

# BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email [info.bmjopen@bmj.com](mailto:info.bmjopen@bmj.com)

# BMJ Open

## The premature closure of ROMPA Clinical Trial. Presentation of the results concerning the 49 randomized patients before the study closure.

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2019-030139
Article Type:	Original research
Date Submitted by the Author:	28-Feb-2019
Complete List of Authors:	Giménez-Esparza, Carola; Vega Baja Hospital of Orihuela, Intensive Care Unit Portillo-Requena, Cristina; Vega Baja Hospital of Orihuela, Intensive Care Unit Colomina-Climent, Francisco; Miguel Hernández University, Clinical Medicine 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 Mármol-Peis, Enrique; University Hospital of San Juan de Alicante, Intensive Care Unit Dólera-Moreno, Cristina; 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 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 Palazón-Bru, Antonio; Miguel Hernández University, Clinical Medicine Gil-Guillen, Vicente F.; Miguel Hernández University, Clinical Medicine
Keywords:	INFECTIOUS DISEASES, Adult intensive & critical care < INTENSIVE &

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

	CRITICAL CARE, Clinical trials < THERAPEUTICS

SCHOLARONE™  
Manuscripts

**TITLE PAGE**

Title: The premature closure of ROMPA Clinical Trial. Presentation of the results concerning the 49 randomized patients before the study closure.

Short title: The closure of ROMPA Clinical Trial.

Authors: Carola Giménez-Esparza [1], Cristina Portillo-Requena [1], Francisco Colomina-Climent [2], José Manuel Allegue-Gallego [3], María Galindo-Martínez [3], Cristina Mollà-Jiménez [4], José Luis Antón-Pascual [4], Enrique Mármol-Peis [4], Cristina Dolera-Moreno [4], Manuel Rodríguez-Serra [5], José Luis Martín-Ruiz [5], Pablo Juan Fernández-Arroyo [6], Eugenia María Blasco-Císcar [6], José Cánovas-Robles [7], Enrique González-Hernández [8], Fernando Sánchez-Morán [8], Manuel Solera-Suárez [9], Jesús Torres-Tortajada [9], Antonio Palazón-Bru [2], Vicente Francisco Gil-Guillén [2].

Institutions:

1. Intensive Care Unit, Vega Baja Hospital of Orihuela, Orihuela, Alicante, Spain.
2. Department of Clinical Medicine, Miguel Hernández University, San Juan de Alicante, 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.

1  
2  
3 7. Intensive Care Unit, General University Hospital of Alicante, Alicante, Alicante, Spain.  
4

5 8. Intensive Care Unit, La Plana Hospital of Villarreal, Villarreal, Castellón, Spain.  
6

7 9. Intensive Care Unit, Francesc de Borja Hospital of Gandía, Gandía, Valencia, Spain.  
8  
9

10  
11  
12  
13 Corresponding author: Prof. Antonio Palazón-Bru, PhD. Department of Clinical Medicine,  
14 Miguel Hernández University, Carretera de Valencia - Alicante S/N, 03550, San Juan de  
15 Alicante (Spain). Phone number: +34 965919449. Fax number: +34 965919450. E-mail:  
16 [antonio.pb23@gmail.com](mailto:antonio.pb23@gmail.com)  
17  
18  
19  
20  
21  
22

23 Keywords: Shock, Septic; Coupled Plasma Filtration Adsorption; Mortality; Intensive Care  
24 Units; Clinical Trials.  
25  
26

27  
28 Word count: 2746.  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## ABSTRACT

Objectives: Coupled Plasma Filtration and Adsorption (CPFA) use in septic shock remains controversial. The objective is to clarify whether the application of high dosis of CPFA in addition to the current clinical practice could reduce hospital mortality in septic shock patients in Intensive Care Units at 28 days and 90 days follow up.

Design: We designed a prospective randomized clinical trial, ROMPA (Reducción de la Mortalidad Plasma-Adsorción), to demonstrate an absolute mortality reduction of 20% [ $\alpha=0.05$ ;  $1-\beta=0.8$ ;  $n=190(95 \times 2)$ ].

Setting: Being aware of the pitfalls associated with previous medical device trials, we developed a training program to improve CPFA use (especially clotting problems). The protocol was approved by the ethics committees of all participating centers. Circumstances beyond our control produced a change in recruitment conditions unacceptable to ROMPA researchers and the trial was discontinued.

Participants: By closure, 5 centres from an initial 10 fulfilled the necessary trial criteria, with 49 patients included, 30 control group (CG) and 19 intervention group (IG).

Intervention: CPFA.

Main outcome measures: Hospital mortality at 28 days and 90 days follow up

Results: After 28 days, 14 patients died (46.7%) from the CG and 11 (57.9%) from the IG, not reaching statistical significance ( $p=0.444$ ). At 90 days 19 patients had died (63.3%) from the CG and 11 patients (57.9%) from the IG, ( $p=0.878$ ). The adjustment by propensity score or the use of the Kaplan Meier technique failed to achieve statistical difference, neither in the Intention to Treat Approach nor by the Actual Intervention Received.

1  
2  
3 Conclusion: We herewith present the results gained from the prematurely-closed trial. The  
4  
5 results are inconclusive due to low statistical power but we consider that this data is of  
6  
7 interest for the scientific community and potentially necessary for any ensuing debate.  
8  
9

10 Register: NCT02357433 in [clinicaltrials.gov](http://clinicaltrials.gov)  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For peer review only

### STRENGTHS AND LIMITATIONS OF THIS STUDY

- Randomised control clinical trial testing the efficacy of CPFA in septic shock.
- Premature closure of the trial by circumstances beyond the trial.
- Scarce sample size: underpowered trial.

For peer review only



## INTRODUCTION

Sepsis is still a leading cause of mortality in Intensive Care Units (ICU) patients, with a 20-50% mortality rate of sepsis and septic shock [1]. There exists a feeling of frustration generated by the large series of negative randomized clinical trials (RCTs) in septic shock treatment (especially in targeting mortality) during the past 30 years [2]. Patients included in these trials have a wide variability in their probability of death translating into differences in benefits to be derived from specific therapy application, producing a handicap to sample size calculation. This can lead to the trial having less power than initially planned increasing risk of a type 2 error and undoubtedly this is the origin of unexpected results.[3] It questions the use of subgroups in an attempt to extract some kind of useful information in negative RCTs.[4]

The COMPACT 1, a multicentre RCT study, failed to show benefit by using Coupled Plasma Filtration and Adsorption (CPFA) therapy in a population with septic shock. In a per protocol analysis, patients treated with CPFA at treated plasma volume superior to 0.20 l/kg/day showed a reduction in mortality rate [5]. Although an interesting finding, our group considered it was necessary to carry out a RCT to confirm this hypothesis.

The response to this question was the ROMPA (Reducción de la Mortalidad Mediante Plasma-Adsorción en Shock séptico), a multicenter RCT carried out in ICUs of southeastern Spain. The ROMPA Study (NCT02357433 in [clinicaltrials.gov](http://clinicaltrials.gov)) tried to clarify whether the application of high doses CPFA in addition to the current clinical practice was able to reduce hospital mortality in septic shock patients in ICUs. The protocol of ROMPA has been published in a free access support and the details of the protocol could be consulted without restrictions.[6]

1  
2  
3 In October 2017, COMPACT 2 (NCT01639664 in clinical trials.gov) trial investigators, a  
4 similar study to ROMPA conducted in Italian ICUs,[7] reported the premature closure of the  
5 study for having detected an increase in early mortality (3 first days) in the intervention  
6 branch, 6/42 (12.5%) vs 19/58 (32.8%)  $p=0.020$ , not having reached the sample size prefixed  
7 in the protocol (350 patients). The adjusted odds ratio (OR) of the treatment yielded by  
8 logistic regression is 2.1 (95% CI: 0.7-6.6,  $p=0.19$ ) and the adjusted hazard ratio (HR)  
9 yielded by the Cox model is 2.5 (95% CI: 1.4- 4.4,  $p=0.002$ ). This information was  
10 immediately reported to our Ethical Committee and these results were published on the  
11 research group website in Italian.[8] Subsequent events, including a provisional warning by  
12 the product supplier, motivated us to take the final decision of closing ROMPA. At that time,  
13 of the 10 initial hospitals only 5 had exceeded the technical capacity requirements and  
14 availability of resources required to access the randomization portal. In this paper and as a  
15 result of events of such severity, our group shows the data collected to date and the results  
16 from the 49 enrolled patients (30 control and 19 intervention groups).

## 39 METHODS

### 42 Protocol

43 The full study protocol was previously published.[6] A synthesis of it is made in this section  
44 (Methods) .

### 51 Setting and participants

52 The study was performed in 5 ICUs, in the southeast of Spain, that follow the same protocol  
53 in the treatment of septic shock, based on the recommendations of the Surviving Sepsis  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 Campaign with the participation of the following centers: Vega Baja Hospital of Orihuela,  
4  
5 General University Santa Lucía Hospital of Cartagena, University Hospital of San Juan de  
6  
7 Alicante, Lluís Alcanyís Hospital of Xàtiva and Francesc de Borja Hospital of Gandía.  
8  
9

10  
11 The ROMPA study is a multi-centric, randomized, prospective, open clinical trial with 28-  
12  
13 and 90-day follow-up and allocation ratio 1:1, assessing the mortality reduction by CPFA in  
14  
15 patients with septic shock. Furthermore, we analyzed 3-day mortality to compare our results  
16  
17 with the Italian group.  
18  
19

20  
21 Each center obtained technical proficiency with the machine and CPFA treatment before they  
22  
23 could become “activated” for enrolment by the investigator monitoring team. This was done  
24  
25 to avoid similar problems as those reported for the first COMPACT study,[4] and also  
26  
27 because CPFA is not routinely done in Spain and a new machine with improved  
28  
29 anticoagulation support was subsequently developed and used for this trial.  
30  
31

### 32 33 **Participants**

34  
35  
36 Patients  $\geq 18$  years old admitted to the ICU of the participant hospitals, with a diagnosis of  
37  
38 septic shock can be included in the study. The inclusion and exclusion criteria are detailed in  
39  
40 the published protocol.  
41  
42

### 43 44 **Interventions**

45  
46  
47 The patient is considered registered once the informed consent form has been obtained by the  
48  
49 patient or legal representative. The recruitment process ends with the patient randomization.  
50  
51 Patients were divided randomly into two arms (control and intervention). ROMPA has a  
52  
53 stratified randomization based on gender, age ( $\leq 65$  or  $>65$  years) and SAPS III score ( $<50$  or  
54  
55  $\geq 51$ ). On the one hand, in the control group we followed the suggestions provided by the  
56  
57  
58  
59  
60

1  
2  
3 recent surviving sepsis guidelines, as well as standard care guidelines typically followed in  
4 Spain. On the other hand, in the CPFA group, we applied the same protocol plus high doses  
5 of CPFA in the first 3 days after randomization.  
6  
7  
8

## 9 10 **Variables and measurements**

### 11 12 **Primary and Secondary Outcomes**

13  
14  
15 The primary outcome variable is all-cause of mortality assessed at 3, 28 and 90 days from the  
16 recruitment of the patient. Moreover, at the descriptive level and in order to check  
17 homogeneity of both groups, the following variables will be collected at the time of  
18 recruitment: birth year, gender, height, dry weight, body temperature, heart rate, blood  
19 pressure, blood cell count, coagulation values, glucose level, plasma creatinine,  
20 bilirubinemia, plasma C reactive protein, procalcitonin level, blood gas analysis, lactate,  
21 urinary output (ml/kg/h), Pa O<sub>2</sub>/FiO<sub>2</sub> ratio, APACHE II, SOFA and SAPSIII scores.  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32

### 33 34 **Sample Size**

35  
36  
37 Originally, a sample size of 190 patients was calculated to determine differences in mortality  
38 rates in both groups with a power-of-contrast of 80%. A partial analysis with the first 49  
39 patients has been carried out as described in this paper. Using the data from the initial sample  
40 size calculation, these patients represent an approximate power-of-contrast of 30%.  
41  
42  
43  
44  
45  
46

### 47 48 **Statistical analysis**

49  
50 Initially, the calculation of the indicators of clinical relevance (relative risk, RR, absolute risk  
51 reduction, ARR, relative risk reduction, RRR, number needed to treat, NNT, by intent to  
52 treat, ITT) was planned. Without having the sample size calculated for the study  
53 (intermediate analysis) and having made the allocation based on a set of variables, the  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 homogeneity of the groups was not able to be established. To minimize this problem, the  
4 propensity scores as a population overlap weight technique was applied with the objective of  
5 overcoming the problem caused by the lack of homogeneity between the two groups.[9] The  
6 adjustment variables were APACHE II, previous lactate levels and the presence of urinary  
7 sepsis. Finally, although it was not established in the study protocol, Kaplan-Meier survival  
8 curves were analyzed to determine differences in mortality in the analyzed groups (log-rank  
9 test). Since a significant number of patients died in the first three days and were unable to  
10 receive the technique (n = 3) we decided to perform the analysis by actual intervention  
11 received (AIR).  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22

### 23 24 25 **Ethical issues**

26  
27  
28 The study was originally approved by all Ethics Committees of the different Hospitals  
29 participating in the study. There was a general agreement that the trial closure was the best  
30 option, since the decision adopted by the Italian group to close its trial had been made public  
31 through its website and the supplier consequently marked their product used for the test with  
32 a warning.  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42

### 43 44 **RESULTS**

45  
46 A total of 49 patients were included in the final analysis (30 in the control group and 19 in the  
47 intervention group) (Figure 1). The randomization tables are displayed in Table 1. Parametric  
48 statistics did not allow us to establish significant differences between the analyzed factors due  
49 to the small sample size. However, we can see a mean difference between the two groups of  
50 1.9 on an APACHE II score, 0.6 mmol/l of lactate levels and 10.9% in the prevalence of  
51 urinary sepsis. All these factors have been used in the propensity score test.  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 With regard to mortality (without adjusting by propensity score), 7 patients (23.3%) died in  
4 the first three days from the control group and 8 patients (40.6%) died from the intervention  
5 group (p=0.146). After 28 days, 14 patients died (46.7%) from the control group and 11  
6 patients died (57.9%) from the intervention group, not reaching statistical significance  
7 (p=0.444). At 90 days 19 patients had died (63.3%) from the control group and 11 patients  
8 had died (57.9%) from the intervention group, which is to say no patient died from the  
9 intervention group between 28 and 90 days (p=0.878). Adjusting by propensity score and  
10 using the Kaplan-Meier technique (Figure 2), statistical significant difference was not  
11 reached, neither in the ITT (Table 2) approach nor by the AIR approach (Table 3).  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24

25 In patients who died in the first three days, we found that the base-line levels of lactate were  
26 higher compared with the rest (in mmol/L):  $7.96 \pm 4.79$  vs  $4.43 \pm 2.41$ ,  $p=0.015$ . This situation  
27 was similar in the APACHE score:  $29.7 \pm 5.1$  vs  $27.5 \pm 5.5$ ,  $p=0.194$ , although this variable was  
28 not significant.  
29  
30  
31  
32  
33  
34  
35  
36  
37

## 38 **DISCUSSION**

### 39 **Summary**

40  
41  
42 Our results seem to indicate that the patient who received CPFA had less chance of mortality  
43 in the long term (90 days), whether by ITT analysis or AIR analysis. However, in the short  
44 and medium term during ITT analysis, CPFA had a detrimental effect and when using AIR  
45 analysis the effect was protected. In any case, the statistical power to obtain conclusions from  
46 these results was low.  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56

### 57 **Limitations of the study**

1  
2  
3 This RCT was designed to determine medium and long-term differences between the CPFA  
4 and the standard care. For this purpose, a sample size of 190 patients was pre-determined. In  
5  
6 these partial results, the sample size of 190 was not reached and therefore the statistical  
7  
8 power of the comparison contrast is very low (~ 30%). In addition, as the randomization  
9  
10 process was done based on the baseline characteristics of the patient, this can produce  
11  
12 differences between the groups. Moreover, we can observe that the sample sizes of the two  
13  
14 groups are not similar (the control group has approximately 50% more patients). All this has  
15  
16 led to the use of propensity score adjustment in order to obtain results similar to an RCT  
17  
18 (totally homogeneous groups, except in the intervention received). [9] However, even if we  
19  
20 apply this technique we still have a low power of contrast. Despite this limitation, we want to  
21  
22 communicate our partial results following the premature closure of the RCT COMPACT 2.  
23  
24  
25  
26  
27  
28

### 29 **Comparison with the existing literature**

30  
31  
32 We agreed with the Ethics Committee to review the incidence of early mortality in our trial  
33  
34 on account of the findings communicated to us by the COMPACT 2 team. It should be  
35  
36 emphasised that the ROMPA investigators were not given any impression of these  
37  
38 COMPACT 2 findings during their own clinical practice. In any case, the analysis of what  
39  
40 happened in the ROMPA sample collected up to that moment was carried out having a  
41  
42 statistical power of only 30%, as expressed previously. Therefore, from a methodological  
43  
44 point of view, it cannot have more value than the purely descriptive one. The results reported  
45  
46 by the group of researchers of COMPACT 2 here deserve a special mention [8]. In these  
47  
48 results, as occurred in our group, a preliminary analysis was developed that is far from the  
49  
50 sample size initially calculated and therefore with low statistical power of contrast (not  
51  
52 indicated by them in their report). In addition, as in our study, the COMPACT 2 group used a  
53  
54 randomization system based on prognostic scores, [6] which means that the groups will not  
55  
56  
57  
58  
59  
60

1  
2  
3 be similar until the end of recruitment (which is reason to introduce the propensity score in  
4 our results).  
5  
6

7  
8 In this situation, subgroup analysis has the problem of introducing analytic challenges and  
9 can lead to overstated and misleading results, [10] and as such we have to consider the  
10 remarkably low mortality of the control group, together with a remarkably high mortality of  
11 the intervention group. These results seem to be far removed from those that are obtained in  
12 usual clinical practice. This situation was not observed in the first COMPACT trial [5] and  
13 we have not heard of a retrospective analysis to explain these results.  
14  
15  
16  
17  
18  
19  
20  
21  
22

23 In our group, patients who died in the first 72 h had significantly higher initial lactate values  
24 than the rest of the patients included in the trial ( $7.96\pm 4.79$  vs  $4.43\pm 2.41$ ,  $p=0.015$ ). Increased  
25 blood lactate in sepsis or trauma reflects anaerobic glycolysis due to hypoperfusion, and / or  
26 increased aerobic glycolysis.[11] In septic shock it mainly reflects hypoperfusion. At the  
27 present time, there is solid evidence about the predictive role of high lactate levels with  
28 respect to mortality in septic shock patients and our results are reflecting this.[12-18]  
29  
30  
31  
32  
33  
34  
35  
36  
37

38 Lastly, we would like to comment on the margin of time chosen by the Italian group to carry  
39 out its partial results. We think it is important to assess the patient's mortality, but this  
40 mortality should be assessed with a global calculation. In other words, for a technique to be  
41 effective, it must decrease the patient's mortality in a reasonable period of time in order to  
42 allow the healing of sepsis and its possible subsequent consequences. For this reason, the  
43 period of 28 and 90 days was fixed by our protocol. Consequently, for the sake of conducting  
44 an effective clinical trial, it is not of relevance that the patient unfortunately dies early, but  
45 whether the patient dies in a period of time where he has a high mortality risk due to sepsis.  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56 In addition, in the calculation of the sample size of the Italian group, this was not  
57  
58  
59  
60



1  
2  
3 contemplated and could be a result of random error or heterogeneous groups in the treatment  
4 allocation. At this point, it must be stated that the ROMPA investigators are not at any  
5 moment criticising the COMPACT 2 decision to halt their trial. ROMPA's researchers  
6 remain aware of the complexity of such a decision and that it involves multiple factors, the  
7 most important being the security of the patients.  
8  
9  
10  
11  
12  
13  
14

### 15 **Implications to research**

16  
17  
18 Our study was halted prematurely for the reasons we have previously explained when only 49  
19 patients had been randomized (out of a target 190 patients). In the intervention arm, 19  
20 patients were randomized and 30 patients randomized in the control arm. In both approaches  
21 (ITT and real intervention), we have not found evidence of either benefit or harmful effect in  
22 the tested treatment and, of course, this comes as no surprise due to the premature  
23 termination.  
24  
25  
26  
27  
28  
29  
30  
31  
32

33 At this level of recruitment and with a power of 30% our sample is absolutely exposed to the  
34 random effect, resulting in a lack of homogeneity in the levels of basal risk. This lack of  
35 homogeneity pre-determines that the technique can be presented as either beneficial or  
36 harmful. In fact the technique appears less beneficial in the subgroup (not predefined) of  
37 patients who died in 72 hours and that, logically, were patients with an elevated basal risk,  
38 primarily expressed through lactate levels and APACHE 2 score .  
39  
40  
41  
42  
43  
44  
45  
46  
47

48 We would like to comment on a controversial issue. Three patients who had been randomized  
49 to the intervention group died in the first 72 hrs and did not receive the CPFA treatment. The  
50 rapid hemodynamic deterioration of the patients did not allow the connection to the  
51 extracorporeal circuit. It is obvious that in the ITT analysis these patients are considered to all  
52 effects as belonging to the intervention group, assuming the great negative impact they will  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 have on the efficacy analysis. It should always be borne in mind that these 3 patients,  
4  
5 representing 20% of total intervention group who died early, did not actually receive  
6  
7 treatment. Undoubtedly, adequate sample size management would minimize the problem. But  
8  
9 if what we are considering is the possible harmful effect of the technique in a non pre-  
10  
11 specified subgroup of an underpowered sample we cannot ignore this situation. It seems  
12  
13 reasonable to think that if we talk about the possible harmful action of a device, the technique  
14  
15 in question should have actually been applied.  
16  
17  
18  
19  
20  
21  
22

## 23 **CONCLUSIONS**

24  
25  
26 In this paper we have presented the results of the 49 patients randomized in our trial up until  
27  
28 the moment of closure. As a consequence of the procedure being underpowered, it was not  
29  
30 possible to do an analysis of contrast of hypothesis and under this inconvenience, we present  
31  
32 the results obtained for the interest of all concerned in knowing what has happened in our  
33  
34 trial. When all is taken into consideration, we have not found a difference in mortality  
35  
36 between the two groups.  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## AUTHORS' CONTRIBUTIONS

CG drafted the paper of the protocol, CP 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.

## REFERENCES

1. Gaieski DF, Edwards JM, Kallan MJ, et al. Benchmarking the incidence and mortality of severe sepsis in the United States. *Crit Care Med* 2013;41:1167–74.
2. Opal SM, Dellinger RP, Vincent JL, et al. 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.
3. Wong JL, Mason AJ, Gordon AC, Bret SJ. Are large randomised controlled trials in severe sepsis and septic shock statistically disadvantaged by repeated inadvertent underestimates of required sample size? *BMJ Open* 2018;8:e020068.
4. Vincent JL, Marini JJ, Pesenti A. Do trials that report a neutral or negative treatment effect improve the care of critically ill patients? No. *Intensive Care Med* 2018;44:1989–91.
5. Livigni S, Bertolini G, Rossi C, et al. Efficacy of coupled plasma filtration and adsorption (CPFA) in patients with septic shock: a multicenter randomised controlled clinical trial. *BMJ Open* 2014;4:e003536.
6. Colomina-Climent F, Gimenez-Esparza C, Portillo-Jimenez C, et al. Mortality Reduction in Septic Shock by Plasma Adsorption ((ROMPA): a protocol for a randomised clinical trial. *BMJ Open* 2016;6:e011856.
7. Gruppo Italiano per la Valutazione degli Interventi in Terapia Intensiva. COMPACT-2: COMbining Plasmafiltration and Adsorption Clinical Trial-2. Available from <http://www.giviti.marionegri.it/COMPACT2.asp> [updated July 6, 2018; accessed November 27, 2018].

- 1  
2  
3 8. Gruppo Italiano per la Valutazione degli Interventi in Terapia Intensiva. Chiusura  
4 anticipata dello Studio COMPACT-2. Available from  
5  
6 <http://www.giviti.marionegri.it/Download/COMPACT-2%20Chiusura%20anticipata.pdf>  
7  
8 [updated October 23, 2017; accessed November 27, 2018].  
9  
10  
11  
12  
13 9. Stuart BL, Grebel LE, Butler CC, et al. Comparison between treatment effects in a  
14 randomised controlled trial and an observational study using propensity scores in primary  
15 care. *Br J Gen Pract* 2017;67:e643–9.  
16  
17  
18 10. Wang R, Lagakos SW, Ware JH, Hunter DJ, Drazen JM. Statistics in Medicine –  
19 Reporting of Subgroup Analyses in Clinical Trials. *N Engl J Med* 2007;357:2189–94.  
20  
21  
22  
23 11. James JH, Luchette FA, McCarter FD, Fischer JE. Lactate is an unreliable indicator of  
24 tissue hypoxia in injury or sepsis. *Lancet* 1999;354:505–8  
25  
26  
27 12. Cochran A, Edelman LS, Saffle JR, Morris SE. The relationship of serum lactate and base  
28 deficit in burn patients to mortality. *J Burn Care Res* 2007;28:231–40.  
29  
30  
31 13. Koliski A, Cat I, Giraldo DJ, Cat ML. Blood lactate concentration as prognostic marker in  
32 critically ill children. *J Pediatr (Rio J)* 2005;81:287–92.  
33  
34  
35 14. Shapiro NI, Howell MD, Talmor D, et al. Serum lactate as a predictor of mortality in  
36 emergency department patients with infection. *Ann Emerg Med* 2005;45:524–8.  
37  
38  
39 15. Trzeciak S, Dellinger RP, Chansky ME, et al. Serum lactate as a predictor of mortality in  
40 patients with infection. *Intensive Care Med* 2007;33:970–7.  
41  
42  
43 16. Mikkelsen ME, Miltiades AN, Gaieski DF, et al. Serum lactate is associated with  
44 mortality in severe sepsis independent of organ failure and shock. *Crit Care Med*  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 17. Nichol AD, Egi M, Pettila V, et al. Relative hyperlactatemia and hospital mortality in  
4 critically ill patients: a retrospective multi-centre study. *Crit Care* 2010;14:R25.  
5  
6  
7

8 18. Kang YR, Um SW, Koh WJ, et al. Initial lactate level and mortality in septic shock  
9 patients with hepatic dysfunction. *Anaesth Intensive Care* 2011;39:862–7.  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For peer review only

1  
2  
3 **FIGURE LEGENDS:**  
4

5  
6 Figure 1: Flow chart of the clinical trial (partial results).  
7  
8  
9

10  
11  
12 Figure 2: Survival analysis using the Kaplan-Meier estimator comparing both groups.  
13  
14

15 Red, intervention; Blue, control.  
16  
17

18 A, intention to treat; B, real intervention.  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

**TABLES:**

Table 1: Comparison between the intervention and the control group.

Variable	Control group n=30 n(%) / x±s	CPFA n=19 n(%) / x±s	p-value
Gender male	18(60.0)	11(57.9)	0.884
Abdominal sepsis	12(40.0)	8(42.1)	0.884
Cancer	11(36.7)	7(36.8)	0.990
Community-acquired pneumonia	5(16.7)	3(15.8)	>0.999
Nosocomial pneumonia	3(10.0)	3(15.8)	0.665
Diabetes	9(30.0)	5(26.3)	0.781
Urinary sepsis	8(26.7)	3(15.8)	0.492
APACHE II	28.9±5.6	27.0±5.1	0.244
SOFA	12.8±3.3	12.2±4.4	0.541
SAPS II	74.5±20.9	70.7±21.0	0.587
Lactate (mmol/l)	5.3±3.4	5.9±4.1	0.580
Age (years)	70.0±13.6	71.0±14.5	0.812

Abbreviations: APACHE, Acute Physiology And Chronic Health Evaluation; CPFA, Coupled Plasma Filtration Adsorption; n(%), absolute frequency (relative frequency); SAPS, Simplified Acute Physiology Score; SOFA, Sequential Organ Failure Assessment; x±s, mean ± standard deviation.



Table 2: Clinical relevance of the intervention (intention-to-treat) in the patients with septic shock (adjusted by propensity scores as a population overlap weight).

Outcome	RR (95% CI)	RRR (95% CI)	ARR (95% CI)	NNT/NNH*	p-value
3-day mortality	1.67(0.51-5.46)	-0.67(-4.46 to 0.49)	-0.17(-0.54 to 0.20)	6 (H)	0.667
28-day mortality	1.28(0.57-2.87)	-0.28(-1.87 to 0.43)	-0.13(-0.53 to 0.28)	8 (H)	0.537
90-day mortality	0.92(0.48-1.76)	0.08(-0.76 to 0.52)	0.05(-0.35 to 0.45)	19 (T)	>0.999

Abbreviations: ARR, Absolute Risk Reduction; CI, confidence interval; H, Harm; NNH, Number Needed to Harm; NNH, Number Needed to Treat; RR, relative risk; RRR, Relative Risk Reduction; T, Treat.

\*, not possible to compute the confidence interval (division by zero).

bmjopen-2019-030129 on 3 December 2019. Downloaded from <http://bmjopen.bmj.com/> on April 19, 2024 by guest. Protected by copyright.

Table 3: Clinical relevance of the intervention (real group) in the patients with septic shock (adjusted by propensity scores as a population overlap weight).

Outcome	RR (95% CI)	RRR (95% CI)	ARR (95% CI)	NNT	p-value
3-day mortality	0.84(0.26-2.73)	0.16(-1.73 to 0.74)	0.06(-0.32 to 0.44)	18	>0.999
28-day mortality	0.93(0.42-2.06)	0.07(-1.06 to 0.58)	0.04(-0.37 to 0.45)	26	>0.999
90-day mortality	0.72(0.35-1.48)	0.28(-0.48 to 0.65)	0.19(-0.21 to 0.59)	6	0.417

Abbreviations: ARR, Absolute Risk Reduction; CI, confidence interval; NNT, Number Needed to Treat; RR, relative risk; RRR, Relative Risk Reduction.

\*, not possible to compute the confidence interval (division by zero).

Enrollment

BMJ Open  
Assessed for eligibility (n=72)

Excluded (n=32)  
◆ Not meeting inclusion criteria (n=13)  
◆ Declined to participate (n=1)  
◆ Other reasons (n=8)

Randomized (n=49)

Allocation

Allocated to intervention (n=19)  
◆ Received allocated intervention (n=16)  
◆ Did not receive allocated intervention (premature death) (n=3)

Allocated to intervention (n=30)  
◆ Received allocated intervention (n=30)  
◆ Did not receive allocated intervention (n=0)

Follow-Up

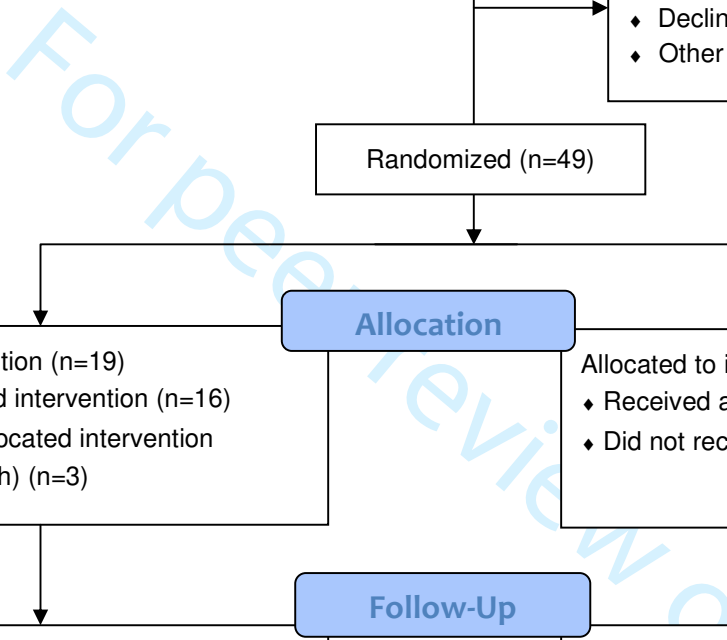
Lost to follow-up (give reasons) (n=0)  
Discontinued intervention (give reasons) (n=0)

Lost to follow-up (give reasons) (n=0)  
Discontinued intervention (give reasons) (n=0)

Analysis

Analysed (n=19)  
◆ Excluded from analysis (n=0)

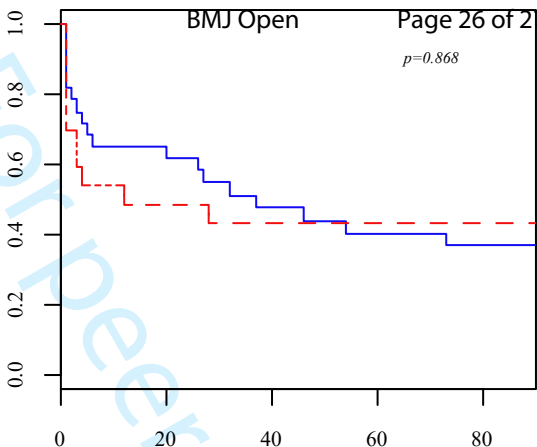
Analysed (n=30)  
◆ Excluded from analysis (n=0)



1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36

$p=0.868$ 

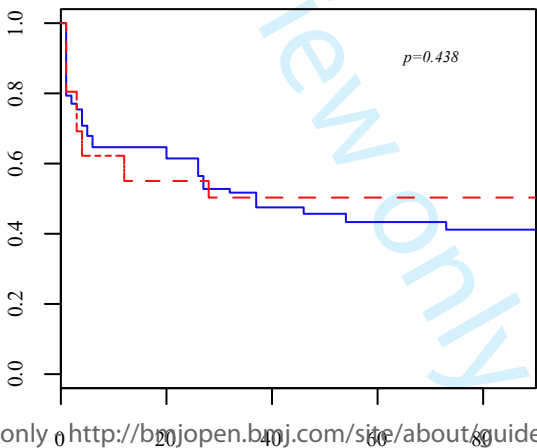
Accumulated survival

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12

Follow-up time (days)

**A**

Accumulated survival

17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33

Follow-up time (days)

**B**



# CONSORT 2010 checklist of information to include when reporting a randomised trial\*

Section/Topic	Item No	Checklist item	Reported on page No
<b>Title and abstract</b>			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	3
<b>Introduction</b>			
Background and objectives	2a	Scientific background and explanation of rationale	6-7
	2b	Specific objectives or hypotheses	7
<b>Methods</b>			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	7-8
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	7-10
Participants	4a	Eligibility criteria for participants	7-8
	4b	Settings and locations where the data were collected	7-8
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	8-9
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	9
	6b	Any changes to trial outcomes after the trial commenced, with reasons	9
Sample size	7a	How sample size was determined	9
	7b	When applicable, explanation of any interim analyses and stopping guidelines	
<b>Randomisation:</b>			
Sequence generation	8a	Method used to generate the random allocation sequence	Protocol
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	Protocol
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	Protocol
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	Protocol
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	Protocol

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	N/A
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	9-10
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	9-10
<b>Results</b>			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	10
	13b	For each group, losses and exclusions after randomisation, together with reasons	10
Recruitment	14a	Dates defining the periods of recruitment and follow-up	7-8
	14b	Why the trial ended or was stopped	6-7
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	21
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	11
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	11
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	11
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	11
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	11
<b>Discussion</b>			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	12
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	14-15
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	14-15
<b>Other information</b>			
Registration	23	Registration number and name of trial registry	4
Protocol	24	Where the full trial protocol can be accessed, if available	7
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	16

\*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see [www.consort-statement.org](http://www.consort-statement.org).

# BMJ Open

## The premature closure of ROMPA Clinical Trial. Presentation of the results concerning the 49 randomized patients before the study closure.

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2019-030139.R1
Article Type:	Original research
Date Submitted by the Author:	12-Sep-2019
Complete List of Authors:	Giménez-Esparza, Carola; Vega Baja Hospital of Orihuela, Intensive Care Unit Portillo-Requena, Cristina; Vega Baja Hospital of Orihuela, Intensive Care Unit Colomina-Climent, Francisco; Miguel Hernández University, Clinical Medicine 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 Mármol-Peis, Enrique; University Hospital of San Juan de Alicante, Intensive Care Unit Dólera-Moreno, Cristina; University Hospital of San Juan de Alicante, Intensive Care Unit Rodríguez-Serra, 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 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 Palazón-Bru, Antonio; Miguel Hernández University, Clinical Medicine Gil-Guillen, Vicente F.; Miguel Hernández University, Clinical Medicine
<b>Primary Subject	Intensive care

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

Heading</b>:	
Secondary Subject Heading:	Intensive care, Infectious diseases
Keywords:	INFECTIOUS DISEASES, Adult intensive & critical care < INTENSIVE & CRITICAL CARE, Clinical trials < THERAPEUTICS





**TITLE PAGE**

Title: The premature closure of ROMPA Clinical Trial. Presentation of the results concerning the 49 randomized patients before the study closure.

Short title: The closure of ROMPA Clinical Trial.

Authors: Carola Giménez-Esparza [1], Cristina Portillo-Requena [1], Francisco Colomina-Climent [2], José Manuel Allegue-Gallego [3], María Galindo-Martínez [3], Cristina Mollà-Jiménez [4], José Luis Antón-Pascual [4], Enrique Mármol-Peis [4], Cristina Dolera-Moreno [4], Manuel Rodríguez-Serra [5], José Luis Martín-Ruiz [5], Pablo Juan Fernández-Arroyo [6], Eugenia María Blasco-Císcar [6], José Cánovas-Robles [7], Enrique González-Hernández [8], Fernando Sánchez-Morán [8], Manuel Solera-Suárez [9], Jesús Torres-Tortajada [9], Antonio Palazón-Bru [2], Vicente Francisco Gil-Guillén [2].

Institutions:

1. Intensive Care Unit, Vega Baja Hospital of Orihuela, Orihuela, Alicante, Spain.
2. Department of Clinical Medicine, Miguel Hernández University, San Juan de Alicante, 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.

1  
2  
3 7. Intensive Care Unit, General University Hospital of Alicante, Alicante, Alicante, Spain.  
4

5 8. Intensive Care Unit, La Plana Hospital of Villarreal, Villarreal, Castellón, Spain.  
6

7 9. Intensive Care Unit, Francesc de Borja Hospital of Gandía, Gandía, Valencia, Spain.  
8  
9

10  
11  
12  
13 Corresponding author: Prof. Antonio Palazón-Bru, PhD. Department of Clinical Medicine,  
14 Miguel Hernández University, Carretera de Valencia - Alicante S/N, 03550, San Juan de  
15 Alicante (Spain). Phone number: +34 965919449. Fax number: +34 965919450. E-mail:  
16 [antonio.pb23@gmail.com](mailto:antonio.pb23@gmail.com)  
17  
18  
19  
20  
21  
22

23 Keywords: Shock, Septic; Coupled Plasma Filtration Adsorption; Mortality; Intensive Care  
24 Units; Clinical Trials.  
25  
26

27  
28 Word count: 2846.  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## ABSTRACT

Objectives: Coupled Plasma Filtration and Adsorption (CPFA) use in septic shock remains controversial. The objective is to clarify whether the application of high dosis of CPFA in addition to the current clinical practice could reduce hospital mortality in septic shock patients in Intensive Care Units at 28 days and 90 days follow up.

Design: We designed a prospective randomized clinical trial, ROMPA (Reducción de la Mortalidad Plasma-Adsorción), to demonstrate an absolute mortality reduction of 20% [ $\alpha=0.05$ ;  $1-\beta=0.8$ ;  $n=190(95 \times 2)$ ].

Setting: Being aware of the pitfalls associated with previous medical device trials, we developed a training program to improve CPFA use (especially clotting problems). The protocol was approved by the ethics committees of all participating centers. Circumstances beyond our control produced a change in recruitment conditions unacceptable to ROMPA researchers and the trial was discontinued.

Participants: By closure, 5 centres from an initial 10 fulfilled the necessary trial criteria, with 49 patients included, 30 control group (CG) and 19 intervention group (IG).

Intervention: CPFA.

Main outcome measures: Hospital mortality at 28 days and 90 days follow up

Results: After 28 days, 14 patients died (46.7%) from the CG and 11 (57.9%) from the IG, not reaching statistical significance ( $p=0.444$ ). At 90 days 19 patients had died (63.3%) from the CG and 11 patients (57.9%) from the IG, ( $p=0.878$ ). The adjustment by propensity score or the use of the Kaplan Meier technique failed to achieve statistical difference, neither in the Intention to Treat Approach nor by the Actual Intervention Received.

1  
2  
3 Conclusion: We herewith present the results gained from the prematurely-closed trial. The  
4  
5 results are inconclusive due to low statistical power but we consider that this data is of  
6  
7 interest for the scientific community and potentially necessary for any ensuing debate.  
8  
9

10 Register: NCT02357433 in [clinicaltrials.gov](http://clinicaltrials.gov)  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For peer review only

### STRENGTHS AND LIMITATIONS OF THIS STUDY

- Randomised control clinical trial testing the efficacy of CPFA in septic shock.
- Premature closure of the trial by circumstances beyond the trial.
- Scarce sample size: underpowered trial.

For peer review only

## INTRODUCTION

Sepsis is still a leading cause of mortality in Intensive Care Units (ICU) patients, with a 20-50% mortality rate of sepsis and septic shock [1]. There exists a feeling of frustration generated by the large series of negative randomized clinical trials (RCTs) in septic shock treatment (especially in targeting mortality) during the past 30 years [2]. Patients included in these trials have a wide variability in their probability of death translating into differences in benefits to be derived from specific therapy application, producing a handicap to sample size calculation. This can lead to the trial having less power than initially planned increasing risk of a type 2 error and undoubtedly this is the origin of unexpected results.[3] It questions the use of subgroups in an attempt to extract some kind of useful information in negative RCTs.[4]

The COMPACT 1, a multicentre RCT study, failed to show benefit by using Coupled Plasma Filtration and Adsorption (CPFA) therapy in a population with septic shock. In a per protocol analysis, patients treated with CPFA at treated plasma volume superior to 0.20 l/kg/day showed a reduction in mortality rate [5]. Although an interesting finding, our group considered it was necessary to carry out a RCT to confirm this hypothesis.

The response to this question was the ROMPA (Reducción de la Mortalidad Mediante Plasma-Adsorción en Shock séptico), a multicenter RCT carried out in ICUs of southeastern Spain. The ROMPA Study (NCT02357433 in [clinicaltrials.gov](http://clinicaltrials.gov)) tried to clarify whether the application of high doses CPFA in addition to the current clinical practice was able to reduce hospital mortality in septic shock patients in ICUs. The protocol of ROMPA has been published in a free access support and the details of the protocol could be consulted without restrictions.[6]

1  
2  
3 In October 2017, COMPACT 2 (NCT01639664 in clinical trials.gov) trial investigators, a  
4 similar study to ROMPA conducted in Italian ICUs,[7] reported the premature closure of the  
5 study for having detected an increase in early mortality (3 first days) in the intervention  
6 branch, 6/42 (12.5%) vs 19/58 (32.8%)  $p=0.020$ , not having reached the sample size prefixed  
7 in the protocol (350 patients). The adjusted odds ratio (OR) of the treatment yielded by  
8 logistic regression is 2.1 (95% CI: 0.7-6.6,  $p=0.19$ ) and the adjusted hazard ratio (HR)  
9 yielded by the Cox model is 2.5 (95% CI: 1.4- 4.4,  $p=0.002$ ). This information was  
10 immediately reported to our Ethical Committee and these results were published on the  
11 research group website in Italian.[8] Subsequent events, including a provisional warning by  
12 the product supplier, motivated us to take the final decision of closing ROMPA. At that time,  
13 of the 10 initial hospitals only 5 had exceeded the technical capacity requirements and  
14 availability of resources required to access the randomization portal. In this paper and as a  
15 result of events of such severity, our group shows the data collected to date and the results  
16 from the 49 enrolled patients (30 control and 19 intervention groups).

## 39 METHODS

### 42 Protocol

45 The full study protocol was previously published.[6] A synthesis of it is made in this section  
46 (Methods) .

### 51 Setting and participants

54 The study was performed in 5 ICUs, in the southeast of Spain, that follow the same protocol  
55 in the treatment of septic shock, based on the recommendations of the Surviving Sepsis  
56  
57  
58  
59  
60

1  
2  
3 Campaign with the participation of the following centers: Vega Baja Hospital of Orihuela,  
4  
5 General University Santa Lucía Hospital of Cartagena, University Hospital of San Juan de  
6  
7 Alicante, Lluís Alcanyís Hospital of Xàtiva and Francesc de Borja Hospital of Gandía.  
8  
9

10  
11 The ROMPA study is a multi-centric, randomized, prospective, open clinical trial with 28-  
12  
13 and 90-day follow-up and allocation ratio 1:1, assessing the mortality reduction by CPFA in  
14  
15 patients with septic shock. Furthermore, we analyzed 3-day mortality to compare our results  
16  
17 with the Italian group.  
18  
19

20  
21 Each center obtained technical proficiency with the machine and CPFA treatment before they  
22  
23 could become “activated” for enrolment by the investigator monitoring team. This was done  
24  
25 to avoid similar problems as those reported for the first COMPACT study (coagulation of the  
26  
27 extracorporeal circuit, technical problems intimately linked to the management of a complex  
28  
29 extracorporeal circuit, problems related to necessary logistic that require an extracorporeal  
30  
31 technique such as CPFA as necessary and problems related to the need for specialized  
32  
33 personnel),[4] and also because CPFA is not routinely done in Spain and a new machine with  
34  
35 improved anticoagulation support was subsequently developed and used for this trial.  
36  
37  
38  
39

#### 40 **Participants**

41  
42  
43 Patients  $\geq 18$  years old admitted to the ICU of the participant hospitals, with a diagnosis of  
44  
45 septic shock can be included in the study. This was defined as documented or suspected  
46  
47 infection with systemic manifestations of infection accompanied by signs of organ failure, or  
48  
49 tissue hypoperfusion with persistent hypotension despite administration of adequate fluid  
50  
51 resuscitation (at least 30ml/kg crystalloides) and in the absence of other causes of  
52  
53 hypotension. The inclusion and exclusion criteria are detailed in the published protocol.[6]  
54  
55  
56  
57

#### 58 **Interventions**



1  
2  
3 The patient is considered registered once the informed consent form has been obtained by the  
4 patient or legal representative. The recruitment process ends with the patient randomization.  
5  
6  
7 The time between septic shock diagnosis and randomization was established in 12 hours,  
8  
9  
10 because this window adjusts much more to the reality of the clinical scenario, at least that of  
11  
12 the hospitals that participated in the ROMPA study. The researchers of the COMPACT 2  
13  
14 study reached the same conclusion.[7]  
15  
16

17  
18 Patients were divided randomly into two arms (control and intervention). ROMPA has a  
19  
20 stratified randomization based on gender, age ( $\leq 65$  or  $>65$  years) and SAPS III score ( $<50$  or  
21  
22  $\geq 51$ ). On the one hand, in the control group we followed the suggestions provided by the  
23  
24 recent surviving sepsis guidelines, as well as standard care guidelines typically followed in  
25  
26 Spain. On the other hand, in the CPFA group, we applied the same protocol plus high doses  
27  
28 of CPFA in the first 3 days after randomization.  
29  
30  
31

### 32 **Variables and measurements**

### 34 **Primary and Secondary Outcomes**

35  
36  
37 The primary outcome variable is all-cause of mortality assessed at 3, 28 and 90 days from the  
38  
39 recruitment of the patient. The analysis of 3-day mortality, although it was not initially pre-  
40  
41 specified in the protocol, it was a recommendation of our Ethical Committee after knowing  
42  
43 the data of the Italian group.[8]  
44  
45  
46  
47

48  
49 Moreover, at the descriptive level and in order to check homogeneity of both groups, the  
50  
51 following variables will be collected at the time of recruitment: birth year, gender, height, dry  
52  
53 weight, body temperature, heart rate, blood pressure, blood cell count, coagulation values,  
54  
55 glucose level, plasma creatinine, bilirubinemia, plasma C reactive protein, procalcitonin  
56  
57  
58  
59  
60

1  
2  
3 level, blood gas analysis, lactate, urinary output (ml/kg/h), Pa O<sub>2</sub>/FiO<sub>2</sub> ratio, APACHE II,  
4  
5 SOFA and SAPSIII scores.  
6  
7

### 8 **Sample Size**

9  
10  
11 Originally, a sample size of 190 patients was calculated to determine differences in mortality  
12 rates in both groups with a power-of-contrast of 80%. The assumed control mortality rate was  
13 50% and we tried to demonstrate a reduction in mortality of 20% with the intervention  
14 (similar to the COMPACT I results).[4] A partial analysis with the first 49 patients has been  
15 carried out as described in this paper. Using the data from the initial sample size calculation,  
16 these patients represent an approximate power-of-contrast of 30%.  
17  
18  
19  
20  
21  
22  
23  
24  
25

### 26 **Statistical analysis**

27  
28  
29 Initially, the calculation of the indicators of clinical relevance (relative risk, RR, absolute risk  
30 reduction, ARR, relative risk reduction, RRR, number needed to treat, NNT, by intent to  
31 treat, ITT) was planned. Without having the sample size calculated for the study  
32 (intermediate analysis) and having made the allocation based on a set of variables, the  
33 homogeneity of the groups was not able to be established. To minimize this problem, the  
34 propensity scores as a population overlap weight technique was applied with the objective of  
35 overcoming the problem caused by the lack of homogeneity between the two groups.[9] The  
36 adjustment variables were APACHE II, previous lactate levels and the presence of urinary  
37 sepsis. Finally, although it was not established in the study protocol, Kaplan-Meier survival  
38 curves were analyzed to determine differences in mortality in the analyzed groups (log-rank  
39 test). Since a significant number of patients died in the first three days and were unable to  
40 receive the technique (n = 3, 15.8%) we decided to perform the analysis by actual  
41 intervention received (AIR). Although initially we did not plan this analysis  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

(clinicaltrials.gov), the fact that one out of six patients did not receive the intervention could produce results completely different from its real effect.

### **Ethical issues**

The study was originally approved by all Ethics Committees of the different Hospitals participating in the study. There was a general agreement that the trial closure was the best option, since the decision adopted by the Italian group to close its trial had been made public through its website and the supplier consequently marked their product used for the test with a warning. A Data and Safety Monitoring Board periodically review and evaluate the study data for the safety of the patients. It was formed by the Principal Investigator, the Senior Investigator and the Biostatistician of the project.

### **Patient and Public Involvement**

Patients were not involved.

## **RESULTS**

A total of 49 patients were included in the final analysis (30 in the control group and 19 in the intervention group) (Figure 1). The randomization tables are displayed in Table 1. Parametric statistics did not allow us to establish significant differences between the analyzed factors due to the small sample size. However, we can see a mean difference between the two groups of 1.9 on an APACHE II score, 0.6 mmol/l of lactate levels and 10.9% in the prevalence of urinary sepsis. All these factors have been used in the propensity score test.

1  
2  
3 With regard to mortality (without adjusting by propensity score), 7 patients (23.3%) died in  
4 the first three days from the control group and 8 patients (40.6%) died from the intervention  
5 group (p=0.146). After 28 days, 14 patients died (46.7%) from the control group and 11  
6 patients died (57.9%) from the intervention group, not reaching statistical significance  
7 (p=0.444). At 90 days 19 patients had died (63.3%) from the control group and 11 patients  
8 had died (57.9%) from the intervention group, which is to say no patient died from the  
9 intervention group between 28 and 90 days (p=0.878). Adjusting by propensity score and  
10 using the Kaplan-Meier technique (Figure 2), statistical significant difference was not  
11 reached, neither in the ITT (Table 2) approach nor by the AIR approach (Table 3).  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24

25 In patients who died in the first three days, we found that the base-line levels of lactate were  
26 higher compared with the rest (in mmol/L):  $7.96 \pm 4.79$  vs  $4.43 \pm 2.41$ ,  $p=0.015$ . This situation  
27 was similar in the APACHE score:  $29.7 \pm 5.1$  vs  $27.5 \pm 5.5$ ,  $p=0.194$ , although this variable was  
28 not significant.  
29  
30  
31  
32  
33  
34  
35  
36  
37

## 38 DISCUSSION

### 41 Summary

42  
43  
44 Our results seem to indicate that the patient who received CPFA had less chance of mortality  
45 in the long term (90 days), whether by ITT analysis or AIR analysis. However, in the short  
46 and medium term during ITT analysis, CPFA had a detrimental effect and when using AIR  
47 analysis the effect was protected. In any case, the statistical power to obtain conclusions from  
48 these results was low and these were non-significant, consequently we are only describing the  
49 estimation of the analyzed parameters (HR and proportions).  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

### Limitations of the study

This RCT was designed to determine medium and long-term differences between the CPFA and the standard care. For this purpose, a sample size of 190 patients was pre-determined. In these partial results, the sample size of 190 was not reached due to the cessation of the trial and therefore the statistical power of the comparison contrast is very low (~ 30%). As a consequence, the ARR of 20% is much too high and overly ambitious. This combined with the low sample size yields an extraordinarily low power. In addition, as the randomization process was done based on the baseline characteristics of the patient, this can produce differences between the groups. Moreover, we can observe that the sample sizes of the two groups are not similar (the control group has approximately 50% more patients). All this has led to the use of propensity score adjustment in order to obtain results similar to an RCT (totally homogeneous groups, except in the intervention received). [9] However, even if we apply this technique we still have a low power of contrast. Despite this limitation, we are obliged to communicate our partial results following the premature closure of the RCT COMPACT 2.

### Comparison with the existing literature

We agreed with the Ethics Committee to review the incidence of early mortality in our trial on account of the findings communicated to us by the COMPACT 2 team. It should be emphasised that the ROMPA investigators were not given any impression of these COMPACT 2 findings during the ROMPA clinical trial. The results reported by the group of researchers of COMPACT 2 here deserve a special mention [8]. In these results, as occurred in our group, a preliminary analysis was developed that is far from the sample size initially calculated and therefore with low statistical power of contrast (not indicated by them in their report). In addition, as in our study, the COMPACT 2 group used a randomization system

1  
2  
3 based on prognostic scores, [6] which means that the groups will not be similar until the end  
4 of recruitment (which is reason to introduce the propensity score in our results).  
5  
6  
7

8 In this situation, subgroup analysis has the problem of introducing analytic challenges and  
9 can lead to overstated and misleading results, [10] and as such we have to consider the  
10 remarkably low mortality of the control group, together with a remarkably high mortality of  
11 the intervention group. These results seem to be far removed from those that are obtained in  
12 usual clinical practice. This situation was not observed in the first COMPACT trial [5] and  
13 we have not heard of a retrospective analysis to explain these results.  
14  
15  
16  
17  
18  
19  
20  
21  
22

23 Lastly, we would like to comment on the margin of time chosen by the Italian group to carry  
24 out its partial results. We think it is important to assess the patient's mortality, but this  
25 mortality should be assessed with a global calculation. For a technique to be effective, it must  
26 decrease the patient's mortality in a reasonable period of time in order to allow the healing of  
27 sepsis and its possible subsequent consequences. For this reason, the period of 28 and 90 days  
28 was fixed by our protocol. Consequently, for the sake of conducting an effective clinical trial,  
29 it is not of relevance that the patient unfortunately dies early, but whether the patient dies in a  
30 period of time where he has a high mortality risk due to sepsis. In addition, in the calculation  
31 of the sample size of the Italian group, this was not contemplated and could be a result of  
32 random error or heterogeneous groups in the treatment allocation. At this point, it must be  
33 stated that the ROMPA investigators are not at any moment criticising the COMPACT 2  
34 decision to halt their trial. ROMPA's researchers remain aware of the complexity of such a  
35 decision and that it involves multiple factors, the most important being the security of the  
36 patients.  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55

### 56 **Implications to research**

57  
58  
59  
60

1  
2  
3 Our study was halted prematurely for the reasons we have previously explained when only 49  
4 patients had been randomized (out of a target 190 patients). In the intervention arm, 19  
5 patients were randomized and 30 patients randomized in the control arm. In both approaches  
6 (ITT and real intervention), we have not found evidence of either benefit or harmful effect in  
7 the tested treatment and, of course, this comes as no surprise due to the premature  
8 termination.

9  
10  
11  
12  
13  
14  
15  
16  
17  
18 At this level of recruitment and with a power of 30% our sample is absolutely exposed to the  
19 random effect, resulting in a lack of homogeneity in the levels of basal risk. This lack of  
20 homogeneity pre-determines that the technique can be presented as either beneficial or  
21 harmful. In fact the technique appears less beneficial in the subgroup (not predefined) of  
22 patients who died in 72 hours and that, logically, were patients with an elevated basal risk,  
23 primarily expressed through lactate levels and APACHE 2 score.

24  
25  
26  
27  
28  
29  
30  
31  
32 We would like to comment on a controversial issue. Three patients who had been randomized  
33 to the intervention group (20%) died in the first 72 hrs and did not receive the CPFA  
34 treatment. The rapid hemodynamic deterioration of the patients did not allow the connection  
35 to the extracorporeal circuit. Undoubtedly adequate sample size management minimized this  
36 problem, but if what we are considering is the possible harmful of the technique in a non-pre-  
37 specified subgroup of an underpowered sample we cannot ignore this situation of the  
38 technique not being applied.

## 39 40 41 42 43 44 45 46 47 48 49 50 51 52 **CONCLUSIONS**

53  
54  
55 In this paper we have presented the results of the 49 patients randomized in our trial up until  
56 the moment of closure. As a consequence of the procedure being underpowered, it was not

1  
2  
3 possible to do an analysis of contrast of hypothesis and under this inconvenience, we present  
4  
5 the results obtained for the interest of all concerned in knowing what has happened in our  
6  
7 trial. When all is taken into consideration, we have not found a difference in mortality  
8  
9  
10 between the two groups.  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For peer review only



## **AUTHORS' CONTRIBUTIONS**

CG designed the study and drafted the paper of the protocol; CP participated in the study design and helped draft the paper; FC, JMA, MG, CM, José LAP, EM, CD, MR, JLM, PJA, EMB, JC, EG, FS, MS, JT and VFG participated in the study design and reviewed critically the manuscript; AP participated in the study design, performed the statistical analysis and reviewed critically the manuscript. All the authors approved the final version of the text to be submitted for publication.

## **FUNDING STATEMENT**

This work was supported by Belco 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.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from Francisco Colomina-Climent, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of all the Ethics Committee which approved the study.

For peer review only

## REFERENCES

1. Gaieski DF, Edwards JM, Kallan MJ, et al. Benchmarking the incidence and mortality of severe sepsis in the United States. *Crit Care Med* 2013;41:1167–74.
2. Opal SM, Dellinger RP, Vincent JL, et al. 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.
3. Wong JL, Mason AJ, Gordon AC, Bret SJ. Are large randomised controlled trials in severe sepsis and septic shock statistically disadvantaged by repeated inadvertent underestimates of required sample size? *BMJ Open* 2018;8:e020068.
4. Vincent JL, Marini JJ, Pesenti A. Do trials that report a neutral or negative treatment effect improve the care of critically ill patients? No. *Intensive Care Med* 2018;44:1989–91.
5. Livigni S, Bertolini G, Rossi C, et al. Efficacy of coupled plasma filtration and adsorption (CPFA) in patients with septic shock: a multicenter randomised controlled clinical trial. *BMJ Open* 2014;4:e003536.
6. Colomina-Climent F, Gimenez-Esparza C, Portillo-Jimenez C, et al. Mortality Reduction in Septic Shock by Plasma Adsorption ((ROMPA): a protocol for a randomised clinical trial. *BMJ Open* 2016;6:e011856.
7. Gruppo Italiano per la Valutazione degli Interventi in Terapia Intensiva. COMPACT-2: COMbining Plasmafiltration and Adsorption Clinical Trial-2. Available from <http://www.giviti.marionegri.it/COMPACT2.asp> [updated July 6, 2018; accessed November 27, 2018].

- 1  
2  
3 8. Gruppo Italiano per la Valutazione degli Interventi in Terapia Intensiva. Chiusura  
4 anticipata dello Studio COMPACT-2. Available from  
5  
6 <http://www.giviti.marionegri.it/Download/COMPACT-2%20Chiusura%20anticipata.pdf>  
7  
8 [updated October 23, 2017; accessed November 27, 2018].  
9  
10  
11  
12  
13 9. Stuart BL, Grebel LE, Butler CC, et al. Comparison between treatment effects in a  
14 randomised controlled trial and an observational study using propensity scores in primary  
15 care. *Br J Gen Pract* 2017;67:e643–9.  
16  
17  
18  
19  
20  
21 10. Wang R, Lagakos SW, Ware JH, Hunter DJ, Drazen JM. Statistics in Medicine –  
22 Reporting of Subgroup Analyses in Clinical Trials. *N Engl J Med* 2007;357:2189–94.  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 **FIGURE LEGENDS:**  
4

5  
6 Figure 1: Flow chart of the clinical trial (partial results).  
7  
8  
9

10  
11  
12 Figure 2: Survival analysis using the Kaplan-Meier estimator comparing both groups.  
13  
14

15  
16 Red, intervention; Blue, control.  
17

18  
19 A, intention to treat; B, real intervention.  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

**TABLES:**

Table 1: Comparison between the intervention and the control group.

Variable	Control group n=30 n(%) / x±s	CPFA n=19 n(%) / x±s	p-value
Gender male	18(60.0)	11(57.9)	0.884
Abdominal sepsis	12(40.0)	8(42.1)	0.884
Cancer	11(36.7)	7(36.8)	0.990
Community-acquired pneumonia	5(16.7)	3(15.8)	>0.999
Nosocomial pneumonia	3(10.0)	3(15.8)	0.665
Diabetes	9(30.0)	5(26.3)	0.781
Urinary sepsis	8(26.7)	3(15.8)	0.492
APACHE II	28.9±5.6	27.0±5.1	0.244
SOFA	12.8±3.3	12.2±4.4	0.541
SAPS II	74.5±20.9	70.7±21.0	0.587
Lactate (mmol/l)	5.3±3.4	5.9±4.1	0.580
Age (years)	70.0±13.6	71.0±14.5	0.812

Abbreviations: APACHE, Acute Physiology And Chronic Health Evaluation; CPFA, Coupled Plasma Filtration Adsorption; n(%), absolute frequency (relative frequency); SAPS, Simplified Acute Physiology Score; SOFA, Sequential Organ Failure Assessment; x±s, mean ± standard deviation.

Table 2: Clinical relevance of the intervention (intention-to-treat) in the patients with septic shock (adjusted by propensity scores as a population overlap weight).

Outcome	RR (95% CI)	RRR (95% CI)	ARR (95% CI)	NNT/NNH*	p-value
3-day mortality	1.67(0.51-5.46)	-0.67(-4.46 to 0.49)	-0.17(-0.54 to 0.20)	6 (H)	0.667
28-day mortality	1.28(0.57-2.87)	-0.28(-1.87 to 0.43)	-0.13(-0.53 to 0.28)	8 (H)	0.537
90-day mortality	0.92(0.48-1.76)	0.08(-0.76 to 0.52)	0.05(-0.35 to 0.45)	19 (T)	>0.999

Abbreviations: ARR, Absolute Risk Reduction; CI, confidence interval; H, Harm; NNH, Number Needed to Harm; NNH, Number Needed to Treat; RR, relative risk; RRR, Relative Risk Reduction; T, Treat.

\*, not possible to compute the confidence interval (division by zero).

Table 3: Clinical relevance of the intervention (real group) in the patients with septic shock (adjusted by propensity scores as a population overlap weight).

Outcome	RR (95% CI)	RRR (95% CI)	ARR (95% CI)	NNT	p-value
3-day mortality	0.84(0.26-2.73)	0.16(-1.73 to 0.74)	0.06(-0.32 to 0.44)	18	>0.999
28-day mortality	0.93(0.42-2.06)	0.07(-1.06 to 0.58)	0.04(-0.37 to 0.45)	26	>0.999
90-day mortality	0.72(0.35-1.48)	0.28(-0.48 to 0.65)	0.19(-0.21 to 0.59)	6	0.417

Abbreviations: ARR, Absolute Risk Reduction; CI, confidence interval; NNT, Number Needed to Treat; RR, relative risk; RRR, Relative Risk Reduction.

\*, not possible to compute the confidence interval (division by zero).



**Enrollment**

BMJ Open  
Assessed for eligibility (n=72)

Excluded (n=23)  
◆ Not meeting inclusion criteria (n=13)  
◆ Declined to participate (n=1)  
◆ Other reasons (n=9)

Randomized (n=49)

**Allocation**

14 Allocated to intervention (n=19)  
15  
16 Received allocated intervention (n=16)  
17  
18 Did not receive allocated intervention  
19 (premature death) (n=3)  
20

Allocated to intervention (n=30)  
◆ Received allocated intervention (n=30)  
◆ Did not receive allocated intervention (n=0)

**Follow-Up**

24 Lost to follow-up (give reasons) (n=0)  
25  
26 Discontinued intervention (give reasons) (n=0)  
27

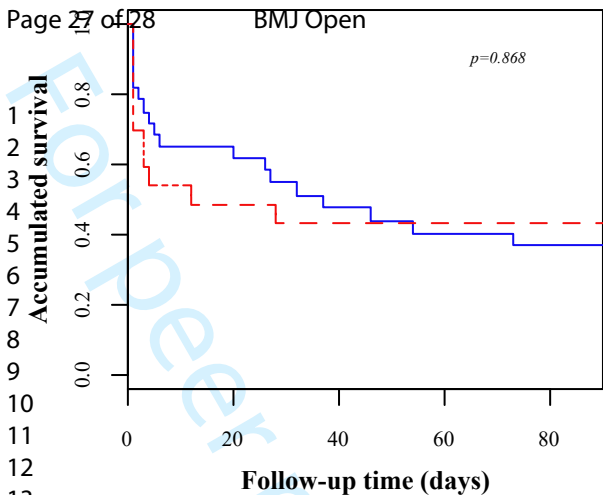
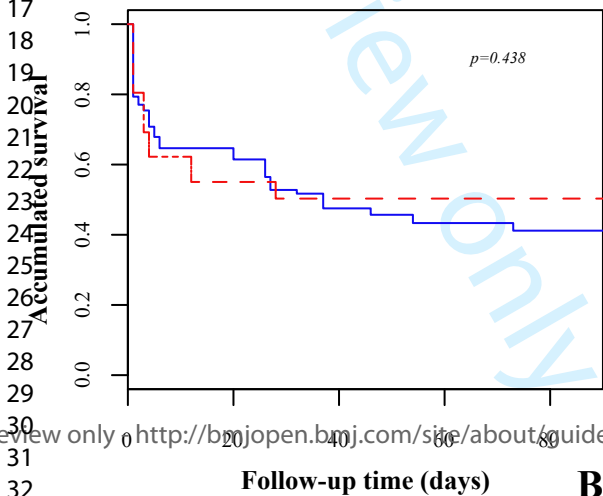
Lost to follow-up (give reasons) (n=0)  
Discontinued intervention (give reasons) (n=0)

**Analysis**

32 Analysed (n=19)  
33  
34 Excluded from analysis (n=0)  
35

Analysed (n=30)  
◆ Excluded from analysis (n=0)

For peer review only - <http://bmjopen.bmj.com/site/about/guidelines.xhtml>

**A****B**



# CONSORT 2010 checklist of information to include when reporting a randomised trial\*

Section/Topic	Item No	Checklist item	Reported on page No
<b>Title and abstract</b>			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	3
<b>Introduction</b>			
Background and objectives	2a	Scientific background and explanation of rationale	6-7
	2b	Specific objectives or hypotheses	7
<b>Methods</b>			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	7-8
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	7-10
Participants	4a	Eligibility criteria for participants	7-8
	4b	Settings and locations where the data were collected	7-8
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	8-9
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	9-10
	6b	Any changes to trial outcomes after the trial commenced, with reasons	9-10
Sample size	7a	How sample size was determined	9-10
	7b	When applicable, explanation of any interim analyses and stopping guidelines	
<b>Randomisation:</b>			
Sequence generation	8a	Method used to generate the random allocation sequence	Protocol
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	Protocol
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	Protocol
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	Protocol
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	Protocol

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	N/A
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	10-11
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	10-11
<b>Results</b>			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	11
	13b	For each group, losses and exclusions after randomisation, together with reasons	11
Recruitment	14a	Dates defining the periods of recruitment and follow-up	7-8
	14b	Why the trial ended or was stopped	6-7
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	21
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	11
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	12
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	12
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	12
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	12
<b>Discussion</b>			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	13
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	13-16
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	13-16
<b>Other information</b>			
Registration	23	Registration number and name of trial registry	4
Protocol	24	Where the full trial protocol can be accessed, if available	7
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	17

\*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see [www.consort-statement.org](http://www.consort-statement.org).

# BMJ Open

## The premature closure of ROMPA Clinical Trial: Mortality Reduction in Septic Shock by Plasma Adsorption.

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2019-030139.R2
Article Type:	Original research
Date Submitted by the Author:	17-Oct-2019
Complete List of Authors:	Giménez-Esparza, Carola; Vega Baja Hospital of Orihuela, Intensive Care Unit Portillo-Requena, Cristina; Vega Baja Hospital of Orihuela, Intensive Care Unit Colomina-Climent, Francisco; Miguel Hernández University, Clinical Medicine 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 Mármol-Peis, Enrique; University Hospital of San Juan de Alicante, Intensive Care Unit Dólera-Moreno, Cristina; University Hospital of San Juan de Alicante, Intensive Care Unit Rodríguez-Serra, 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 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 Palazón-Bru, Antonio; Miguel Hernández University, Clinical Medicine Gil-Guillen, Vicente F.; Miguel Hernández University, Clinical Medicine
<b>Primary Subject Heading</b>:	Intensive care

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

Secondary Subject Heading:	Intensive care, Infectious diseases
Keywords:	INFECTIOUS DISEASES, Adult intensive & critical care < INTENSIVE & CRITICAL CARE, Clinical trials < THERAPEUTICS



**TITLE PAGE**

Title: The premature closure of ROMPA Clinical Trial: Mortality Reduction in Septic Shock by Plasma Adsorption.

Short title: The closure of ROMPA Clinical Trial.

Authors: Carola Giménez-Esparza [1], Cristina Portillo-Requena [1], Francisco Colomina-Climent [2], José Manuel Allegue-Gallego [3], María Galindo-Martínez [3], Cristina Mollà-Jiménez [4], José Luis Antón-Pascual [4], Enrique Mármol-Peis [4], Cristina Dolera-Moreno [4], Manuel Rodríguez-Serra [5], José Luis Martín-Ruíz [5], Pablo Juan Fernández-Arroyo [6], Eugenia María Blasco-Císcar [6], José Cánovas-Robles [7], Enrique González-Hernández [8], Fernando Sánchez-Morán [8], Manuel Solera-Suárez [9], Jesús Torres-Tortajada [9], Antonio Palazón-Bru [2], Vicente Francisco Gil-Guillén [2].

Institutions:

1. Intensive Care Unit, Vega Baja Hospital of Orihuela, Orihuela, Alicante, Spain.
2. Department of Clinical Medicine, Miguel Hernández University, San Juan de Alicante, 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.

1  
2  
3 7. Intensive Care Unit, General University Hospital of Alicante, Alicante, Alicante, Spain.  
4

5 8. Intensive Care Unit, La Plana Hospital of Villarreal, Villarreal, Castellón, Spain.  
6

7 9. Intensive Care Unit, Francesc de Borja Hospital of Gandía, Gandía, Valencia, Spain.  
8  
9

10  
11  
12  
13 Corresponding author: Prof. Antonio Palazón-Bru, PhD. Department of Clinical Medicine,  
14 Miguel Hernández University, Carretera de Valencia - Alicante S/N, 03550, San Juan de  
15 Alicante (Spain). Phone number: +34 965919449. Fax number: +34 965919450. E-mail:  
16 [antonio.pb23@gmail.com](mailto:antonio.pb23@gmail.com)  
17  
18  
19  
20  
21  
22

23 Keywords: Shock, Septic; Coupled Plasma Filtration Adsorption; Mortality; Intensive Care  
24 Units; Clinical Trials.  
25  
26

27  
28 Word count: 2886.  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60



## ABSTRACT

Objectives: Coupled Plasma Filtration and Adsorption (CPFA) use in septic shock remains controversial. The objective is to clarify whether the application of high doses of CPFA in addition to the current clinical practice could reduce hospital mortality in septic shock patients in Intensive Care Units at 28 days and at 90 days follow-up.

Design: We designed a prospective randomized clinical trial, ROMPA (Reducción de la Mortalidad Plasma-Adsorción), to demonstrate an absolute mortality reduction of 20% [ $\alpha=0.05$ ;  $1-\beta=0.8$ ;  $n=190(95 \times 2)$ ].

Setting: Being aware of the pitfalls associated with previous medical device trials, we developed a training program to improve CPFA use (especially clotting problems). The protocol was approved by the ethics committees of all participating centers. Circumstances beyond our control produced a change in recruitment conditions unacceptable to ROMPA researchers and the trial was discontinued.

Participants: By closure, 5 centers from an initial 10 fulfilled the necessary trial criteria, with 49 patients included, 30 in the control group (CG) and 19 in the intervention group (IG).

Intervention: CPFA.

Main outcome measures: Hospital mortality at 28 days and 90 days follow-up.

Results: After 28 days, 14 patients died (46.7%) from the CG and 11 (57.9%) from the IG, not reaching statistical significance ( $p=0.444$ ). At 90 days, 19 patients had died (63.3%) from the CG and 11 patients (57.9%) from the IG, ( $p=0.878$ ). The adjustment by propensity score or the use of the Kaplan Meier technique failed to achieve statistical difference, neither by Intention to Treat nor by the Actual Intervention Received.

1  
2  
3 Conclusion: We herewith present the results gained from the prematurely closed trial. The  
4  
5 results are inconclusive due to low statistical power but we consider that this data is of  
6  
7 interest for the scientific community and potentially necessary for any ensuing debate.  
8  
9

10 Register: NCT02357433 in [clinicaltrials.gov](http://clinicaltrials.gov)  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For peer review only

### STRENGTHS AND LIMITATIONS OF THIS STUDY

- Randomized control clinical trial testing the efficacy of CPFA in septic shock.
- Premature closure due to circumstances beyond the control of the trial.
- Scarce sample size: underpowered trial.

For peer review only

## INTRODUCTION

Sepsis is still a leading cause of mortality in Intensive Care Unit (ICU) patients, with a 20-50% mortality rate from sepsis and septic shock [1]. There has been a feeling of frustration generated by the large amount of negative randomized clinical trials (RCTs) in septic shock treatment (especially in those targeting mortality) over the past 30 years [2]. Patients included in these trials vary widely in their probability of death. This translates into differences in the benefits derived from specific therapy application, which in turn handicaps sample size calculation. This can lead to the trial having less statistical power than initially planned, increasing the risk of a type 2 error and this is the origin of unexpected results. [3] It questions the use of subgroups in an attempt to extract some kind of useful information in negative RCTs. [4]

The COMPACT 1, a multicenter RCT study, failed to show any benefits when using Coupled Plasma Filtration and Adsorption (CPFA) therapy in a population with septic shock. In a per-protocol analysis, patients treated with CPFA using a volume of treated plasma superior to 0.20 l/kg/day demonstrated a reduction in mortality rate [5]. Although an interesting result, our group considered it was necessary to carry out a RCT to confirm this hypothesis.

The response to this question was ROMPA (Reducción de la Mortalidad Mediante Plasma-Adsorción en Shock séptico), a multicenter RCT carried out in ICUs of southeastern Spain. The ROMPA Study (NCT02357433 in clinicaltrials.gov) tried to clarify whether the application of high doses of CPFA in addition to the current clinical practice was able to reduce hospital mortality in septic shock patients in ICUs. The protocol of ROMPA has been published in a free access journal and the details of the protocol can be consulted without restrictions. [6]

1  
2  
3 In October 2017, the trial investigators of COMPACT 2 (NCT01639664 in clinicaltrials.gov),  
4 a similar study to ROMPA conducted in Italian ICUs [7], reported the premature closure of  
5 the study for having detected an increase in early mortality (3 first days) in the intervention  
6 branch (6/42 (12.5%) vs 19/58 (32.8%)  $p=0.020$ , not reaching the 350 patient sample size  
7 prefixed in the protocol). The adjusted odds ratio (OR) of the treatment yielded by logistic  
8 regression is 2.1 (95% CI: 0.7-6.6,  $p=0.19$ ) and the adjusted hazard ratio (HR) yielded by the  
9 Cox model is 2.5 (95% CI: 1.4- 4.4,  $p=0.002$ ). This information was immediately reported to  
10 our Ethical Committee and these results were published on the research group website in  
11 Italian [8]. Subsequent events, including a provisional warning by the product supplier, led us  
12 to close ROMPA. At that time, of the 10 initial hospitals, only 5 had exceeded the technical  
13 capacity requirements and availability of resources required to access the randomization  
14 portal. Due to the severity of the events, our group wishes to show the data collected so far  
15 and the results from the 49 enrolled patients (30 control and 19 intervention groups).

## 36 **METHODS**

### 39 **Protocol**

40 The full study protocol has been published previously. [6] In this section, a synthesis of the  
41 protocol is given (Methods).

### 44 **Setting and participants**

45 The study was performed in 5 ICUs in the southeast of Spain, all following the same protocol  
46 in the treatment of septic shock, which is based on the recommendations of the Surviving  
47 Sepsis Campaign. The following centers participated: Vega Baja Hospital of Orihuela,

1  
2  
3 General University Santa Lucía Hospital of Cartagena, University Hospital of San Juan de  
4  
5 Alicante, Lluís Alcanyís Hospital of Xàtiva and Francesc de Borja Hospital of Gandía.  
6  
7

8  
9 The ROMPA study is a multi-center, randomized, prospective, open clinical trial with 28-  
10  
11 and 90-day follow-up and allocation ratio 1:1, assessing the mortality reduction by CPFA in  
12  
13 patients with septic shock. Furthermore, we analyzed 3-day mortality to compare our results  
14  
15 with the Italian group.  
16  
17

18  
19 Each center obtained technical proficiency with the machine and CPFA treatment before they  
20  
21 could become “activated” for enrolment by the investigator-monitoring team. This was done,  
22  
23 firstly, in order to avoid similar problems as those reported in the first COMPACT study  
24  
25 (coagulation of the extracorporeal circuit; technical problems intimately linked to the  
26  
27 management of a complex extracorporeal circuit; logistical problems which required an  
28  
29 extracorporeal technique such as CPFA; problems related to the need for specialized  
30  
31 personnel). [4] Secondly, as CPFA is not routinely administered in Spain, a new machine  
32  
33 with improved anticoagulation support was developed and used for this trial.  
34  
35  
36  
37

### 38 **Participants**

39  
40  
41 Patients  $\geq 18$  years-old with a diagnosis of septic shock and admitted to the ICU of the  
42  
43 participant hospitals are eligible to be included in the study. Diagnosis of septic shock was  
44  
45 defined as documented or suspected infection with systemic manifestations of infection  
46  
47 accompanied by signs of organ failure, or tissue hypoperfusion with persistent hypotension  
48  
49 despite administration of adequate fluid resuscitation (at least 30ml/kg crystalloides) and in  
50  
51 the absence of other causes of hypotension. The inclusion and exclusion criteria are detailed  
52  
53 in the published protocol. [6]  
54  
55  
56  
57

### 58 **Interventions**

1  
2  
3 The patient is registered once the informed consent form has been obtained by the patient or  
4 legal representative. The recruitment process ends with the patient randomization. The time  
5  
6 between septic shock diagnosis and randomization was established in 12 hours, because this  
7  
8 window adjusts much more to the reality of the clinical situation, at least that of the hospitals  
9  
10 that participated in the ROMPA study. The researchers of the COMPACT 2 study reached  
11  
12 the same conclusion. [7]  
13  
14  
15

16  
17 Patients were divided randomly into two arms (control and intervention). ROMPA has a  
18  
19 stratified randomization based on gender, age ( $\leq 65$  or  $>65$  years) and SAPS III score ( $<50$  or  
20  
21  $\geq 51$ ). On the one hand, in the control group we followed the suggestions provided by the  
22  
23 recent surviving sepsis guidelines, as well as standard care guidelines typically followed in  
24  
25 Spain. On the other hand, in the CPFA group, we applied the same protocol plus high doses  
26  
27 of CPFA in the first 3 days after randomization.  
28  
29  
30

### 31 32 **Variables and measurements**

### 33 34 **Primary and Secondary Outcomes**

35  
36 The primary outcome variable is all-cause mortality assessed at 28 and 90 days after the  
37  
38 recruitment of the patient. The analysis of 3-day mortality, although not initially specified in  
39  
40 the protocol, was an added recommendation by our Ethical Committee once the data of the  
41  
42 Italian group had become known. [8]  
43  
44  
45

46  
47 Moreover, at the descriptive level and in order to check homogeneity of both groups, the  
48  
49 following variables will be collected at the time of recruitment: birth year, gender, height, dry  
50  
51 weight, body temperature, heart rate, blood pressure, blood cell count, coagulation values,  
52  
53 glucose level, plasma creatinine, bilirubinemia, plasma C reactive protein, procalcitonin  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 level, blood gas analysis, lactate, urinary output (ml/kg/h), Pa O<sub>2</sub>/FiO<sub>2</sub> ratio, APACHE II,  
4  
5 SOFA and SAPSIII scores.  
6  
7

### 8 **Sample Size**

9  
10  
11 Originally, a sample size of 190 patients was calculated to determine differences in mortality  
12 rates in both groups with a power-of-contrast of 80%. The assumed control group mortality  
13 rate was 50% and we tried to demonstrate a reduction in mortality of 20% in the intervention  
14 group (similar to the COMPACT I results). [4] A partial analysis with the first 49 patients has  
15 been carried out as described in this paper. Using the data from the initial sample size  
16 calculation, these patients represent an approximate power-of-contrast of 30%.  
17  
18  
19  
20  
21  
22  
23  
24  
25

### 26 **Statistical analysis**

27  
28  
29 Initially, the calculation of the indicators of clinical relevance (relative risk, RR, absolute risk  
30 reduction, ARR, relative risk reduction, RRR, number needed to treat, NNT, by intent to  
31 treat, ITT) was planned. Without having the sample size calculated for the study  
32 (intermediate analysis) and having made the allocation based on a set of variables, the  
33 homogeneity of the groups could not be established. The propensity scores as a population  
34 overlap weight technique was applied with the objective of overcoming the problem caused  
35 by the lack of homogeneity between the two groups.[9] The adjustment variables were  
36 APACHE II, previous lactate levels and the presence of urinary sepsis. Finally, although not  
37 established in the study protocol, Kaplan-Meier survival curves were analyzed to determine  
38 differences in mortality in the analyzed groups (log-rank test). Since a significant number of  
39 patients died in the first three days and were unable to receive the technique (n = 3, 15.8%)  
40 we decided to perform the analysis by actual intervention received (AIR). Although **this**  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60



1  
2  
3 analysis was not initially planned (clinicaltrials.gov), the fact that one out of six patients did  
4  
5 not receive the intervention necessitated it.  
6  
7

### 8 **Ethical issues**

9  
10  
11 The study was originally approved by all Ethics Committees of the Hospitals participating in  
12  
13 the study. There was a general agreement that the trial closure was the best option, since the  
14  
15 decision adopted by the Italian group to close its trial had been made public through its  
16  
17 website resulting in the device supplier marking their product used for the test with a  
18  
19 warning. A Data and Safety Monitoring Board was set up to periodically review and evaluate  
20  
21 the study data for the safety of the patients. It was formed by the Principal Investigator, the  
22  
23 Senior Investigator and the Biostatistician of the project.  
24  
25  
26  
27

### 28 **Patient and Public Involvement**

29  
30  
31 This research was done without patient involvement. Patients were not invited to comment  
32  
33 on the study design and were not consulted to develop patient relevant outcomes or interpret  
34  
35 the results. Patients were not invited to contribute to the writing or editing of this document  
36  
37 for readability or accuracy.  
38  
39  
40  
41  
42  
43  
44

## 45 **RESULTS**

46  
47  
48 A total of 49 patients were included in the final analysis (30 in the control group and 19 in the  
49  
50 intervention group) (Figure 1). The randomization tables are displayed in Table 1. Parametric  
51  
52 statistics did not allow us to establish significant differences between the analyzed factors due  
53  
54 to the small sample size. However, we can see a mean difference between the two groups  
55  
56 based on three variables: 1.9 on an APACHE II score, 0.6 mmol/l of lactate levels and 10.9%  
57  
58  
59  
60

1  
2  
3 in the prevalence of urinary sepsis. All these factors have been used in the propensity score  
4  
5 test.  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For peer review only

1  
2  
3 With regard to mortality (without adjusting by propensity score), 7 patients (23.3%) had died  
4 in the first three days from the control group and 8 patients (40.6%) had died from the  
5 intervention group ( $p=0.146$ ). After 28 days, 14 patients had died (46.7%) from the control  
6 group and 11 patients had died (57.9%) from the intervention group, not reaching statistical  
7 significance ( $p=0.444$ ). At 90 days 19 patients had died (63.3%) from the control group and  
8 11 patients had died (57.9%) from the intervention group, which is to say no patient died  
9 from the intervention group between 28 and 90 days ( $p=0.878$ ). Adjusting by propensity  
10 score and using the Kaplan-Meier technique (Figure 2), statistical significant difference was  
11 not reached, neither by ITT (Table 2) nor by the AIR. (Table 3).  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24

25 In patients who died in the first three days, we found that the base-line levels of lactate were  
26 higher compared with the rest of the patients (in mmol/L):  $7.96\pm 4.79$  vs  $4.43\pm 2.41$ ,  $p=0.015$ .  
27 A similar situation was revealed in the APACHE score:  $29.7\pm 5.1$  vs  $27.5\pm 5.5$ ,  $p=0.194$ ,  
28 although this variable was not significant.  
29  
30  
31  
32  
33  
34  
35  
36  
37

## 38 DISCUSSION

### 41 Summary

42  
43  
44 Our results seem to indicate that the patients who received CPFA had less chance of mortality  
45 in the long term (90 days), whether by ITT analysis or AIR analysis. However, in the short  
46 and medium term during ITT analysis, CPFA had a detrimental effect and when using AIR  
47 analysis the effect was protective. In any case, the statistical power to obtain conclusions  
48 from these results was low and therefore non-significant. As a consequence, we are only  
49 describing the estimation of the analyzed parameters (HR and proportions).  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

### **Limitations of the study**

This RCT was designed to determine medium and long-term differences between CPFA and standard care. For this purpose, a sample size of 190 patients was pre-determined. In these partial results, the sample size of 190 was not reached due to the cessation of the trial and therefore the statistical power of the comparison contrast is very low (~ 30%). As a consequence, the ARR of 20% is much too high and unrealistic. Combined with the low sample size, this yields a very low statistical power. In addition, as the randomization process was undertaken based on the baseline characteristics of the patient, this can produce differences between the groups. Moreover, we can observe that the sample sizes of the two groups are not similar (the control group has approximately 50% more patients). All this has led to the use of propensity score adjustment in order to obtain results similar to an RCT (homogeneous groups, except in the intervention received). [9] However, even if we apply this technique we still have a low power of contrast. Despite this limitation, we are obliged to communicate our partial results following the premature closure of the RCT COMPACT 2.

### **Comparison with the existing literature**

We agreed with the Ethics Committee to review the incidence of early mortality in our trial after the findings communicated to us by the COMPACT 2 team. It should be emphasized that the ROMPA investigators were not given any impression of these COMPACT 2 findings during the ROMPA clinical trial. The results reported by the group of researchers of COMPACT 2 here deserve a special mention [8]. In these results, as occurred in our group, a preliminary analysis was developed that is far from the sample size initially calculated and therefore with low statistical power of contrast (not indicated by them in their report). In addition, as in our study, the COMPACT 2 group used a randomization system based on

1  
2  
3 prognostic scores, [6] which means that the groups will not be similar until the end of  
4  
5 recruitment (which is reason to introduce the propensity score in our results).  
6  
7

8  
9 In this situation, subgroup analysis has the problem of introducing analytic challenges and  
10  
11 can lead to overstated and misleading results, [10] and, as such, we have to consider the  
12  
13 remarkably low mortality of the control group, together with a remarkably high mortality of  
14  
15 the intervention group. These results seem to be far removed from those that are obtained in  
16  
17 usual clinical practice. This situation was not observed in the first COMPACT trial [5] and  
18  
19 we have not heard of a retrospective analysis to explain these results.  
20  
21  
22

23  
24 Lastly, we would like to comment on the margin of time chosen by the Italian group to carry  
25  
26 out its partial results. We think it is important to assess the patient's mortality, but this  
27  
28 mortality should be assessed with a global calculation. For a technique to be effective, it must  
29  
30 decrease the patient's mortality in a reasonable period of time in order to allow the healing of  
31  
32 sepsis and its possible consequences. For this reason, the periods of 28 days and 90 days were  
33  
34 fixed by our protocol. Consequently, for the sake of conducting an effective clinical trial, it is  
35  
36 not of relevance that the patient dies early, but whether the patient dies in a period of time  
37  
38 where he has a high mortality risk due to sepsis. Additionally, in the calculation of the sample  
39  
40 size of the Italian group, mortality at three days was not contemplated and could be a result of  
41  
42 either random error or heterogeneous groups in the treatment allocation. At this point, it must  
43  
44 be stated that the ROMPA investigators are not at any moment criticizing the COMPACT 2  
45  
46 decision to halt their trial. ROMPA's researchers remain aware of the complexity of such a  
47  
48 decision and that it involves multiple factors, the most important being the security of the  
49  
50 patients.  
51  
52  
53  
54

### 55 56 **Implications to research** 57 58 59 60

1  
2  
3 Our study was halted prematurely for the reasons we have previously explained when only 49  
4 patients had been randomized (out of a target 190 patients). In the intervention arm, 19  
5 patients were randomized and 30 patients in the control arm. In both approaches (ITT and  
6 real intervention), we have not found evidence of either benefit or harmful effect in the tested  
7 treatment and, of course, this comes as no surprise due to the premature termination.  
8  
9

10  
11  
12 At this level of recruitment and with a statistical power of 30%, our sample is exposed to the  
13 random effect, resulting in a lack of homogeneity in the levels of basal risk. This lack of  
14 homogeneity pre-determines that the technique can be presented as either beneficial or  
15 harmful. In fact the technique appears less beneficial in the subgroup (not predefined) of  
16 patients who died in 72 hours and these were patients with an elevated basal risk, primarily  
17 expressed through lactate levels and APACHE 2 score.  
18  
19

20  
21  
22 We would like to comment on a controversial issue. Three patients who had been randomized  
23 to the intervention group (20%) died in the first 72 hours and did not receive the CPFA  
24 treatment. The rapid hemodynamic deterioration of the patients did not allow the connection  
25 to the extracorporeal circuit. Undoubtedly, adequate sample size management minimized this  
26 problem, but if what we are considering is the potential harmfulness of the technique in a  
27 non-pre-specified subgroup of an underpowered sample size, we cannot ignore the fact that  
28 the technique was not applied.  
29  
30

## 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 **CONCLUSIONS**

51  
52  
53 In this paper we have presented the results of the 49 patients randomized in our trial up until  
54 the moment of closure. As a consequence of the procedure being underpowered, it was not  
55 possible to do an analysis of contrast of hypothesis and under this inconvenience, we present  
56  
57  
58  
59  
60

1  
2  
3 the results obtained for the interest of all who are concerned about what happened in our trial.  
4

5 When all is taken into consideration, we have not found a difference in mortality between the  
6

7  
8 two groups.  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For peer review only

## **AUTHORS' CONTRIBUTIONS**

CG designed the study and drafted the paper of the protocol; CP participated in the study design and helped draft the paper; FC, JMA, MG, CM, José LAP, EM, CD, MR, JLM, PJA, EMB, JC, EG, FS, MS, JT and VFG participated in the study design and reviewed critically the manuscript; AP participated in the study design, performed the statistical analysis and reviewed critically the manuscript. All the authors approved the final version of the text to be submitted for publication.

## **FUNDING STATEMENT**

This work was supported by Bellco, who provided all the devices and materials related to the use of CPFA for the treatment group. This entity did not play any role in study design; collection, management, analysis, and interpretation of data; writing of this report; 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 have participated in our study.



### DATA AVAILABILITY STATEMENT

The complete data that supports the findings of this study is available from Francisco Colomina-Climent. Upon reasonable request and with the permission of all the Ethics Committees who approved the study, this data may be freely accessed by the authors.

For peer review only

## REFERENCES

1. Gaieski DF, Edwards JM, Kallan MJ, et al. Benchmarking the incidence and mortality of severe sepsis in the United States. *Crit Care Med* 2013;41:1167–74.
2. Opal SM, Dellinger RP, Vincent JL, et al. 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.
3. Wong JL, Mason AJ, Gordon AC, Bret SJ. Are large randomised controlled trials in severe sepsis and septic shock statistically disadvantaged by repeated inadvertent underestimates of required sample size? *BMJ Open* 2018;8:e020068.
4. Vincent JL, Marini JJ, Pesenti A. Do trials that report a neutral or negative treatment effect improve the care of critically ill patients? No. *Intensive Care Med* 2018;44:1989–91.
5. Livigni S, Bertolini G, Rossi C, et al. Efficacy of coupled plasma filtration and adsorption (CPFA) in patients with septic shock: a multicenter randomised controlled clinical trial. *BMJ Open* 2014;4:e003536.
6. Colomina-Climent F, Gimenez-Esparza C, Portillo-Jimenez C, et al. Mortality Reduction in Septic Shock by Plasma Adsorption ((ROMPA): a protocol for a randomised clinical trial. *BMJ Open* 2016;6:e011856.
7. Gruppo Italiano per la Valutazione degli Interventi in Terapia Intensiva. COMPACT-2: COMbining Plasmafiltration and Adsorption Clinical Trial-2. Available from <http://www.giviti.marionegri.it/COMPACT2.asp> [updated July 6, 2018; accessed November 27, 2018].

1  
2  
3 8. Gruppo Italiano per la Valutazione degli Interventi in Terapia Intensiva. Chiusura  
4 anticipata dello Studio COMPACT-2. Available from

5  
6  
7 <http://www.giviti.marionegri.it/Download/COMPACT-2%20Chiusura%20anticipata.pdf>

8  
9  
10 [updated October 23, 2017; accessed November 27, 2018].

11  
12  
13 9. Stuart BL, Grebel LE, Butler CC, et al. Comparison between treatment effects in a  
14 randomised controlled trial and an observational study using propensity scores in primary  
15 care. *Br J Gen Pract* 2017;67:e643–9.

16  
17  
18 10. Wang R, Lagakos SW, Ware JH, Hunter DJ, Drazen JM. Statistics in Medicine –  
19 Reporting of Subgroup Analyses in Clinical Trials. *N Engl J Med* 2007;357:2189–94.  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 **FIGURE LEGENDS:**  
4

5  
6 Figure 1: Flow chart of the clinical trial (partial results).  
7  
8  
9

10  
11  
12 Figure 2: Survival analysis using the Kaplan-Meier estimator comparing both groups.  
13  
14

15 Red, intervention; Blue, control.  
16  
17

18 A, intention to treat; B, real intervention.  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For peer review only

**TABLES:**

Table 1: Comparison between the intervention and the control group.

Variable	Control group n=30 n(%) / x±s	CPFA n=19 n(%) / x±s	p-value
Gender male	18(60.0)	11(57.9)	0.884
Abdominal sepsis	12(40.0)	8(42.1)	0.884
Cancer	11(36.7)	7(36.8)	0.990
Community-acquired pneumonia	5(16.7)	3(15.8)	>0.999
Nosocomial pneumonia	3(10.0)	3(15.8)	0.665
Diabetes	9(30.0)	5(26.3)	0.781
Urinary sepsis	8(26.7)	3(15.8)	0.492
APACHE II	28.9±5.6	27.0±5.1	0.244
SOFA	12.8±3.3	12.2±4.4	0.541
SAPS II	74.5±20.9	70.7±21.0	0.587
Lactate (mmol/l)	5.3±3.4	5.9±4.1	0.580
Age (years)	70.0±13.6	71.0±14.5	0.812

Abbreviations: APACHE, Acute Physiology And Chronic Health Evaluation; CPFA, Coupled Plasma Filtration Adsorption; n(%), absolute frequency (relative frequency); SAPS, Simplified Acute Physiology Score; SOFA, Sequential Organ Failure Assessment; x±s, mean ± standard deviation.

Table 2: Clinical relevance of the intervention (intention-to-treat) in the patients with septic shock (adjusted by propensity scores as a population overlap weight).

Outcome	RR (95% CI)	RRR (95% CI)	ARR (95% CI)	NNT/NNH*	p-value
3-day mortality	1.67(0.51-5.46)	-0.67(-4.46 to 0.49)	-0.17(-0.54 to 0.20)	6 (H)	0.667
28-day mortality	1.28(0.57-2.87)	-0.28(-1.87 to 0.43)	-0.13(-0.53 to 0.28)	8 (H)	0.537
90-day mortality	0.92(0.48-1.76)	0.08(-0.76 to 0.52)	0.05(-0.35 to 0.45)	19 (T)	>0.999

Abbreviations: ARR, Absolute Risk Reduction; CI, confidence interval; H, Harm; NNH, Number Needed to Harm; NNH, Number Needed to Treat; RR, relative risk; RRR, Relative Risk Reduction; T, Treat.

\*, not possible to compute the confidence interval (division by zero).

Table 3: Clinical relevance of the intervention (real group) in the patients with septic shock (adjusted by propensity scores as a population overlap weight).

Outcome	RR (95% CI)	RRR (95% CI)	ARR (95% CI)	NNT	p-value
3-day mortality	0.84(0.26-2.73)	0.16(-1.73 to 0.74)	0.06(-0.32 to 0.44)	18	>0.999
28-day mortality	0.93(0.42-2.06)	0.07(-1.06 to 0.58)	0.04(-0.37 to 0.45)	26	>0.999
90-day mortality	0.72(0.35-1.48)	0.28(-0.48 to 0.65)	0.19(-0.21 to 0.59)	6	0.417

Abbreviations: ARR, Absolute Risk Reduction; CI, confidence interval; NNT, Number Needed to Treat; RR, relative risk; RRR, Relative Risk Reduction.

\*, not possible to compute the confidence interval (division by zero).

**Enrollment**

BMJ Open  
Assessed for eligibility (n=72)

Excluded (n=23)  
◆ Not meeting inclusion criteria (n=13)  
◆ Declined to participate (n=1)  
◆ Other reasons (n=9)

Randomized (n=49)

**Allocation**

Allocated to intervention (n=19)  
◆ Received allocated intervention (n=16)  
◆ Did not receive allocated intervention (premature death) (n=3)

Allocated to intervention (n=30)  
◆ Received allocated intervention (n=30)  
◆ Did not receive allocated intervention (n=0)

**Follow-Up**

Lost to follow-up (give reasons) (n=0)  
Discontinued intervention (give reasons) (n=0)

Lost to follow-up (give reasons) (n=0)  
Discontinued intervention (give reasons) (n=0)

**Analysis**

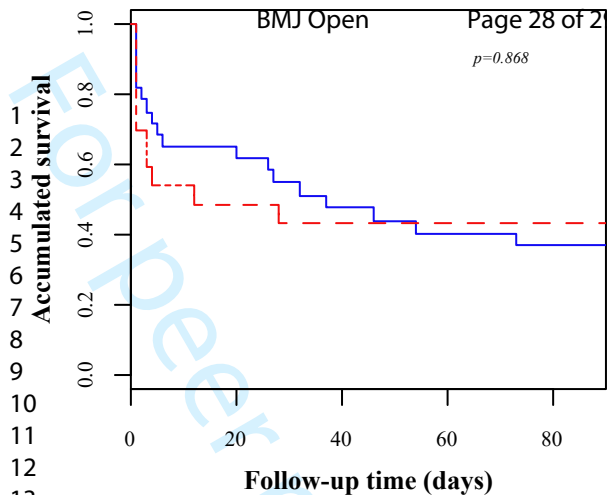
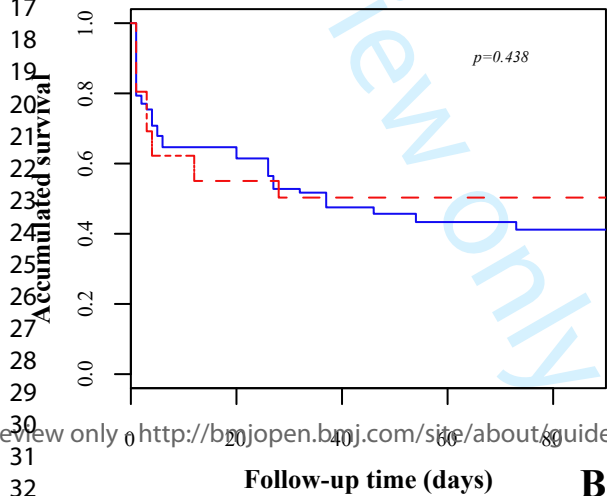
Analysed (n=19)  
◆ Excluded from analysis (n=0)

Analysed (n=30)  
◆ Excluded from analysis (n=0)

For peer review only - <http://bmjopen.bmj.com/site/about/guidelines.xhtml>

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36



$p=0.868$  $p=0.438$ 



# CONSORT 2010 checklist of information to include when reporting a randomised trial\*

Section/Topic	Item No	Checklist item	Reported on page No
<b>Title and abstract</b>			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	3
<b>Introduction</b>			
Background and objectives	2a	Scientific background and explanation of rationale	6-7
	2b	Specific objectives or hypotheses	7
<b>Methods</b>			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	7-8
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	7-10
Participants	4a	Eligibility criteria for participants	7-8
	4b	Settings and locations where the data were collected	7-8
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	8-9
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	9-10
	6b	Any changes to trial outcomes after the trial commenced, with reasons	9-10
Sample size	7a	How sample size was determined	9-10
	7b	When applicable, explanation of any interim analyses and stopping guidelines	
<b>Randomisation:</b>			
Sequence generation	8a	Method used to generate the random allocation sequence	Protocol
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	Protocol
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	Protocol
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	Protocol
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	Protocol

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	N/A
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	10-11
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	10-11
<b>Results</b>			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	11
	13b	For each group, losses and exclusions after randomisation, together with reasons	11
Recruitment	14a	Dates defining the periods of recruitment and follow-up	7-8
	14b	Why the trial ended or was stopped	6-7
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	21
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	11
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	12
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	12
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	12
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	12
<b>Discussion</b>			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	13
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	13-16
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	13-16
<b>Other information</b>			
Registration	23	Registration number and name of trial registry	4
Protocol	24	Where the full trial protocol can be accessed, if available	7
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	17

\*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see [www.consort-statement.org](http://www.consort-statement.org).

## Correction: *The premature closure of ROMPA clinical trial: mortality reduction in septic shock by plasma adsorption*

Giménez-Esparza C, Portillo-Requena C, Colomina-Climent F, *et al.* The premature closure of ROMPA clinical trial: mortality reduction in septic shock by plasma adsorption. *BMJ Open* 2019;9:e030139. doi: 10.1136/bmjopen-2019-030139.

This article was previously published with an error.

The following statement in the discussion section is incorrect: 'In addition, as in our study, the COMPACT 2 group used a randomisation system based on prognostic scores,<sup>6</sup> which means that the groups will not be similar until the end of recruitment (which is reason to introduce the propensity score in our results).' The COMPACT 2 group used a blocked randomization schedule (randomly permuting blocks of four and six), with stratification according to site and the presence of septic shock at admission.

**Open access** This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

© Author(s) (or their employer(s)) 2020. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

*BMJ Open* 2020;10:e030139corr1. doi:10.1136/bmjopen-2019-030139corr1

