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Assessing efficacy of CytoSorb haemoadsorber for prevention of organ dysfunction in cardiac surgery patients with infective endocarditis: REMOVE-protocol for randomised controlled trial

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ABSTRACT

Introduction Infective endocarditis (IE) is associated with high mortality and morbidity. Multiple organ failure is the main cause of death after surgery for IE. Cardiopulmonary bypass (CPB) can cause a systemic inflammatory response. In a pilot study (REMOVE-pilot (Revealing mechanisms and investigating efficacy of hemoad-sorption for prevention of vasodilatory shock in cardiac surgery patients with infective endocarditis – a multicentric randomized controlled group sequential trial)), we found that plasma profiles of cytokines during and after CPB were higher in patients with IE compared with patients with non-infectious valvular heart disease. Sequential Organ Failure Assessment (SOFA) scores on the first and second postoperative days and in-hospital mortality were also higher in IE patients. This protocol describes the design of the REMOVE trial on cytokine-adsorbing columns, for example, CytoSorb, for non-selective removal of cytokines. The aim of the REMOVE study is to demonstrate efficacy of CytoSorb on the prevention of multiorgan dysfunction in patients with IE undergoing cardiac surgery.

Methods and analysis The REMOVE study is an interventional randomised controlled multicenter trial with a group sequential (Pocock) design for assessing efficacy of CytoSorb in patients undergoing cardiac surgery for IE. The change in mean total SOFA (Δ SOFA) score between preoperative and postoperative care will be used as primary endpoint. Data on 30-day mortality, changes in cytokines levels, duration of mechanical ventilation, length of intensive care unit and hospital stay, and postoperative stroke will be collected as secondary endpoints. An interim analysis will be conducted after including 25 participating patients per study arm (with a focus on feasibility of the recruitment as well as differences in cytokines and cell-free DNA levels).

Ethics and dissemination The protocol was approved by the institutional review board and ethics committee of the University of Jena as well as by the corresponding ethics committee of each participating study centre. The results will be published in a renowned international medical journal, irrespective of the outcomes of the study.

Trial registration number The ClinicalTrials.gov registry (NCT03266302).

Strengths and limitations of this study

- The topic of the study is clinically relevant, as the mortality after surgery for infective endocarditis (IE) is still very high and there is a need for new treatment modalities.
- Strict patient selection guided by the modified Duke Criteria for the diagnosis of IE; low-risk patients with EuroSCORE II≤3 will be excluded.
- This is the first randomised multicenter study assessing the efficacy of CytoSorb in patients with infective endocarditis undergoing cardiac surgery.
- The primary endpoint chosen in this study is the Δ mean total Sequential Organ Failure Assessment Score which has been used in a number of previous clinical trials in sepsis.
- The study is not blinded; however, we are not expecting that to cause bias, because the primary endpoint is calculated based on clinical and laboratory parameters which are routinely measured in the intensive care unit.

INTRODUCTION

Infective endocarditis (IE) affects 1–10/100 000 persons per year worldwide and is associated with up to 40% in-hospital mortality.[1–3] Surgical treatment is necessary in about 50% of patients and is associated with in-hospital mortality as high as 15%–25% and 1-year mortality of 40%.[1 4] The postoperative course of patients with IE is often complicated with a varying degree of circulatory failure, that is, hypotension, decreased systemic vascular resistance, despite high cardiac output, adequate fluid resuscitation and adrenergic vasopressor administration which can progress to septic shock in up to 10%–28% of cases.[5–7] If septic shock complicates the course of the disease mortality can reach up

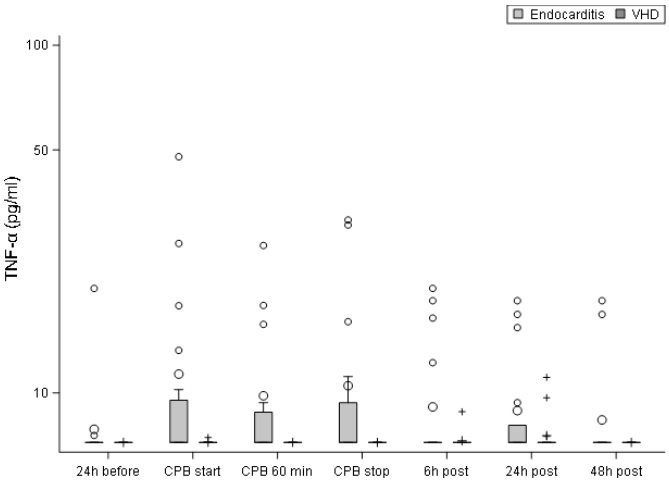

Figure 1 Boxplots of TNF-α plasma concentrations before, during and after cardiac surgery in patients with infective endocarditis and valvular heart disease.[15] Before, before surgery; CPB, cardiopulmonary bypass; post, after surgery; TNF, tumour necrosis factor; VHD, valvular heart disease.

to 75%–100% in some studies.[7 8] We previously showed that septic shock leading to multiple organ failure was the main cause of death in 78.7% of patients who died after surgical procedures for IE.[9]

The mechanism of circulatory failure complicating the postoperative course of endocarditis has not been completely elucidated. Some presumed mechanisms include a combination of endothelial injury, arginine-vasopressin-system dysfunction and release of vasodilatatory mediators.[10] The mechanism that triggers septic shock in IE patients is also not fully understood and warrants further investigation.[11] Interleukin-6 (IL-6), IL-8, IL-18 and IL-1β are proinflammatory cytokines participating in the development of the innate immunity and are associated with unfavourable outcome in severe sepsis.[12] However, available information on the role of these cytokines in IE is scarce. Bustamante *et al* reported elevated IL-6, IL-8 and interferon-γ (IFN-γ)plasma levels to be associated with an unfavourable outcome in patients with prosthetic-valve IE.[13] In addition, Ekdahl *et al* investigated human valves from IE patients for the presence of IL-8 and tumour necrosis factor-alpha (TNF-α) containing cells. They suggested the local occurrence of IL-8 containing cells as a potential marker of disease activity.[14] A further potential mechanism of postoperative circulatory failure and septic shock may be related to the liberation of infective material at the time of surgical removal of the infected tissues.

Surgery using cardiopulmonary bypass (CPB) initiates a systemic inflammatory response induced by extrinsic (eg, anaesthesia, contact activation within the extracorporeal circuit and endotoxemia) and intrinsic (eg, tissue damage, endothelial cell activation and ischaemia-reperfusion injury of the myocardium) factors. All of these factors may delay weaning from the ventilator, recovery of organ function and discharge from intensive care unit (ICU) and increase perioperative mortality. Thus measures to decrease the inflammatory process have the potential to improve the perioperative outcome.

As part of the preparatory work for this study, we performed a case–control pilot study.[15] We investigated the release profiles of inflammatory and vasoactive mediators before, during and after cardiac surgery in patients with IE as well as in patients with non-infectious valvular heart disease (VHD). We found that plasma profiles of cytokines during and after CPB were significantly higher in patients with IE than in patients with non-infectious VHD. Figure 1 shows that TNF-α levels increased rapidly after CPB initiation in the IE group, while in the VHD group it was not detectable. Sequential Organ Failure Assessment (SOFA) scores on the first and second postoperative days were higher in IE group than the VHD group. In addition, in-hospital mortality was higher in the IE group (35%) than in VHD group (5%).

Cytokine-adsorbing columns, for example, CytoSorb, are specifically designed for the non-selective removal of cytokines. They are composed of beads that are able to capture and adsorb cytokines by size exclusion chromatography and non-selective hydrophobic interactions. Small molecules, below 5 kDa, travel through the pores of the beads while larger molecules and cells, above 60 kDa, pass around the beads. In experimental endotoxemia in the rat, haemoadsorption with CytoSorb removed cytokines, reduced nuclear factor (NF)-κB DNA binding in liver cells and improved short-term survival.[16] In cecal ligation and puncture- induced septic rats haemoadsorption reduced circulating cytokines, improved mean arterial pressure and resulted in increased short-term survival.[17] CytoSorb has been tested in a multicenter randomised controlled study including 43 patients with sepsis and acute lung injury.[18] The use of the cytokine-adsorbing column reduced IL-6. Mortality did not differ between the two groups, but the study was not powered for this endpoint. In another study, 37 patients undergoing elective surgery with CPB were randomly assigned to CytoSorb haemoadsorption or a control group.[19] The primary outcome was difference of cytokine levels (IL-1β, IL-6, IL-18, TNF-α and IL-10) within the first five postoperative days. There was no reduction in cytokines level detectable following treatment. Nonetheless, strong interindividual differences in cytokine levels among patients (all low-risk patients) were reported. The authors argued that the inclusion of patients with higher risk might be considered in future studies.[19] In another randomised study investigating CytoSorb to eliminate cytokines during cardiac surgery on 30 patients, there was no difference in cytokine levels between patients treated with CytoSorb and a control group.[20] In the REMOVE trial, we address several of these limitations: We assess efficacy of CytoSorb haemoadsorption in a larger high-risk group of IE patients undergoing heart surgery using CPB in a two-arm multicenter, non-blinded, randomised, controlled, group sequential clinical trial.

METHODS AND ANALYSIS

Objectives

Primary objective

The primary objective of this study is to demonstrate efficacy of a cytokines haemoadsorption device (CytoSorb) in contrast to no device on the development of multiple organ dysfunction syndrome in cardiac surgery patients with IE.

Secondary objectives

To study the mechanisms of IE-induced vasodilatory shock in patients undergoing cardiac surgery using CPB for IE. This secondary objective is the main focus of the planned interim analysis after 25 patients per study arm at which changes of vasoactive and inflammatory mediator and cell-free DNA (cfDNA) levels will be explored in blood samples.

Endpoints

The primary confirmatory endpoint of REMOVE is the change in mean total SOFA (Δ SOFA) score between the mean total postoperative SOFA score and the SOFA score 24 hours before surgery. The SOFA score is measured on a scale ranging from 0 to 4 for each of six organ systems, with an aggregate score from 0 to 24 and higher scores indicating more severe organ dysfunction (online supplementary file 4).[21]The mean total postoperative SOFA score will be assessed from the first postoperative day until discharge from the ICU or intermediate care (maximally to the ninth postoperative day). The mean total SOFA score is a well-established endpoint used in a number of previous clinical trials in sepsis[22 23] and can be used as surrogate for the assessment of short-term mortality.[24]

The secondary endpoints of the study are as follows:

- 30-day mortality rate defined as mortality, in the hospital or anywhere after discharge, within 30-day postoperative.
- Changes in vasoactive and inflammatory mediators and cfDNA levels in the blood samples at start of surgery (skin incision), 30 and 60 min after starting CPB, at the end of CPB and 24 hours after surgery (skin closure).
- SOFA subscores operationalised as the primary endpoint.
- Cumulative incidence of stroke within 30 days after surgery.
- Duration of mechanical ventilation, vasopressor and renal replacement therapy within 30 days after surgery.
- Length of in-hospital and ICU stay.

Study design

This study is designed as a multicenter, non-blinded, randomised, controlled, group sequential clinical trial with two groups designed for assessing superiority. Figure 2 shows the flowchart of the study. In the experimental study arm the CytoSorb haemoadsorption device will be integrated into the CPB during cardiac surgery as shown in online supplementary figure 1 . Patients in the control group will be treated according to the standard of care (no CytoSorb).

We will perform a planned interim analysis after 2×25 patients focusing on an explorative comparison of vasoactive and inflammatory mediators and cfDNA levels in the interventional and control groups. The second aim of the interim analysis is to check feasibility of recruitment during the planed study period. These 50 patients will be part of the overall analysed population (a pocock-type group sequential design, details below). The results of the interim evaluation of the Δ mean SOFA score, the primary outcome of the study, will only be made available to the data monitoring safety committee.

Time schedule and study duration

The study duration is planned as 36 months: 24 months of recruitment and 1 month for follow-up and another 6 months for data analysis and publication. The first patient's first visit is planned for the third-quarter (Q3)/2017. Interim analysis with 2×25 patients is planned for the end of Q1/2018. Accordingly, last patient's first visit shall be reached Q2/2019 and last patient's last visit in Q3/2019. The final report and publication should be available in Q2/2020.

Study population

Patients diagnosed with IE according to the modified Duke criteria[25] undergoing cardiac surgery using CPB.

Inclusion criteria

- Infective endocarditis according to the modified Duke criteria with an indication for surgery in accordance with the European Guidelines for IE treatment.[26]
- Age≥18.
- Signed informed consent.

Exclusion criteria

- Low-risk patients with European System for cardiac operative risk evaluation (EuroScore II)≤3.
- Current participation in another interventional trial.
- Pregnancy.
- Current immunosuppressive or immunomodulatory therapy (with dosing of glucocorticoids over cushing threshold).
- Previous participation in the REMOVE study.

Obtaining informed consent

The nature of the study must be explained to each subject (or legally authorised representative) before inclusion in the study. Obtaining of informed consent will then be carried out according to § 28 of the Declaration of Helsinki (online supplementary file 3).

Screening and randomisation

All patients with IE referred to cardiac surgery in the participating centres will be screened. Patients will be 1:1 randomised into one of the two treatment groups stratified by centre.

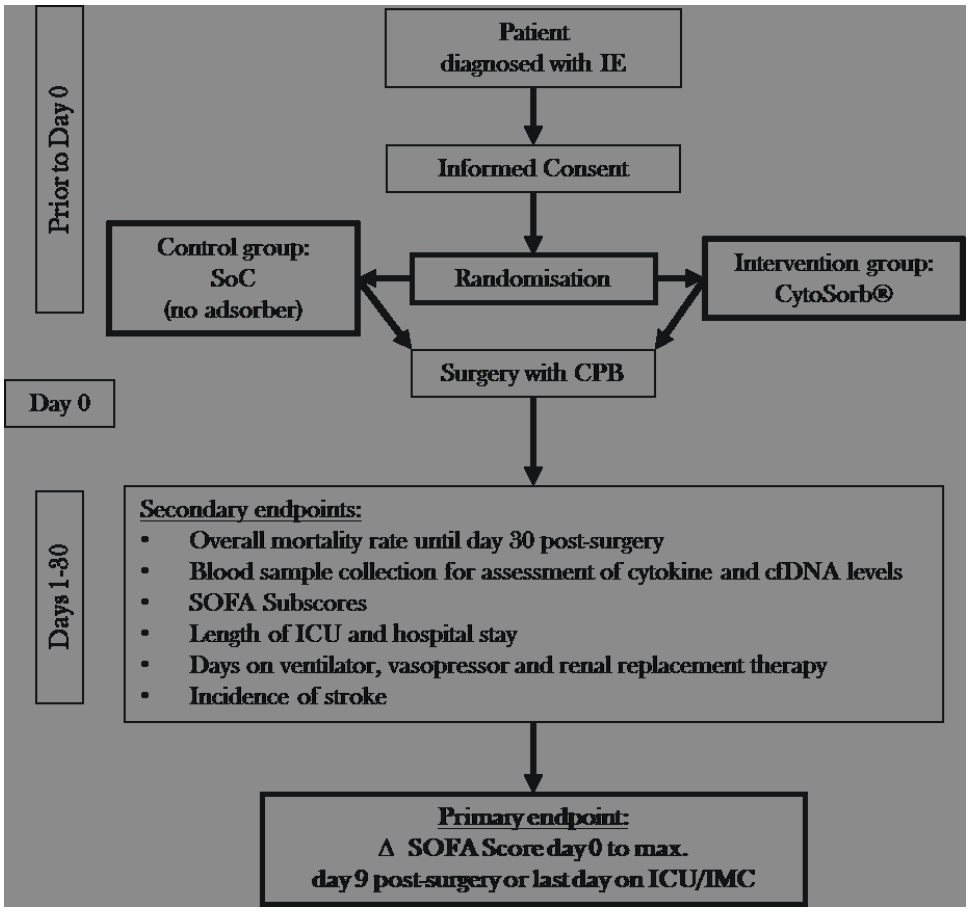

Figure 2 Flowchart of the study procedure. CPB, cardiopulmonary bypass; ICU, intensive care unit; IE, infective endocarditis; IMC, intermediate care unit; SoC, standard of care.

Frequency and scope of study visits

Table 1 shows the study visits. Sample collection for cytokines measurement will be done at skin incision, 30 and 60 min after starting CPB, at the end of CPB and 24 hours after surgery (only for the first 25 patients in each study arm). Sample collection for cfDNA will be done for the first five patients in each study arm only at the study site of the Jena University Hospital at skin incision, 60 min after starting CPB and 24 hours after surgery. SOFA score will be assessed within 24 hours before surgery and from the first postoperative day until discharge from the ICU or intermediate care (maximally to the ninth postoperative day). Follow-up of patients will be done on the 30th postoperative day.

Cytokine and cfDNA measurements

All blood samples for external partners will be taken during surgery and 24-hour post-surgery using a central venous catheter. The following vasoactive and inflammatory mediators will be examined:

- IL-1beta, IL-6, IL-10, IL-18 and TNF-α, procalcitonin (PCT), C-reactive protein (CRP).
- C-terminal proendothelin-1 (CT-proET-1), midregional pro-Adrenomedullin(MR-proADM), copeptin pro-Arginine Vasopressin (CT-proAVP), midregional pro-Atrial natriureticPeptide (MR-proANP).

The measurements will be carried out centrally in the laboratory of the external cooperation partner B.R.A.H.M.S (part of ThermoFisher Scientific).

Microbial cfDNA analysis and microbial transcriptome analysis will be carried out at the Fraunhofer Institute for Interfacial Engineering and Biotechnology, Department of Molecular Biotechnology/Functional Genomics Stuttgart, Germany. Blood sampling for microbial transcriptome analysis will only be conducted in 2×5 patients in Jena as part of a routine blood sampling.

Possible complications and/or risks

No additional risks for the patients due to study participation are expected.[19 27 28] For the assessment of safety of the study, a focus will be on the documentation of the following events:

- Death.
- Safety of the medical device:
  - Breakage of the medical device.
  - Malfunction of the medical device.
  - Inadequacy in labelling or the instructions for use.
- Intraoperative and postoperative complications.
- Renal replacement therapy.
- Mechanical ventilation.
- Abnormal laboratory values (only laboratory values assessed for SOFA score).

Table 1 Frequency and scope of REMOVE study visit

	Time point									
Flowchart	**Within 24 hours before surgery**	**Start surgery (=skin incision)**	**30 min after start CPB**	**60 min after start CPB**	**End of CPB**	**Day 0 (end of surgery to start first complete day after surgery)**	**Day 1 (sample taking 24 hours postsurgery=24 hours after skin closure)**	**Day 2 to max. day 9 after surgery or last day on ICU/ IMC**	**Discharge from ICU/ hospital**	**30-day post surgery**
Check inclusion criteria; Informed consent; randomisation; pregnancy test; demographic data	x									
Operative risk assessment (EuroScore*)	x									
Duke criteria	x									
Cardiac status incl. endocarditis, SIRS, risk factors, organ dysfunction	x									
Charlson comorbidity assessment†	x									
Concomitant medication ‡	x									
Microbiology and antimicrobial treatment ‡ §	x									
Blood culture testing ‡ ¶	x									
Brain natriuretic peptide, troponin and liver values ‡	x									
Neurological status ‡	X									
Organ dysfunction assessment (SOFA)	x					x	x	x		
Blood sampling for mediator profiling**		x	x	x	x		x			
Blood sampling for cfDNA profiling/transcriptome analysis**	x	x		x			x			
Valve tissue sampling ††			x							
Details of surgery and CPB incl. complications					x	x	x			x
Incidence of stroke										x
Length of ICU and in-hospital stay									x	x
Total days on ventilation, vasopressor and renal replacement therapy										x
Mortality									x	x
Blood sampling for MinEd study‡‡		x								
Cardiovascular incidents or fatal events							X			
Protocol deviations							X			

Continued

Table 1 Continued

Flowchart	Time point									
	Within 24 hours before surgery	Start surgery (=skin incision)	30 min after start CPB	60 min after start CPB	End of CPB	Day 0 (end of surgery to start first complete day after surgery)	Day 1 (sample taking 24 hours postsurgery=24 hours after skin closure)	Day 2 to max. day 9 after surgery or last day on ICU/ IMC	Discharge from ICU/ hospital	30-day post surgery

*According to http://www.euroscore.org/calc.html.
†According to http://www.fpnotebook.com/prevent/Exam/ChrlsnCmrbdtyIndx.htm.
‡Concomitant medication, antimicrobial treatment, blood culture testing, additional liver values, neurological status: if and as far as indicated.
Concomitant Medication: only immunomodulating therapies.
§Antimicrobial treatment: substance, application, dose, duration.
¶Blood culture testing: time point blood sampling, infectious agent, growing time, resistance.
**Blood sampling only of the first 50 patients for interim.
††Valve tissue sampling (incl. pathological examination) will only be done if infected tissue is removed during surgery.
‡‡Blood sampling includes 4.9 mL serum. See section five for further information on MinEd study.
CPB, cardiopulmonary bypass; ICU, intensive care unit; IMC, intermediate care unit; SIRS, systemic inflammatory response syndrom; SOFA, sequential organ failure assessment.

Any of the above-mentioned adverse event (AE) is considered as serious adverse event (SAE) if it is directly or indirectly caused, may have caused in the past or may cause in the future death or a serious aggravation of the state of health of a patient, user or another person without taking into consideration if the incident was caused by the medical device. The events will be recorded from the moment the medical device is unpacked for surgery until follow-up at day 30 post-surgery.

Statistical considerations and methods

Sample size

Sample size calculations were performed for the primary outcome of Δ mean SOFA score until day 9 postsurgery. The sample size calculation was done for a pocock-type group sequential design with a planned interim analysis for 2×25 patients (20% of the total sample size) and a final analysis. It should be noted that the focus of the interim analysis is exploring perioperative plasma profiles of cytokines and vasoactive mediators . The study is designed as a group sequential study in order to be able to test the primary endpoint for superiority at the interim and final analysis. The null hypothesis states that there is no difference between study groups regarding the primary outcome (ie, H0: $\mu1=\mu2$). Therefore the two-sided alternative hypothesis is H1: $\mu1\neq\mu2$. A claim in favour of superiority for the experimental group can be made if H0 can be rejected and if the direction of the effect is in favour of the experimental group. Data from previous studies[22 23] have shown that a 1.4-point lower SOFA score in the intervention group would be of clinical relevance. We assume a common SD of 3.8 points which results in a standardised effect size of 0.368 SD.[29] To achieve 80% power at an overall two-sided significance level of $\alpha=5\%$ while including an interim analysis after 2×25 patients ($\alpha1=0.0147$) and a final analysis ($\alpha2=0.0378$), 125 patients need to be included per study arm (two-sided group-sequential z-test; nQuery Advisor V.7.0 Statistical Solutions). Based on a previous study,[22] a drop-out rate of 15% is expected, leading to a total of 296 (2×148) patients that need to be randomised.

Statistical analyses

The analysis of the primary outcome will be a comparison of the experimental group with CytoSorb adsorber and the control group with standard care with regard to differences in mean total SOFA score until day 9 postsurgery. Note that we consider a two-sided test with $\alpha=0.05$ ($\alpha1=0.0147$ (2×25 patients) and $\alpha2=0.0378$ (final analysis)), as both superiority of the experimental and superiority of the control group are of interest (ie, a potential harm of the device). The confirmatory analysis on the intention-to-treat analysis set will be performed by a linear mixed model including surgeon and baseline SOFA as fixed effect covariates and centre as random effect. The null hypothesis can be rejected if the p value related to the Wald test statistic for the treatment effect is equal or smaller than $\alpha1$ or $\alpha2$. We will perform explorative sensitivity analysis for the primary outcome such as analyses in the per-protocol analysis set and worst/ best-case scenario analyses in case of missing data on the primary outcome.

All secondary analyses will be done exploratively, that is, without adjustment for multiplicity. We will use adequate standard descriptive and inferential statistical techniques. To be more specific for the changes in vasoactive and inflammatory mediator and cfDNA levels at the interim analysis we will follow the preclinical sepsis models by Peng *et al*.[17] We expect a group difference in intraindividual changes of either IL-1β, IL-6 or IL-10 after 60 min, and at the end of CPB. At least one of these three comparisons should meet an explorative significance level of $\alpha_{cytokine}=0.05$. Such a result could serve as an indicator of the mechanistic mode of action of the medical devices and would link the rodent model data of Peng *et al* to human data. A patient who for any reason (except death) fails to continue in the trial until the last visit is a drop out.

Methods against bias

Randomisation and (concealment of) treatment allocation

To address 'concealment of allocation', randomisation will be done centrally. Patients will be randomised, and whoever receives one of the compared treatments is part of the full analysis set (intention-to-treat analysis set). To achieve balanced prognostic factor distributions for the factor centre, we propose to apply a center-stratified 1:1 block randomisation of variable block sizes.

Methods against treatment bias

This study has a non-blinded study design and assesses real-life treatment strategies. Systematic differences due to differing expertise of participating surgeons will be minimised but cannot be totally ruled out and will be explored in posthoc statistical modelling of their potential effect. All participating sites are certified cardiothoracic centres and have a quality management system. Investigators have to be trained in good clinical practice (GCP). All surgeons should be qualified cardiac surgeons and hold the appropriate national diploma or at least operate under surveillance of a senior cardiac surgeon. Proof of qualification should be given before being acknowledged in participating in the study.

Methods against measurement bias

At each visit, the occurrence of possible outcomes will be documented in the case report forms (as shown in the online supplementary file 1). In addition, all patients will be followed-up after surgery. Finally, monitoring (on-site and central) will be done during the trial by staff of the Center for Sepsis Control and Care and the Center for Clinical Studies, Jena University Hospital.

Data management

Data assessment/case report forms

Data acquisition will be done via web application into the study management software OpenClinica. The software meets the regulatory requirements (GCP, 21CFR Part11). The data will be entered via encrypted connection in web browser input masks. Each subject will be given an unambiguous patient identification number to ensure pseudonymised data analysis.

ETHICS AND DISSEMINATION

The study was approved in September 2017 by the institutional review board and ethics committee of the Friedrich Schiller University (No.: 5240-08/17) as well as by the corresponding ethics committee for each participating centre (online supplementary file 2).

Privacy, collection and processing of data

The data obtained in the course of the study will be treated pursuant to the appropriate Data Protection Law. During the study, subjects will be identified solely by an individual identification code (subject number). Study findings stored on a computer/server will be stored in accordance with local data protection law and will be handled in strictest confidence.

Dissemination

The results of this study will be published in a renowned international medical journal, irrespective of the outcomes of the study.

DISCUSSION

CytoSorb is a haemoadsorption medical device which is capable of removing molecules between 5 and 60 kDa including cytokines, and a wide range of inflammatory mediators. However, the efficacy of CytoSorb is still controversial. While experimental studies on animal models have shown encouraging results,[16 17] clinical studies provided conflicting results.[20 27 30 31] Small patient samples, non-randomised studies, and the inclusion of low-risk patients were limitations that may explain these discrepancies. In REMOVE we are going to investigate the efficacy of CytoSorb by a randomised trial in a larger patient sample with IE with an established clinical confirmatory surrogate endpoint related to organ dysfunction. Demonstrating efficacy of the use of CytoSorb haemoadsorption during CPB in high-risk patients with IE would be a first evidence-based step forward for this difficult-to-treat patient population.

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of safety and efficacy data. Members of this board are: Matthias Loebe. Miami Transplant institute, Memorial Jackson Health System, University of Miami. John A. Kellum, Department of Critical Care Medicine, University of Pittsburgh. Peter U. Heuschmann, Institute for Clinical Epidemiology and Biometry, University of Würzburg.

Contributors MD is the principal investigator. MD, SP, FMB, AS and CS wrote the protocol. AS was involved in the design and sample-sized considerations; TL is the responsible biometrician. TD, MB, FMB, AG, AS and SH are scientific advisors who participated in reviewing the protocol. SP is the project manager and monitor. MD and IV are responsible for patients' recruitment at theUniversity Hospital of Jena. All coauthors read and proved the final manuscript.

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Competing interests FMB reports grants and personal fees from CytoSorbents Europe,outside the submitted work.

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

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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