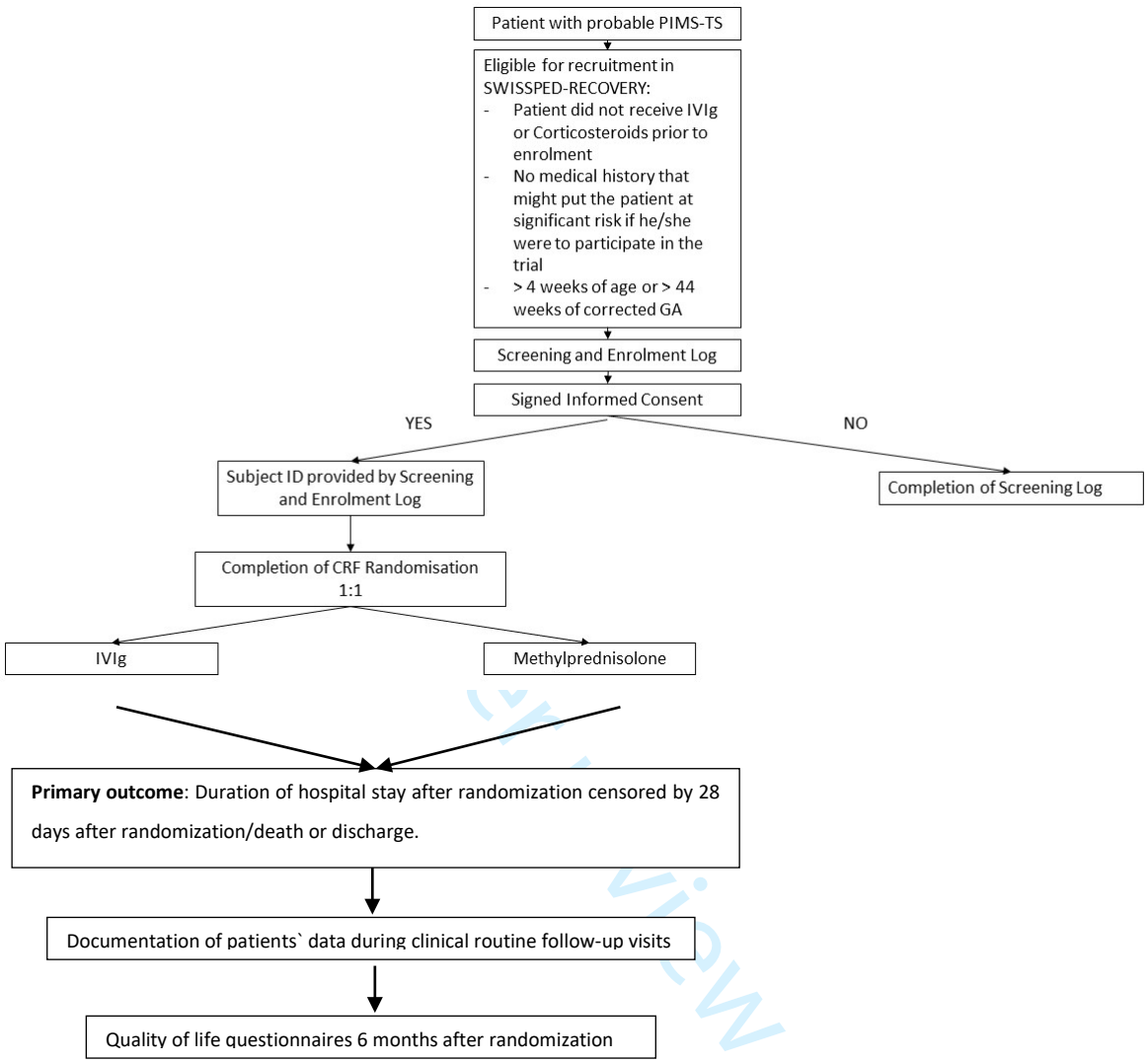
| CONTENT | DETAILS OF BRC |
|---|---|
| **7. Decision making** | |
| What is reviewed by the trial physician in advance of BRC meetings? | All events of non-trial systemic anti-inflammatory treatment reported by Swissped-RECOVERY trial sites. |
| What decisions are open to the trial physician in advance of BRC meetings | The information available for all events of non-trial systemic anti-inflammatory treatment will be screened by the trial physician in advance of a meeting of the BRC. Where the trial physician feels there is sufficient clinical information for a decision to be made by the BRC, the event will be referred to the BRC for review. Where it is felt there is insufficient clinical information for a decision, the event will be referred back to the reporting site for additional narrative and clinical information.<br>No adjudications on the endpoint will be made by the trial physician during this screening process. |
| What is reviewed at meetings of the BRC | All events of non-trial systemic anti-inflammatory treatment, referred by the trial physician following initial screening. |
| What decisions will be open to the BRC | Based on discussions within meetings of the BRC, for each event the following decisions should be made and recorded on the BRC form:<br>• Provide assessment of clinical events that might influence trial endpoints, as follows:<br>- adjudicate based on the clinical case vignettes<br>○ Disease classification<br>○ Likelihood that non-trial systemic anti-inflammatory treatment was indicated<br>○ if anti-inflammatory treatment is indicated<br>▪ Reason why<br>Guidelines for completion of the BRC form are provided in annex 4. |
| How decisions or recommendations will be reached within the BRC | The final decision will be made by members of the BRC present at the meeting. Every effort should be made to achieve consensus. The role of the Chair is to summarise discussions and encourage consensus; therefore, it is usually best for the Chair to give their own opinion last. |
| When the BRC is quorate for decision-making | (see section 5) |
| Any specific issues relating to the trial design that might influence the proceedings | (See Section 2) |
| **8. Reporting** | |
| To whom will the BRC report their recommendations/decisions, and in what form | The BRC will report their decisions using the approved BRC form (see annex 4 for guidelines on completion of the BRC form). A paper example of the BRC form will be sent with the meeting agenda via facilitator for illustrative purposes. The BRC form is programmed in Redcap and will be filled in electronically supported by the facilitator during the meeting.. A central log of all BRC adjudications and the decisions made will also be stored securely by the facilitator.<br>Following a meeting of the BRC, all completed BRC forms will be reviewed by the facilitator and/or data manager. Any resulting queries will be raised with the BRC for resolution at a subsequent |

| CONTENT | DETAILS OF BRC |
|---|---|
| | meeting. |
| **9. After the trial** | |
| The information about the BRC that will be included in published trial reports | BRC members will be named and their affiliations listed in the main report, unless they explicitly request otherwise. |
| Any constraints on BRC members divulging information about their deliberations after the trial has been published | The BRC members should not discuss issues relating to their involvement in the trial until 12 months after the primary trial results have been published. |

**Abbreviations and glossary**

| | |
|---|---|
| AE | Adverse event |
| AR | Adverse reaction |
| CF | Consent form |
| BRC | Blinded Review Commitee |
| CI | Chief Investigator |
| CRF | Case Report Form |
| CTA | Clinical Trials Authorisation |
| DMC | Data Monitoring Committee |
| HE | Health Economics |
| IB | Investigator's Brochure |
| IDMC | Independent Data Monitoring Committee |
| ISRCTN | International standard randomised controlled trial number |
| MHRA | Medicines and Healthcare products Regulatory Authority |
| MRC | Medical Research Council |
| NHS | National Health Service |
| PI | Principal Investigator |
| PIS | Patient information Sheet |
| PIMS-TS | Paediatric inflammatory multisystem syndrome-temporally associated with SARS-CoV-2 |
| QL | Quality of life |
| SAE | Serious adverse event |
| SAR | Serious adverse reaction |
| SOP | Standard operating procedures |
| SPC | Summary of product characteristics |
| SSA | Site specific assessment |
| SUSAR | Suspected unexpected serious adverse reaction |
| TMG | Trial Management Group |
| TSC | Trial Steering Committee |
| UAR | Unexpected adverse reaction |

**Figure 1: Diagram summarizing trial**



# Annexe 1: Agreement and competing interests form for independent members

**<u>Swissped-RECOVERY Blinded Review Committee</u>: Agreement to join the Blinded Review Committee as an independent member and disclosure of potential competing interests**

Please complete the following document and return to the BRC Facilitator.

(please initial box to agree)

| | |
|---|---|
| | I have read and understood the BRC Charter version V1.2, dated 18 July 2022 |
| | I agree to join the Blinded Review Committee for this trial as an independent member |
| | I agree to treat all sensitive trial data and discussions confidentially |

The avoidance of any perception that independent members of an BRC may be biased in some fashion is important for the credibility of the decisions made by the BRC and for the integrity of the trial.

Potential competing interests should be disclosed. In many cases simple disclosure up front should be sufficient. Otherwise, the (potential) independent BRC member should remove the conflict or stop participating in the BRC. **Table 1** lists potential competing interests.

| | |
|---|---|
| | **No,** I have no potential competing interests to declare |
| | **Yes,** I have potential competing interests to declare (please detail below) |

Please provide details of any potential competing interests:

_____

_____

_____

Name: _____

Signed: _____ Date: _____

**Table 1: Potential competing interests for independent members**

- Stock ownership in any commercial company manufacturing amoxicillin
- Stock transaction in any commercial company involved (if previously holding stock)
- Consulting arrangements with the Sponsor/Funder
- Ongoing advisory role to a company manufacturing amoxicillin
- Career tied up in a product or technique assessed by trial
- Hands-on participation in the trial
- Involvement in the running of the trial
- Emotional involvement in the trial
- Intellectual conflict e.g. strong prior belief in the trial's experimental arm
- Involvement in regulatory issues relevant to the trial procedures
- Investment (financial or intellectual) or career tied up in competing products
- Involvement in the writing up of the main trial results in the form of authorship

# Annexe 2: Agreement and confidentiality agreement for observers

**<u>Swissped-RECOVERY Blinded Review Committee</u>: Agreement to attend the Blinded Review Committee and treat all information confidentially**

Please complete the following document and return to the Facilitator.

(please initial box to agree)

| | |
|---|---|
| | I have received a copy of the BRC Charter version V1.2, dated 18 July 2022 |
| | I agree to attend the Endpoint Review Committee meeting on ____/_____/_____ |
| | I agree to treat as confidential any sensitive information gained during this meeting unless explicitly permitted |

Name: _____

Signed: _____ Date: _____

# Annexe 3: Summarise changes from previous version

**Version 1.0**

This is version 1.0 of the BRC charter for this trial. There are no changes to be reported.

**Version 1.1**

This is version 1.1 of the BRC charter for this trial. Names for the BRC members have been added and BRC form has been updated

**Version 1.2**

This is version 1.2 of the BRC charter for this trial. BRC charter has been updated in line with the shared decisions, which have been made during the first BRC meeting that : 1) reporting: the facilitator will capture BRC decisions in RedCap, no release of the BRC chair is required, 2) Decision: if non-randomized systemic anti-inflammatory treatment is indicated the BRC don`t have to find consensus which anti-inflammatory treatment is indicated, 3) deviation time will be reported as treatment initiation + XX hours, 4) critically ill is defined as involvement of two organ systems.

# Annex 4: BRC Form Completion Guidelines

**Blinded Review Form**

**Meeting details section will be completed by the BRC facilitator during the BRC meeting.**

Question 1 – Event number

- A unique number allocated to the event being adjudicated by the Swissped-RECOVERY BRC is noted.

Question 2 – date of BRC review

- The date of review will be noted.

**Form details section will be completed by the BRC facilitator during the BRC meeting.**

Question 3 – Type of Review

- Initial will be selected for events being reviewed by the BRC for the first time. Where an event has previously been reviewed by the BRC and referred back to the site for more information, follow-up will be selected when the event is reviewed again with the additional information supplied by site. The follow-up number will be recorded as 1 for the first time an event is reviewed after being referred back to site for additional information, 2 for the second time etc.

**BRC Adjudication section**

The BRC is blinded to the randomized anti-inflammatory trial treatment. The question 4 to 6 will be discussed by the independent members of the BRC. There is only one possible answer for each question. The selected answer will be communicated to the facilitator. The facilitator will document the selected answer in the database during the meeting.

Question 4 – Classification of disease at time of event

Based on provided clinical and laboratory information the BRC should adjudge type of PIMS-TS

A) Shocked PIMS-TS

B) KD-like PIMS-TS

C) Undifferentiated PIMS-TS

D) Other disease (no further action needed)

Question 5 – Likelihood that non-trial systemic anti-inflammatory treatment was clinically indicated.

Based on provided clinical and laboratory data and additional examinations (echo, ECG) the BRC should determine whether non-trial systemic anti-inflammatory treatment was clinically indicated.

A) Definitely

B) Probably/Possibly

C) Unlikely (no further action needed)

D) No (no further action needed)

E) Too little info (no further action needed)

(Definition: Definitely >80% likely, Possibly >50 -80% likely, Unlikely >20-50% likely, No < 20% likely)

Question 6 – Primary reason for non-trial systemic ant-inflammatory treatment

The BRC should adjudicate why non-trial systemic anti-inflammatory treatment is indicated:

A) Evidence of ongoing PIMS-TS inflammation even if patients is in a stable condition
B) Evidence of ongoing PIMS-TS inflammation and worsening of the general condition
C) Evidence of ongoing PIMS-TS inflammation and critically ill patient
D Intolerance to the IMP/Adverse event
E) Other:_____

**BRC Outcome section will be completed by the facilitator during the BRC meeting**

Question 7 and 8 – Can a decision be reached today?

- If the BRC has reached a decision based on the information available in questions 4 – 6, this should be answered as "Yes".
- If the BRC has not been able to reach a decision based on the information available in questions 4 – 6, this should be answered in question 8 as "No, further information needed". The BRC facilitator will follow-up with the relevant site and requests additional information. When the additional information has been provided by the site, the case will be reviewed again by the BRC.

**Attendance section will be completed by the facilitator during the BRC meeting**

Question 9 –Attendance

The facilitator will document the attendance of the BRC members at each meeting.

**Final approval section will be completed during or up to one week after the BRC meeting by the BRC chair**

Question 10 – Final approval

- Facilitator will indicate at the e CRF that form is completed

## Annex 5: BRC Reference Documents

1) Current version of the Swissped-RECOVERY protocol (Version 1.3, 18.01.2022);
2) Current version of the BRC Forms