


BMJ Open Cytokine adsorption in patients with severe COVID-19 pneumonia requiring extracorporeal membrane oxygenation: protocol for a randomised, controlled, open-label intervention, multicentre trial

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ABSTRACT

Introduction Venovenous extracorporeal membrane oxygenation (V-V ECMO) is a last resort treatment option in patients with severe COVID-19 related acute respiratory distress syndrome (ARDS). Mortality in these critically ill patients is high. Elevated interleukin-6 (IL-6) levels in these severe courses are associated with poor outcome. Extracorporeal cytokine adsorption is an approach to lower elevated IL-6 levels. However, there is no randomised controlled data on the efficacy of cytokine adsorption and its effect on patient outcome in severe COVID-19 related ARDS requiring V-V ECMO support.

Methods and analysis We here report the protocol of a 1:1 randomised, controlled, parallel group, open-label intervention, superiority multicentre trial to evaluate the effect of extracorporeal cytokine adsorption using the CytoSorb device in severe COVID-19 related ARDS treated with V-V ECMO. We hypothesise that extracorporeal cytokine adsorption in these patients is effectively reducing IL-6 levels by 75% or more after 72 hours as compared with the baseline measurement and also reducing time to successful V-V ECMO explantation. We plan to include a total of 80 patients at nine centres in Germany.

Ethics and dissemination The protocol of this study was approved by the ethical committee of the University of Freiburg as the leading institution (EK 285/20). Additional votes will be obtained at all participating centres.

Trial registration numbers NCT04385771 and DRKS 00021248.

INTRODUCTION

In December 2019, a series of unexplained cases of pneumonia in the city of Wuhan in China has come to light. In virological analyses of samples from the patients' respiratory tracts, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was isolated. The coronavirus disease 2019 (COVID-19) spread rapidly in the city of Wuhan in early 2020 and soon beyond.¹ On 30 January 2020, the Director-General of the WHO declared the

Strengths and limitations of this study

- This trial is a 1:1 randomised, controlled, parallel group, open-label intervention, superiority multicentre trial.
- It is designed to evaluate the effect of extracorporeal cytokine adsorption using the CytoSorb device in severe COVID-19 related acute respiratory distress syndrome treated with venovenous extracorporeal membrane oxygenation.
- We plan to include a total of 80 patients at nine centres in Germany.
- Only very severe cases of COVID-19 will be examined in this study.
- We hypothesise that extracorporeal cytokine adsorption using a CytoSorb adsorber is effectively reducing interleukin-6 levels by 75% or more after 72 hours as compared with the baseline measurement and also reducing the time to successful extracorporeal membrane oxygenation explantation.

outbreak a public health emergency of international concern, and on 11 March 2020, the WHO declared the virus a pandemic.² In humans, an infection with the virus can cause only mild respiratory tract infections or even very severe pneumonia; these serious cases often end fatally, especially in old and prediseased patients.^{1 3} To date, there are only few specific therapeutic options available. Therefore, therapy, especially intensive care treatment for very severe courses, must concentrate on supportive treatment of lung failure and other complications.⁴⁻⁶

About a quarter of inpatient cases will be admitted to intensive care units (ICUs), 10%–17% require invasive mechanical ventilation, and venovenous extracorporeal membrane oxygenation (V-V ECMO) is

used in 2%–4% of inpatient cases.^{3 7–11} Patients requiring extracorporeal membrane oxygenation (ECMO) have a high mortality rate in the studies published so far.^{3 8 12–15} In severe cases, a pronounced release of vasoactive cytokines was repeatedly observed.^{8 16 17} High interleukin-6 (IL-6) levels were identified as a potential predictor of fatal outcome.^{16 18 19}

Data from preclinical trials give evidence for the technical efficiency of the CytoSorb adsorber (CytoSorbents Corporation, Monmouth Junction, New Jersey, USA) in extracting circulating cytokines from the blood.²⁰ IL-6 is also an important factor in the pathophysiology of severe septic shock and excessive immune response in haemophagocytic lymphohistiocytosis; for both indications, it has been shown that extracorporeal adsorption of IL-6 and other vasoactive substances in a CytoSorb adsorber leads to a significant reduction of these cytokines in patient blood.^{21–24} Clinical experience shows that the CytoSorb adsorber can also be safely integrated into a V-V ECMO system.^{25–27} First experience with cytokine adsorption in patients with COVID-19 treated with V-V ECMO at our centre suggests that cytokine adsorption may result in a more pronounced decrease of IL-6 after initiation of ECMO compared with patients treated without a CytoSorb adsorber.²⁸ However, the database for a substantial effect on clinically relevant endpoints remains weak, and strong evidence from sufficiently powered randomised controlled trials is missing.

The aim of this trial is to investigate the influence of extracorporeal cytokine adsorption on IL-6 levels and time to successful ECMO explantation in patients with severe COVID-19 and V-V ECMO. We hypothesise that extracorporeal cytokine adsorption using a CytoSorb adsorber is effectively reducing the IL-6 levels by 75% or more after 72 hours as compared with the baseline measurement and also reducing the time to successful ECMO explantation.

METHODS AND ANALYSIS

This 1:1 randomised, controlled, parallel group, open-label intervention, superiority multicentre trial will be conducted at nine sites in Germany. The coordinating investigator is located at the Medical Center of the University of Freiburg, which is the leading site.

Inclusion/exclusion criteria

Adult patients (≥ 18 years) with reverse transcriptase PCR (rtPCR) confirmed SARS-CoV-2 infection and V-V ECMO are eligible for study inclusion. Exclusion criteria are a known or presumed patient will against participation in the study or against the measures applied in the study or a decision (made prior to inclusion of the patient in this trial) to terminate the treatment within the next 24 hours. The decision for initiation of V-V ECMO will be made independent from the potential participation in the study by the treating physicians and prior to inclusion in the study according to established criteria.^{5 6}

Enrolment of subjects into the study

If a patient appears to be eligible for the trial, the investigator will include the patient into the trial based on fulfilment of inclusion and exclusion criteria and based on the consent procedure described below.

Trial duration

The planned duration of the trial is 18 months. The trial started in July 2020 and is planned to end in December 2021.

Interventions

Participants will be allocated to the intervention group or to the control group. In the intervention group only, a CytoSorb adsorber is incorporated into the V-V ECMO system for 72 hours as an add-on to standard treatment. The CytoSorb adsorber is applied as given by the manufacturer's instructions. It will be inserted into the ECMO circuit via Luer-Lock connections in a way that patient blood flows through it from bottom to top. The adsorber is usually installed in the system as part of the preparation of the ECMO system before the system is connected to the patient circuit, but at the latest within 4 hours after initiation of the ECMO.

Recommended flow rates through the adsorber are between 100 mL/min and 700 mL/min. The adsorber can be left in the system for 24 hours and must then be replaced. Adsorber replacement after 24 and after 48 hours is possible during operation, as is removal of the adsorber after 72 hours. Alternatively, the cytokine adsorber may also be incorporated into a continuous renal replacement treatment circuit in patients requiring renal replacement therapy.

As a supplement to routine diagnostics, four additional blood samples are necessary within the scope of the study at the times 1 hour, 24 hours, 48 hours and 72 hours after initiation of cytokine adsorption; the last three blood samples should be taken within the first hour after replacing the adsorber. The blood samples are taken at the same time points in the control group (figure 1). The reference time (t_0) is the start of cytokine adsorption in the intervention group and the start of V-V ECMO therapy in the control group. In general, the CytoSorb adsorber is connected to the ECMO system before implantation of the V-V ECMO so that in the intervention group the connection of the V-V ECMO to the patient's blood circuit and the start of cytokine adsorption take place simultaneously. However, the study design allows the CytoSorb adsorber to be installed within the first 4 hours of ECMO therapy; in this case, the reference time for blood sampling is the start of CytoSorb therapy. This will only take place in exceptional cases if, for organisational or logistical reasons, a CytoSorb adsorber is not immediately available for installation in the ECMO system in case of urgent implantation of V-V ECMO.

The blood samples will be analysed for standard clinical laboratory parameters such as blood count, electrolytes, kidney and liver function parameters and coagulation

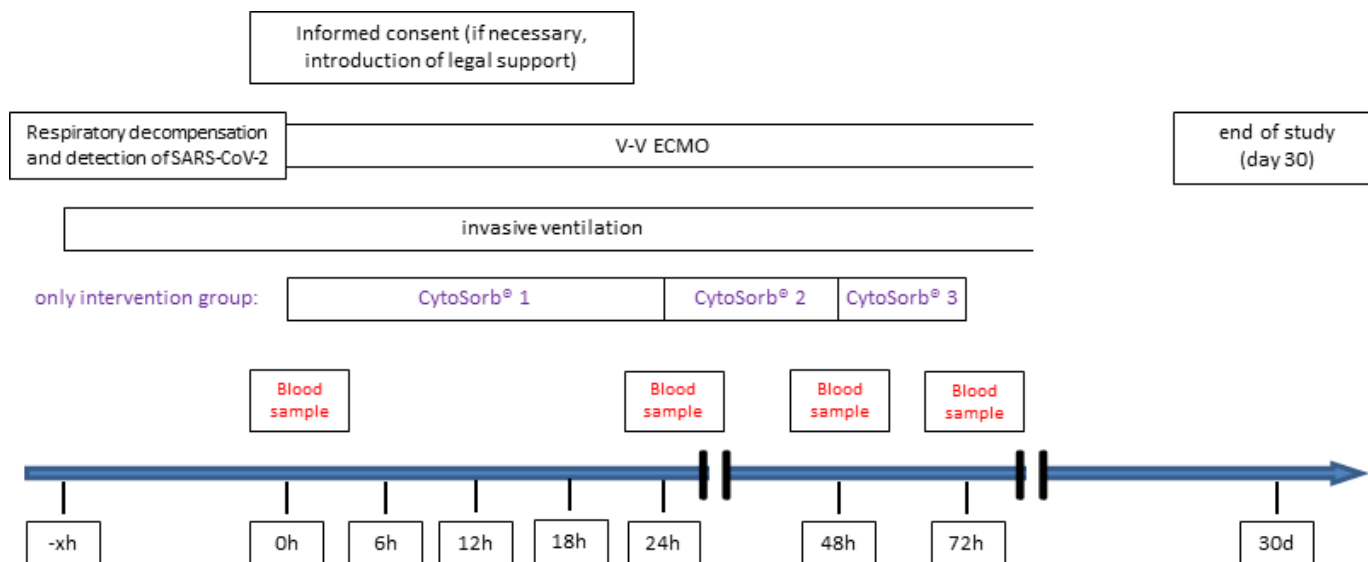


Figure 1 Participant timeline. Schedule for enrolment, interventions and assessments. V-V ECMO, veno-venous extracorporeal membrane oxygenation.

parameters. In addition, the levels of interleukins and cytokines will be determined (table 1). The blood samples are analysed in the local laboratories at the participating centres.

Clinical data

Besides patient-specific demographic and personal data (e.g., age and height), medical preconditions, previous treatment in another hospital before referral to the hospital of study inclusion and previous medication will be documented. Furthermore, several clinical scores established in intensive care medicine (eg, Sequential Organ Failure Assessment (SOFA), Respiratory Extracorporeal Membrane Oxygenation Survival Prediction (RESP), Predicting Death for Severe ARDS on V-V ECMO (PRESERVE), Simplified Acute Physiology Score II (SAPS II) and Acute Physiology And Chronic Health Evaluation II (APACHE II))^{29–32} as well as ECMO and ventilation parameters will be documented at baseline and at timepoints 24, 48 and 72 hours). Beyond this, clinical and treatment-related data will be collected during the study (table 2). All clinical data will be retrieved from the patients' files.

Standard of care

Both groups will receive therapy of sepsis and acute respiratory distress syndrome including therapy with V-V ECMO according to current international standards and guidelines. These standards and guidelines describe, among other things, criteria and target values for the control of fluid resuscitation and catecholamine therapy, ventilation approaches and patient positioning. These standards and instructions are applied within the intervention and control group; that is, this treatment in both groups does not deviate from the established and guideline-based routine therapy.

In both groups, V-V ECMO therapy will be continued as long as clinically indicated. Specifically, criteria for successful termination and explantation of the V-V ECMO will be a reduction of sweep gas flow of the V-V ECMO to 0 L/min for several hours, usually for approximately 6 hours (functional interruption of V-V ECMO support) while still achieving sufficient oxygenation and decarboxylation of the patient blood.

Allocation of the participants to the study groups

Allocation to the intervention and control groups is carried out by centre-stratified 1:1 randomisation with blocks of variable length within strata. The block lengths will be documented separately and will not be disclosed to the investigators. The allocation sequence for the study groups will be based on a computer-generated random list.

Concealment mechanism

The allocation sequence will be implemented by using opaque, sealed envelopes sequentially numbered per centre. The random list will not be accessible to the principal investigator or other members of the study team responsible for patient enrolment. The Clinical Trials Unit (CTU) will prepare the randomisation envelopes according to the random list. The envelopes will be stored in a secure place to which the perfusionists or the physicians who prepare the ECMO circuits before implantation will have access.

Implementation

When a patient with COVID-19 is selected for V-V ECMO, an ECMO circuit will be prepared according to the centre's standard on request of the responsible ECMO physician. When preparing the system for connection to the patient, the perfusionist or responsible physician will open a randomisation envelope following the sequential order, starting

Table 1 List of laboratory parameters to be collected

	0 hour	1 hour	24 hours	48 hours	72 hours
A. Laboratory parameters assessed at different time points during the study. The parameters from 0 hour will be taken from clinical routine measurements before initiation of V-V ECMO					
Leukocytes (thous./ μ L)	x	x	x	x	x
Thrombocytes (thous./ μ L)	x	x	x	x	x
Haemoglobin (g/dL)	x	x	x	x	x
Haematocrit (%)	x	x	x	x	x
Lymphocytes (thous./ μ L)	x	x	x	x	x
Neutrophils (thous./ μ L)	x	x	x	x	x
Monocytes (thous./ μ L)	x	x	x	x	x
INR (international normalized ratio)	x	x	x	x	x
PTT (s) (partial thromboplastin time)	x	x	x	x	x
D-dimers (mg/L)	x	x	x	x	x
Fibrinogen (Clauss method) (mg/dL)	x	x	x	x	x
Willebrand factor activity (%)	x	x	x	x	x
Willebrand factor antigene (%)	x	x	x	x	x
Ferritin (ng/mL)	x	x	x	x	x
Urea (mg/dL)	x	x	x	x	x
Creatinine (mg/dL)	x	x	x	x	x
Uric acid (mg/dL)	x	x	x	x	x
LDH (U/L) (lactate dehydrogenase)	x	x	x	x	x
CK (U/L) (creatine kinase)	x	x	x	x	x
CK-MB (U/L) (creatine kinase, MB isoenzyme)	x	x	x	x	x
Myoglobin (U/L)	x	x	x	x	x
Troponin T (ng/mL)	x	x	x	x	x
NT-proBNP (pg/mL) (aminoterminal form brain natriuretic peptide)	x	x	x	x	x
AST (U/L) (aspartate aminotransferase)	x	x	x	x	x
ALT (U/L) (alanine aminotransferase)	x	x	x	x	x
AP (U/L) (alkaline phosphatase)	x	x	x	x	x
g-GT (U/L) (gamma-glutamyltransferase)	x	x	x	x	x
Bilirubin (mg/dL)	x	x	x	x	x
CRP (mg/L) (C-reactive protein)	x	x	x	x	x
PCT (ng/mL) (procalcitonin)	x	x	x	x	x
Total serum protein (g/dL)	x	x	x	x	x
Albumin (g/dL)	x	x	x	x	x
IL-6 (pg/mL) (interleukin-6)	x	x	x	x	x
Triglycerides (mg/dL)	x	x	x	x	x
Cholesterine (mg/dL)	x	x	x	x	x
LDL-cholesterine (mg/dL) (low-density lipoprotein cholesterine)	x	x	x	x	x
HDL-cholesterine (mg/dL) (high-density lipoprotein cholesterine)	x	x	x	x	x
B. Point-of-care tests collected during the study. The parameters from 0 hour will be taken from clinical routine measurements before initiation of V-V ECMO					
pH	x	x	x	x	x
pCO ₂ (mm Hg) (partial pressure of carbon dioxide)	x	x	x	x	x
pO ₂ (mm Hg) (partial pressure of oxygen)	x	x	x	x	x
sO ₂ (%) (oxygen saturation)	x	x	x	x	x

Continued

Table 1 Continued

	0 hour	1 hour	24 hours	48 hours	72 hours
SBC (mmol/L) (standard bicarbonate)	×	×	×	×	×
Lactate (mmol/L)	×	×	×	×	×
Sodium (mmol/L)	×	×	×	×	×
Potassium (mmol/L)	×	×	×	×	×
Chloride (mmol/L)	×	×	×	×	×
Calcium (mmol/L)	×	×	×	×	×

thous, thousand; V-V ECMO, veno-venous extracorporeal membrane oxygenation.

with the envelope displaying the lowest available number (eg, first: R001, second: R002 and third: R003).

The envelope contains the randomisation form on which the randomised treatment is noted. The perfusionist or authorised randomising investigator will manually enter the individual patient identification code assigned for the trial on the randomisation form and will confirm randomisation by dating and signing the form. Trial treatment can then be initiated according to the randomisation result. The trial patient must be registered at CTU of the Medical Center, University of Freiburg, within 24 hours after opening the randomisation envelope.

Blinding (masking)

The trial is an open-label trial; therefore, there is no blinding, neither for participants nor for the care providers or the study team.

Criteria for discontinuing or modifying allocated interventions for a given trial participant

In case of harms or complications discovered during cytokine adsorption, this treatment can be terminated or interrupted at any time. As in any extracorporeal

circulation, blood clotting can occur and result in loss of function of the device. Continuous blood flow measurement in the ECMO system and in the bypass for the Cyto-Sorb adsorber will allow for early detection of clotting that will result in reduced blood flow. In this case, the adsorber may be exchanged at any time during ongoing operation of the V-V ECMO. On request of the participant or authorised relatives, cytokine adsorption treatment can be terminated or interrupted at any time.

Strategies to improve adherence to intervention protocols

All patients included in this study are treated on an ICU and in general deeply analgesedated. Therefore, adherence to the intervention protocols depends primarily on the treating physicians. The study team will be responsible for monitoring protocol adherence.

Relevant concomitant care and interventions that are permitted or prohibited during the trial

Besides cytokine adsorption and collection of study-associated additional blood samples, the treatment of the

Table 2 List of clinical treatment data to be collected during the study

	0 hour	1 hour	24 hours	48 hours	72 hours
Fluid balance (mL)	×	×	×	×	×
Administration of albumin 5% (mL)	×	×	×	×	×
Administration of albumin 20% (mL)	×	×	×	×	×
Supply of red cell concentrates (number)	×	×	×	×	×
Supply of thrombocyte concentrates (number)	×	×	×	×	×
Supply of fresh frozen plasma (number)	×	×	×	×	×
Dosage of norepinephrine (10 mg/50 mL)	×	×	×	×	×
Dosage of dobutamine (250 mg/50 mL)	×	×	×	×	×
Dosage of epinephrine (10 mg/50 mL)	×	×	×	×	×
Dosage of vasopressin (40 IE/40 mL)	×	×	×	×	×
RRsys (mm Hg)	×	×	×	×	×
RRdia (mm Hg)	×	×	×	×	×
Mean arterial pressure (mm Hg)	×	×	×	×	×
Heart rate (1/min)	×	×	×	×	×

Data will be retrieved from the hospital's electronic patient charts.

patients will follow established standards. There are no specific interventions that are prohibited during the trial.

Primary endpoints

The trial has two primary endpoints: (1) IL-6 reduction by 75% or more after 72 hours as compared with the baseline measurement and (2) time to successful ECMO explantation within 30 days after randomisation.

Endpoint 1 is defined as successful IL-6 reduction if the ratio between the IL-6 measurement after 72 hours divided by the IL-6 measurement at baseline is 0.25 or less. The baseline IL-6 measurement is the start of CytoSorb therapy in the intervention group and the start of V-V ECMO therapy in the control group. Usually, the CytoSorb adsorber is connected to the ECMO system before implantation of the V-V ECMO, so that in the intervention group, the connection of the V-V ECMO to the patient circuit and the start of CytoSorb therapy take place simultaneously. However, the study design allows for the possibility that the CytoSorb adsorber can also be installed within the first 4 hours of ECMO therapy; in this case, the reference time for blood sampling is the start of CytoSorb therapy. This will only take place in exceptional cases if, for organisational or logistical reasons, a CytoSorb adsorber is not immediately available for installation in the ECMO system in the case of urgent implantation of a V-V ECMO. Endpoint 1 was chosen as it is considered as a clinically relevant IL-6 reduction and as realistically achievable according to reports from the international CytoSorb Registry, where IL-6 levels in patients with severe infections could be reduced by more than 80% by adsorption in the CytoSorb adsorber.²⁴

Endpoint 2 is defined as time from randomisation to successful ECMO explantation within 30 days after randomisation. Death within 30 days will be analysed as competing event. For patients who do not experience one of the events successful ECMO explantation or death, time to last follow-up will be analysed as censored observation. In the unexpected case that patients who were explanted from ECMO will have to be reimplanted later or who will die within 30 days, the ECMO explantation will not be counted as successful.

Secondary endpoints

The following endpoints are secondary efficacy endpoints:

- ▶ Ventilator-free days (VFDs) in the first 30 days after randomisation, where invasive mechanical ventilation, non-invasive ventilation and ECMO are defined as ventilator days. VFD=0, if the patient dies in the first 30 days after randomisation.
- ▶ Time until the end of mechanical ventilation and explantation from ECMO. Death under ventilation and/or ECMO will be analysed as a competing event. The time will be censored at the time of last visit for surviving patients under ventilation and/or ECMO.
- ▶ Overall survival time, defined as time from randomisation to death. The time will be censored at the time of last visit for surviving patients.

- ▶ Days on ICU.
- ▶ Vasopressor dosage of epinephrine, norepinephrine, vasopressin and dobutamine at 24, 48 and 72 hours.
- ▶ Fluid substitution and fluid balance at 24, 48 and 72 hours.
- ▶ Serum lactate at 24, 48 and 72 hours. Urine output at 24, 48 and 72 hours.
- ▶ Willebrand factor at 24, 48 and 72 hours.
- ▶ D-dimers at 24, 48 and 72 hours.
- ▶ IL-6 levels at 24, 48 and 72 hours.
- ▶ SOFA score at 24, 48 and 72 hours.

The following endpoints are secondary safety endpoints: adverse events of special interest (AESI), such as, for example, device-related events like air in the ECMO system, blood clotting in the ECMO system or major bleeding complications.

Participant retention and follow-up

As already described, adherence to intervention protocols and participant retention primarily depends on the treating physicians. Therefore, no specific measures need to be taken to increase patient retention. Since no specific follow-up is planned in this study, no specific measures need to be taken in this respect, either.

Data management

Study data will be entered in pseudonymised form in a study database by authorised and trained members of the study team via electronic case report forms (eCRFs). The electronic data capture system REDCap (<https://projectredcap.org/>) is used for data acquisition. This system uses built-in security features to prevent unauthorised access to patient data, including an encrypted transport protocol for data transmission from the participating sites to the study database. Employees of the CTU charged with hosting the eCRF and the study database are obliged to maintain data confidentiality and to comply with data protection regulation. Access will be granted to authorised personnel only and only if they have received appropriate training.

Statistical methods

Sample size

Sample size calculation and power considerations are based on the two primary endpoints: (1) IL-6 reduction by 75% or more after 72 hours as compared with the baseline measurement and (2) time to successful ECMO explantation within 30 days after randomisation. If there is no difference between treatment arms with respect to endpoint 1, that is, a clinically relevant IL-6 reduction, it is assumed that there is also no difference between treatment arms with respect to the clinically relevant endpoint 2. Therefore, statistical comparisons (at two-sided significance level alpha of 0.05) between treatment arms will be performed in this a priori specified sequence, that is, the statistical comparison with respect to endpoint 2 will only be performed if a difference between treatment arms with respect to endpoint 1 had been shown at a two-sided

significance level alpha of 0.05. Thus, no alpha correction of the individual statistical tests is necessary.

For sample size calculation with respect to endpoint 1, it is assumed that the probability of IL-6 reduction by 75% or more after 72 hours is 80% in the intervention group and 50% in the control group. This assumption is based on the results in the first 10 patients of the ongoing CYCOV I trial (NCT04324528 and DRKS00021300). In the intervention group, IL-6 could be reduced by 75% or more in three out of four patients; the fourth patient was considered as not representative due to pretreatment and extremely high IL-6 values at baseline. In the control group, IL-6 could be reduced by 75% or more in two out of six patients. Under this assumption, a sample size of 39 patients per treatment arm would be required to show a difference in the probability of IL-6 reduction between treatments at two-sided significance level of 0.05 with a power of 80%. This was calculated with formula '[3]' in Campbell *et al*³³ for the χ^2 test of the hypothesis that the difference between the probabilities is equal to zero using nQuery V.8.3.1 (Module PTT0), which is adequate also for the analysis with logistic regression.³⁴ Therefore, the 1:1 randomisation of a total of 80 patients between treatment arms is planned.

With respect to endpoint 2, nothing is known about the expected treatment effect. It is assumed that the mortality within 30 days is high and that only a small difference between treatment arms can be expected (probability of 0.7 in the intervention group and of 0.75 in the control group). With regard to the probability of successful ECMO explantation within 30 days after randomisation, an analysis of the time to successful ECMO explantation considering death as a competing event using a Fine and Gray model will be performed. With a total of 80 patients, a difference between treatment arms can be shown at two-sided significance level of 0.05 with a power of 80%, if the probability of successful ECMO explantation within 30 days after randomisation is 0.30 in the intervention group and 0.08 in the control group.³⁵ This corresponds to a subdistribution HR of 4.28 and a required number of 15 patients with successful ECMO explantation.

Statistical methods for analysing primary and secondary outcomes

Efficacy analyses will be performed primarily in the full analysis set according to the intention-to-treat principle addressing the treatment policy estimand. This means that the patients will be analysed in the treatment arms to which they were randomised, irrespective of whether they refused or discontinued the treatment or whether other protocol violations are revealed.

The treatment effect with respect to the primary endpoint 1 IL-6 reduction by 75% or more after 72 hours as compared with the baseline measurement will be estimated and tested within a logistic regression model. The model will include the treatment arm, centre, age and the baseline IL-6 level as independent variables. For quantification of the treatment effect, the OR will be estimated with 95% CI. The two-sided test on difference between

treatment arms at significance level 5% will be based on the two-sided 95% CI. In the primary analysis, for patients with missing 72 hours IL-6 level, the 48 hours IL-6 level will be used for calculation of IL-6 reduction. If both the 72 hours and the 48 hours IL-6 levels are missing, the patient will be counted as no success with respect to IL-6 reduction. In an additional sensitivity analysis, for patients with missing 72 hours IL-6, the missing data will be filled by multiple imputation techniques. In the multiple imputation model, the parameters centre, age and baseline IL-6 level will be included.

The statistical comparison with respect to primary endpoint 2 time to successful ECMO-explantation within 30 days after randomisation will only be performed if a difference between treatment arms with respect to endpoint 1 had been shown at a two-sided significance level alpha of 0.05. If this had not been the case, the analysis with respect to endpoint 2 will be interpreted as exploratory.

The treatment effect with respect to the primary endpoint 2 time to successful ECMO-explantation within 30 days after randomisation will be estimated and tested within the Fine and Gray model considering death as a competing event. The model will include the treatment arm, centre, age in years and the baseline IL-6 level as independent variables. For quantification of the treatment effect, the subdistribution HR will be estimated with 95% CI. The two-sided test on difference between treatment arms at significance level 5% will be based on the two-sided 95% CI. The probability of successful ECMO explantation will be estimated by the Aalen-Johansen estimator considering death as a competing event.

The relationship between IL-6 reduction and time to successful ECMO explantation within 30 days after randomisation will be analysed within the Fine and Gray model considering death as a competing event. The model will include the treatment arm, centre, age in years, the baseline IL-6 level and IL-6 reduction (yes/no) after 72 hours as independent variables. In additional analyses, an interaction between randomised treatment and the IL-6 reduction will be investigated as well as the effect of IL-6 reduction as a continuous covariate.

Descriptive analyses of the secondary endpoints will be performed in similar regression models as for the primary endpoints, as appropriate for the respective type of data. Differences between treatment groups will be calculated with 95% CIs. Incidences of AESI will be calculated with 95% CIs. All p values relating to the secondary endpoints are interpreted purely descriptively.

No efficacy interim analysis will be performed. Before enrolment of all patients and the end of the trial, no early confirmatory conclusion of superior efficacy of the intervention can be drawn.

All statistical programming for analysis will be performed with the Statistical Analysis System (V 9.4).

Monitoring procedure

Monitoring will be performed by the CTU, Medical Center, University of Freiburg. Adapted monitoring will be done according to applicable GCP guidelines and standard operating procedures.

Monitoring will be performed as a combination of on-site visits (as far as possible according to social distancing provisions and travel restrictions) and remote monitoring procedures drawing on a risk-based quality management approach. Details will be specified in a monitoring plan.

Data monitoring committee

An independent Data Monitoring Committee (DMC) will be established. The function of the DMC is to monitor the course of the trial and, if necessary, to give a recommendation to the coordinating investigator for discontinuation, modification or continuation of the trial. It is the task of the DMC to examine whether the conduct of the trial is still ethically justifiable and whether the patients' safety is ensured. The composition and responsibilities of the DMC as well as the structure and procedures of its meetings will be laid down in a DMC charter.

Harms

Applicable German medical device regulation will be followed in the documentation and reporting of adverse events. Furthermore, AESI will be documented in the eCRF, for example, serious adverse events considered related to the investigational device (ie, serious adverse device effects), air in the ECMO system, blood clotting in the ECMO system or major bleeding complications.

Auditing

Auditing may be performed to the extent deemed appropriate by the quality assurance department of the Medical Center – University of Freiburg or of the participating sites.

ETHICS AND DISSEMINATION

The protocol of this study was approved by the ethical committee of the University of Freiburg (EK 285/20, online supplemental material 1). Additional votes will be obtained at all participating centers. All relevant protocol modifications will be submitted to the University of Freiburg's Ethics Committee and all other local ethics committees for approval. No changes will be implemented before ethical approval.

Consent or assent

Patients with severe COVID-19 who are eligible for therapy with V-V ECMO are usually endotracheally intubated, mechanically ventilated and therefore analgosedated at the time of study inclusion, so that it is usually not possible to educate these patients in the acute phase. Based on the reports of previous cases, the clinical condition of patients requiring invasive ventilation and V-V ECMO deteriorates rapidly within a short period of time, and at the same time,

a relevant increase in IL-6 is observed in these patients.⁸ The first few hours after initiation of V-V ECMO therapy are crucial for the course of the study, as this is when the excessive release of vasoactive cytokines begins. The aim of the study is to investigate whether a rapid reduction of these excessive cytokines in the blood circulation of the patients can facilitate the stabilisation of the circulation and control of the inflammatory reaction in the context of SARS-CoV-2 infection and thus positively influence the further course of the disease. For this reason, rapid study inclusion and assignment of patients to the intervention and control groups is necessary, even without prior clarification and without the prior consent of the patient, a relative or a legal representative. Likewise, in most cases, the blood sample must be taken at the time 1 hour after installation of the adsorber, without the prior consent of the patient, a relative or a legal representative.

For critically ill patients who are admitted to intensive care with severe respiratory failure, the medical care team (doctors and nursing staff of the ICUs of the participating sites) will ensure rapid contact with their relatives; this happens independent from any potential study participation. In general, relatives can be identified and contacted quickly within the first hours after admission of a patient. If these initial attempts are unsuccessful, the police may attempt to contact them. In cases in which no relatives of the patient exist or can be identified, a request is made as soon as possible to the local court to obtain a legal representative (examples of the consent forms for legal representatives in online supplemental materials 2 and 3).

Invasively ventilated patients in severe lung failure who require additional support with ECMO are usually only able to give consent after significant stabilisation and recovery over the course of a few days, so in these cases, a legal guardian is appointed as part of clinical routine; in most cases, this is a close relative of the patient. This guardian is then informed about the current research project. After regaining consciousness and the ability to give consent before the end of the examination period, the patient is informed himself or herself. The following table (table 3) shows the different options for obtaining informed consent.

Even in the case of dying patients, the relatives are informed about the study inclusion. Since no further dangers for the patient can arise here and participation in the study ends with death, in this case, no detailed explanation of the expected risks is necessary.

Confidentiality

Study data are entered into the eCRF in pseudonymised form only. Pseudonymisation is carried out directly in the raw data before any further processing, so that only the pseudonyms are recognisable in all evaluations. Pseudonymisation is done using a list where each patient is assigned a study-specific ID. This study ID list is kept separately and confidential in the local investigator site file; only authorised study personnel at the respective site have access to this list.

Table 3 Variants of informed consent for study inclusion

Variant	Condition of the patient at the time of provisional study enrolment	Action for possible legitimisation of participation in the study	Result	Forms to be used
1	Patient is able to give consent.	Discuss study participation with patient.	Patient decides according to own standards.	▶ Patient information. ▶ Consent form.
2	Patient is not able to give consent and has a legal guardian for health issues.	Discuss study participation with legal guardian.	Legal guardian decides (according to the welfare and presumed will of the person being cared for).	▶ Information for the legal guardian and declaration of consent for the study participation of the person being cared for.
3	Patient is not able to give consent and has no legal guardian for health issues.	Ask relatives (or legal guardian with other responsibilities) about the presumed patient will.	The presumed will justifies measures that are necessary as long as the incapacity to give consent exists or a legal guardian is appointed.	▶ Information for the relatives and explanation of the presumed will of the patient.
4	Patient will become able to give consent during the study.	Discuss further study participation with patient.	Patient decides according to own standards.	▶ Patient information. ▶ Consent form.

Patient and public involvement

No patient involved in the development of the research question, study design, outcome measures and conduction of the study.

Access to data

All members of the study team and all researchers involved in data collection, evaluation and writing of the scientific publication(s) related to this study will have full access to all data collected. There are no contractual agreements with anyone that would limit the access to the data by any means.

Ancillary and post-trial care

Since there are no harms to be expected resulting specifically from the trial-specific interventions, no special provisions are made for trial-specific ancillary or post-trial care. Post-trial care is at the discretion of the treating physician. In this study, the CytoSorb adsorber is used within the scope of the intended purpose of the medical device with CE marking.

Dissemination policy

The results of this study will be presented at symposia and conferences and published in peer-reviewed journals. Authorship eligibility will follow the recommendation provided by the International Committee of Medical Journal Editors.³⁶

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Contributors AS is the coordinating investigator, and DD is the deputy of the coordinating investigator. AS developed the idea for this study, and AS, CS, DD and MR designed the study. Statistical analyses and sample size calculation were performed by CS. CB, TW, JR and DS advised in study design. AS, MR, FS, CvS-M and CS wrote the study protocol that served as the draft for this manuscript.

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