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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 10 secondary and tertiary paediatric hospitals in Switzerland

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NS and CS contributed equally.

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For numbered affiliations see end of article.

Correspondence to
Dr Julia Anna Bielicki; JuliaAnna.Bielicki@ukbb.ch

Nina Schöbi ,[1] Carlos Sanchez ,[2] Tatjana Welzel,[2,3] Alasdair Bamford ,[4,5] Kate Webb,[6] Pablo Rojo,[7] Adriana Tremoulet,[8] Andrew Atkinson,[2,9] Luregn J Schlapbach,[10,11] Julia Anna Bielicki,[2,12] The Swissped-RECOVERY trial group

ABSTRACT

Objectives In trials of acute severe infections or inflammations frequent administration of non-randomised treatment (ie, 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 10 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 numbers SNCTP000004720 and 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 resulted in an improvement in 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 (ICE) 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 ICE, 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.

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 International Council for Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use E9(R1) Addendum on Estimands and Sensitivity Analysis 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 postrandomisation patient management. The ICH Addendum outlines the importance of explicit preplanned 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 IVIG became the mainstay of treatment informed by the resemblance of PIMS-TS cases and Kawasaki disease. Phenotype classification, that is, 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 ClinicalTrials.gov (NCT 04826588)), an investigator-initiated randomised multicentre open-label two-arm trial (IVIG vs IVMP) in children hospitalised with PIMS-TS at 10 Swiss paediatric hospitals (Aarau, Basel, Bellinzona, Bern, Fribourg, Geneva, Lausanne, Lucerne, St. Gallen and Zurich).[2] We aimed to determine clinical indications 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 ICEs

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 IAC

The IAC consisted of four international PIMS-TS experts who met virtually in five sessions between 6 June 2022 and 9 August 2022. The work of the IAC was governed by a dedicated charter (online supplemental file 1), 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 on IAC request. IAC consensus decisions were required by the 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 (ECG, 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 the 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]: (1) Shock-like PIMS-TS, (2) Kawasaki disease-like PIMS-TS, (3) undifferentiated PIMS-TS and (4) other disease; in case of (5), 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 (1–3), the first question was followed by the likelihood that the ICE was clinically indicated: (1) definitely >80%, (2) probably 51%–80%, (3) unlikely 21%–50%, (4) not <21%, (5) too little information. ICEs classified as (5) were represented to the IAC on receipt of additional narrative information. ICEs considered to be in category (1) or (2) 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 (IQR) for continuous variables. Between-group differences were investigated using the χ^2 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 (V.4.2.2).[5]

RESULTS

Between 21 May 2021 and 15 April 2022, a total of 76 patients were enrolled. Of these, 75 patients were included in the primary analysis (37 were allocated to IVMP and 38 were allocated 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 with 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).

IAC 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 with IVIG (2/12). Of note, while patients considered to show a Shock-like 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

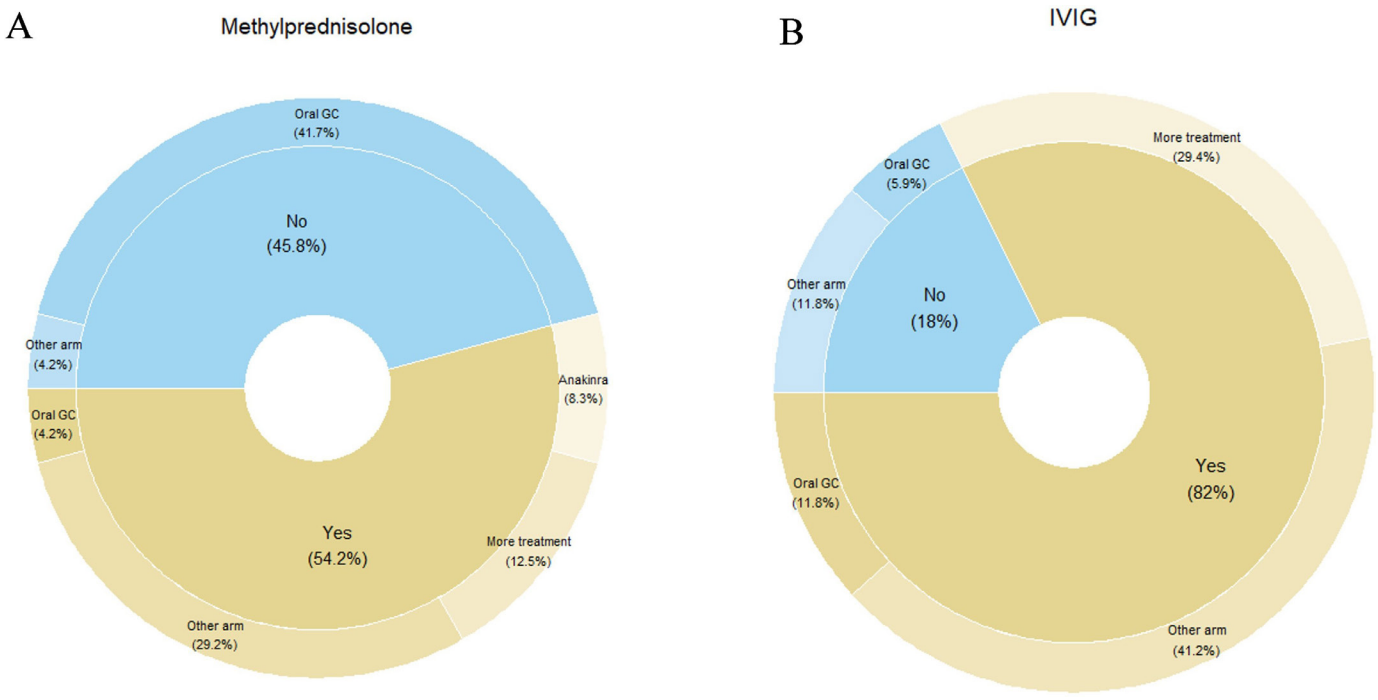

Figure 1 (A) A total of 24 ICEs reported; considered clinically indicated 13/24, with administration of IVIG in 7/13 clinically indicated ICEs; considered non-indicated 11/24, with administration of oral glucocorticoids in 10/11 non-indicated ICEs. (B) A total of 17 ICEs reported; considered clinically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

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; IVIG, intravenous immunoglobulin; IVMP, intravenous methylprednisolone.

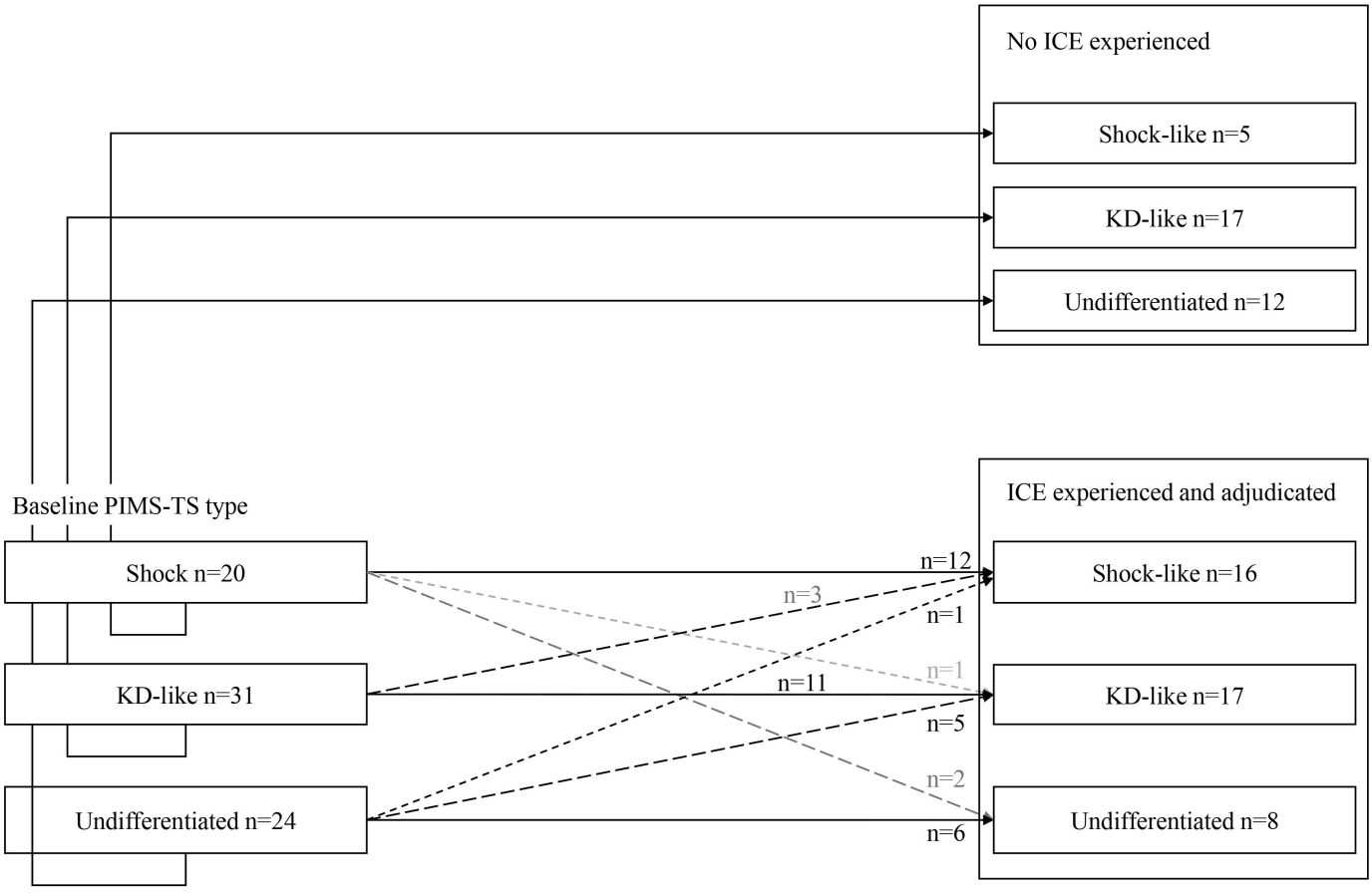

Figure 2 Patients considered to show a Shock-like or Kawasaki disease-like clinical phenotype of PIMS-TS at baseline most displayed the same phenotype at the time of receipt of non-randomised anti-inflammatory treatment (12/15 Shock-like PIMS-TS, 11/14 Kawasaki disease-like PIMS-TS), this was not the 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). ICE, intercurrent event; PIMS-TS, Paediatric Inflammatory Multisystem Syndrome Temporally Associated with SARS-CoV-2.

a clinically indicated versus 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 with 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 the first randomised treatment.

While we did not identify a relevant difference in effectiveness between the 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 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 regimen 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

Table 2 (A and B) Baseline characteristics stratified by the presence or absence of an ICE (A) and stratified by the IAC consensus (B)

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, µg/L	4249.50 (1868.00, 6355.75)	1840.00 (1233.50, 3491.25)	0.01
Ferritin, µg/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
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, µg/L	2440.00 (1834.50, 5310.25)	4458.50 (2306.75, 6747.25)	0.27
Ferritin, µg/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

A: Difference in baseline characteristics for patients with and without ICEs in lymphocytopaenia, thrombocytopaenia, ferritin, D-dimers and need for inotropic support.
B: Difference in baseline characteristics for patients with a clinically indicated vs non-indicated ICE in longer fever duration.
IAC, independent adjudication committee; ICE, intercurrent event; NTproBNP, N-Terminal Pro-B-Type Natriuretic Peptide.

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 undertreating 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 reclassified 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 the 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 the 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 prespecified analyses and will help to improve the interpretation of trial findings.

Author affiliations
[1]Paediatrics, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland
[2]Paediatric Research Centre, University Children's Hospital Basel, University of Basel, Basel, Switzerland
[3]Pediatric Rheumatology, University Children's Hospital Basel, University of Basel, Basel, Switzerland
[4]Paediatric Infectious Diseases, Great Ormond Street Hospital for Children NHS Foundation Trust, London, UK
[5]Infection, Immunity and Inflammation, UCL Great Ormond Street Institute of Child Health, London, UK
[6]Division of Paediatric Rheumatology, School of Child and Adolescent Health, Red Cross War Memorial Children's Hospital, University of Cape Town, Cape Town, South Africa
[7]Pediatrics, Hospital Universitario Doce de Octubre. Universidad Complutense. Instituto de Investigación 12 Octubre, Madrid, Spain
[8]Paediatrics, University of California San Diego, Rady Children's Hospital San Diego, San Diego, California, USA
[9]Infectious Diseases, Washington University in St. Louis School of Medicine, St. Louis, St Louis, Missouri, USA
[10]Department of Intensive Care and Neonatalogy, and Children's Research Center, University Children's Hospital Zürich, Zurich, Switzerland
[11]Child Health Research Centre, The University of Queensland, and Paediatric Intensive Care Unit, Queensland Children's Hospital, Saint Lucia, Queensland, Australia
[12]Centre for Neonatal and Paediatric Infection, St George's University, London, UK

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Collaborators Maya C Andre, MD, PhD, Division of Respiratory and Critical Care Medicine, University Children's Hospital Basel, University of Basel, Basel, Switzerland, Douggl G N Bailey, MD, Paediatric and Neonatal Intensive Care Unit, Children's Hospital of Eastern Switzerland, St. Gallen, Switzerland, Geraldine Blanchard-Rohner, MD, Paediatric Immunology and Vaccinology Unit, Division of General Paediatrics, Department of Child, Woman and Adolescent Medicine, Faculty of Medicine, Geneva University Hospitals, Geneva, Switzerland, Michael Buettcher, MD, Paediatric Infectious Diseases Unit, Department of Paediatrics, Cantonal Hospital Lucerne, Lucerne, Switzerland, Serge Grazioli, MD, Division of Neonatal and Paediatric Intensive Care, Department of Child, Woman and Adolescent Medicine, Faculty of Medicine, Geneva University Hospitals, Geneva, Switzerland, Henrik Koehler, MD, MHBA, Department of Paediatrics, Cantonal Hospital Aarau, Aarau, Switzerland, Maria-Helena Perez, MD, Paediatric Intensive Care Unit, Lausanne University Hospital and Lausanne University, Lausanne, Switzerland, Johannes Trück, MD, DPhil, Division of Immunology and Children's Research Center, University Children's Hospital Zurich, University of Zurich, Zurich, Switzerland, Federica Vanoni, PD, Institute of Paediatric of Southern Switzerland, Ente Ospedaliero Cantonale, Bellinzona, Switzerland, Petra Zimmermann, MD, PhD, Department of Paediatrics, University of Fribourg and Fribourg Hospital, Fribourg, Switzerland acted as PIs at local sites, performed patient recruitment, data collection and approved the final version of the manuscript.

Contributors JAB, TW and CS planned and implemented the masked review of intercurrent events. JAB and NS contributed to the first draft, approved the final version and took responsibility for the accuracy of the reported findings. JAB acts a guarantor. AB, KW, AT, PR, TW, LJS, AA and CS contributed to the draft and approved the final version. JAB acts as guarantor. CS performed the analysis and is the data manager for Swissped-RECOVERY.

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Competing interests JAB 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

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Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval 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 (ie, Bern, Geneva, Eastern Switzerland, Ticino, Vaud and Zurich). Written informed consent has been obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. Deidentified participant data will be shared on 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.

ORCID iDs
Nina Schöbi http://orcid.org/0000-0001-5240-5016
Carlos Sanchez http://orcid.org/0000-0002-1572-7590
Alasdair Bamford http://orcid.org/0000-0003-4764-229X

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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). **Interventions** Children and adolescents will be randomised to: Randomisation 1: Methylprednisolone 10 mg/kg/dose (maximum dose 1000 mg per day) for three days once daily Randomisation 2: IVIG 2 g/kg/dose (maximum dose 100 g) as a single dose given as a slow infusion **Objectives** *Primary objective:* The primary objective is to compare the effect of study treatments on the duration of hospital stay after randomization. *Secondary objectives* Secondary objectives are to assess the effects of study treatments on • all-cause mortality at 28 days or discharge from hospital (whichever occurs first). • among patients *not* on invasive mechanical ventilation at baseline, the composite endpoint of all-cause death or need for invasive mechanical ventilation or ECMO. • the need for ventilation support (excluding O2 supplementation). • duration of invasive mechanical ventilation. • among patients not on inotropes at baseline, the endpoint of need for any inotropic support. • the need for renal replacement therapy. • cardiac outcomes. *Other objectives* • To measure the rate of major bleeding and thrombotic events in the cohort and by study treatment. • 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. • To explore changes in markers of inflammation (fever, C-reactive protein) in the cohort and by study treatment. • To assess health status and functional outcome as measured by the SDQ 6 months post randomisation. • 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. 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. 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: - adjudicate based on the clinical case vignettes o Disease classification o Likelihood that non-trial systemic anti-inflammatory treatment was indicated o if anti-inflammatory treatment is indicated ▪ Reason why • Maintain confidentiality of all trial information that is not already in the public domain • Review and approve the BRC form • 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. • 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 • 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). The members of the BRC for this trial are: (1) Alasdair Bamford - BRC Chair (Independent) (2) Adriana Tremoulet – Independent member (3) Pablo Rojo Conejo – Independent member (4) Kate Webb – Independent member 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). 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. 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: • Blinded trial data relevant to adjudication of the event. This data will be downloaded from the trial database by the data manager • 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.

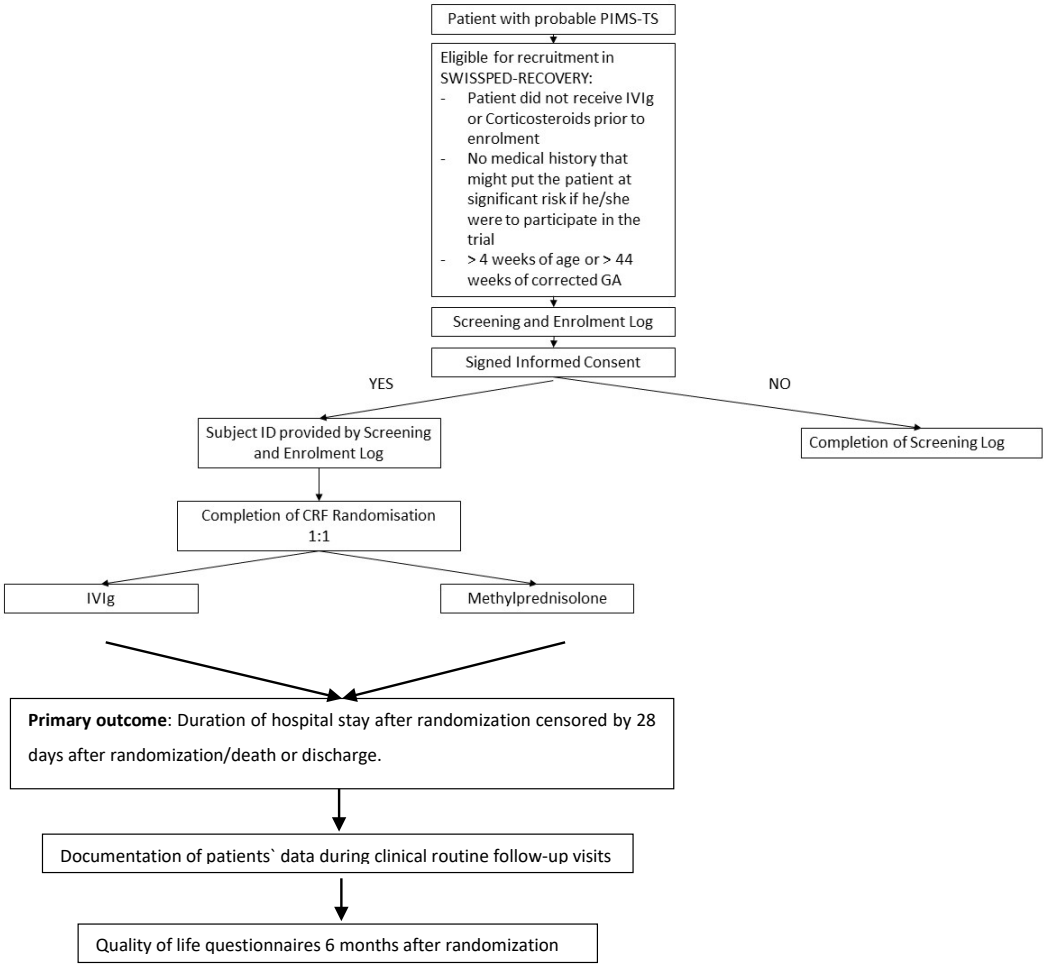
CONTENT	DETAILS OF BRC
7. Decision making	
What is reviewed by the trial physician in advance of BRC meetings?	All events of non-trial systemic anti-inflammatory treatment reported by Swissped-RECOVERY trial sites.
What decisions are open to the trial physician in advance of BRC meetings	The information 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. 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: • Provide assessment of clinical events that might influence trial endpoints, as follows: - adjudicate based on the clinical case vignettes o Disease classification o Likelihood that non-trial systemic anti-inflammatory treatment was indicated o if anti-inflammatory treatment is indicated ▪ Reason why 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. 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