BMJ Open

Mortality Reduction in Septic Shock by Plasma Adsorption (ROMPA): a protocol for a randomized clinical trial.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-011856
Article Type:	Protocol
Date Submitted by the Author:	10-Mar-2016

Complete List of Authors:	Colomina-Climent, Francisco; Miguel Hernández University, Clinical Medicine Giménez-Esparza, Carola; Vega Baja Hospital of Orihuela, Intensive Care Unit Portillo-Requena, Cristina; Vega Baja Hospital of Orihuela, Intensive Care Unit Allegue-Gallego, José; General University Santa Lucía Hospital of Cartagena, Intensive Care Unit Galindo-Martínez, María; General University Santa Lucía Hospital of Cartagena, Intensive Care Unit Mollà-Jiménez, Cristina; University Hospital of San Juan de Alicante, Intensive Care Unit Antón-Pascual, José; University Hospital of San Juan de Alicante, Intensive Care Unit Rodríguez-Serna, Manuel; Lluís Alcanyís Hospital of Xàtiva, Intensive Care Unit Martín-Ruíz, José; Lluís Alcanyís Hospital of Xàtiva, Intensive Care Unit Fernández-Arroyo, Pablo; Marina Baixa Hospital of Villajoyosa, Intensive Care Unit Blasco-Císcar, Eugenia; Marina Baixa Hospital of Villajoyosa, Intensive Care Unit Cánovas-Robles, José; General University Hospital of Alicante, Intensive Care Unit Herrera-Murillo, Miguel; General University Hospital of Alicante, Intensive Care Unit González-Hernández, Enrique; La Plana Hospital of Villarreal, Intensive Care Unit Sánchez-Morán, Fernando; La Plana Hospital of Villarreal, Intensive Care Unit Solera-Suárez, Manuel; Francesc de Borja Hospital of Gandía, Intensive Care Unit Torres-Tortajada, Jesús; Francesc de Borja Hospital of Gandía, Intensive Care Unit Nuñez-Martínez, José; Vinalopó University Hospital of Elche, Intesive Care Unit Martín-Langerwerf, David; Vinalopó University Hospital of Elche, Intesive Care Unit Herrero-Gutiérrez, Eugenio; University Hospital of Torrevieja, Intensive Care Unit Sebastián-Muñoz, Isabel; University Hospital of Torrevieja, Intensive Care Unit

	Palazón-Bru, Antonio; Miguel Hernández University, Clinical Medicine Gil-Guillen, Vicente F.; Miguel Hernández University, Clinical Medicine
Primary Subject Heading:	Intensive care
Secondary Subject Heading:	Infectious diseases, Intensive care
Keywords:	INFECTIOUS DISEASES, Adult intensive & critical care < INTENSIVE & CRITICAL CARE, STATISTICS & RESEARCH METHODS

TITLE PAGE:

Title: Mortality Reduction in Septic Shock by Plasma Adsorption (ROMPA): a protocol for a randomized clinical trial.

Running head: The ROMPA study.

Authors: Francisco Colomina-Climent [1], Carola Giménez-Esparza [2], Cristina Portillo-Requena [2], José Manuel Allegue-Gallego [3], María Galindo-Martínez [3], Cristina Mollà-Jiménez [4], José Luis Antón-Pascual [4], Manuel Rodríguez-Serra [5], José Luis Martín-Ruíz [5], Pablo Juan Fernández-Arroyo [6], Eugenia María Blasco-Císcar [6], José Cánovas-Robles [7], Miguel Herrera-Murillo [7], Enrique González-Hernández [8], Fernando Sánchez-Morán [8], Manuel Solera-Suárez [9], Jesús Torres-Tortajada [9], José María Nuñez-Martínez [10], David Martín-Langerwerf [10], Eugenio Herrero-Gutiérrez [11], Isabel Sebastián-Muñoz [11], Antonio Palazón-Bru [1], Vicente Francisco Gil-Guillén [1].

Institutions:

1. Department of Clinical Medicine, Miguel Hernández University, San Juan de Alicante, Alicante, Spain.

2. Intensive Care Unit, Vega Baja Hospital of Orihuela, Orihuela, Alicante, Spain.

3. Intensive Care Unit, General University Santa Lucía Hospital of Cartagena, Cartagena, Murcia, Spain.

4. Intensive Care Unit, University Hospital of San Juan de Alicante, San Juan de Alicante, Alicante, Spain.

5. Intensive Care Unit, Lluís Alcanyís Hospital of Xàtiva, Xàtiva, Valencia, Spain.

6. Intensive Care Unit, Marina Baixa Hospital of Villajoyosa, Villajoyosa, Alicante, Spain.

7. Intensive Care Unit, General University Hospital of Alicante, Alicante, Alicante, Spain.

8. Intensive Care Unit, La Plana Hospital of Villarreal, Villarreal, Castellón, Spain.

9. Intensive Care Unit, Francesc de Borja Hospital of Gandía, Gandía, Valencia, Spain.

10. Intensive Care Unit, Vinalopó University Hospital of Elche, Elche, Alicante, Spain.

11. Intensive Care Unit, University Hospital of Torrevieja, Torrevieja, Alicante, Spain.

Corresponding author: Prof. Antonio Palazón-Bru, PhD. Department of Clinical Medicine, Miguel Hernández University, Carretera de Valencia - Alicante S/N, 03550, San Juan de Alicante (Spain). Phone number: +34 965919449. Fax number: +34 965919450. E-mail: antonio.pb23@gmail.com

Keywords: Shock, Septic; Coupled Plasma Filtration Adsorption; Mortality; Intensive Care Units; Clinical Trials.

Word count: 2878.

ABSTRACT:

Introduction: There is a lack of evidence in the efficacy of the coupled plasma filtration adsorption (CPFA) to reduce the mortality rate in septic shock. To fill this gap, we have designed the ROMPA study (Mortality Reduction in Septic Shock by Plasma Adsorption), to confirm whether treatment with an adequate dose of treated plasma by CPFA could confer a clinical benefit.

Methods and analysis: Our study is a multi-centric randomized clinical trial with 28- and 90-day follow-up and allocation ratio 1:1. Its aim is to clarify whether the application of high doses of CPFA (treated plasma ≥0.20 l/kg/day) in the first 3 days after randomization in addition to the current clinical practice is able to reduce hospital mortality in septic shock patients in intensive care units (ICUs) at 28 and 90 days after initiation of the therapy. The study will be performed in 10 ICUs in the Southeast of Spain which follow the same protocol in this disease (based on the Surviving Sepsis Campaign). Our trial is designed to be able to demonstrate an absolute mortality reduction of 20% [α=0.05; 1-β=0.8; n=190(95x2)]. The severity of the process, ensuring the recruitment of patients with high probability of death (50% in the control group), will be achieved through an adequate stratification by using both, severity scores and classical definitions of severe sepsis/septic shock and dynamic parameters. Our centers are fully aware of the many pitfalls associated with previous medical device trials. Trying to reduce these problems, we have developed a training program to improve the CPFA use (especially clotting problems).

Ethics and dissemination: The protocol was approved by the ethics committees of all the participant centers. The findings of the trial will be disseminated through peer-reviewed journals, national and international conference presentations.

Trial registration: NCT02357433 (clinicaltrials.gov).

INTRODUCTION

Sepsis is a clinical syndrome characterized by systemic inflammation due to infection.[1] Experimental studies show that infusion of bacterial products leads to rapid systemic release of an array of pro-inflammatory mediators.[2] These mediators are thought to play a role in consequent organ injury or death. Although initially much of the interest in sepsis focused on the pro-inflammatory response or single inflammatory mediators,[3-6] it is now clear that infection often triggers a complex, variable, and prolonged host response.[7,8] While both pro-inflammatory and anti-inflammatory mechanisms can contribute to the resolution of infection and tissue recover, an inappropriate response consisting of an excess (or deficiency) of mediators, inappropriate timing or location can lead to organ injury and secondary infections.

Sepsis is still a leading cause of mortality in intensive care units (ICUs) patients with a mortality rate of severe sepsis and septic shock ranging from 20-50%.[9] The Surviving Sepsis Campaign, an international consortium of professional societies involved in critical care treatment of infectious diseases, and emergency medicine, recently issued the third edition of the clinical guidelines for the management of severe sepsis and septic shock.[10] However, despite the high prevalence, there is still not a consensus on the concise definition and poor evidence for many therapeutic strategies.[11-14]

One of the great disappointments during the past 30 years has been the failure to apply advances in our understanding of the biological features of sepsis into effective new therapies. Many reasons have been proposed for the numerous failed therapeutic approaches and clinical trials. These include inappropriate targets,

targeting specific molecules that are part of redundant pathways, inappropriate timing and incorrect translation of oversimplified animal models to the more complex conditions and timing of human sepsis. In addition, many trials have been strongly criticized for incorrect trial design or execution.[13]

Theoretically, extracorporeal therapies can be used to remove septic mediators from the bloodstream of critically ill patients.[14,15] In practice however, inflammatory mediators are often poorly removed by conventional diffusion or convection due to the large molecular weight or biophysical size of many cytokines. Even with very high filtration volumes, many cytokines are not able to pass through the pores of commonly used filters.[16] Additionally, use of high permeable membranes or excess filtration can be associated with loss of albumin and other physiologic proteins and components. A recent systemic review found there was no evidence for clinical benefit of high volume hemofiltration for sepsis.[17]

Over the last several years, there has been an increased interest in the use of adsorption to aid in the removal of mediators during extracorporeal therapies.[14,15] This can be done by adsorption to a membrane during passage of blood through a hemofilter (hemoperfusion), where mediators are adsorbed to the membrane surface; or by adsorption with a cartridge containing resin in either hemo – or plasma perfusion. Although adsorptive techniques have been used for nearly 50 years, there is a relative lack of data regarding clinical efficacy for conditions such as sepsis.

Coupled plasma filtration adsorption (CPFA) has been proposed as one method to non-specifically remove both pro- and anti-inflammatory mediators.[18,19] This technique consists of a combination of filters and a resin cartridge to remove a number of different cytokines including TNF-α, Il-6 and Il-10, while simultaneously

providing continuous renal replacement therapy (CRRT) for renal/fluid support. The entire CPFA process can be divided into four phases: (a) the partial separation of plasma from the whole blood by a plasma filter; (b) the removal of sepsis mediators by a cartridge containing miniature spheres of a synthetic hydrophobic resin, (c) reinfusion of the purified plasma before the hemofilter and finally d) hemofiltration (Figures 1 and 2).

CPFA was first used in the late 90's with subsequent publications of several small observational clinical reports and case studies.[20-26] A few years ago, a large randomized multicenter controlled trial performed by a group of Italian intensive care physicians, GiViTI, but the trial was stopped for futility.[27] Factors leading to early stopping were extensively analyzed by the investigators and focused primarily on technical problems and inability to achieve an appropriate dose of treated plasma. Nearly 50% of the patients did not achieve the target goal of 10 hours of treatment/day. In a per protocol analysis the COMPACT I patients treated with CPFA with a dose of treated plasma superior to 0.20 l/kg/day showed a reduction in the mortality rate compared to control patients or those that received a lesser dose of treated plasma. Although this was an interesting finding, it is necessary to carry out a randomized clinical trial to confirm whether treatment with an adequate dose of treated plasma by CPFA could confer a clinical benefit.

The aim of the ROMPA Study (Reduccion de la Mortalidad Mediante Plasma-Adsorción en Shock séptico -- Mortality Reduction in Septic Shock by Plasma Adsorption) is to clarify whether the application of high doses CPFA in addition to the current clinical practice is able to reduce hospital mortality in septic shock patients in ICUs.

Primary and Secondary Outcomes

Primary Outcome: The main objective is to assess whether the treatment of septic shock associated with standard clinical practice, with the addition of CPFA at high doses (treated plasma volume equal or superior to 0.2 l/kg/day), is able to reduce hospital mortality of patients with septic shock at 28 and 90 days after initiation of therapy.

Secondary Outcome: Resolution time of septic shock, expressed in terms of normalization of plasma lactate, weaning from vasoactive medications and reduction of ICU length of stay (expressed as number of days without septic shock) on the intervention group compared to the control group.

METHODS

Setting and participants

The study will be performed in 10 ICUs, in the southeast of Spain, that follow the same protocol in the treatment of septic shock, based on the recommendations of the Surviving Sepsis Campaign with the participation of the following centers: Vega Baja Hospital of Orihuela, General University Santa Lucía Hospital of Cartagena, University Hospital of San Juan de Alicante, Lluís Alcanyís Hospital of Xàtiva, Marina Baixa Hospital of Villajoyosa, General University Hospital of Alicante, La Plana Hospital of Villarreal, Francesc de Borja Hospital of Gandía, Vinalopó University Hospital of Elche and University Hospital of Torrevieja.

The ROMPA study is a multi-centric, randomized, prospective, open clinical trial with 28- and 90-day follow-up and allocation ratio 1:1, assessing the mortality reduction by CPFA in patients with septic shock.

Each center must obtain technical proficiency with the machine and CPFA treatment before they can become “activated” for enrolment by the investigator monitoring team. This was done to avoid similar problems as those reported for COMPACT 1, and also because CPFA is not routinely done in Spain and there is a new generation machine now used for CPFA with improved anticoagulation support.

Participants and Sample Size

Patients ≥18 years old admitted to the ICU of the participant hospitals, with a diagnosis of septic shock can be included in the study. Definition of septic shock is: documented or probable infection with systemic manifestations, accompanied by signs of organ dysfunction or tissue hypoperfusion and with persistent hypotension despite adequate fluid resuscitation (at least 30 ml/kg of crystalloid), in the absence of other causes of hypotension.

Moreover the inclusion criteria comprises: (i) identification of the source of infection in the first 12 hours of diagnosis. (ii) severity of clinical situation, defined by APACHE II Score, which must be between 20 and 37 points; (iii) the time between septic shock diagnosis and randomization is 12 hours maximum.

The probability of death in this population in the internal experience of the participating centers is about 50%. We have a higher mortality than what is typically reported in recent literature due to a high percentage of abdominal surgical patients.

Finally, we will exclude pregnant patients, those with pathologies for which expected survival is <90 days, or in presence of contraindications (absolute or relative) to CRRT and lack of informed consent.

We plan to enroll 190 patients with the diagnosis of septic shock in order to demonstrate a reduction in mortality of 20% (similar to that of a subgroup of COMPACT I patients in which the volumes of treated plasma reach a level of at least 0.20 l/kg/day) with an alfa of 0.05 and a power of the contrast of 80%.[28]

Retrospective analysis of the clinical activity of the ICU involved in the previous year, allowed us to expect a total admission of 300 cases per year in all participating hospitals. As only one third of these patients are likely to meet the inclusion/exclusion requirements, we could complete the clinical trial within two years. The recruitment period is preset between March 2015 and March 2017.

Given the characteristics of the study population, with expectations of a long hospital stay (at best) and consequence (comorbidity), which also determine the need for the patients to remain in contact with the hospital system, we do not expect losses to follow up at 28 and 90 days.

Interventions

The patient is considered registered once informed consent form has been obtained by the patient or legal representative. The recruitment process ends with the patient randomization.

Patients will be divided randomly into two arms (control and intervention).

ROMPA has a stratified randomization based on gender, age (≤ 65 or > 65 years) and SAPS III score (<50 or ≥51).

The characteristics of the groups are:

control group: Treatment according to the clinical practice of treating septic shock, following the protocol of the Surviving Sepsis Campaign.

intervention group: Same protocol plus high doses CPFA in the first 3 days after randomization.

The scheme of the trial is displayed in Figure 3.

Variables and measurements

The primary outcome variable is all-cause of mortality assessed at 28 and 90 days from the recruitment of the patient. Moreover, at the descriptive level and in order to check homogeneity of both groups, the following variables will be collected at the time of recruitment: birth year, gender, height, dry weight, body temperature, heart rate, blood pressure, count blood cell, coagulation values (PT, APTT, INR), glucose level, plasma creatinine, bilirubinemia, plasma C reactive protein, procalcitonin level, blood gas analysis (BGA), lactate, urinary output (ml/kg/h), Pa O_2/FiO_2 ratio. APACHE II, SOFA and SAPSIII scores.

Finally, for surviving patients, the following variables will be obtained at a descriptive level: length of stay in ICU (days), normalizing times for lactate levels and vasoactive support suspension expressed in hours.

Statistical analysis

The descriptive analysis will be performed using means and standard deviations for quantitative variables and absolute and relative frequencies for qualitative variables. To verify the homogeneity of both groups chi-square (Pearson or Fisher) and t-test will be used. To determine the benefit of our intervention, the clinical relevance indicators will be calculated: Relative Risk (RR), Absolute Risk Reduction (ARR), Relative Risk Reduction (RRR), Number Needed to Treat (NNT).

All analyses will be performed with a significance of 5% and the associated Confidence Interval (IC) of each relevant parameter will be calculated. The statistical software used will be the IBM SPSS Statistics 22

The entire analysis will be undertaken with “the intention to treat” principle, even though we have foreseen a “by protocol” analysis. Only patients who have received at least the minimum established doses of CPFA treatment in the experimental arm will be evaluated.

The “by protocol” analysis will include the fulfillment of the following requirements: 1) at least 3 CPFA sessions; 2) Total volume of treated plasma > 0.2 l/kg day in a minimum of 66% of total sessions; 3) Total volume of treated plasma throughout the total number of sessions, once divided by the number of sessions, should result in a mean treated plasma of ≥0.18 l/kg/day.

DISCUSSION

The present study should hopefully confirm the hypothesis showed by "per protocol" analysis of COMPACT-1 study and provide answers about the efficacy of early (less than 12 hours from diagnosis) high dose CPFA treatment in septic shock patients.

All cause mortality is an adequate and unavoidable target in a clinical trial like ours, where we expect a mortality rate of about 50% in the control group. The question however remains as to what time point to use to verify a treatment effect, and how to reveal whether an improved survival from treatment can be distinguished from the high background mortality (and often wide range of serious comorbidities) in the critically ill patient with septic shock. Our study analyzes mortality at both 28 days and 90 days.

28-day mortality has been used as a main objective in most of the relevant trials in severe sepsis from 1991 to 2009.[29] Patients with sepsis are classically considered to be patients who have a high risk of morbid complications and death. This is in large part owing to the organ dysfunction caused by sepsis, and the attendant complications of treating the organ dysfunction.[30] The corollary of this situation in terms of mortality is that hospital mortality may be higher than 28-day mortality but is likely lower than 90-day mortality.[31]

For this reason, analysis of mortality at 90 days has to be considered as essential to assess the clinical impact of a new therapeutic measure in septic shock treatment. The mortality with sepsis, particularly related to treating organ dysfunction, remains a priority to clinicians worldwide and deserves greater public health attention.

A source of potential weakness in the study design is the expected high mortality in the control group. We acknowledge that this can vary widely. A recent meta-analysis

showed mortality rates in the control arms, ranging from 17% to 61%, which impacted the results, resulting in a benefit in the studies with the highest rates.[32] We expect that our trial should be able to recruit only patients with high mortality risks based on previous patient data from our centers. We will try to meet this objective through an adequate stratification by using both , severity scores and classical definitions of severe sepsis /septic shock (that by themselves have all clearly failed to this end) and dynamic parameters, i.e., persistence and/or worsening signs of hypoperfusion after adequate infection source control, goal directed fluid therapy, and vasopressor infusion.

So-called secondary objectives (average stay, time to resolution of septic shock), but with an undoubted clinical interest, should help to shape the theoretical advantages of this technique.

Why do we think we can carry out this test?

All ICUs participating in this project have extensive experience in using CRRT techniques in critically ill patients. The investigators are fully aware of the challenge of treating patients with septic shock, and have particular experience in the treatment of septic shock due to an abdominal origin (the main type of patient treated for septic shock in our centers). The high mortality of this group consumes a huge amount of resources and has generated awareness of the need for efficacy studies. This is coupled with a strong commitment from the investigators to address this issue.

In addition, our centers are fully aware of the many pitfalls associated with previous medical device trials for extracorporeal therapies. In particular, there have been

many discussions centered on whether investigators and nursing staff from previous failed/negative trials were fully familiar and trained in using the technique and associated support (anticoagulation, vascular access…). As an example the first large randomized CPFA trial, COMPACT-1 had a complication rate of anticoagulation or other technical issues in nearly 50% of the patients.[27]

To overcome these hurdles, we have taken several steps to address the issue of familiarity with the technique. These include:

-Practical hands-on workshops and intensive training for CPFA in each participating hospitals. In these workshops doctors and nurses have perfected their knowledge and skills in the art. In particular we have put a lot of emphasis in including our nursing and technical professionals in the study design and execution.

-Requirement of successful completion of at least two cycles of CPFA treatments for patients similar to those with the inclusion requirements before the hospital can be authorized to officially start the trial and have access to the randomization portal.

-Formation of an intra-network 24/7 support group among the investigators. Investigators are able to call a core team (from the investigators team) to help in treatment or patient issues.

-Participating centers meet on a quarterly basis to monitor trial progress and share incidents that have occurred during the study.

ETHICS AND DISSEMINATION

Research ethics approval

This study has a clinicaltrials.gov identifier of NCT02357433. Currently, all participating centers have obtained Ethical Committee approval to participate in the trial.

Consent or assent

The Consent Form acknowledges the participant will for accepting or declining participation on ROMPA clinical trial. The request for the signing of this document is always a function of accredited doctors to participate in the trial.

Confidentiality

All participants´ personal information will be encrypted with the objective of keeping personal data on condition of anonymity.

Declaration of interests

The authors declare no conflict of interest.

Access to data

Any access to information regarding these procedures can only be accessed by the primary investigator as well as the team responsible for processing data.

Ancillary and post-trial care

Any side effects, which could have been produced while participating in the trial, can be assisted upon through the specific insurance policy (HDI Hannover International, policy number 130/002/001903) related to the trial procedures.

Dissemination policy

The findings of the trial will be disseminated through peer-reviewed journals, national and international conference presentations.

AUTHORS' CONTRIBUTIONS

FC drafted the paper of the protocol, AP helped draft the paper, and the rest of the authors critically reviewed the paper before sending it to *BMJ Open*.

FUNDING STATEMENT

This work was supported by Bellco which provided all the devices and materials related to the use of CPFA for the treatment group and will pay the open access fee for publication in *BMJ Open*. This entity did not play any role in study design; collection, management, analysis, and interpretation of data; writing of this report; and the decision to submit this report for publication.

COMPETING INTERESTS STATEMENT

The authors declare no conflict of interest.

ACKNOWLEDGMENTS

The authors thank all the health professionals integrated in the ROMPA research group and those who will participate in our study. The copyright holder (Bellco) has approved the utilization of Figures 1-2.

REFERENCES

1) Angus DC, van der Poll T. Severe sepsis and septic shock. N Engl J Med 2013; 369:840-51.

2) van der Poll T, Opal SM. Host-pathogen interactions in sepsis. Lancet Infect Dis 2008;8:32-43.

3) Bone RC, Grodzin CJ, Balk RA. Sepsis: A new hypothesis for pathogenesis of the disease process. Chest 1997;112:235-43.

4) McCloskey RV, Straube RC, Sanders C, Smith SM, Smith CR. Treatment of septic shock with human monoclonal antibody HA-1A. A randomized, double-blind, placebo-controlled trial. CHESS trial study group. Ann Intern Med 1994;121:1-5.

5) Beutler B, Greenwald D, Hulmes JD, et al. Identity of tumour necrosis factor and the macrophage-secreted factor cachectin. Nature 1985;316:552-4.

6) Bernard GR, Wheeler AP, Russell JA, et al. The effects of ibuprofen on the physiology and survival of patients with sepsis. The ibuprofen in sepsis study group. N Engl J Med 1997;336:912-8.

7) Wiersinga WJ, Leopold SJ, Cranendonk DR, van der Poll T. Host innate immune responses to sepsis. Virulence 2014;5:36-44.

8) Hotchkiss RS, Monneret G, Payen D. Immunosuppression in sepsis: A novel understanding of the disorder and a new therapeutic approach. Lancet Infect Dis 2013;13:260-8.

9) Gaieski DF, Edwards JM, Kallan MJ, Carr BG. Benchmarking the incidence and mortality of severe sepsis in the united states. Crit Care Med 2013;41:1167-74.

10) Dellinger RP, Levy MM, Rhodes A, et al. Surviving sepsis campaign: International guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med 2013;41:580-637.

11) Angus DC. The search for effective therapy for sepsis: Back to the drawing board? JAMA 2011;306:2614-5.

12) Drewry AM, Hotchkiss RS. Sepsis: Revising definitions of sepsis. Nat Rev Nephrol 2015;11:326-8.

13) Opal SM, Dellinger RP, Vincent JL, Masur H, Angus DC. The next generation of sepsis clinical trial designs: What is next after the demise of recombinant human activated protein C? Crit Care Med 2014;42:1714-21.

14) Rimmelé T, Kellum JA. Clinical review: Blood purification for sepsis. Crit Care 2011;15:205.

15) Panagiotou A, Gaiao S, Cruz DN. Extracorporeal therapies in sepsis. J Intensive Care Med 2013;28:281-95.

16) Rimmelé T, Kellum JA. High-volume hemofiltration in the intensive care unit: A blood purification therapy. Anesthesiology 2012;116:1377-87.

17) Clark E, Molnar AO, Joannes-Boyau O, Honoré PM, Sikora L, Bagshaw SM. High-volume hemofiltration for septic acute kidney injury: A systematic review and meta-analysis. Crit Care 2014;18:R7.

18) Tetta C, Cavaillon JM, Schulze M, et al. Removal of cytokines and activated complement components in an experimental model of continuous plasma filtration coupled with sorbent adsorption. Nephrol Dial Transplant 1998;13:1458-64.

19) Ronco C, Brendolan A, d'Intini V, Ricci Z, Wratten ML, Bellomo R. Coupled plasma filtration adsorption: Rationale, technical development and early clinical experience. Blood Purif 2003;21:409-16.

20) Hassan J, Cader RA, Kong NC, Mohd M, Rahman AR, Hod R. Coupled plasma filtration adsorption (CPFA) plus continuous veno-venous haemofiltration (CVVH) versus CVVH alone as an adjunctive therapy in the treatment of sepsis. Excli J 2013;12:681-92.

21) Abdul Cader R, Abdul Gafor H, Mohd R, Yen Kong W, Arshad N, Kong N. Coupled plasma filtration and adsorption (CPFA): A single center experience. Nephrourol Mon 2013;5:891-6.

22) Formica M, Olivieri C, Livigni S, Cesano G, Vallero A, Maio M, Tetta C. Hemodynamic response to coupled plasmafiltration-adsorption in human septic shock. Intensive Care Med 2003;29:703-8.

23) Ronco C, Brendolan A, Lonnemann G, et al. A pilot study of coupled plasma filtration with adsorption in septic shock. Crit Care Med 2002;30:1250-5.

24) Moretti R, Scarrone S, Pizzi B, Bonato V, Vivaldi N. Coupled plasma filtration-adsorption in weil's syndrome: Case report. Minerva Anestesiol 2011;77:846-9.

25) Berlot G, Agbedjro A, Tomasini A, Bianco F, Gerini U, Viviani M, Giudici F. Effects of the volume of processed plasma on the outcome, arterial pressure and

blood procalcitonin levels in patients with severe sepsis and septic shock treated with coupled plasma filtration and adsorption. Blood Purif 2014;37:146-51.

26) Fabbri LP, Macchi A, Lecchini R, Antonella P. Post influenza vaccination guillain-barré syndrome. An exceptional recovery case after cardiac arrest for two hours in hyperthermia and septic shock. Anesthesia, Pain & Intensive Care 2015;18:166-9.

27) Livigni S, Bertolini G, Rossi C, et al. Efficacy of coupled plasma filtration adsorption (CPFA) in patients with septic shock: A multicenter randomised controlled clinical trial. BMJ Open 2014;4:e003536.

28) Chow S, Wang H, Shao J. Sample Size Calculations in Clinical Research. New York, NY: Chapman & Hall/CRC 2008.

29) Stevenson EK, Rubenstein AR, Radin GT, Wiener RS, Walkey AJ. Two decades of mortality trends among patients with severe sepsis: a comparative meta-analysis. Crit Care Med 2014;42:625-31.

30) Martin GS. Sepsis, severe sepsis and septic shock: changes in incidence, pathogens and outcomes. Expert Rev Anti Infect Ther 2012;10:701-6.

31) Kaukonen KM, Bailey M, Suzuki S, Pilcher D, Bellomo R. Mortality Related to Severe Sepsis and Septic Shock Among Critically Ill Patients in Australia and New Zealand, 2000- 2012. JAMA 2014;311:1308-16.

32) Asfar P, Claessens YE, Duranteau J, Kipnis E, Leone M, Levy B; French Opinion Group in Sepsis (FrOGS). Residual rates of mortality in patients with severe sepsis: a fatality or a new challenge? Ann Intensive Care 2013;3:27.

FIGURE LEGENDS:

Figure 1: Amplya system from Bellco Societa unipersonales a r.l.

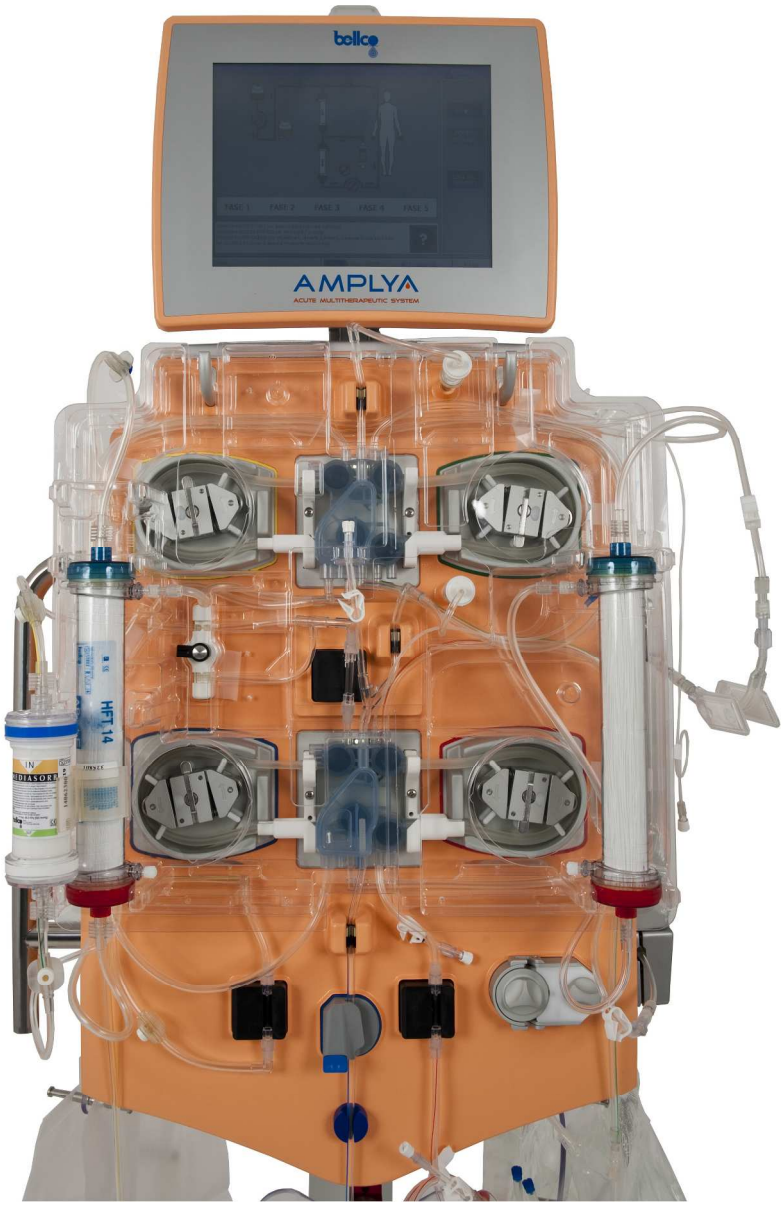
The resin cartridge and plasmafilter are in position and ready for use. The copyright holder (Bellco) has approved the utilization of this figure.

Figure 2: Schematic representation of CPFA circuit.

The extracorporeal circuit consisting of plasma filter (A), a resin cartridge (B) and a high-flux dialyzer (C). Blood pass through a plasma filter, extracted plasma is purified by adsorption on a resin cartridge and the reconstituted blood (●) through a high-permeability hemofilter, in which convective exchanges are realized in a post-dilution mode (substitution). The copyright holder (Bellco) has approved the utilization of this figure.

Figure 3: Study Diagram.

This shows the general study design and includes: 1) Registration: The patient is considered "enrolled" once informed consent has been obtained. 2) Recruitment Phase: must occur within the first 12 hours of Septic Shock diagnosis. 3) Randomization: Group A (CPFA) or Group B (Control). 4) Statistical evaluations: at the end of the study and after follow-up.



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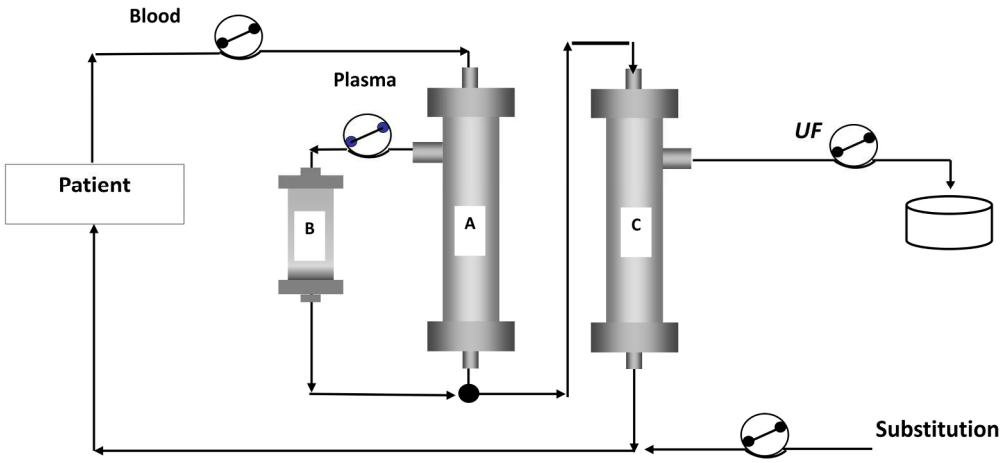


Figure 2: Schematic representation of CPFA circuit.
The extracorporeal circuit consisting of plasma filter (A), a resin cartridge (B) and a high-flux dialyzer (C). Blood pass through a plasma filter, extracted plasma is purified by adsorption on a resin cartridge and the reconstituted blood (•) through a high-permeability hemofilter, in which convective exchanges are realized in a post-dilution mode (substitution). The copyright holder (Bellco) has approved the utilization of this figure.
105x48mm (600 x 600 DPI)

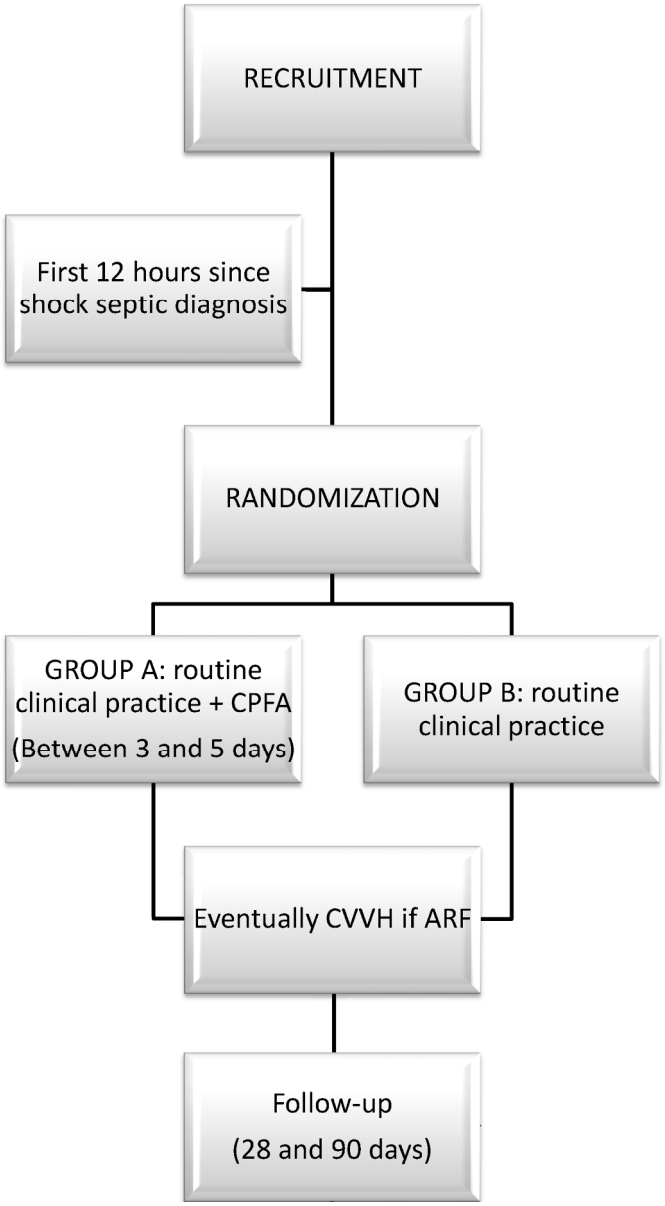


Figure 3: Study Diagram.
This shows the general study design and includes: 1) Registration: The patient is considered "enrolled" once informed consent has been obtained. 2) Recruitment Phase: must occur within the first 12 hours of Septic Shock diagnosis. 3) Randomization: Group A (CPFA) or Group B (Control). 4) Statistical evaluations: at the end of the study and after follow-up.
225x398mm (300 x 300 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym ✓
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry ✓
	2b	All items from the World Health Organization Trial Registration Data Set N/A
Protocol version	3	Date and version identifier ✓
Funding	4	Sources and types of financial, material, and other support ✓
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors ✓
	5b	Name and contact information for the trial sponsor ✓
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities ✓
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention ✓
	6b	Explanation for choice of comparators ✓
Objectives	7	Specific objectives or hypotheses ✓
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) ✓

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained ✓
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) ✓
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered ✓
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) ✓
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) ✓
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial ✓
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended ✓
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) ✓
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations ✓
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size ✓

Methods: Assignment of interventions (for controlled trials)

Allocation:		
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions ✓

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned ✓
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions ✓
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol ✓
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols ✓
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol ✓
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol ✓
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) ✓
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) ✓
Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial ✓
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct ✓
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor ✓
Ethics and dissemination		
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval ✓
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) ✓
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) ✓
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable ✓
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial ✓
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site ✓
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators ✓
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation ✓
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions ✓
	31b	Authorship eligibility guidelines and any intended use of professional writers ✓
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code ✓

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates ✓
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Mortality Reduction in Septic Shock by Plasma Adsorption (ROMPA): a protocol for a randomized clinical trial.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-011856.R1
Article Type:	Protocol
Date Submitted by the Author:	03-May-2016

Complete List of Authors:	Colomina-Climent, Francisco; Miguel Hernández University, Clinical Medicine Giménez-Esparza, Carola; Vega Baja Hospital of Orihuela, Intensive Care Unit Portillo-Requena, Cristina; Vega Baja Hospital of Orihuela, Intensive Care Unit Allegue-Gallego, José; General University Santa Lucía Hospital of Cartagena, Intensive Care Unit Galindo-Martínez, María; General University Santa Lucía Hospital of Cartagena, Intensive Care Unit Mollà-Jiménez, Cristina; University Hospital of San Juan de Alicante, Intensive Care Unit Antón-Pascual, José; University Hospital of San Juan de Alicante, Intensive Care Unit Rodríguez-Serna, Manuel; Lluís Alcanyís Hospital of Xàtiva, Intensive Care Unit Martín-Ruíz, José; Lluís Alcanyís Hospital of Xàtiva, Intensive Care Unit Fernández-Arroyo, Pablo; Marina Baixa Hospital of Villajoyosa, Intensive Care Unit Blasco-Císcar, Eugenia; Marina Baixa Hospital of Villajoyosa, Intensive Care Unit Cánovas-Robles, José; General University Hospital of Alicante, Intensive Care Unit Herrera-Murillo, Miguel; General University Hospital of Alicante, Intensive Care Unit González-Hernández, Enrique; La Plana Hospital of Villarreal, Intensive Care Unit Sánchez-Morán, Fernando; La Plana Hospital of Villarreal, Intensive Care Unit Solera-Suárez, Manuel; Francesc de Borja Hospital of Gandía, Intensive Care Unit Torres-Tortajada, Jesús; Francesc de Borja Hospital of Gandía, Intensive Care Unit Nuñez-Martínez, José; Vinalopó University Hospital of Elche, Intesive Care Unit Martín-Langerwerf, David; Vinalopó University Hospital of Elche, Intesive Care Unit Herrero-Gutiérrez, Eugenio; University Hospital of Torrevieja, Intensive Care Unit Sebastián-Muñoz, Isabel; University Hospital of Torrevieja, Intensive Care Unit

	Palazón-Bru, Antonio; Miguel Hernández University, Clinical Medicine Gil-Guillen, Vicente F.; Miguel Hernández University, Clinical Medicine
Primary Subject Heading:	Intensive care
Secondary Subject Heading:	Infectious diseases, Intensive care
Keywords:	INFECTIOUS DISEASES, Adult intensive & critical care < INTENSIVE & CRITICAL CARE, STATISTICS & RESEARCH METHODS

TITLE PAGE:

Title: Mortality Reduction in Septic Shock by Plasma Adsorption (ROMPA): a protocol for a randomized clinical trial.

Running head: The ROMPA study.

Authors: Francisco Colomina-Climent [1], Carola Giménez-Esparza [2], Cristina Portillo-Requena [2], José Manuel Allegue-Gallego [3], María Galindo-Martínez [3], Cristina Mollà-Jiménez [4], José Luis Antón-Pascual [4], Manuel Rodríguez-Serra [5], José Luis Martín-Ruíz [5], Pablo Juan Fernández-Arroyo [6], Eugenia María Blasco-Císcar [6], José Cánovas-Robles [7], Miguel Herrera-Murillo [7], Enrique González-Hernández [8], Fernando Sánchez-Morán [8], Manuel Solera-Suárez [9], Jesús Torres-Tortajada [9], José María Nuñez-Martínez [10], David Martín-Langerwerf [10], Eugenio Herrero-Gutiérrez [11], Isabel Sebastián-Muñoz [11], Antonio Palazón-Bru [1], Vicente Francisco Gil-Guillén [1].

Institutions:

1. Department of Clinical Medicine, Miguel Hernández University, San Juan de Alicante, Alicante, Spain.

2. Intensive Care Unit, Vega Baja Hospital of Orihuela, Orihuela, Alicante, Spain.

3. Intensive Care Unit, General University Santa Lucía Hospital of Cartagena, Cartagena, Murcia, Spain.

4. Intensive Care Unit, University Hospital of San Juan de Alicante, San Juan de Alicante, Alicante, Spain.

5. Intensive Care Unit, Lluís Alcanyís Hospital of Xàtiva, Xàtiva, Valencia, Spain.

6. Intensive Care Unit, Marina Baixa Hospital of Villajoyosa, Villajoyosa, Alicante, Spain.

7. Intensive Care Unit, General University Hospital of Alicante, Alicante, Alicante, Spain.

8. Intensive Care Unit, La Plana Hospital of Villarreal, Villarreal, Castellón, Spain.

9. Intensive Care Unit, Francesc de Borja Hospital of Gandía, Gandía, Valencia, Spain.

10. Intensive Care Unit, Vinalopó University Hospital of Elche, Elche, Alicante, Spain.

11. Intensive Care Unit, University Hospital of Torrevieja, Torrevieja, Alicante, Spain.

Corresponding author: Prof. Antonio Palazón-Bru, PhD. Department of Clinical Medicine, Miguel Hernández University, Carretera de Valencia - Alicante S/N, 03550, San Juan de Alicante (Spain). Phone number: +34 965919449. Fax number: +34 965919450. E-mail: antonio.pb23@gmail.com

Keywords: Shock, Septic; Coupled Plasma Filtration Adsorption; Mortality; Intensive Care Units; Clinical Trials.

Word count: 2878.

ABSTRACT:

Introduction: There is a lack of evidence in the efficacy of the coupled plasma filtration adsorption (CPFA) to reduce the mortality rate in septic shock. To fill this gap, we have designed the ROMPA study (Mortality Reduction in Septic Shock by Plasma Adsorption), to confirm whether treatment with an adequate dose of treated plasma by CPFA could confer a clinical benefit.

Methods and analysis: Our study is a multi-centric randomized clinical trial with 28- and 90-day follow-up and allocation ratio 1:1. Its aim is to clarify whether the application of high doses of CPFA (treated plasma ≥0.20 l/kg/day) in the first 3 days after randomization in addition to the current clinical practice is able to reduce hospital mortality in septic shock patients in intensive care units (ICUs) at 28 and 90 days after initiation of the therapy. The study will be performed in 10 ICUs in the Southeast of Spain which follow the same protocol in this disease (based on the Surviving Sepsis Campaign). Our trial is designed to be able to demonstrate an absolute mortality reduction of 20% [α=0.05; 1-β=0.8; n=190(95x2)]. The severity of the process, ensuring the recruitment of patients with high probability of death (50% in the control group), will be achieved through an adequate stratification by using both, severity scores and classical definitions of severe sepsis/septic shock and dynamic parameters. Our centers are fully aware of the many pitfalls associated with previous medical device trials. Trying to reduce these problems, we have developed a training program to improve the CPFA use (especially clotting problems).

Ethics and dissemination: The protocol was approved by the ethics committees of all the participant centers. The findings of the trial will be disseminated through peer-reviewed journals, national and international conference presentations.

Trial registration: NCT02357433 (clinicaltrials.gov).

INTRODUCTION

Sepsis is a clinical syndrome characterized by systemic inflammation due to infection.[1] Experimental studies show that infusion of bacterial products leads to rapid systemic release of an array of pro-inflammatory mediators.[2] These mediators are thought to play a role in consequent organ injury or death. Although initially much of the interest in sepsis focused on the pro-inflammatory response or single inflammatory mediators,[3-6] it is now clear that infection often triggers a complex, variable, and prolonged host response.[7,8] While both pro-inflammatory and anti-inflammatory mechanisms can contribute to the resolution of infection and tissue recover, an inappropriate response consisting of an excess (or deficiency) of mediators, inappropriate timing or location can lead to organ injury and secondary infections.

Sepsis is still a leading cause of mortality in intensive care units (ICUs) patients with a mortality rate of severe sepsis and septic shock ranging from 20-50%.[9] The Surviving Sepsis Campaign, an international consortium of professional societies involved in critical care treatment of infectious diseases, and emergency medicine, recently issued the third edition of the clinical guidelines for the management of severe sepsis and septic shock.[10] However, despite the high prevalence, there is still not a consensus on the concise definition and poor evidence for many therapeutic strategies.[11-14]

One of the great disappointments during the past 30 years has been the failure to apply advances in our understanding of the biological features of sepsis into effective new therapies. Many reasons have been proposed for the numerous failed therapeutic approaches and clinical trials. These include inappropriate targets,

targeting specific molecules that are part of redundant pathways, inappropriate timing and incorrect translation of oversimplified animal models to the more complex conditions and timing of human sepsis. In addition, many trials have been strongly criticized for incorrect trial design or execution.[13]

Theoretically, extracorporeal therapies can be used to remove septic mediators from the bloodstream of critically ill patients.[14,15] In practice however, inflammatory mediators are often poorly removed by conventional diffusion or convection due to the large molecular weight or biophysical size of many cytokines. Even with very high filtration volumes, many cytokines are not able to pass through the pores of commonly used filters.[16] Additionally, use of high permeable membranes or excess filtration can be associated with loss of albumin and other physiologic proteins and components. A recent systemic review found there was no evidence for clinical benefit of high volume hemofiltration for sepsis.[17]

Over the last several years, there has been an increased interest in the use of adsorption to aid in the removal of mediators during extracorporeal therapies.[14,15] This can be done by adsorption to a membrane during passage of blood through a hemofilter (hemoperfusion), where mediators are adsorbed to the membrane surface; or by adsorption with a cartridge containing resin in either hemo – or plasma perfusion. Although adsorptive techniques have been used for nearly 50 years, there is a relative lack of data regarding clinical efficacy for conditions such as sepsis.

Coupled plasma filtration adsorption (CPFA) has been proposed as one method to non-specifically remove both pro- and anti-inflammatory mediators.[18,19] This technique consists of a combination of filters and a resin cartridge to remove a number of different cytokines including TNF-α, Il-6 and Il-10, while simultaneously

providing continuous renal replacement therapy (CRRT) for renal/fluid support. The entire CPFA process can be divided into four phases: (a) the partial separation of plasma from the whole blood by a plasma filter; (b) the removal of sepsis mediators by a cartridge containing miniature spheres of a synthetic hydrophobic resin, (c) reinfusion of the purified plasma before the hemofilter and finally d) hemofiltration (Figures 1 and 2).

CPFA was first used in the late 90's with subsequent publications of several small observational clinical reports and case studies.[20-26] A few years ago, a large randomized multicenter controlled trial performed by a group of Italian intensive care physicians, GiViTI, but the trial was stopped for futility.[27] Factors leading to early stopping were extensively analyzed by the investigators and focused primarily on technical problems and inability to achieve an appropriate dose of treated plasma. Nearly 50% of the patients did not achieve the target goal of 10 hours of treatment/day. In a per protocol analysis the COMPACT I patients treated with CPFA with a dose of treated plasma superior to 0.20 l/kg/day showed a reduction in the mortality rate compared to control patients or those that received a lesser dose of treated plasma. Although this was an interesting finding, it is necessary to carry out a randomized clinical trial to confirm whether treatment with an adequate dose of treated plasma by CPFA could confer a clinical benefit.

The aim of the ROMPA Study (Reduccion de la Mortalidad Mediante Plasma-Adsorción en Shock séptico -- Mortality Reduction in Septic Shock by Plasma Adsorption) is to clarify whether the application of high doses CPFA in addition to the current clinical practice is able to reduce hospital mortality in septic shock patients in ICUs.

Primary and Secondary Outcomes

Primary Outcome: The main objective is to assess whether the treatment of septic shock associated with standard clinical practice, with the addition of CPFA at high doses (treated plasma volume equal or superior to 0.2 l/kg/day), is able to reduce hospital mortality of patients with septic shock at 28 and 90 days after initiation of therapy.

Secondary Outcome: Resolution time of septic shock, expressed in terms of normalization of plasma lactate, weaning from vasoactive medications and reduction of ICU length of stay (expressed as number of days without septic shock) on the intervention group compared to the control group.

METHODS

Setting and participants

The study will be performed in 10 ICUs, in the southeast of Spain, that follow the same protocol in the treatment of septic shock, based on the recommendations of the Surviving Sepsis Campaign with the participation of the following centers: Vega Baja Hospital of Orihuela, General University Santa Lucía Hospital of Cartagena, University Hospital of San Juan de Alicante, Lluís Alcanyís Hospital of Xàtiva, Marina Baixa Hospital of Villajoyosa, General University Hospital of Alicante, La Plana Hospital of Villarreal, Francesc de Borja Hospital of Gandía, Vinalopó University Hospital of Elche and University Hospital of Torrevieja.

The ROMPA study is a multi-centric, randomized, prospective, open clinical trial with 28- and 90-day follow-up and allocation ratio 1:1, assessing the mortality reduction by CPFA in patients with septic shock.

Each center must obtain technical proficiency with the machine and CPFA treatment before they can become “activated” for enrolment by the investigator monitoring team. This was done to avoid similar problems as those reported for COMPACT 1, and also because CPFA is not routinely done in Spain and there is a new generation machine now used for CPFA with improved anticoagulation support.

Participants and Sample Size

Patients ≥18 years old admitted to the ICU of the participant hospitals, with a diagnosis of septic shock can be included in the study. Definition of septic shock is: documented or probable infection with systemic manifestations, accompanied by signs of organ dysfunction or tissue hypoperfusion and with persistent hypotension despite adequate fluid resuscitation (at least 30 ml/kg of crystalloid), in the absence of other causes of hypotension.

Moreover the inclusion criteria comprises: (i) identification of the source of infection in the first 12 hours of diagnosis. (ii) severity of clinical situation, defined by APACHE II Score, which must be between 20 and 37 points; (iii) the time between septic shock diagnosis and randomization is 12 hours maximum. The choice of timing to start was based on previous experience from the COMPACT study and actual clinical use of routine users (data provided by manufacturer). We think however that an early start is better for the patient to avoid further amplification of the inflammatory cascade.

The probability of death in this population in the internal experience of the participating centers is about 50%. We have a higher mortality than what is typically reported in recent literature due to a high percentage of abdominal surgical patients. The observation of a high mortality rate in patients with septic shock from abdominal origin is a classic finding in the scientific papers.[28] European and North American experience of intra-abdominal sepsis is similar, with reported mortality rates for this condition ranging between 30% and 60%. Irrespective of the surgical strategies employed, laparotomy in the critically ill is associated with significant morbidity and mortality, the incidence of which increases with each re-laparotomy.[29]

Finally, we will exclude: a) patients under the age of 18 years; b) pregnant patients; c) patients with pathologies for which expected survival is <90 days (we analyze the mortality at 28 and 90 days. So we thought that it makes sense to exclude patients with comorbidities involving a life expectancy less than that period of time. In any case this prognosis would not be set by the ICU team but by the respective medical teams treating these pathologies); d) presence of contraindications (absolute or relative) to extrarenal depuration techniques; and e) lack of informed consent.

We plan to enroll 190 patients with the diagnosis of septic shock in order to demonstrate a reduction in mortality of 20% (similar to that of a subgroup of COMPACT I patients in which the volumes of treated plasma reach a level of at least 0.20 l/kg/day) with an alfa of 0.05 and a power of the contrast of 80%.[30] Our work hypothesis is based in COMPACT I observation that in intention-to-treat analysis there was no statistical difference in hospital mortality (47.3%, controls; 45.1%, CPFA; p=0.76), but in a subgroup analysis patients who could get a dose of treated plasma superior than 0.20 l/kg/day had a lower mortality compared with controls

(OR=0.36, 95% CI: 0.13-0.99).[27] The limits of this per protocol analysis are evident (definition for the per protocol analysis was based on characteristics measured after randomization, the subgroup allocation may have been influenced by the outcome...). In consequence our objective is to test this hypothesis in a clinical trial with enough power and potency.

Retrospective analysis of the clinical activity of the ICU involved in the previous year, allowed us to expect a total admission of 300 cases per year in all participating hospitals. As only one third of these patients are likely to meet the inclusion/exclusion requirements, we could complete the clinical trial within two years. The recruitment period is preset between March 2015 and March 2017.

Given the characteristics of the study population, with expectations of a long hospital stay (at best) and consequence (comorbidity), which also determine the need for the patients to remain in contact with the hospital system, we do not expect losses to follow up at 28 and 90 days.

Interventions

The patient is considered registered once informed consent form has been obtained by the patient or legal representative. The recruitment process ends with the patient randomization.

Patients will be divided randomly into two arms (control and intervention).

ROMPA has a stratified randomization based on gender, age (≤ 65 or > 65 years) and SAPS III score (<50 or ≥51).

The characteristics of the groups are:

control group: Treatment following the suggestions provided by the recent surviving sepsis guidelines, as well as standard care guidelines typically followed in Spain. CRRT, CVVH for both renal (such as AKI) or non-renal (such as fluid overload) are permitted in both trial arms if these are routinely used. We will not permit the introduction of non-routine extracorporeal or pharmaceutical agents for sepsis during the study to avoid confounding factors.

intervention group: Same protocol plus high doses CPFA in the first 3 days after randomization. Once the patient is placed in the CPFA group, he/she will receive treatment with CPFA in immediately. The treatment time will be the necessary to achieve the treated plasma dose of 0.2 l/kg/day. Patients will receive a minimum of 3 sessions and a maximum of 5. Regarding the 3 day duration of CPFA this was also suggested from the manufacturer as the typical shorter usage of CPFA. It is possible for the physician to use CPFA for a longer period if necessary.

The scheme of the trial is displayed in Figure 3.

Variables and measurements

The primary outcome variable is all-cause of mortality assessed at 28 and 90 days from the recruitment of the patient. Moreover, at the descriptive level and in order to check homogeneity of both groups, the following variables will be collected at the time of recruitment: birth year, gender, height, dry weight, body temperature, heart rate, blood pressure, count blood cell, coagulation values (PT, APTT, INR), glucose level, plasma creatinine, bilirubinemia, plasma C reactive protein, procalcitonin level, blood gas analysis (BGA), lactate, urinary output (ml/kg/h), Pa O_2/FiO_2 ratio. APACHE II, SOFA and SAPSIII scores.

Finally, for surviving patients, the following variables will be obtained at a descriptive level: length of stay in ICU (days), normalizing times for lactate levels and vasoactive support suspension expressed in hours.

Statistical analysis

The descriptive analysis will be performed using means and standard deviations for quantitative variables and absolute and relative frequencies for qualitative variables. To verify the homogeneity of both groups chi-square (Pearson or Fisher) and t-test will be used. To determine the benefit of our intervention, the clinical relevance indicators will be calculated: Relative Risk (RR), Absolute Risk Reduction (ARR), Relative Risk Reduction (RRR), Number Needed to Treat (NNT).

All analyses will be performed with a significance of 5% and the associated Confidence Interval (IC) of each relevant parameter will be calculated. The statistical software used will be the IBM SPSS Statistics 22

The entire analysis will be undertaken with “the intention to treat” principle, even though we have foreseen a “by protocol” analysis. Only patients who have received at least the minimum established doses of CPFA treatment in the experimental arm will be evaluated.

The “by protocol” analysis will include the fulfillment of the following requirements: 1) at least 3 CPFA sessions; 2) Total volume of treated plasma > 0.2 l/kg day in a minimum of 66% of total sessions; 3) Total volume of treated plasma throughout the total number of sessions, once divided by the number of sessions, should result in a mean treated plasma of ≥0.18 l/kg/day.

DISCUSSION

The present study should hopefully confirm the hypothesis showed by "per protocol" analysis of COMPACT-1 study and provide answers about the efficacy of early (less than 12 hours from diagnosis) high dose CPFA treatment in septic shock patients.

All cause mortality is an adequate and unavoidable target in a clinical trial like ours, where we expect a mortality rate of about 50% in the control group. The question however remains as to what time point to use to verify a treatment effect, and how to reveal whether an improved survival from treatment can be distinguished from the high background mortality (and often wide range of serious comorbidities) in the critically ill patient with septic shock. Our study analyzes mortality at both 28 days and 90 days.

28-day mortality has been used as a main objective in most of the relevant trials in severe sepsis from 1991 to 2009.[31] Patients with sepsis are classically considered to be patients who have a high risk of morbid complications and death. This is in large part owing to the organ dysfunction caused by sepsis, and the attendant complications of treating the organ dysfunction.[32] The corollary of this situation in terms of mortality is that hospital mortality may be higher than 28-day mortality but is likely lower than 90-day mortality.[33]

For this reason, analysis of mortality at 90 days has to be considered as essential to assess the clinical impact of a new therapeutic measure in septic shock treatment. The mortality with sepsis, particularly related to treating organ dysfunction, remains a priority to clinicians worldwide and deserves greater public health attention.

A source of potential weakness in the study design is the expected high mortality in the control group. We acknowledge that this can vary widely. A recent meta-analysis showed mortality rates in the control arms, ranging from 17% to 61%, which impacted the results, resulting in a benefit in the studies with the highest rates.[34] We expect that our trial should be able to recruit only patients with high mortality risks based on previous patient data from our centers. We will try to meet this objective through an adequate stratification by using both, severity scores and classical definitions of severe sepsis /septic shock (that by themselves have all clearly failed to this end) and dynamic parameters, i.e., persistence and/or worsening signs of hypoperfusion after adequate infection source control, goal directed fluid therapy, and vasopressor infusion.

So-called secondary objectives (average stay, time to resolution of septic shock), but with an undoubted clinical interest, should help to shape the theoretical advantages of this technique.

Why do we think we can carry out this test?

All ICUs participating in this project have extensive experience in using CRRT techniques in critically ill patients. The investigators are fully aware of the challenge of treating patients with septic shock, and have particular experience in the treatment of septic shock due to an abdominal origin (the main type of patient treated for septic shock in our centers). The high mortality of this group consumes a huge amount of resources and has generated awareness of the need for efficacy studies. This is coupled with a strong commitment from the investigators to address this issue.

In addition, our centers are fully aware of the many pitfalls associated with previous medical device trials for extracorporeal therapies. In particular, there have been many discussions centered on whether investigators and nursing staff from previous failed/negative trials were fully familiar and trained in using the technique and associated support (anticoagulation, vascular access…). As an example the first large randomized CPFA trial, COMPACT-1 had a complication rate of anticoagulation or other technical issues in nearly 50% of the patients.[27]

To overcome these hurdles, we have taken several steps to address the issue of familiarity with the technique. These include:

-Practical hands-on workshops and intensive training for CPFA in each participating hospitals. In these workshops doctors and nurses have perfected their knowledge and skills in the art. In particular we have put a lot of emphasis in including our nursing and technical professionals in the study design and execution. Clotting problems have to be taken into account in order to really be able to evaluate the efficacy of CPFA. Clotting was a major issue in the first COMPACT study.[27] All investigators and staff in our study underwent a very extensive training program for use of the machine (AMPLYA and the CPFA technique). This was one of the reasons that we had a relatively slow start for enrolment, as it was mandatory for the center to become experience before starting enrolment. Clotting can be due to many factors including: patient related factors, inappropriate anticoagulation choice or lack of anti-coagulation monitoring, and machine alarms/problems. We have increased awareness of all these issues. So far in our study, we have not had significant problems related to clotting.

-Requirement of successful completion of at least two cycles of CPFA treatments for patients similar to those with the inclusion requirements before the hospital can be authorized to officially start the trial and have access to the randomization portal.

-Formation of an intra-network 24/7 support group among the investigators. Investigators are able to call a core team (from the investigators team) to help in treatment or patient issues.

-Participating centers meet on a quarterly basis to monitor trial progress and share incidents that have occurred during the study.

ETHICS AND DISSEMINATION

Research ethics approval

This study has a clinicaltrials.gov identifier of NCT02357433. Currently, all participating centers have obtained Ethical Committee approval to participate in the trial.

Consent or assent

The Consent Form acknowledges the participant will for accepting or declining participation on ROMPA clinical trial. The request for the signing of this document is always a function of accredited doctors to participate in the trial.

Confidentiality

All participants´ personal information will be encrypted with the objective of keeping personal data on condition of anonymity.

Declaration of interests

The authors declare no conflict of interest.

Access to data

Any access to information regarding these procedures can only be accessed by the primary investigator as well as the team responsible for processing data.

Ancillary and post-trial care

Any side effects, which could have been produced while participating in the trial, can be assisted upon through the specific insurance policy (HDI Hannover International, policy number 130/002/001903) related to the trial procedures.

Dissemination policy

The findings of the trial will be disseminated through peer-reviewed journals, national and international conference presentations.

AUTHORS' CONTRIBUTIONS

FC drafted the paper of the protocol, AP helped draft the paper, and the rest of the authors critically reviewed the paper before sending it to *BMJ Open*.

FUNDING STATEMENT

This work was supported by Bellco which provided all the devices and materials related to the use of CPFA for the treatment group and will pay the open access fee

for publication in *BMJ Open*. This entity did not play any role in study design; collection, management, analysis, and interpretation of data; writing of this report; and the decision to submit this report for publication.

COMPETING INTERESTS STATEMENT

The authors declare no conflict of interest.

ACKNOWLEDGMENTS

The authors thank all the health professionals integrated in the ROMPA research group and those who will participate in our study. The copyright holder (Bellco) has approved the utilization of Figures 1-2.

REFERENCES

1) Angus DC, van der Poll T. Severe sepsis and septic shock. N Engl J Med 2013; 369:840-51.

2) van der Poll T, Opal SM. Host-pathogen interactions in sepsis. Lancet Infect Dis 2008;8:32-43.

3) Bone RC, Grodzin CJ, Balk RA. Sepsis: A new hypothesis for pathogenesis of the disease process. Chest 1997;112:235-43.

4) McCloskey RV, Straube RC, Sanders C, Smith SM, Smith CR. Treatment of septic shock with human monoclonal antibody HA-1A. A randomized, double-blind, placebo-controlled trial. CHESS trial study group. Ann Intern Med 1994;121:1-5.

5) Beutler B, Greenwald D, Hulmes JD, et al. Identity of tumour necrosis factor and the macrophage-secreted factor cachectin. Nature 1985;316:552-4.

6) Bernard GR, Wheeler AP, Russell JA, et al. The effects of ibuprofen on the physiology and survival of patients with sepsis. The ibuprofen in sepsis study group. N Engl J Med 1997;336:912-8.

7) Wiersinga WJ, Leopold SJ, Cranendonk DR, van der Poll T. Host innate immune responses to sepsis. Virulence 2014;5:36-44.

8) Hotchkiss RS, Monneret G, Payen D. Immunosuppression in sepsis: A novel understanding of the disorder and a new therapeutic approach. Lancet Infect Dis 2013;13:260-8.

9) Gaieski DF, Edwards JM, Kallan MJ, Carr BG. Benchmarking the incidence and mortality of severe sepsis in the united states. Crit Care Med 2013;41:1167-74.

10) Dellinger RP, Levy MM, Rhodes A, et al. Surviving sepsis campaign: International guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med 2013;41:580-637.

11) Angus DC. The search for effective therapy for sepsis: Back to the drawing board? JAMA 2011;306:2614-5.

12) Drewry AM, Hotchkiss RS. Sepsis: Revising definitions of sepsis. Nat Rev Nephrol 2015;11:326-8.

13) Opal SM, Dellinger RP, Vincent JL, Masur H, Angus DC. The next generation of sepsis clinical trial designs: What is next after the demise of recombinant human activated protein C? Crit Care Med 2014;42:1714-21.

14) Rimmelé T, Kellum JA. Clinical review: Blood purification for sepsis. Crit Care 2011;15:205.

15) Panagiotou A, Gaiao S, Cruz DN. Extracorporeal therapies in sepsis. J Intensive Care Med 2013;28:281-95.

16) Rimmelé T, Kellum JA. High-volume hemofiltration in the intensive care unit: A blood purification therapy. Anesthesiology 2012;116:1377-87.

17) Clark E, Molnar AO, Joannes-Boyau O, Honoré PM, Sikora L, Bagshaw SM. High-volume hemofiltration for septic acute kidney injury: A systematic review and meta-analysis. Crit Care 2014;18:R7.

18) Tetta C, Cavaillon JM, Schulze M, et al. Removal of cytokines and activated complement components in an experimental model of continuous plasma filtration coupled with sorbent adsorption. Nephrol Dial Transplant 1998;13:1458-64.

19) Ronco C, Brendolan A, d'Intini V, Ricci Z, Wratten ML, Bellomo R. Coupled plasma filtration adsorption: Rationale, technical development and early clinical experience. Blood Purif 2003;21:409-16.

20) Hassan J, Cader RA, Kong NC, Mohd M, Rahman AR, Hod R. Coupled plasma filtration adsorption (CPFA) plus continuous veno-venous haemofiltration (CVVH) versus CVVH alone as an adjunctive therapy in the treatment of sepsis. Excli J 2013;12:681-92.

21) Abdul Cader R, Abdul Gafor H, Mohd R, Yen Kong W, Arshad N, Kong N. Coupled plasma filtration and adsorption (CPFA): A single center experience. Nephrourol Mon 2013;5:891-6.

22) Formica M, Olivieri C, Livigni S, Cesano G, Vallero A, Maio M, Tetta C. Hemodynamic response to coupled plasmafiltration-adsorption in human septic shock. Intensive Care Med 2003;29:703-8.

23) Ronco C, Brendolan A, Lonnemann G, et al. A pilot study of coupled plasma filtration with adsorption in septic shock. Crit Care Med 2002;30:1250-5.

24) Moretti R, Scarrone S, Pizzi B, Bonato V, Vivaldi N. Coupled plasma filtration-adsorption in weil's syndrome: Case report. Minerva Anestesiol 2011;77:846-9.

25) Berlot G, Agbedjro A, Tomasini A, Bianco F, Gerini U, Viviani M, Giudici F. Effects of the volume of processed plasma on the outcome, arterial pressure and

blood procalcitonin levels in patients with severe sepsis and septic shock treated with coupled plasma filtration and adsorption. Blood Purif 2014;37:146-51.

26) Fabbri LP, Macchi A, Lecchini R, Antonella P. Post influenza vaccination guillain-barré syndrome. An exceptional recovery case after cardiac arrest for two hours in hyperthermia and septic shock. Anesthesia, Pain & Intensive Care 2015;18:166-9.

27) Livigni S, Bertolini G, Rossi C, et al. Efficacy of coupled plasma filtration adsorption (CPFA) in patients with septic shock: A multicenter randomised controlled clinical trial. BMJ Open 2014;4:e003536.

28) Schoenberg MH, Weiss M, Radermacher P. Outcome of patients with sepsis and septic shock after ICU treatment. Langenbecks Arch Surg 1998;383:44-8. Review.

29) Wakefield CH, Fearon KCH. Laparotomy for abdominal sepsis in the critically ill. In: Holzheimer RG, Mannick JA, eds. Surgical Treatment: Evidence-Based and Problem-Oriented. Munich: Zuckschwerdt 2001.

30) Chow S, Wang H, Shao J. Sample Size Calculations in Clinical Research. New York, NY: Chapman & Hall/CRC 2008.

31) Stevenson EK, Rubenstein AR, Radin GT, Wiener RS, Walkey AJ. Two decades of mortality trends among patients with severe sepsis: a comparative meta-analysis. Crit Care Med 2014;42:625-31.

32) Martin GS. Sepsis, severe sepsis and septic shock: changes in incidence, pathogens and outcomes. Expert Rev Anti Infect Ther 2012;10:701-6.

33) Kaukonen KM, Bailey M, Suzuki S, Pilcher D, Bellomo R. Mortality Related to Severe Sepsis and Septic Shock Among Critically Ill Patients in Australia and New Zealand, 2000- 2012. JAMA 2014;311:1308-16.

34) Asfar P, Claessens YE, Duranteau J, Kipnis E, Leone M, Levy B; French Opinion Group in Sepsis (FrOGS). Residual rates of mortality in patients with severe sepsis: a fatality or a new challenge? Ann Intensive Care 2013;3:27.

FIGURE LEGENDS:

Figure 1: Amplya system from Bellco Societa unipersonales a r.l.

The resin cartridge and plasmafilter are in position and ready for use. The copyright holder (Bellco) has approved the utilization of this figure.

Figure 2: Schematic representation of CPFA circuit.

The extracorporeal circuit consisting of plasma filter (A), a resin cartridge (B) and a high-flux dialyzer (C). Blood pass through a plasma filter, extracted plasma is purified by adsorption on a resin cartridge and the reconstituted blood (●) through a high-permeability hemofilter, in which convective exchanges are realized in a post-dilution mode (substitution). The copyright holder (Bellco) has approved the utilization of this figure.

Figure 3: Study Diagram.

This shows the general study design and includes: 1) Registration: The patient is considered "enrolled" once informed consent has been obtained. 2) Recruitment Phase: must occur within the first 12 hours of Septic Shock diagnosis. 3) Randomization: Group A (CPFA) or Group B (Control). 4) Statistical evaluations: at the end of the study and after follow-up.

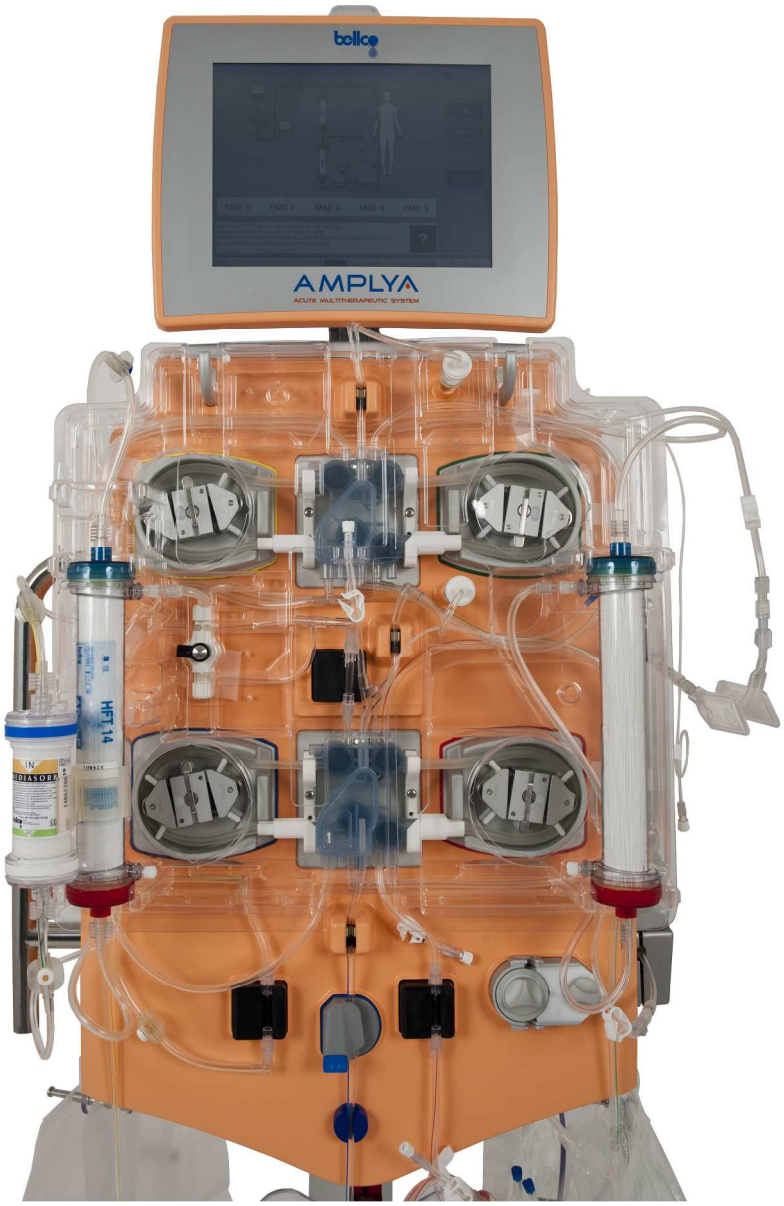
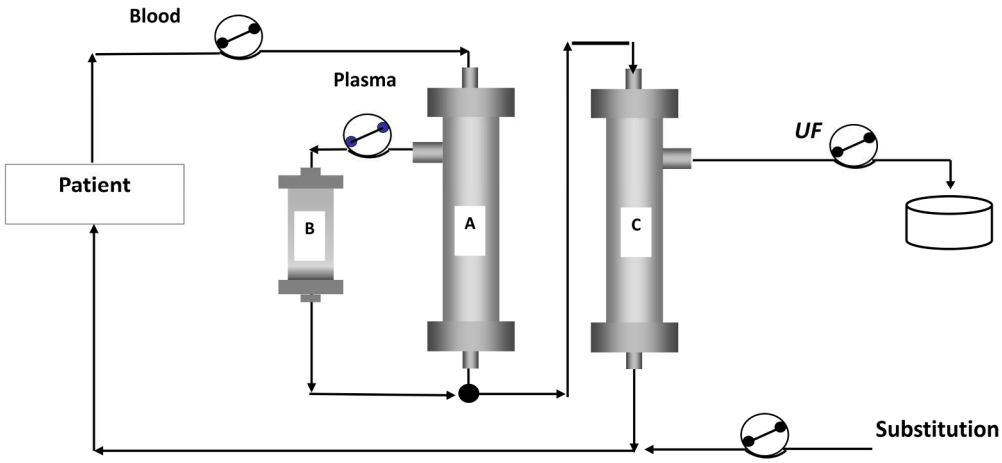


Figure 1: Amplya system from Bellco Societa unipersonales a r.l.
The resin cartridge and plasmafilter are in position and ready for use. The copyright holder (Bellco) has approved the utilization of this figure.
231x308mm (300 x 300 DPI)



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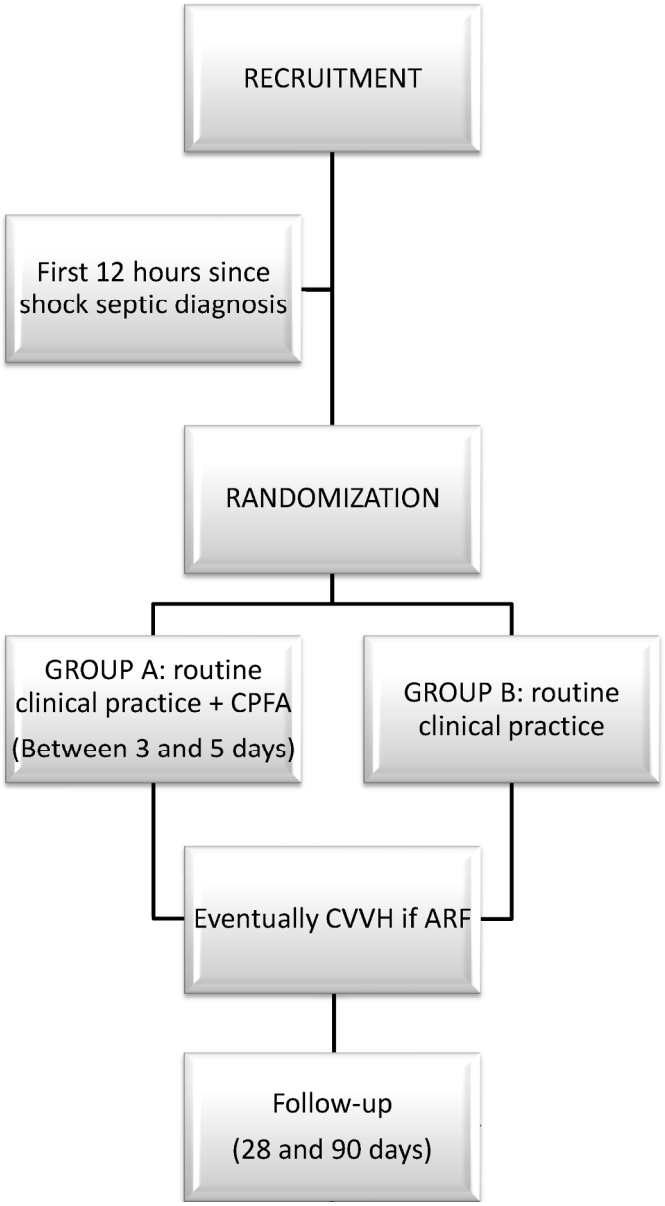
105x48mm (600 x 600 DPI)



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225x398mm (300 x 300 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym **page 1**
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry **page 17**
	2b	All items from the World Health Organization Trial Registration Data Set N/A
Protocol version	3	Date and version identifier **page 17**
Funding	4	Sources and types of financial, material, and other support **page 18-19**
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors **page 18**
	5b	Name and contact information for the trial sponsor **pages 18-19**
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities **pages 18-19**
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) N/A
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention **pages 5-8**
	6b	Explanation for choice of comparators **pages 11-12**
Objectives	7	Specific objectives or hypotheses **pages 7-8**

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) **pages 8-9**
Methods: Participants, interventions, and outcomes		
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained **pages 8-9**
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) **pages 9-11**
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered **pages 11-12**
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) **pages 11-12**
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) **pages 11-12**
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial **pages 11-12**
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended **pages 12-13**
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) **pages 9-11**
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations **pages 10-11**
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size **page 11**
Methods: Assignment of interventions (for controlled trials)		
Allocation:		

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions **page 11**
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned **page 11**
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions **page 11**
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how **pages 17-18**
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial **pages 17-18**
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol **pages 12-13**
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols **pages 12-13**
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol **pages 17-18**
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol **page 13**
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) **pages 13**
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) **page 13**

Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed **pages 17-18**
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial **pages 17-18**
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct **pages 17-18**
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor **pages 17-18**
Ethics and dissemination		
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval **pages 17-18**
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) **pages 17-18**
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) **pages 17-18**
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable **pages 17-18**
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial **pages 17-18**
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site **pages 17-18**
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators **pages 17-18**

Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation **pages 17-18**
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions **pages 17-18**
	31b	Authorship eligibility guidelines and any intended use of professional writers **pages 17-18**
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code **pages 17-18**
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.