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:

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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.

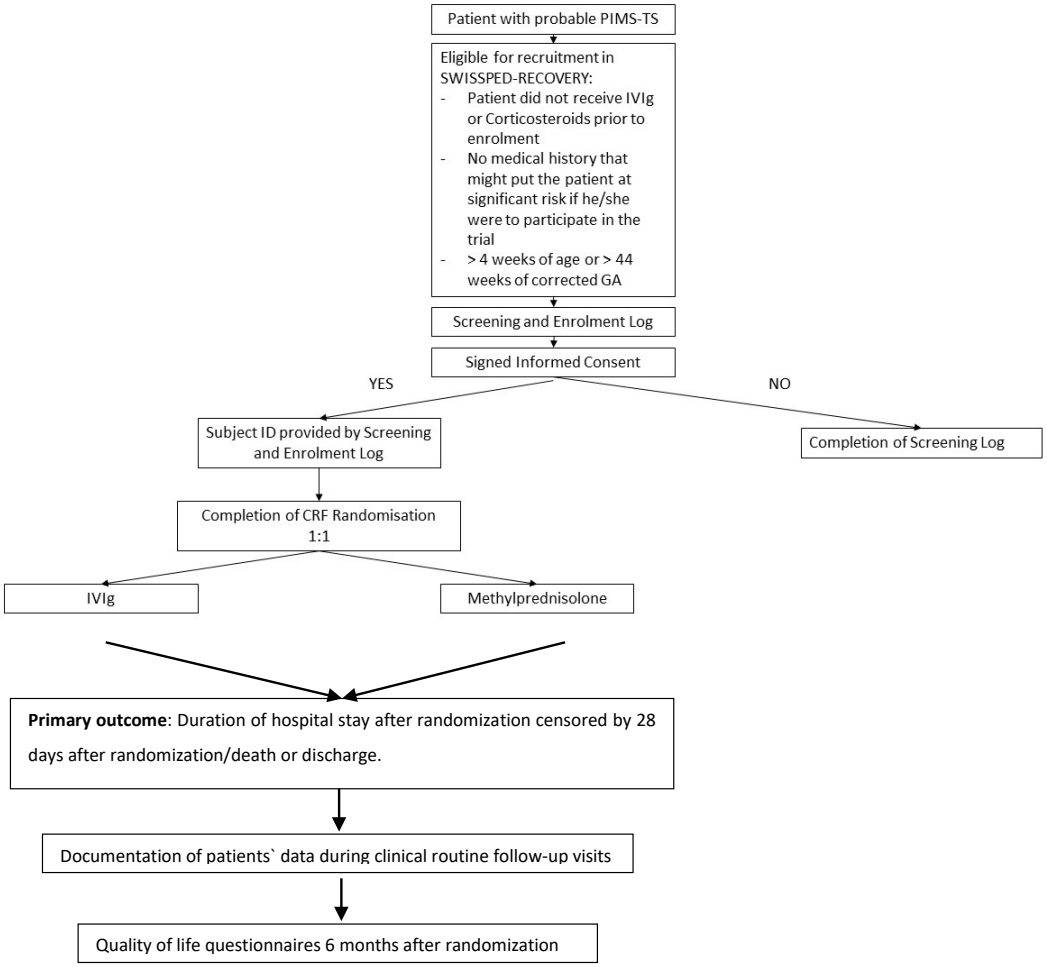
CONTENT	DETAILS OF BRC
7. Decision making	
What is reviewed by the trial physician in advance of BRC meetings?	All events of non-trial systemic anti-inflammatory treatment reported by Swissped-RECOVERY trial sites.
What decisions are open to the trial physician in advance of BRC meetings	The information 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