Randomised Evaluation of COVID-19 Therapy (RECOVERY)

Amendment (18.01.2022, V1.3) to Amendment (16.06.2021 V1.2)

Summary
This is an amendment to the amendment (Version 1.2, 16.06.2021) to the addendum (Version 1.1, 23.03.2021) to the RECOVERY international protocol (Version 13.0, 26-01-2021) providing further information relevant to the implementation of the study at Swiss study sites. The following aspects are covered:

1. Study synopsis
2. Study administrative structure in Switzerland
3. Ethical and Regulatory aspects
4. Study population
5. Relevant randomisations
6. Screening and enrolment
7. Local substudies
8. Data collection
9. Regulatory aspects and safety
10. Quality control and data protection
11. Monitoring
12. Funding

The RECOVER UK Paediatric Trial Management Group has reviewed and approved these aspects.

Study Type: Adaptive platform trial (Sister trial to the paediatric arms in RECOVERY UK)

Study Categorisation: A

Study Identifier: SWISSPED-RECOVERY

Sponsor-investigator:
Name: Dr. Julia Bielicki, MD MPH PhD
Paediatric Infectious Diseases and Vaccinology
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Phone + 41 61 7041212, Fax +41 61 704 12 13
Email: julia.bielicki@ukbb.ch

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Place/Date Signature

Co-Chief Investigator (Switzerland):

Name: Prof. Luregn Schlapbach

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Place/Date Signature

Signature Pages

Study Title Randomised Evaluation of COVID-19 Therapy (RECOVERY)

The Sponsor-Investigator, Co-Chief Investigator and Trial Statistician have approved the International Protocol Version 13.0, 26-01-2021 and the Amendment (Version 1.3, dated 18. January 2022) , and confirm hereby to conduct the study according to the protocol, current version of the World Medical Association Declaration of Helsinki, ICH-GCP guidelines or ISO 14155 norm if applicable and the local legally applicable requirements.

Sponsor-Investigator:

Dr. Julia Bielicki, MD MPH PhD

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Place/Date Signature

Co-Chief Investigator:

Prof. Luregn Schlapbach

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Place/Date Signature

Statistician:

Andrew Atkinson, PhD

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Place/Date Signature

Local Principal Investigator at study site:

I have read and understood this trial protocol and agree to conduct the trial as set out in this study protocol, the current version of the World Medical Association Declaration of Helsinki, ICH-GCP guidelines or ISO 14155 norm and the local legally applicable requirements.

Site	*University of Basel Children's Hospital*
	Spitalstrasse 33
	4056 Basel
Principal investigator	*PD Dr. med. Maya André*

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Place/Date Signature

Local Principal Investigator at study site:

I have read and understood this trial protocol and agree to conduct the trial as set out in this study protocol, the current version of the World Medical Association Declaration of Helsinki, ICH-GCP guidelines or ISO 14155 norm and the local legally applicable requirements.

Site	*University Children`s Hospital Zuerich*
	Steinwiesstr. 75
	8032 Zuerich
Principal investigator	*PD Dr. med. PhD Johannes Trueck*

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Place/Date Signature

Local Principal Investigator at study site:

I have read and understood this trial protocol and agree to conduct the trial as set out in this study protocol, the current version of the World Medical Association Declaration of Helsinki, ICH-GCP guidelines or ISO 14155 norm and the local legally applicable requirements.

Site	*Department of Pediatrics, University of Bern*
	Inselspital
	3010 Bern
Principal investigator	*Dr. med. Nina Schoebi*

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Place/Date Signature

Local Principal Investigator at study site:

I have read and understood this trial protocol and agree to conduct the trial as set out in this study protocol, the current version of the World Medical Association Declaration of Helsinki, ICH-GCP guidelines or ISO 14155 norm and the local legally applicable requirements.

Site	*Children's Hospital of Eastern Switzerland, St. Gallen*
	Claudiusstrasse 6
	9006 St. Gallen
	+41 71 243 13 77
Principal investigator	*Dr. med. univ. Douggl G N Bailey*

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Place/Date Signature

Local Principal Investigator at study site:

I have read and understood this trial protocol and agree to conduct the trial as set out in this study protocol, the current version of the World Medical Association Declaration of Helsinki, ICH-GCP guidelines or ISO 14155 norm and the local legally applicable requirements.

Site	*Department of Pediatrics, Cantonal Hospital Fribourg*
	Chemin des Pensionnats 2-6
	1752 Villars-sur-Glâne
	0041 260 306 3542
Principal investigator	*Dr. med. Petra Zimmermann*

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Place/Date Signature

Local Principal Investigator at study site:

I have read and understood this trial protocol and agree to conduct the trial as set out in this study protocol, the current version of the World Medical Association Declaration of Helsinki, ICH-GCP guidelines or ISO 14155 norm and the local legally applicable requirements.

Site	*Department of Pediatrics, Cantonal Hospital Luzern*
	Spitalstrasse
	Postfach
	6000 Luzern 16
Principal investigator	*Dr. med. Michael Buettcher*

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Place/Date Signature

Local Principal Investigator at study site:

I have read and understood this trial protocol and agree to conduct the trial as set out in this study protocol, the current version of the World Medical Association Declaration of Helsinki, ICH-GCP guidelines or ISO 14155 norm and the local legally applicable requirements.

Site	*Pediatric Intensive Care Unit* *Department of Pediatrics,* *University Hospital of Lausanne (CHUV)* *Lausanne, Switzerland* *+41 79 556 40 82*
Principal investigator	*Dr. Marie-Helene Perez*

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Place/Date Signature

Local Principal Investigator at study site:

I have read and understood this trial protocol and agree to conduct the trial as set out in this study protocol, the current version of the World Medical Association Declaration of Helsinki, ICH-GCP guidelines or ISO 14155 norm and the local legally applicable requirements.

Site	Division of Neonatal and Pediatric Intensive Care, Department of Child, Woman and, Adolescent Medecine, Geneva University Hospitals and Faculty of Medicine, Geneva, Switzerland +41 79 55 34 486
Principal investigator	*Dr. med. Serge Grazioli*

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Place/Date Signature

Local Principal Investigator at study site:

I have read and understood this trial protocol and agree to conduct the trial as set out in this study protocol, the current version of the World Medical Association Declaration of Helsinki, ICH-GCP guidelines or ISO 14155 norm and the local legally applicable requirements.

Site	*Cantonal hospital Aarau* *Department of paediatrics* *Tellstrasse 25* *5001 Aarau*
Principal investigator	*Prof. Dr. med. Henrik Köhler*

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Place/Date Signature

Local Principal Investigator at study site:

I have read and understood this trial protocol and agree to conduct the trial as set out in this study protocol, the current version of the World Medical Association Declaration of Helsinki, ICH-GCP guidelines or ISO 14155 norm and the local legally applicable requirements.

Site	*Ente Ospedaliero Cantonale Ticino (EOC)*
	Pediatrica
	6500 Bellinzona
Principal investigator	*Dr. med. Federica Vanoni*

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Place/Date Signature

1. Study synopsis

Sponsor / Sponsor-Investigator	Dr. Julia Bielicki, MD MPH PhD Paediatric Infectious Diseases and Vaccinology Universität-Kinderspital beider Basel (UKBB)
Study Title:	Swiss Pediatric Randomised Evaluation of COVID-19 Therapy
Short Title / Study ID:	SWISSPED-RECOVERY
Protocol Version and Date:	International Protocol Version 13.0, 26-01-2021 Swiss Addendum V1.1, 23 March 2021 Amendment to the Swiss Addendum V1.3, 18. January 2022
Trial registration:	NCT04826588
Study category and Rationale	A, since pharmacological products will be used according to their SmPCs in an open-label design (kofam categorizer 11.02.2021).
Clinical Phase:	The randomization described in that part is risk category A The original Recovery Protocol is a Complex clinical trial (phase III-IV)
Background and Rationale:	In 2019 a novel coronavirus-disease (COVID-19) emerged in Wuhan, China. A month later the Chinese Center for Disease Control and Prevention identified a new beta-coronavirus (SARS coronavirus 2, or SARS-CoV-2) as the aetiological agent. The clinical manifestations of COVID-19 range from asymptomatic infection or mild, transient symptoms to severe viral pneumonia with respiratory failure. In May 2020 a new COVID-associated inflammatory syndrome in children was identified, Paediatric Inflammatory Multisystem Syndrome - Temporally associated with SARS-CoV-2 (PIMS-TS).5 A rapid international consensus process identified the need to evaluate corticosteroids and intravenous immunoglobulin (IVIg) as initial therapies in PIMS-TS, and confirmed tocilizumab and anakinra as biological anti-inflammatory agents to be evaluated as a second line therapy.
Objective(s):	The primary objective is to compare the effect of study treatments on the duration of hospital stay after randomization. The secondary objectives are to assess the effects of study treatments on all-cause mortality at 28 days; and, among patients not on invasive mechanical ventilation at baseline, the composite endpoint of death or need for invasive mechanical ventilation or ECMO. Other objectives include the assessment of the effects of study treatments on the need for any ventilation (and duration of invasive mechanical ventilation), renal replacement therapy and thrombotic events and cardiac, neurological long-term outcome and quality of life post-infection as well as vaccine coverage.

Outcome(s):	Primary outcome: Duration of hospital stay after randomisation. Secondary outcomes: all-cause mortality 28 days after randomization, hospitalization status, use of ventilation including days of use and type and use of renal dialysis or hemofiltration at 28 days after randomization. Echocardiography and quality of life 6 months after randomization
Study design:	Swissped-Recovery is a sister trial to RECOVERY. The protocol describes an overarching trial design to provide reliable evidence on the efficacy of candidate therapies for children hospitalised with PIMS-TS. It is an adaptive pragmatic platform trial with an open-label randomisation as described below. New trial arms can be added as evidence emerges that other candidate therapeutics should be evaluated. The protocol is deliberately flexible so that it is suitable for a wide range of settings, allowing: - a broad range of patients to be enrolled in large numbers; - randomisation between only those treatment arms that are both available at the hospital and not believed by the enrolling doctor to be contraindicated (e.g. by particular co-morbid conditions or concomitant medications); - treatment arms to be added or removed according to the emerging evidence; and - additional substudies may be added to provide more detailed information on side effects or sub-categorisation of patient types but these are not the primary objective and are not required for participation.
Inclusion / Exclusion criteria:	Patients are eligible for the study if all of the following are true: (i) Hospitalised children (aged <18 years old) (ii) SARS-CoV-2 infection associated disease (clinically suspected or laboratory confirmed) with evidence of single or multi-organ dysfunction (called Paediatric Multisystem Inflammatory Syndrome temporally associated with COVID-19 [PIMS-TS]). (iii) No medical history that might, in the opinion of the attending clinician, put the patient at significant risk if he/she were to participate in the trial Neonates/infants with a corrected gestational age of <= 44 weeks will be excluded. In addition, if the attending clinician believes that there is a specific contra-indication to one of the active drug treatment arms or that the patient should definitely be receiving one of the active drugs, patient will not be available for randomisation.

Measurements and procedures:	All eligible patients are randomly allocated to two treatment arms in the participating hospital: Methylprednisolone 10mg/kg intravenous for three days vs intravenous immunoglobulin (main randomisation part A). The UK study allows a subsequent randomisation for children with PIMS-TS **not covered by the current Swiss addendum** (hyper-inflammatory state associated with COVID-19). For patients for whom not all the trial arms are appropriate or at locations where not all are available, randomisation will be between fewer arms. To facilitate participation, patient enrolment and all other trial procedures are greatly streamlined. Informed consent is simple and data entry is minimal. Follow-up information is recorded at a single timepoint and may be ascertained by contacting participants in person, by phone or electronically, or by review of medical records and databases. At randomisation, information will be collected on the identity of the randomising clinician and of the patient, age, sex, major co-morbidity, pregnancy, COVID-19 onset date and severity, and any contraindications to the study treatments. The main outcomes will be death (with date and probable cause), discharge (with date), need for ventilation (with number of days recorded) and need for renal replacement therapy. Reminders will be sent if outcome data have not been recorded by 28 days after randomisation.
Study Interventions:	Patients will be randomized 1:1 to the following treatments: - Methylprednisolone 10 mg/kg intravenously once daily for 3 days (max 1 g per dose) - Human normal immunoglobulin (IVIg) 2g/kg intravenously as a single dose in line with guidance for dosing and administration in Kawasaki disease The second stage randomisation specified in the International Protocol is not be available in the Amendment (V1.3, 18. January 2022) of the Swissped-Recovery Addendum V1.1, 23 March 2021.
Number of Participants with Rationale:	The larger the number randomised the more accurate the results will be, but the numbers that can be randomised will depend critically on the epidemic progress and the influence of vaccination. For the period of the trial, we estimate that between approximately 50 and 120 children across the 10 centres can be recruited. According to expert opinion, the best estimate (i.e. the mode) would be approximately 80 children assigned to each of the arms using 1:1randomisation (i.e. 40 in each arm). Accordingly, for the primary endpoint comparing mean log transformed length of stay for those on Methylprednisolone 10 mg/kg for three days (N=40) to those on Immunoglobulins (N=40) using a two-sided t-test and with a 5% significance level, we would be able to detect a normalized effect size of approximately 0.65 with 80% power.

Study Duration:	The desirable start date for screening is April 2021. Because of the adaptive nature of the trial and the expected epidemiology and key therapeutic questions for PIMS-TS in Switzerland, there is currently no pre-defined stop date for the trial. We expect an initial trial duration of 21 months.
Study Schedule:	April 2021 FPFV December 2022 LPLV
Study Centre(s):	Multi-centre study across ten Swiss centres as represented above.
Statistical Considerations:	For all outcomes, comparisons will be made between all participants randomised to the different treatment arms, irrespective of whether they received their allocated treatment ("intention-to-treat" analyses). For the primary endpoint, the log transformed time to discharge (or death) will be compared between those on methylprednisolone 10mg/kg intravenous or intravenous immunoglobulins. For time-to-event analyses, the treatment groups will be compared using the log-rank test. Kaplan-Meier estimates for the time to event will also be plotted (with associated log-rank p-values). For binary outcomes where the timing is unknown, the risk ratio and absolute risk difference will be calculated with confidence intervals and p-value reported. For the time to event endpoints discharge alive before 28 days will assume safety from the event (unless there is additional data confirming otherwise). Allowance for multiple treatment comparisons will be made. A p-value of less than 0.05 will be considered statistically significant throughout.
GCP Statement:	This study will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki, the ICH-GCP or ISO EN 14155 (as far as applicable) as well as all national legal and regulatory requirements.

2. Study administrative structure in Switzerland

2.1 Sponsor-Investigator and Co-Chief Investigator

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phone +41 44 266 37 90

2.2 Principal Investigators

- University Children`s Hospital Zurich (Kispi ZH): PD Dr. Johannes Trueck,
- University of Basel Children`s Hospital (UKBB): Dr. Maya André
- Department of Pediatrics, Inselspital Bern: Dr. Nina Schoebi,
- Department of Pediatrics, University Hospital Geneva (HUG): Dr. Serge Grazioli
- Department of Pediatrics, Centre Hospitalier Universitaire Vaudois (CHUV): PD Dr. Marie-Helene Perez
- Children`s Hospital of Eastern Switzerland: Dr Douggl Bailey
- Kantonsspital Luzern: Dr. Michael Buettcher
- Kantonsspital Fribourg: Dr. Petra Zimmermann
- Kantonsspital Aarau: Prof. Dr. Henrik Koehler
- Ente Ospedaliero Cantonale Ticino (EOC), pediatrica: Dr. Federica Vanoni

2.3 Statistician

Andrew Atkinson, PhD
Paediatric Research Centre/SwissPedNet Hub Basel
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Spitalstrasse 33, 4056 Basel, CH
Phone + 41 61 7041212, Fax +41 61 704 12 13

2.4 Monitoring Institution

Paediatric Research Centre, UKBB, Spitalstrasse 33, 4056 Basel, CH
Monitoring will be performed according to a monitoring schedule and will strictly involve staff outside of the trial.

2.5 Independent Data Monitoring Committee

The responsibility of the Independent Data Monitoring Committee (IDMC) will be to safeguard the interests of trial participants, assess the safety of the interventions during the trial, and contribute to monitoring the overall conduct of the clinical trial. The IDMC is independent of, but reports to, the TSG. The specific roles of the IDMC are to monitor evidence for treatment harm (e.g. toxicity data, SAEs, deaths), suggest additional data analyses (using blinded data where possible), for example, of main outcome measures, recommend whether the trial should continue to recruit participants or whether recruitment should be stopped due to safety reasons. A statistician or a named independent delegate will produce the report to the IDMC and will participate in IDMC meetings. Further details of IDMC functioning and procedures will be specified in the IDMC Charter agreed and signed by all IDMC members.

2.6 Any other relevant Committee, Person, Organisation, Institution

A Trial Steering Group will be formed comprising sponsor-investigator, other lead investigators (local and international, clinical and non-clinical), the trial manager and members of the Paediatric Research Centre at UKBB. The TSG will be responsible for the day-to-day running and management of the trial. Full details of the TSG functioning, including the frequency of meeting and a list of TSG members will be detailed in the TSG Charter.
To effectively interact with the RECOVERY UK study, the Swiss TSG will co-opt an expert from the RECOVERY trial group (Prof. Saul Faust, proxy Prof. Elizabeth Whittaker) who will be

invited to the regular TSG meetings and cc`d on relevant TSG conversations. In reverse, a delegate from the Swiss TSG is being invited to the regular RECOVERY meetings.
Swiss PedNet (https://www.swisspednet.ch/) will provide infrastructure support for study coordination, GCP, and monitoring.

3. Ethical and Regulatory aspects

Prior to study conduct, protocol, proposed patient information, consent form and other study-specific documents will be submitted to the Ethikkommission Nordwest- und Zentralschweiz (EKNZ) (Ethics Committee Northwest/Central Switzerland), other relevant ethics committees in Switzerland. Any amendment to the protocol will be approved by these institutions.
The decision of the CEC concerning the conduct of the study will be made in writing to the Sponsor-Investigator before commencement of this study. The clinical study can only begin once approval from all required authorities has been received.

3.1 Study registration

This study is registered on the Swiss National Clinical Trials Portal and ClinicalTrial.gov (NCT 04826588). Registration will be updated if amendments are approved.

3.2 Categorisation of the study

The study category is class A, since pharmacological products will be used according to their SmPCs in an open-label design (kofam categorizer 11.02.2021).

3.3 Competent Ethics Committee (CEC)

The responsible investigator at each site ensures that approval from an appropriately constituted CEC is obtained for SWISSPED-RECOVERY.
Reporting duties and allowed time frame (all changes in the research activity and all unanticipated problems involving risks to humans, including in case of planned or premature study end and the final report) and changes made to the protocol will not be made without prior Sponsor and CEC approval, except where necessary to eliminate apparent immediate hazards to study participants.
Premature study end, premature treatment arm end or interruption of the study will be reported within 15 days. The regular end of the study will be reported to the CEC within 90 days, the final study report will be submitted within one year after study end. Amendments are reported according to section 2.10.

3.4 Swissmedic

Not applicable.

3.5 Ethical Conduct of the Study

The study will be carried out in accordance to the protocol and with principles enunciated in the current version of the Declaration of Helsinki, the guidelines of Good Clinical Practice (GCP) issued by ICH, in case of medical device: the European Regulation on medical devices 2017/745 and the ISO Norm 14155 and ISO 14971, the Swiss Law and Swiss regulatory authority's requirements. The CEC and regulatory authorities will receive annual safety and interim reports and be informed about study stop/end in agreement with local requirements.
Study setup, randomization schedule, study conduct, and data capture will be aligned and harmonized with the UK RECOVERY trial to ensure comparability of data and enabling pre-planned later meta-analyses of patient-level data. For this purpose, a data sharing agreement between the Swiss study and RECOVERY will be signed.

3.6 Declaration of interest
There are no potential conflicts of interest to disclose.

3.7 Patient information and Informed Consent
For details please refer to section 7.4 and 7.5

3.8 Participant privacy and confidentiality
The investigator affirms and upholds the principle of the participant's right to privacy and that they shall comply with applicable privacy laws. Especially, anonymity of the participants shall be guaranteed when presenting the data at scientific meetings or publishing them in scientific journals.
Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. Subject confidentiality will be further ensured by utilising subject identification code numbers to correspond to treatment data in the computer files.
For data verification purposes, authorized representatives of the Sponsor-Investigator, a competent authority (e.g. Swissmedic), or an ethics committee may require direct access to parts of the medical records relevant to the study, including participants' medical history.

3.9 Early termination of the study
The Sponsor-Investigator may terminate the study prematurely according to certain circumstances, for example:

- ethical concerns,
- when the safety of the participants is doubtful or at risk, respectively,
- alterations in accepted clinical practice that make the continuation of a clinical trial unwise,
- early evidence of benefit or harm of the experimental intervention.

3.10 Protocol amendments
Substantial amendments are only implemented after approval of the CEC and CA respectively. Amendments affecting the International and national Protocol will be immediately notified to the CEC and CA and implemented as soon as approval has been obtained to ensure alignment with the main RECOVERY/Swissped-Recovery trial.
Under emergency circumstances, deviations from the protocol to protect the rights, safety and well-being of human subjects may proceed without prior approval of the sponsor and the CEC/CA. Such deviations shall be documented and reported to the sponsor and the CEC/CA as soon as possible.
All non-substantial amendments are communicated to the CA as soon as possible if applicable and to the CEC within the Annual Safety Report (ASR).

4. Study objectives

4.1 Primary objective
The primary objective is to provide reliable estimates of the effect of study treatment on hospital length of stay through to 28 days after randomisation.

4.2 Secondary objective
The secondary objectives are to assess the effects of study treatments on (i) all-cause mortality among patients (ii) and on patients not on invasive mechanical ventilation at baseline, the

composite endpoint of death or need for invasive mechanical ventilation or ECMO. Furthermore, other objectives include (iii) the assessment of the effect of study treatments on the need for any ventilation (and duration of invasive mechanical ventilation), (iv) renal replacement therapy and (v) thrombotic events will be studied. Additionally, (vi) quality of life and (vii) potential cardiac and neurological outcome after discharge and (viii) vaccine coverage will be assessed.

5. Study outcomes

Study outcomes will be assessed based on data recorded up to 28 days and up to 6 months after randomization. Furthermore, data from clinical routine-monitoring will be studied (1-2 weeks after discharge, 4-6 weeks after discharge and 3 months after discharge) if clinical routine controls are indicated.

5.1 Primary Outcome

For children with PIMS-TS the hospital length of stay is the primary outcome.

5.2 Secondary Outcomes

Secondary outcomes include (i) all-cause mortality, (ii) the hospitalisation status, (iii) the use of ventilation including days of use and type and (iv) the use of renal dialysis or hemofiltration and (v) thrombotic events at 28 days after randomisation. Furthermore, (vi) quality of life and (vii) potential cardiac and neurological long-term impacts of PIMS-TS and influence of different pharmacological interventions and (v) thrombotic events will be included.

6. Study design

6.1 General study design

The Swissped-Recovery is a sister trial of RECOVERY. The protocol describes an overarching trial design to provide reliable evidence on the efficacy of candidate therapies for children hospitalised with PIMS-TS receiving standard of care. It is an adaptive pragmatic platform trial with an open-label randomisation as described below. New trial arms can be added as evidence emerges that other candidate therapeutics should be evaluated.

The protocol is deliberately flexible so that it is suitable for a wide range of settings, allowing:

- a broad range of patients to be enrolled in large numbers;
- randomisation between only those treatment arms that available at the hospital and not believed by the enrolling doctor to be contraindicated (e.g. by particular co-morbid conditions or concomitant medications);
- treatment arms to be added or removed according to the emerging evidence; and additional substudies may be added to provide more detailed information on side effects or sub-categorisation of patient types but these are not the primary objective and are not required for participation.

6.2. Randomization

Eligible children with PIMS-TS will be randomized 1:1 to methylprednisolone 10 mg/kg intravenous versus intravenous immunoglobulins (IVIG). The patients will not be randomized to other treatment arms specified in section 2.4 of the International Protocol. For patients for whom not all the trial arms are appropriate or at locations where not all trial arms are available, the randomization will be between fewer arms.

The randomization module for SWISSPED-RECOVERY will be identical with that used in the RECOVERY trial in the UK for the randomization stage. The relevant code has been shared

with a trial statistician from SWISSPED-RECOVERY. Randomization will occur online with allocated treatment displayed on screen and available for download.

7. Study population

Pediatric patients are eligible for the study if they fulfil the inclusion criteria.

7.1.Inclusion criteria

- Hospitalised children (aged <18 years old)
- SARS-CoV-2 infection associated disease (clinically suspected or laboratory confirmed) with evidence of single or multi-organ dysfunction (called Pediatric Multisystem Inflammatory Syndrome temporally associated with COVID-19 [PIMS-TS]).
- No medical history that might, in the opinion of the attending clinician, put the patient at significant risk if he/she were to participate in the trial

Exclusion criteria are specified accordingly:

7.2. Exclusion criteria

- Neonates/infants with a corrected gestational age of <= 44 weeks
- If the attending clinician believes that there is a specific contra-indication to one of the active drug treatment arms or that the patient should definitely be receiving one of the active drug treatment arms, then the patient will not be available for randomisation.

7.3 Recruitment and screening

Eligible children will be identified continuously in the emergency department, paediatric wards, and intensive care units of participating paediatric centres by assessment against the eligibility criteria as listed above. Eligibility will be reviewed and documented by an appropriately trained member of staff delegated by the site PI.

7.4 Consent process

Trained investigators and local staff will explain to each participant the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits and any discomfort it may entail. It will be made completely and unambiguously clear that the parent/guardian of a child is free to refuse to participate in all or any aspect of the trial, at any time and for any reason, without incurring any penalty or affecting the treatment of their child. The family will be informed that their child's medical records will be examined by authorized persons other than their treating physician to ascertain trial outcomes.

All participants for the study will be provided a participant information sheet and a consent form describing the study and providing sufficient information for participant to make an informed decision about their participation in the study. Informed consent should be obtained from legal representatives/parents (children < 18 years). In addition, children aged ≥ 14 years should give a written consent. The patient or the next of skin do not always have the capacity to give their consent for the study in advance or at all. In this study included patients will mostly be emergency cases. If the patient/parent lack capacity to give consent due to the severity of their medical condition (e.g. acute respiratory failure or need for immediate ventilation) or prior disease, then consent may be obtained from a relative acting as the patient's legally designated representative. If no suitable relative is available after reasonable efforts to locate one, an independent doctor will declare the patients` suitability for trial participation. As such, the independent physician safeguards the participant interest and insures proper medical care. The signed document of the independent physician is the prevailing condition for inclusion of

the patient in our study. Informed consent will then be sought with the patient or a parent, if they recover sufficiently.

The participant should read and consider the statement before signing and dating the informed consent form, and should be given a copy of the signed document. The consent form must also be signed and dated by the investigator (or his designee) at the same time as the participant signs, and a copy retained as part of the study records.
Deferred or witnessed consent as outlined in section 2.2 of the International Protocol may be used in exceptional circumstances.

The formal consent of a participant, using the approved consent form, will be obtained before the participant is submitted to any study procedure. In addition, the parent/guardian of the child will be informed about the possibility of re-use of health-related data and samples from this trial for other research project. They can consent in a separate form.

7.5 Criteria of withdrawal/discontinuation of participants
The patient or the legal representative has the right to withdrawal at any time point without specifying any reasons for withdrawal.
Subjects may be withdrawn because of the appearance of a new health condition requiring care or medications prohibited by the protocol, unacceptable adverse event, refusal to continue treatment, or at the Investigator's discretion if it is in the subject's best interest. In case a patient or a parent will withdrawal the informed consent or the informed consent will not be given after primary witness consent, the data and samples will be used until time of withdrawal to assure the scientific quality of the trial. After analyse the data will be anonymized and the left-over of samples will be destroyed.

8. Statistical methods

8.1 Hypothesis
Null hypothesis: Mean length of stay is the same for methylprednisolone 10 mg/kg as that on the other treatment
Alternative Hypothesis: Mean length of stay on the methylprednisolone 10 mg/kg arm is not the same as that on the other treatment (two sided).

8.2 Determination of Sample size
The larger the number randomized the more accurate the results will be, but the numbers that can be randomized will depend critically on the progress of the epidemic and the influence of vaccination on children/family groups. For the 13 months period of the trial, we estimate that between approximately 50 and 120 children across the 10 centres can be recruited. According to expert opinion, the best estimate (i.e. the mode) would be approximately 80 children assigned to each of the arms using 1:1 randomization (i.e 40 in each arm). Accordingly, for the primary endpoint comparing mean log transformed length of stay for those on methylprednisolone 10 mg/kg (N=40) to those on intravenous immunoglobulins (N=40) using a two-sided t-test and with a 5% significance level, we would be able to detect a normalized effect size of approximately 0.65 with 80% power.

8.3 Statistical considerations

For all outcomes, comparisons will be made between all participants randomised to the different treatment arms, irrespective of whether they received their allocated treatment

("intention-to-treat" analyses).
For the primary endpoint, the log transformed time to discharge (or death) will be compared between those on methylprednisolone 10 mg/kg and those on intravenous immunoglobulins For time-to-event analyses, each treatment group will be compared using the log-rank test. Kaplan-Meier estimates for the time to event will also be plotted (with associated log-rank p-values). For binary outcomes where the timing is unknown, the risk ratio and absolute risk difference will be calculated with confidence intervals and p-value reported. For the time to event endpoints, discharge alive before 28 days will assume safety from the event (unless there is additional data confirming otherwise).
Allowance for multiple treatment comparisons due to the design will be made. A p-value of less than 0.05 will be considered statistically significant throughout.

9. Study assessments and Data collection

At randomization, information of the patients will be collected (e.g. age, sex, major co-morbidities) and any contraindications to the study treatments. Additional baseline information such as patient`s health conditions will be collected and recorded on the web-based case report form by the attending clinician or delegated study personal. Follow-up information will be ascertained (i) at day 28 after first randomization or (ii) at discharge or (iii) death (whichever is sooner) (please refer to figure 1).

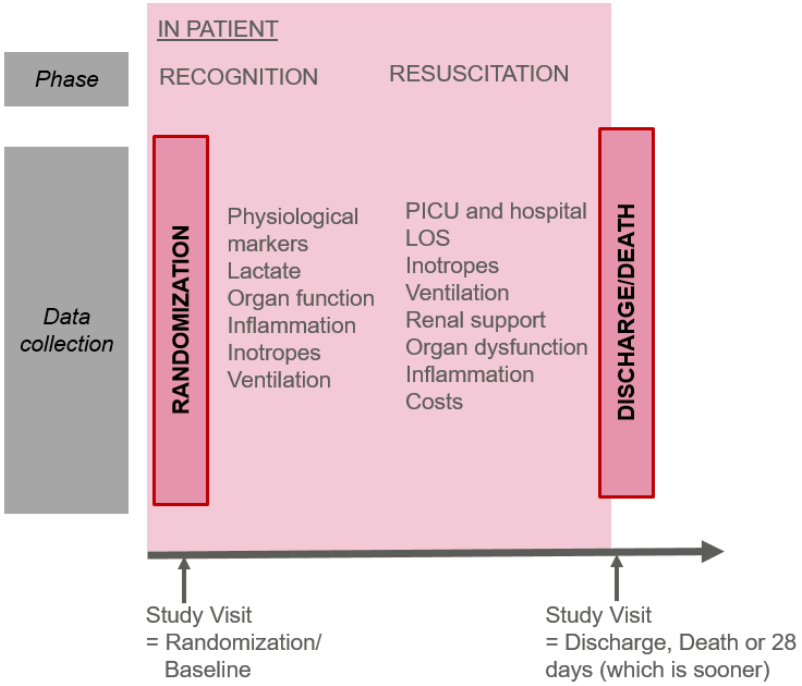

Figure 1: Study assessment and data collection at randomization/baseline and after 28 days, discharge or death (which is sooner)

After discharge/day 28 follow-up information will be collected on all study participants at each site during clinical routine follow-up visits (Figure 2). These clinical follow-up visits are routinely scheduled at 1-2 weeks, 4-6 weeks, and 3-6 months post discharge. During these clinical routine visits, usually a clinical examination, a laboratory assessment and an echocardiography is performed. Individual modification according to the clinician decisions are possible. For these follow-up visits the data collection will be from routine clinical records.

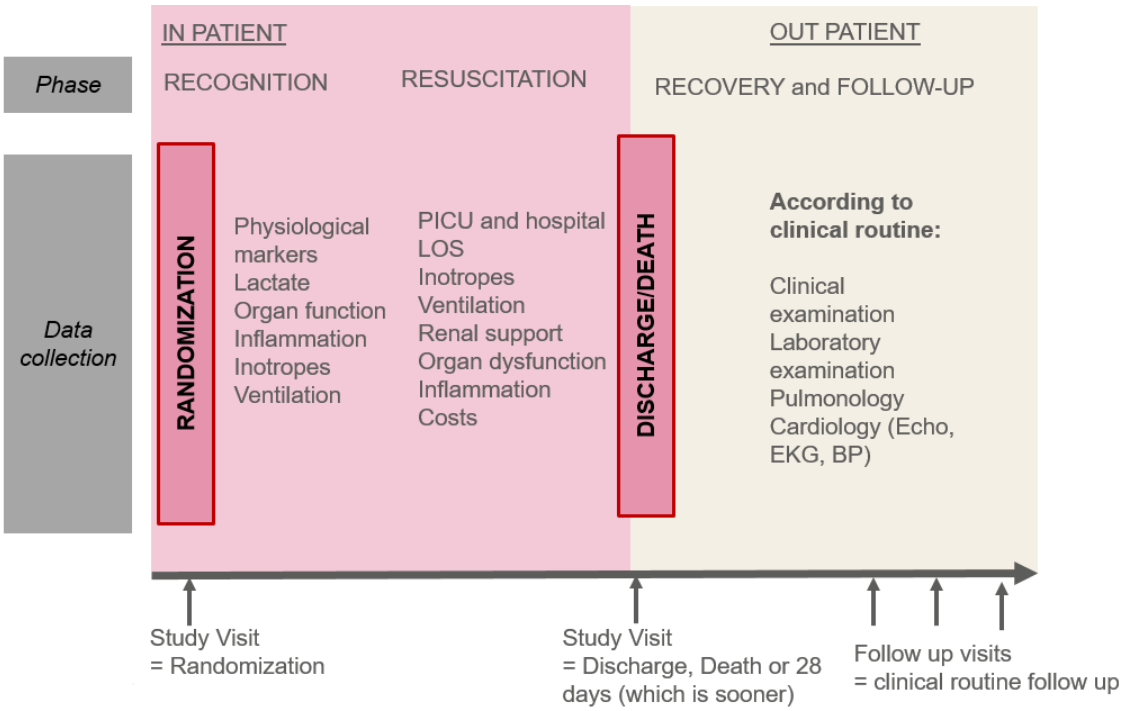

Figure 2: Study assessment and data collection at follow-up

Local substudies

Post-discharge follow-up: Quality of Life, post-traumatic stress disorder, and measures of functional recovery such as school attendance up to six months post PIMS-TS diagnosis will be evaluated. Cardiac function and presence of coronary artery aneurysms will be assessed by echocardiography.

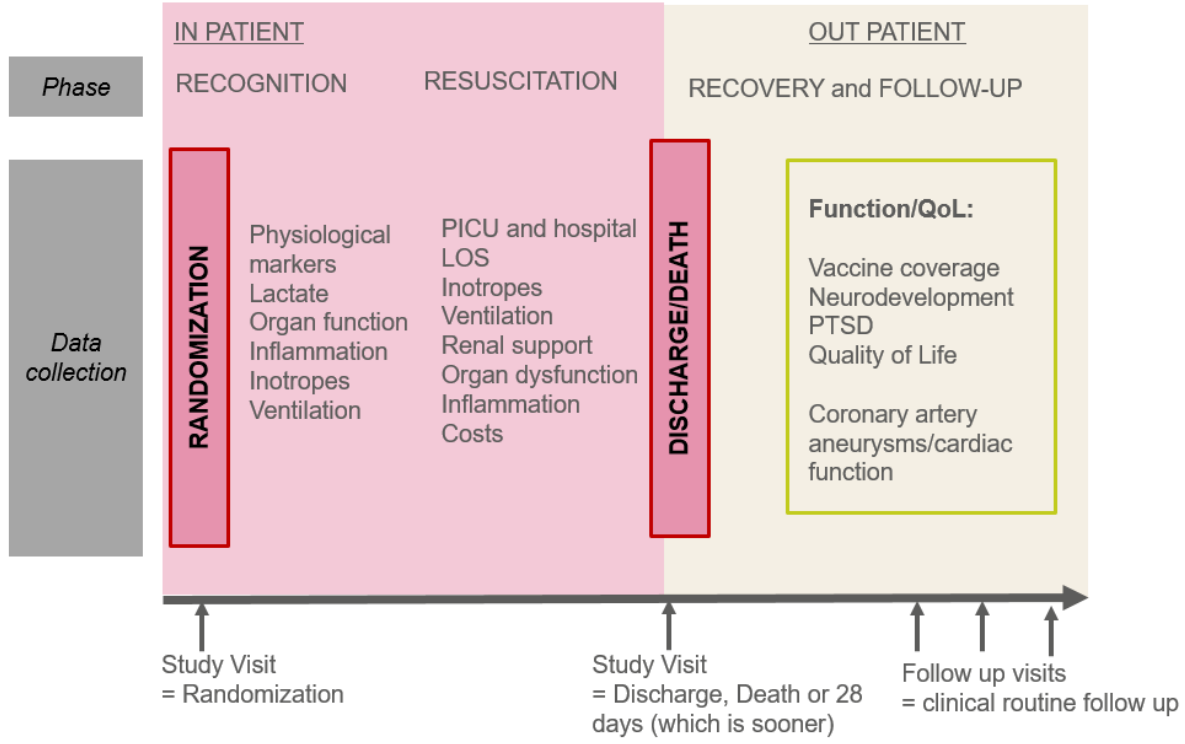

Figure 3: Sub study Quality of Life, post-traumatic stress disorder, and measures of functional recovery paired with vaccine coverage**.**

Health care costs: Direct hospitalization-related costs will be captured for health economic analyses. For each PIMS-TS related hospitalization episode recruited in the study, the total Diagnosis-Related Group (DRG) costs claimed by the respective study site will be extracted from the institutional finance records, and analysed in batch upon completion of recruitment.

Data collection

A simplified study schedule including data of interest and follow-up visits is shown below. For further specification of the data of interest, please see sections 2.3 And 2.7 of the International Protocol. Data collection will be from routine clinical records, except for the extended follow-up.

Study schedule

Days in trial	**Enrolment**	**Randomization**	**Final visit**	**Extended f/u**
	0	**1**	**28[1]**	**At routine outpatient follow-up**
Trial participation				
Eligibility screen	X			
Patient/parent information sheet	X°			
Informed consent	X°			
Trial intervention first randomization		X		
Trial intervention second randomization		X		
Clinical assessments				
Acute and past medical history		X		X
Vital signs		X		
Treatment included in RECOVERY		X	X	
Supportive/directed treatment		X	X	
Specified adverse events		X	X	
Concomitant care/ Healthcare utilization		X	X	X
Disposition/outcome			X	
Quality of Life assessments				X
Vaccine coverage data				x
Laboratory assessments				
SARS-CoV-2 diagnostics	(X)	(X)	(X)	
Haematology	(X)	(X)	(X)	
Biochemistry	(X)	(X)	(X)	
Imaging				
Chest X-ray	(X)	(X)	(X)	
Echocardiography	(X)	(X)	(X)	X

[1]recorded at discharge, upon death or at 28 days (whichever is sooner)

X° Witnessed or deferred consent may be used in exceptional cases.

(X) indicates tests that may be done based on clinical assessment. Results will be collected, if available.

Light grey shading: only relevant for substudies.

10. Regulatory aspects and safety

10.1 Definition and assessment of (serious) adverse events and other safety related events

An **Adverse Event (AE)** is any untoward medical occurrence in a patient or a clinical investigation participant administered a pharmaceutical product and which does not necessarily have a causal relationship with the study procedure. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. [ICH E6 1.2]

A **Serious Adverse Event (SAE)** is classified as any untoward medical occurrence that:

- results in death,
- is life-threatening,
- requires in-patient hospitalization or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity, or
- is a congenital anomaly/birth defect

In addition, important medical events that may not be immediately life-threatening or result in death, or require hospitalisation, but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed above should also usually be considered serious. [ICH E2A].

SAEs should be followed until resolution or stabilisation. Participants with ongoing SAEs at study termination (including safety visit) will be further followed up until recovery or until stabilisation of the disease after termination.

Assessment of Causality

Both Investigator and Sponsor-investigator make a causality assessment of the event to the study drug, based on the criteria listed in the ICH E2A guidelines:

Relationship	Description
Definitely	Temporal relationship Improvement after dechallenge* Recurrence after rechallenge (or other proof of drug cause)
Probably	Temporal relationship Improvement after dechallenge No other cause evident
Possibly	Temporal relationship Other cause possible
Unlikely	Any assessable reaction that does not fulfil the above conditions
Not related	Causal relationship can be ruled out
*Improvement after dechallenge only taken into consideration, if applicable to reaction	

Unexpected Adverse Drug Reaction
An “unexpected” adverse drug reaction is an adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator’s Brochure for drugs that are not yet approved and Product Information for approved drugs, respectively). [ICH E2A]

Suspected Unexpected Serious Adverse Reactions (SUSARs)
The Sponsor-Investigator evaluates any SAE that has been reported regarding seriousness, causality and expectedness. If the event is related to the investigational product and is both serious and unexpected, it is classified as a SUSAR

10.2 Reporting of serious adverse events (SAE) and other safety related events
The focus on severe adverse event (SAE) is on those events are likely to be related with the study medication. Examples include anaphylaxis, Steven Johnson Syndrome or bone marrow failure, where there is no other plausible explanation. Anticipated events, including SAEs, that are either efficacy endpoints or consequences of the underlying disease will be exempted from expedited reporting. Thus, the following events will be exempted from expedited reporting:
(i) Events which are the consequence of COVID-19; and
(ii) Common events which are the consequence of conditions preceding randomisation.

If a **SAE** occurs, it will be reported within a maximum of 24 hours to the Sponsor-Investigator of the study. The Sponsor-Investigator will re-evaluate the SAE. SAEs resulting in death are reported to the Ethics Committee via BASEC within 7 days. The other in the trial involved Ethics Committees receive SAEs resulting in death in Switzerland via Sponsor-Investigator via BASEC within 7 days.

A **SUSAR** needs to be reported to the Ethics Committee (local event via local Investigator) via BASEC within 7 days, if the event is fatal, or within 15 days (all other events). The Sponsor-Investigator must inform all Investigators participating in the clinical study of the occurrence of a SUSAR. All in the trial involved Ethics Committees will be informed about SUSARs in Switzerland via Sponsor-Investigator via BASEC according to the same timelines.

If a sub-protocol or arm is closed early by the sponsor due to a non-favourable benefit-risk balance, the end of such part of the trial should be communicated as an urgent safety measure or as a substantial amendment related to an urgent safety measure. The reason for the early termination and implication for the trial subjects, including description of any intended follow-up activities, should be provided in both cases Urgent safety measure will be reported via BASEC within 7 days according to Art. 37 KlinV.

Substantial changes to the project set-up, the protocol and relevant project documents will be submitted to the Ethics Committee for approval according to KlinV Art. 29 before implementation. Exceptions are measures that have to be taken immediately in order to protect the participants.
Upon project discontinuation, the Ethics Committee is notified within 15 days. Upon project completion, the Ethics Committee is notified within 90 days.

11. Quality control and data protection

The Pediatric Research Centre at UKBB will implement a quality control system on behalf of the sponsor-investigator to ensure adherence to study procedures at all study sites and monitor the conduct of the study. Written standard operating procedures (SOPs) and a manual of operations will be issued to all sites.

All data collected for central analysis in the study, whether clinical data recorded in the electronic data capture (EDC) system or other data, will be coded by a unique randomly generated participant study ID. All personnel involved will be trained in project-related procedures and all-important aspects, including data entry. A project-specific delegation log will be kept to document training and project-related specific responsibilities of staff members. For quality assurance the Ethics Committee may visit the research sites. Direct access to the source data and all project related files and documents must be granted on such occasions.

Relevant clinical study data for each enrolled study participant, i.e. observations, tests and assessments specified in the protocol, are recorded via the web-based EDC system in REDCap™. The REDCap™ database is accessible via the internet. Electronic access is strictly controlled using role-based access permissions defined by the local REDCap™ administrator and by the Principal Investigator. The data are stored on a firewall-protected UKBB server and regularly backed up. All data modifications can be identified through a complete audit trail.

Local investigators registered with the sponsor-investigator will be authorized for the eCRF entries of study participants enrolled at the site. Investigators will be trained to use the EDC system during the site initiation visit. The investigators ensure the accuracy, completeness, and timeliness of the data recorded and provide answers to data queries, as specified in the study protocol and in accordance with additional instructions. The identity of the local investigator entering data and date and time of data entry will be recorded as meta-data in the study database.

The local investigator is required to maintain an accurate medical record of all original documents and data relevant to the study as source documentation. The participant study ID will be noted in the patients' medical record and a copy of the signed informed consent form will be filed in the medical record to identify study participants locally at the study site.

All project data will be handled in accordance with the Ordinance to the Federal Act on Data Protection (DPO) of 14 June 1993 and with uttermost discretion. It is only accessible to authorized personnel who require the data to fulfil their duties within the scope of the research project. All personal and medical information obtained for this study is confidential and disclosure to third parties other than those essential to the implementation of the project or noted below is prohibited.

Clinical source data will be kept at the study sites in the patients' medical records and include demographic and clinical data, medical history, prescribed medication during admission, all clinical examinations and all laboratory and radiological evaluations undertaken as part of routine clinical care. Data which are directly recorded in the eCRF will also be considered as source documents and include detailed documentation of all study eligibility criteria as well as a confirmation that the participant has signed the informed consent form.

All study data will be archived for a minimum of 10 years after study termination or premature termination of the clinical trial. Study-relevant source data and documents will be archived at study sites for a minimum of 10 years.

12. Monitoring

At each participating site, the principal investigator will confirm that the site has adequate facilities and resources to carry out the study. The sponsor-investigator, representatives of the trial management team and a designated external study monitor will conduct a site initiation

visit at each study site to inspect the site facilities, verify qualifications of the local investigators and inform the local teams of responsibilities and the procedures for ensuring adequate and correct documentation and use of the EDC system as well as providing training on implementing all trial activities.
As outlined in the main protocol, monitoring visits at sites are not envisaged. In exceptional circumstances, an onsite monitoring visit may be arranged as considered appropriate based on perceived training needs and the results of central data-based monitoring.

13. Funding

This research project is an investigator-initiated project. We are currently seeking funding from charitable foundations to provide site and trial team support. The study has been endorsed by SwissPedNet. We declare no conflict of interest (independence, intellectual, financial, proprietary).