Emergency Department Resuscitative Endovascular Balloon Occlusion of the Aorta (REBOA) in Trauma Patients with Exsanguinating Hemorrhage

Subtitle: A Randomized Clinical Trial

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KEY POINTS

QUESTION

Does the addition of Resuscitative Endovascular Balloon Occlusion of the Aorta (REBOA) to standard care reduce mortality in trauma patients with exsanguinating hemorrhage?

FINDINGS

In this Bayesian randomized clinical trial that included 90 patients, mortality at 90 days was 54% in the standard care plus REBOA group, and 42% in the standard care group (odds ratio 1.58; 95% credible interval 0.72 to 3.52; posterior probability of increased odds of death with REBOA 86.9%).

MEANING

In trauma patients with exsanguinating hemorrhage, a strategy that includes REBOA, when used in the Emergency Department, does not reduce, and may increase mortality, compared with standard care.

ABSTRACT

IMPORTANCE

Bleeding is the most common cause of preventable death after trauma.

OBJECTIVE

To determine the effectiveness of Resuscitative Endovascular Balloon Occlusion of the Aorta (REBOA), placed in the emergency department, in addition to standard care, compared with standard care alone, on mortality in trauma patients with exsanguinating hemorrhage.

DESIGN

Pragmatic, Bayesian, randomized controlled trial.

SETTING

16 major trauma centers (MTC) in the United Kingdom.

PARTICIPANTS

Trauma patients with exsanguinating hemorrhage. Patients were enrolled between October 2017 and March 2022 and followed up for 90 days.

INTERVENTION

Patients were randomly assigned (1:1 allocation) to a strategy that included REBOA, plus standard care (n=46); or standard care alone (n=44).

MAIN OUTCOME AND MEASURES

The primary outcome was all-cause mortality at 90 days, assessed in the intention-to-treat population. Ten secondary outcomes included mortality at 6 months, while in hospital, and within 24, 6, and 3 hours; the need for definitive hemorrhage control procedures; time to commencement of definitive hemorrhage control procedures; complications; length of stay; blood product use; and cause of death.

RESULTS

Among 90 randomized patients (median age 41 years [Q1-Q3, 31-59], 62 [69%] male, median Injury Severity Score 41 [Q1-Q3, 29-50]), 89 were analyzed. One patient declined to provide consent for continued participation and data collection, 4 days after enrollment. At 90 days, 25 patients (54%) in the standard care plus REBOA group, and 18 patients (42%) in the standard care group had died. The odds ratio (OR) of mortality was 1.58 (95% credible interval 0.72 to 3.52) for patients allocated to standard care plus REBOA, and the posterior probability of an odds ratio of >1 (indicating increased odds of death with REBOA) was 86.9%. Among 10 secondary outcomes, the ORs of mortality, and the posterior probabilities of an OR >1, for 6-month, in-hospital, 24-, 6-, and 3-hour mortality, were all increased in the SC+REBOA group, and increased with earlier mortality endpoints. There were more deaths due to bleeding in the standard care plus REBOA group (8 of 25 patients, 32%) than in standard care alone (3 of 18 patients, 17%), and most occurred within 24 hrs.

INTERPRETATION

In trauma patients with exsanguinating hemorrhage, a strategy that includes REBOA, when used in the Emergency Department, does not reduce, and may increase mortality, compared with standard MTC care.

TRIAL REGISTRATION

The trial is registered with ISRCTN, 16184981.

INTRODUCTION

Hemorrhage is the most common cause of preventable death after trauma.[1] The natural history of uncontrolled bleeding is of falling cardiac output and hypotension and ultimately failure of compensatory mechanisms with consequent cerebral and myocardial hypoperfusion leading to death.[2] In contrast, when hemorrhage is controlled expeditiously, patients often recover.[3] Bleeding originating from within the torso is particularly challenging, because it cannot be controlled without surgery,[4–6] and many patients die before they can be taken to an operating room. Temporary aortic occlusion, to limit hemorrhage and maintain cerebral and myocardial perfusion, until definitive control of hemorrhage can be obtained, is therefore conceptually attractive.[7–9]

Resuscitative Endovascular Balloon Occlusion of the Aorta (REBOA) is a novel technique whereby a percutaneously inserted balloon is inflated in the aorta. Large animal studies have shown REBOA to be highly effective,[10–13] but the current evidence for REBOA in injured humans is limited and conflicting. There are a number of case series;[14–16] cohort studies (retrospective and prospective),[17–20] with divergent results; and several scoping reviews, systematic reviews and meta-analyses.[21–25] There are also military clinical practice guidelines[26] that recommend REBOA for profound shock (defined as a systolic blood pressure <90 mmHg) and some cases of traumatic cardiac arrest (blunt and penetrating); and a position statement from the American College of Emergency Physicians and the American College of Surgeons[27] that recommends REBOA for traumatic life-threatening hemorrhage below the diaphragm in patients in hemorrhagic shock who are unresponsive or transiently responsive to resuscitation, and for patients arriving in arrest from trauma due to presumed life-threatening hemorrhage below the diaphragm. However, there are no randomized clinical trials.

The aim of the UK Resuscitative Endovascular Balloon Occlusion of the Aorta (UK-REBOA) trial was to examine the effectiveness of REBOA, in addition to standard care, as compared with standard care alone, for the management of uncontrolled torso hemorrhage, in specialist Major Trauma Centers (MTCs) in the United Kingdom (UK).

METHODS

STUDY DESIGN AND ELIGIBILITY CRITERIA

The UK-REBOA trial was a multicenter, open, Bayesian, group-sequential, registry-enabled, randomized controlled trial, conducted in 16 MTCs in the UK (Supplement 1, eTable 1). Participants were enrolled under the provisions for adults not able to consent for themselves. The trial protocol was published in advance[28] (Supplement 2) and the statistical analysis plan signed off before data analysis commenced (Supplement 3). The trial was approved by the Greater Manchester Ethics Committee (REC reference: 17/NW/0352).

Trauma patients aged, or believed to be aged, 16 years or older, presenting to specialist MTCs in the UK, were eligible for inclusion. Patients had confirmed or suspected life-threatening torso hemorrhage, which was deemed to be amenable to adjunctive treatment with REBOA. Patients were excluded if they were known or thought to be pregnant or had injuries which were clearly unsurvivable (eTable 2). Consent for continued participation was sought once patients were no longer in a life-threatening condition.

RANDOMIZATION

Participants were randomly assigned in a 1:1 ratio to either a strategy of standard care plus REBOA (SC+REBOA), or standard care (SC) alone. Randomization was performed using a

web-based system, which clinicians could access using cellphones; in permuted blocks of random size (two or four). It was not possible for physicians at the trial sites to be blinded to treatment assignments.

STUDY INTERVENTIONS

The intervention was the technique of endovascular aortic occlusion, for the purpose of resuscitation, as part of an overall resuscitation strategy. The trial sought to evaluate the technique of REBOA rather than a specific brand of device and therefore did not prescribe or mandate a particular product. Clinicians using REBOA as part of the trial had to have completed the trial's training package (supplement 1), and/or subsequent in-house training conducted as part of the establishment of each center's REBOA service. The level of occlusion (zone I, descending thoracic aorta; or zone III, above aortic bifurcation) was left to the attending physician's judgement and their assessment of the likely source of hemorrhage. Patients allocated to the SC group received "standard care", as expected in a specialist MTC. Such treatment typically included intubation, balanced blood product transfusion, interventions such as tourniquet application, and early operative or endovascular hemorrhage control. Treatment could also include open aortic occlusion of the thoracic or abdominal aorta.

PRIMARY AND SECONDARY OUTCOMES

The primary outcome was all-cause mortality at 90 days. Prespecified secondary outcomes included mortality at 6 months, while in hospital, and within 24, 6, and 3 hours; the need for definitive hemorrhage control procedures (defined as an operation that involved resection of a bleeding organ, ligation of a named vessel, interposition grafting, shunt insertion, packing of a cavity; or angiographic embolization); time to commencement of definitive hemorrhage control

procedure; complications; length of stay (hospital- and ICU-free days); blood product use; and causes of death. Baseline data were obtained through linkage to the national Trauma Audit and Research Network (TARN) registry. Primary outcome and most secondary outcome data were collected directly, and from NHS Digital, the National Health Service's data repository (eTable 3).

STATISTICAL ANALYSIS

The output from a Bayesian trial gives a probability for a defined range of treatment effects, given the observed data. We designed the trial around the available number of patients, based on a retrospective study of national registry data.[29] We estimated that 10 high-volume MTCs would admit approximately 80 patients who might benefit from REBOA, per year, approximately half of whom would be enrolled into the trial, over a period of 3 years, giving a target recruitment of 120 participants.

The trial was designed to evaluate the clinical effectiveness of REBOA in the "real-world" clinical setting by answering the question of whether a treatment strategy that includes REBOA reduces the mortality of exsanguinating trauma patients, irrespective of intercurrent events.[30] The main analysis was thus based on the Intention-to-Treat principle.

Our initial design parameters contained an error in the formulation of the variance in calculations, resulting in an overestimation of the operating characteristics. Following consultation with the funder, and external reviewers, we relaxed the success threshold, and added informative priors, resulting in acceptable probabilities of declaring success if REBOA had indeed been beneficial. Given the direction and size of the observed effect size, these changes do not influence interpretation of the findings..

The primary outcome was analyzed using Bayesian logistic regression with a minimally informative prior on the natural log odds ratio (OR) δ of $N(0, 1.28^2)$, which rules out extreme effects, and a non-informative prior on the intercept (i.e. the log odds of survival in standard care) $N(0, 10^2)$. Secondary outcomes were analyzed in the same way, using generalized linear models suitable for the outcome distribution.

We conducted an adjusted analysis – the covariates for which had been selected a priori, without knowledge of the results – to account for potential imbalances between the two groups. Treatment effects were summarized as ORs with 95% credible intervals (CrIs), and posterior probability estimates of the OR being less than 1 (SC+REBOA beneficial) or greater than 1 (SC+REBOA harmful). We also conducted two additional principal stratum analyses, to account for intercurrent events, and an analysis to account for possible learning curve effects. Data missing at baseline are reported as such. All analyses were carried out using Stata 17.[31]

We collected data on complications and Serious Adverse Device Events (SADE). An independent data monitoring committee monitored emerging data (which included two pre-planned interim analyses at 40 and 80 patients). An independent trial steering committee oversaw trial conduct and delivery. The authors vouch for the accuracy and completeness of the data and analyses and for the fidelity of the trial to the protocol.

RESULTS

STUDY TERMINATION

Between October 30, 2017 and March 16, 2022, a total of 90 patients were enrolled. We had originally planned to enroll 120 patients, but the trial was stopped after the second interim analysis, which included 80 patients, because the pre-specified stopping rule for harm was met

(90.1% posterior probability of odds ratio of mortality at 90 days >1; stopping criterion was >90%). Given the time required to collect primary outcome data, a further 10 patients had been enrolled by the time of the interim analysis giving a total of 90 patients. Of these, 46 were randomly assigned to a strategy of SC+REBOA, and 44 to SC (Figure 1). One patient, randomized to SC, declined to provide consent for continued participation and data collection, 4 days after enrollment, and was therefore excluded from analyses from that point forwards.

BASELINE CHARACTERISTICS

Most participants (69%) were male, and most (97%) had suffered blunt trauma, with a median Injury Severity Score (ISS) of 41 (interquartile range (Q1-Q3), 29 to 50; range 0 to 75, a score of >15 indicating severe injury) (table 1). Participants were hypotensive and tachycardic in the prehospital setting (23% required cardiopulmonary resuscitation) and on arrival in Emergency Departments (ED). Overall, the groups were well matched, although those randomized to SC+REBOA were more hypotensive on arrival at ED (median systolic blood pressure 84 mmHg; Q1-Q3, 58-115) than those randomized to SC (median 99 mmHg; Q1-Q3, 72-115), and had a higher median Abbreviated Injury Scales for the head region (eFigures 1 and 2). The distribution of the Abbreviated Injury Scales in other body regions was similar across both groups (eFigures 3-6).

TREATMENT PATHWAYS

Participants randomized to SC+REBOA had a number of REBOA pathways, due to intercurrent events (Figure 3). Of the 46 randomized to this arm, 19 (41%) had a device inserted and inflated. A further 17 (37%) responded to other resuscitative measures while REBOA insertion was being prepared/performed, and progression to full aortic occlusion was no longer deemed necessary.

Two participants (4%) deteriorated before arterial access could be established and in eight (17%), arterial access was attempted, but could not be established. In 10 patients (53%) the balloon was inflated in zone I (descending thoracic aorta), and in 9 participants (47%) in zone III (above aortic bifurcation). The median time from ED arrival to balloon inflation was 32 minutes (Q1-Q3 20-47), and the median duration of inflation was 29 minutes (Q1-Q3 19-64). Partial REBOA (titrated deflation of the balloon to allow some distal perfusion) was used in 8 participants (42%).

PRIMARY OUTCOME

Among 89 patients who provided consent for data analysis, there were 25 deaths (54%) in the SC+REBOA group, and 18 deaths (42%) in the SC group at 90 days after randomization (Table 2). The prespecified primary unadjusted analysis using the minimally informative prior showed that the OR of mortality at 90 days was 1.58 (95% CrI 0.72, 3.52) for patients allocated to SC+REBOA, and the posterior probability of an odds ratio of >1 (indicating increased odds of death with SC+REBOA) was 86.9% (Figure 2, Panel A). The probability that SC+REBOA reduces death by the pre-specified OR of 0.77 (or lower, corresponding to a greater reduction in mortality) was 3.7%. When multivariable regression was used to adjust for differences in baseline characteristics, the odds of 90-day mortality in the SC+REBOA group also remained higher than in the SC group (OR 1.80), but with a wider credible interval (95% CrI 0.59-5.59). The posterior probability of an odds ratio >1 was 84.9%. *Post-hoc* analyses of the impact of individual covariates had only minimal impact on the results. (eTable 4). The results of the principal stratum analyses, to account for intercurrent events, and the learning curve effects analysis did not change the overall findings (Supplement 1).

SECONDARY OUTCOMES

The ORs of mortality, and the posterior probabilities of an OR >1, for 6-month, in-hospital, 24-, 6-, and 3-hour mortality were all increased in the SC+REBOA group and increased with earlier mortality endpoints (Table 2). The survival curves show an early separation of the two groups, but also more deaths in the SC+REBOA group, to day 10 (Figure 2, Panel B). The causes of death, as determined by site investigators, are shown in eTable 5, for each time point. There were more deaths due to bleeding in the SC+REBOA group (8 of 25 patients, 32%) than in the SC group (3 of 18 patients, 17%), and most occurred within 24 hrs.

Fourteen patients in the SC+REBOA group (30%) had a definitive hemorrhage control procedure, compared to 19 (43%) in the SC group. The median time from randomization to definitive hemorrhage control was 19 minutes longer in the SC+REBOA group than in the SC group. Blood transfusion requirements were similar in the two groups (table 2). Patients in the SC group had more ICU- and hospital-free days (Table 2). There were no differences in the number of complications (eTable 6). There were no Serious Adverse Device Effects (SADEs).

DISCUSSION

This is the first randomized trial to examine the potential clinical effectiveness of REBOA for the management of exsanguinating hemorrhage, and there are no other randomized trials of REBOA in trauma patients registered on clinicaltrials.gov (https://clinicaltrials.gov).

Among the 90 patients who were enrolled in our trial, the group that received standard care plus REBOA was observed to have a high probability (86.9%) of higher mortality at 90 days (the primary outcome), compared with the standard care group. It is also noteworthy that the odds and posterior probabilities of increased mortality increased with earlier timepoints, which are

more specific for deaths due to hemorrhage. An adjusted analysis, to account for baseline imbalances, did not alter the findings. The probability that standard care plus REBOA reduces mortality by a worthwhile margin at 90 days was 3.7%, and less so at timepoints within 24 hours.

Our findings are consistent with a number of previously published observational studies. A retrospective, propensity-score matched study from the United States, using data from a national registry, reported a possible detrimental effect of REBOA.[33] Similarly, a retrospective, propensity-score matched study from Japan, also based on national registry data, showed that treatment with REBOA was associated with higher mortality.[20] The findings of these studies had been attributed to unmeasured confounders, but are worthy of re-evaluation, in light of our study. However, there are also a number of other observational studies that have reported positive benefits with REBOA.[22,24]

The survival curves demonstrate the probable harmful early effects of REBOA. The early – within the first few hours – drop in survival likely represents delay in definitively controlling, or failure to definitively control, hemorrhage, as a result of REBOA insertion or attempts at REBOA insertion in the Emergency Department. There were fewer patients who underwent a definitive hemorrhage control procedure in the SC+REBOA group, likely due to the competing risk of early death; and for those who did undergo such a procedure, it took, on average, an additional 19 minutes to commence these procedures. Whilst a small delay to definitive hemorrhage control is to be expected with REBOA, the purported benefit in longer survival was not observed. This can be seen in the increased proportion of early deaths due to uncontrolled hemorrhage. Death due to hemorrhage was more common in the SC+REBOA group, and all of these deaths occurred within 24 hours, and most of them within 3 hours, of randomization. The

excess of early deaths also explains why patients who were allocated to the SC+REBOA strategy had fewer hospital-free and ICU-free days than those who received standard care.

Patients in our trial had higher mortality than those in other studies of hemorrhage control interventions in trauma patients, such as the Pragmatic, Randomized Optimal Platelet and Plasma Ratios (PROPPR) trial. This is, most likely, a result of the inclusion criteria chosen, which selected a more seriously injured group of patients. The median ISS in the PROPPR trial was only 26, compared to a median ISS of 41 in the UK-REBOA trial.

There were a number of pathways experienced by those who were allocated to the REBOA strategy, due to intercurrent events. These findings reflect the challenges in obtaining arterial access in severely shocked patients; and in distinguishing between patients who are experiencing continuing hemorrhage from those in whom bleeding has stopped. These experiences reflect "real life" and highlight the complexity of trauma care, and the challenges inherent in evaluating it.

This trial has a number of strengths. It included a comprehensive training program, which recognized the challenges of evaluating a technology such as REBOA. The trial was pragmatic in design, with simple inclusion criteria that were based on the clinical judgement of experienced clinicians, allowing them to quickly evaluate suitability for the trial, in a pressured clinical setting, and used routinely collected data, minimizing burden on staff.

The trial's limitations include its size, reflecting the relative infrequency and etiology of exsanguinating traumatic hemorrhage in the United Kingdom, where blunt trauma predominates, and most penetrating trauma is the result of stabbings, rather than gunshot wounds. The results may therefore not be translatable to other settings. The reorganization of in-hospital trauma care in England has markedly improved mortality from trauma over the past decade.[32] However,

institutional case volume (and operative case volume for hemorrhage control) is lower than in other countries, reflecting high road safety standards and low levels of inter-personal violence. The responsibility for the control of torso hemorrhage rests with surgeons who do not only provide trauma care, and who are not resident in the hospital. The initial care of trauma patients is the responsibility of senior emergency medicine doctors, but surgeons are called early (even before the arrival of a patient). Nevertheless, these organizational differences may have impacted on the speed with which trauma patients were treated and operated on, if needed.

The relatively low proportion (37%) of patients who underwent a definitive hemorrhage control procedure may be a reflection of the rigorous classification applied. Operations were only counted as definitive hemorrhage control procedures when a bleeding organ had to be resected, a named vessel was ligated, repaired, or shunted, or a cavity was packed. A limitation of this approach is that a bowel resection for mesenteric bleeding, for example, would not have been coded as a definitive hemorrhage control procedure. There were some baseline imbalances between the groups, but adjusted analyses showed these had little effect on the results, and the proportion of deaths attributed to traumatic brain injury, in particular, were similar in the two groups.

CONCLUSIONS

In conclusion, the UK-REBOA trial shows that, in trauma patients with exsanguinating hemorrhage, a strategy that includes REBOA, when used in the Emergency Department, does not reduce, and may increase mortality, compared with standard MTC care.

TABLES

Table 1. Patient characteristics

Variable	SC+REBOA (N=46)	SC (N=44)
Median age (years) [Q1, Q3]	46 [33, 62]	39 [30, 56]
Sex – No. (%)		
Female	18 (39)	10 (23)
Male	28 (61)	34 (77)
Mechanism of injury – No. (%)		
Blunt	44 (96)	43 (98)
Penetrating	2 (4)	1 (2)
Prehospital vital signs (first recorded)		
Prehospital systolic blood pressure		
Median (mmHg) [Q1, Q3]; N	85 [66, 120]; N=34	97 [71, 128]; N=37
<= 90mmHg – n/N (%)	18/34 (53)	17/37 (46)
<= 70mmHg – n/N (%)	11/34 (32)	9/37 (24)
Median prehospital heart rate (beats per minute) [Q1, Q3]; N	113 [94, 133]; N=42	109 [76, 133]; N=40
Median prehospital oxygen saturation (%) [Q1, Q3]; N	88 [80, 95]; N=32	92 [81, 98]; N=43
Median prehospital Glasgow Coma Scale[a] [Q1, Q3]; N	10 [3, 14]; N=42	10 [3, 14]; N=42
Prehospital CPR performed – n/N (%);	10/43 (22)	11 (25)
Method of transport, n/N (%)		
Ambulance	22/45 (49)	19/43 (43)
Helicopter	17/45 (38)	21/43 (49)
Ambulance and helicopter	6/45 (13)	3/43 (7)
Median time from injury to ED arrival (minutes) [Q1, Q3]; N	90 [70, 125]; N=39	97 [78, 119]; N=41
Median time from ED arrival to randomization (minutes) [Q1, Q3]; N [b]	13 [4, 21]; N=39	13 [4, 19]; N=41
ED arrival characteristics		
ED Systolic blood pressure (mmHg)		
Median (mmHg) [Q1, Q3]; N	84 [58, 115]; N=44	99 [72, 115]; N=42
<= 90mmHg – n/N (%)	26/44 (59)	19/42 (45)
<= 70mmHg – n/N (%)	18/44 (41)	9/42 (21)
Median ED heart rate (beats per minute) [Q1, Q3]; N	105 [88, 123]; N=45	120 [87, 135]; N=43

Median ED oxygen saturation (%) [Q1, Q3]; N	99 [90, 100]; N=39	99 [95, 100]; N=40
Median ED Glasgow Coma Scale [Q1, Q3]; N	3 [3, 11]; N=39	3 [3, 15]; N=39
CPR performed on arrival in ED – n/N (%)	4/40 (9)	4/43 (9)
Injury pattern and severity		
Median Injury Severity Score [Q1, Q3]; n*	41 [29, 50]	41 [29, 50]
Injury Severity Score (ISS) band[c], No. (%)		
Very severe (ISS >25)	38 (83)	38 (86)
Severe (16-25)	7 (15)	4 (9)
Moderate (ISS 9-15)	1 (2)	1 (2)
Mild (ISS 1-8)	0 (0)	1 (2)
Injury pattern – Abbreviated Injury Scales[d]		
Head, median [Q1, Q3]	3 [0, 4]	0 [0, 5]
Thorax, median [Q1, Q3]	4 [3, 4]	4 [1, 4]
Abdomen, median [Q1, Q3]	2 [0, 3]	2 [0, 4]
Pelvis, median [Q1, Q3]	2 [0, 5]	2 [0, 5]
Limbs, median [Q1, Q3]	2 [2, 3]	3 [2, 3]

Abbreviations: SC, Standard Care; REBOA, Resuscitative Endovascular Balloon Occlusion of the Aorta; ISS, Injury Severity Score; Q1 25th percentile; Q3 75th percentile

[a] Glasgow Coma Scale (GCS) ranges from 3-15. A GCS of 15 indicates a normal level of consciousness. A GCS of 3 indicates a patient who does not respond to any stimuli, including pain.

[b] Three participants in the SC+REBOA arm and five participants in the SC arm were randomized before arrival, so were given a time of 0 minutes

[c] The Injury Severity Score (ISS) is a global anatomical scoring system that provides a global measure of trauma severity. It is calculated by summing the squares of the three worst-injured body regions (indicated by the highest Abbreviated Injury Scales). ISS ranges from 0 (no injury) to 75 (maximal injury). An Abbreviated Injury Scale of 6 in any region automatically results in an ISS of 75.

[d] The Abbreviated Injury Scale (AIS) is an anatomically-based, consensus-derived severity scoring system that classifies an individual injury, by body region, according to its relative severity, and a six-point scale. (0, no injury; 1, minor injury; 6 maximal injury)

Table 2: Outcomes

	SC+REBOA N=46	SC N=44	Absolute Difference (%) 95% CrI	Effect estimate[b]	95% Credible Interval (CrI)	Posterior Probability (%) of OR>1
Primary outcome						
Death within 90 days, n/N (%)	25/46 (54)	18/43[a] (42)	11.3 (-8.1, 30.1)	1.58	(0.72, 3.52)	86.9
Secondary outcomes						
Mortality at different time points, n/N (%)						
Death within 6 months	25/46 (54)	18/43[a] (42)	11.3 (-8.1, 30.1)	1.58	(0.72, 3.52)	86.9
Death while in hospital	25/46 (54)	1843[a] (42)	11.3 (-8.1, 30.1)	1.58	(0.72, 3.52)	86.9
Death within 24 hours	17/46 (37)	10/44 (23)	12.5 (-5.0, 29.6)	1.85	(0.79, 4.46)	91.8
Death within 6 hours	13/46 (28)	4/44 (9)	15.8 (1.8, 30.4)	3.14	(1.13, 9.76)	98.6
Death within 3 hours	11/46 (24)	2 /44 (5)	15.1 (3.3, 28.4)	4.25	(1.33, 15.99)	99.3
Definitive Hemorrhage Control Procedures (DHCP)						
Patients who underwent a DHCP, No. (%)	14 (30)	19 (43)	-11.5 (-29.6, 7.1)	0.60	(0.26, 1.37)	
Mins from randomization to DHCP, median [Q1, Q3]; N	83 [56, 156]; N=12	64 [34, 83]				
Type of DHCP, No. (%)[c]						
Hemorrhage control laparotomy	7 (50)	12 (63)				
Extremity vascular ligation, shunting, or repair	2 (14)	4 (21)				
Pelvic packing	4 (29)	1 (5)				
Angioembolization	2 (14)	2 (11)				
Hemorrhage control thoracotomy	1 (7)	0 (0)				
Length of Stay						
ICU-free days[d] (at 90 days), median [Q1, Q3]						
Mean (SD); n/N	35 (40)	40 (37)		-4.79	(-20.75, 11.31)	
Median [Q1, Q3] ; n/N	0 [0, 80]	45 [0, 78]				
Hospital-free days[d] (at 90 days), median [Q1, Q3]						
Mean (SD); n/N	22 (30)	41 (39)		-18.58	(-32.86, -3.93)	
Median [Q1, Q3]; n/N	0 [0, 49]	41 [0,82]				
Transfusion requirements						
Red blood cells, units, median [Q1, Q3]						

Mean (SD); n	10 (9)	11 (9)	0.92	(0.66, 1.29)
Median [Q1, Q3]	7 [4, 12]	9 [4, 17]		
Plasma, units, median [Q1, Q3]				
Mean (SD); n	8 (8)	11 (10)	0.73	(0.49, 1.08)
Median [Q1, Q3]	6 [3, 10]	7 [4, 18]		
Platelets, pools, median [Q1, Q3]				
Mean (SD); n	1 (3)	2 (2)	0.87	(0.50, 1.52)
Median [Q1, Q3]	1 [0, 2]	1 [0, 2]		
Cryoprecipitate, units, median [Q1, Q3]				
Mean (SD); n	2 (3)	2 (3)	0.79	(0.41, 1.53)
Median [Q1, Q3]	0 [0, 2]	2 [0, 3]		
Tranexamic acid, mg, median [Q1, Q3]				
Mean (SD); n	1413 (580)	1568 (695)	0.90	(0.70, 1.16)
Median [Q1, Q3]	1000 [1000, 2000]	2000 [1000, 2000]		

Abbreviations: DHCP, Definitive Hemorrhage Control Procedure; Q1 25th percentile; Q3 75th percentile

[a] N=43 in SC as one participant withdrew on day 4

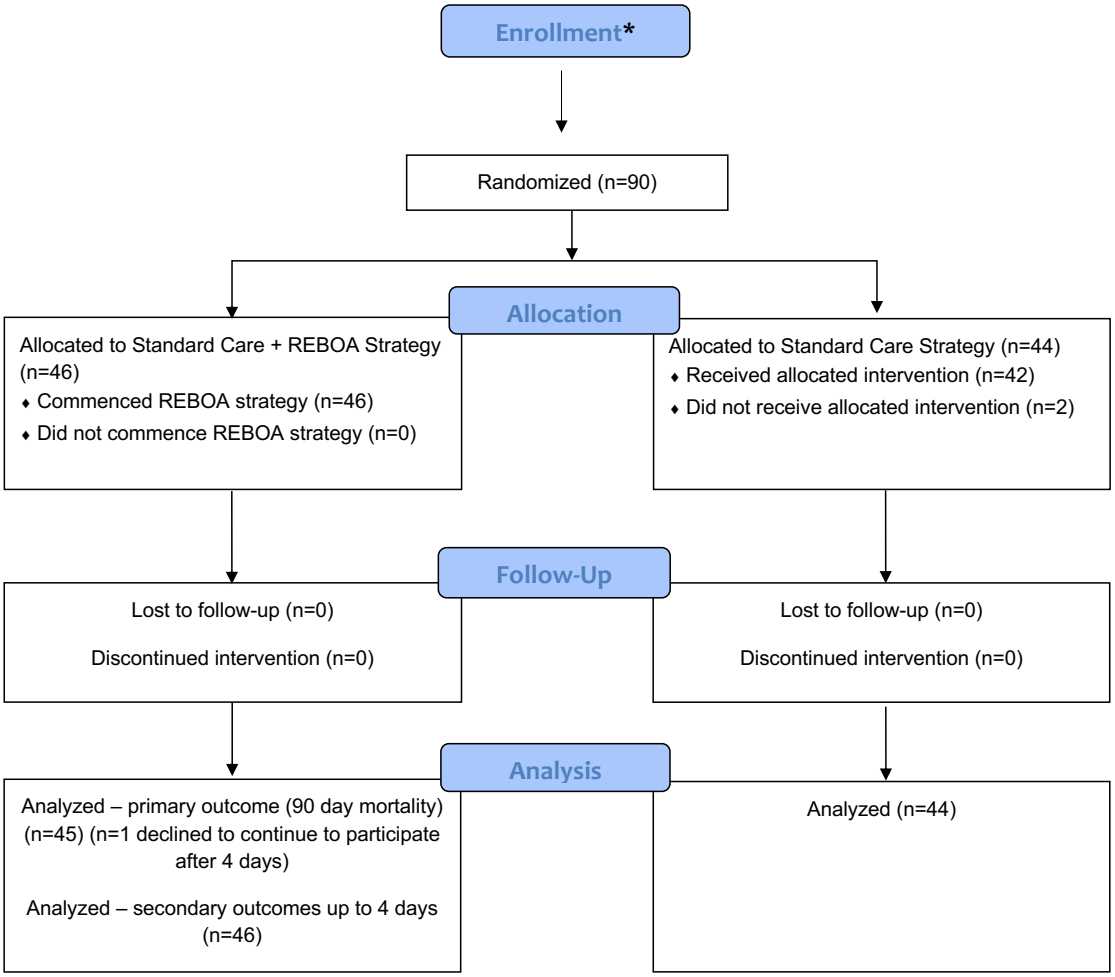
[b] Odds ratio for mortality and hemorrhage control, mean difference for minutes from randomization to hemorrhage control procedure, incident rate ratios for transfusion requirements and mean difference for time from randomisation to hemorrhage control procedure and length of stay.

[c] Some patients underwent more than one DHCP

[d] Zero free days were assigned to participants that died within 90-day follow-up

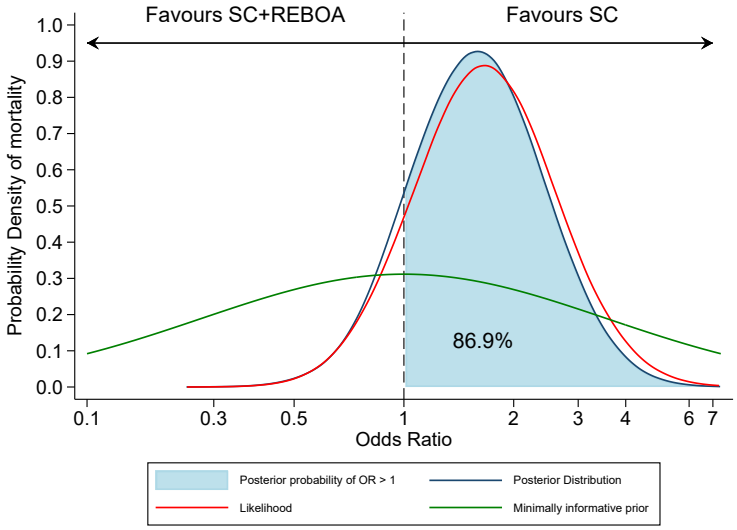
FIGURE LEGENDS

Figure 1. Recruitment, randomization and patient flow in the UK-REBOA trial.



*All trauma patients presenting to participating Emergency Departments were assessed for eligibility. Only those deemed eligible for REBOA were included.

Figure 2. Panel A: Odds Ratio and posterior probability of mortality for death within 90 days (primary outcome) Panel B: Kaplan-Meier survival estimates



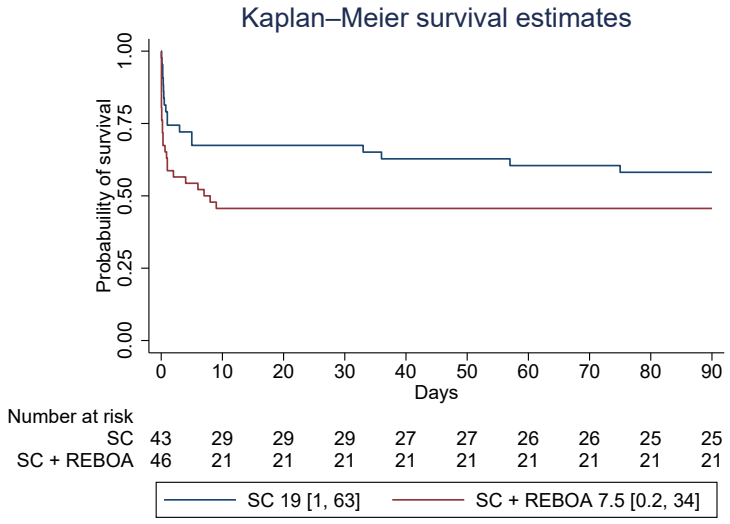
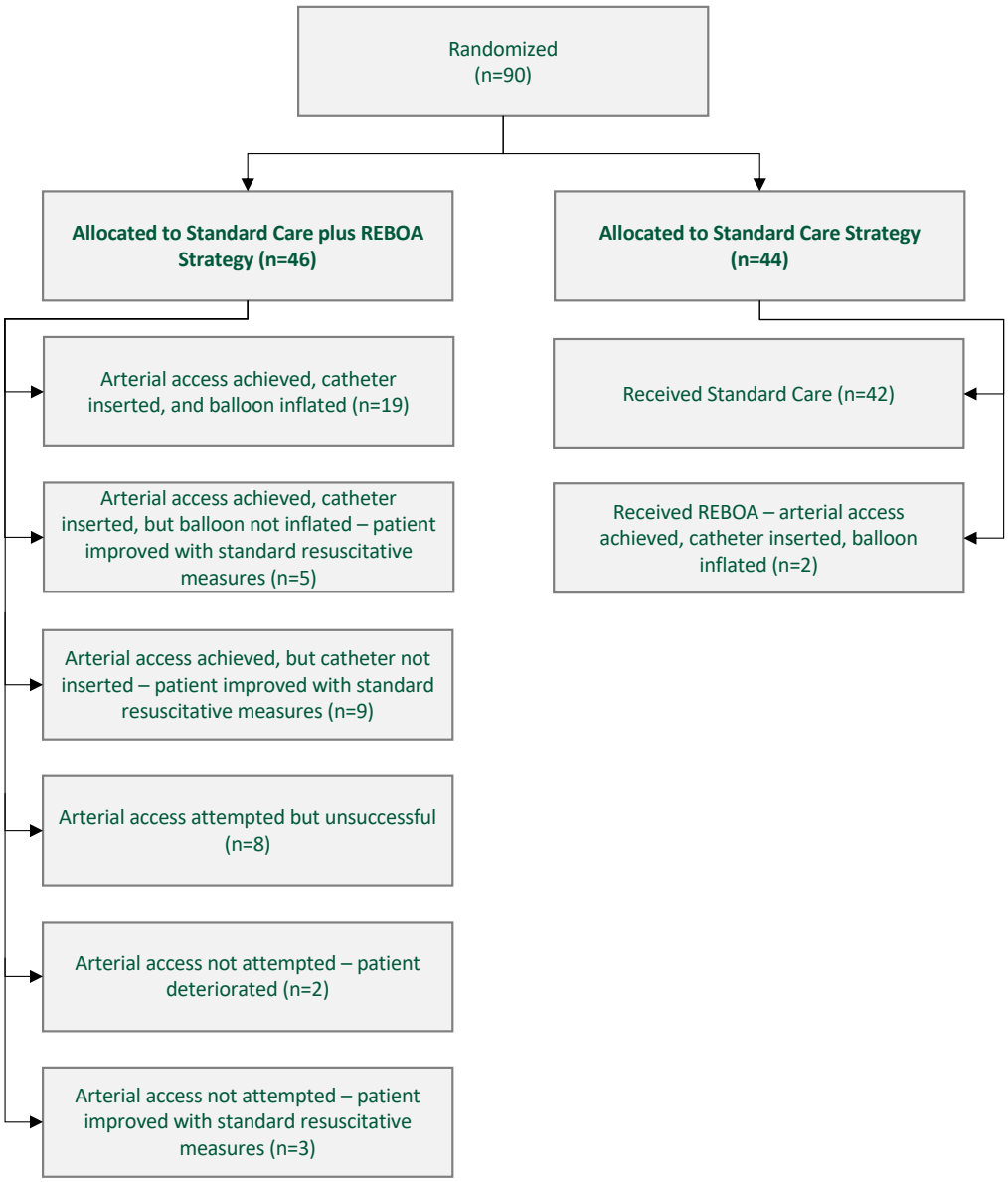


Figure 3. Treatment pathways experienced by patients in the UK-REBOA trial



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CONFLICTS OF INTEREST DISCLOSURE

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SUPPLEMENTARY TABLES

eTable1: Participating major trauma centers and enrollment by site

Site	SC+REBOA	SC	Total
	n (%)	n (%)	n (%)
The Royal London Hospital	7 (15)	7 (16)	14 (16)
St Mary's Hospital, London	1 (2)	1 (2)	2 (2)
Leeds General Infirmary, Leeds	9 (20)	10 (23)	19 (21)
Queen's Medical Centre, Nottingham	3 (7)	4 (9)	7 (8)
Royal Victoria Infirmary, Newcastle	2 (4)	2 (5)	4 (4)
St George's University Hospital	3 (7)	3 (7)	6 (7)
Queen Elizabeth Hospital, Birmingham	5 (11)	6 (14)	11 (12)
University Hospital, Coventry	4 (9)	3 (7)	7 (8)
Aintree University Hospital	2 (4)	1 (2)	3 (3)
Southmead Hospital Bristol	4 (9)	3 (7)	7 (8)
John Radcliffe Hospital, Oxford	4 (9)	3 (7)	7 (8)
Sheffield Teaching Hospital	2 (4)	1 (2)	3 (3)
University Hospitals of North Midlands, Stoke	0 (0)	0 (0)	0 (0)
Hull University Teaching Hospitals, Hull	0 (0)	0 (0)	0 (0)
King’s College Hospital, London	0 (0)	0 (0)	0 (0)
James Cook University Hospital, Middlesbrough	0 (0)	0 (0)	0 (0)

eTable2: Inclusion and exclusion criteria in list form

Inclusion criteria:

1. Adult trauma patients (aged, or believed to be aged, 16 years or older)
2. With confirmed or suspected life-threatening torso hemorrhage
3. Which is thought to be amenable to adjunctive treatment with REBOA (zone I [thoracic aorta] or zone III [aortic bifurcation])

Exclusion criteria:

1. Women known or thought to be pregnant at presentation
2. Children (aged, or believed to be aged 15 or younger)
3. Patients with injuries which are deemed unsurvivable on clinical grounds

eTable3: Definitions of outcomes and sources of data

Primary outcome: 90-day mortality

Definition: Death within 90 days of enrollment/randomization

Source: Case Report Form

Secondary outcome: 3-hour mortality

Definition: Death within 3 hours of enrollment/randomization

Source: Case Report Form

This outcome was added to the protocol (before the recruitment was complete and before the statistical analysis plan finalized) following the publication of the consensus statement on outcomes for hemorrhage control trials in trauma patients.[1]

Secondary outcome: 6-hour mortality

Definition: Death within 6 hours of enrollment/randomization

Source: Case Report Form

Secondary outcome: 24-hour mortality

Definition: Death within 24 hours of enrollment/randomization

Source: Case Report Form

Secondary outcome: 30-day mortality

Definition: Death within 30 days of enrollment/randomization

Source: Case Report Form

Secondary outcome: In-hospital mortality

Definition: Death while in hospital

Source: Case Report Form

Secondary outcome: 6-month mortality

Definition: Death within 6 months of enrollment/randomization

Source: NHS Digital

Secondary outcome: Need for hemorrhage control procedures

Definition: A hemorrhage control procedure was defined as an operation that involved resection of a bleeding organ (e.g. laparotomy with splenectomy, nephrectomy); ligation, repair, or shunting of a named vessel; or packing of a cavity (e.g. abdomen, pelvis); or angioembolization of a bleeding vessel.

Procedural data were independently reviewed by three of the investigators, without knowledge of allocation or outcomes, and categorized as hemorrhage control procedure, or not. Differences were then resolved by discussion and consensus.

Source: Trauma Audit and Research Network

Secondary outcome: Time to commencement of hemorrhage control procedure

Definition: Time from enrollment/randomization to commencement of hemorrhage control procedure.

Source: Trauma Audit and Research Network

Secondary outcome: Complications

Definition: Complications were pre-specified, as per the protocol.

Source: Case Report Form

Secondary outcome: Length of stay (as hospital- and ICU-free days)

Definition: Hospital stay, duration from date/time of arrival in emergency department to date/time of death, or discharge from acute care. ICU stay, total duration of time spent in intensive care unit. Hospital-free days and ICU-free days, at 90 days, were calculated using standard methodology.

Source: Trauma Audit and Research Network

Secondary outcome: Blood product use

Definition: Number of units of Red Blood Cells, Plasma, and Platelets received within first 24 hours

Source: Case Report Form

eTable4: Adjusted intention to treat analysis for 90 day mortality (primary outcome)

	OR	95% CrI	Posterior Probability (%) of OR>1
Age	1.39	(0.59, 3.28)	77.3
Gender	1.53	(0.69, 3.48)	85.1
ISS	1.63	(0.73, 3.77)	88.1
AIS head	1.61	(0.72, 3.79)	87.2
AIS face	1.65	(0.73, 3.75)	88.5
AIS chest	1.68	(0.74, 3.90)	89.5
AIS abdomen	1.50	(0.67, 3.44)	83.6
AIS spine	1.72	(0.76, 4.05)	89.9
AIS pelvic	1.61	(0.71, 3.64)	87.2
AIS limbs	1.69	(0.73, 3.99)	89.0
AIS other	1.60	(0.72, 3.59)	87.4
Pre-hospital CPR[1]	1.69	(0.69, 4.20)	87.4
ED SBP[2]	1.53	(0.69, 3.52)	84.9
CPR on arrival[1]	1.62	(0.72, 3.71)	87.9
Time from arrival to randomisation[3]	1.59	(0.72, 3.71)	87.4
All[4]	1.80	(0.59, 5.59)	84.9
All (removing ISS)[5]	1.67	(0.55, 5.30)	81.6

[1]missing values have been set to no.

[2]mean SBP across group have been used to impute missing values.

[3]for those randomised before arrival, set to 0.

[4]including all the covariates listed above

[5]including all covariates above but removing ISS

The covariates for the adjusted intention to treat analysis were selected before the results were known. Given the collinearity between AIS and ISS, the final analysis was performed with both ISS included, and excluded.

eTable5: Causes of death

	SC+REBOA	SC
Death within 3 hours, n	11	2
Bleeding, n (%)	6 (55)	-
Traumatic brain injury, n (%)	2 (18)	-
Unknown, n (%)	3 (27)	2 (100)
Death within 6 hours, n	13	4
Bleeding, n (%)	7 (54)	2 (50)
Traumatic brain injury, n (%)	3 (23)	-
Unknown, n (%)	3 (23)	2 (50)
Death within 24 hours, n	17	10
Bleeding, n (%)	8 (47)	2 (20)
Traumatic brain injury, n (%)	4 (24)	5 (50)
Unknown, n (%)	5 (29)	3 (30)
Death while in hospital, n	25	18
Traumatic brain injury, n (%)	9 (36)	8 (44)
Bleeding, n (%)	8 (33)	3 (17)
Multi-organ failure, n (%)	2 (8)	3 (17)
Respiratory causes, n (%)	-	1 (6)
Spinal cord injury, n (%)	1 (4)	-
Unknown, n (%)	5 (20)	3 (17)
Death within 90 days (primary outcome), n	25	18
Traumatic brain injury, n (%)	9 (36)	8 (44)
Bleeding, n (%)	8 (32)	3 (17)
Multi-organ failure, n (%)	2 (8)	3 (17)
Respiratory causes, n (%)	-	1 (6)
Spinal cord injury, n (%)	1 (4)	-
Unknown, n (%)	5 (20)	3 (17)
Death within 6 months, n	25	18
Traumatic brain injury, n (%)	9 (36)	8 (44)
Bleeding, n (%)	8 (32)	3 (17)
Multi-organ failure, n (%)	2 (8)	3 (17)
Respiratory causes, n (%)	-	1 (6)
Spinal cord injury, n (%)	1 (4)	-
Unknown, n (%)	5 (20)	3 (17)

“Unknown” includes patients in whom it was not possible to attribute a primary cause of death, and patients for whom postmortem examination reports were outstanding.

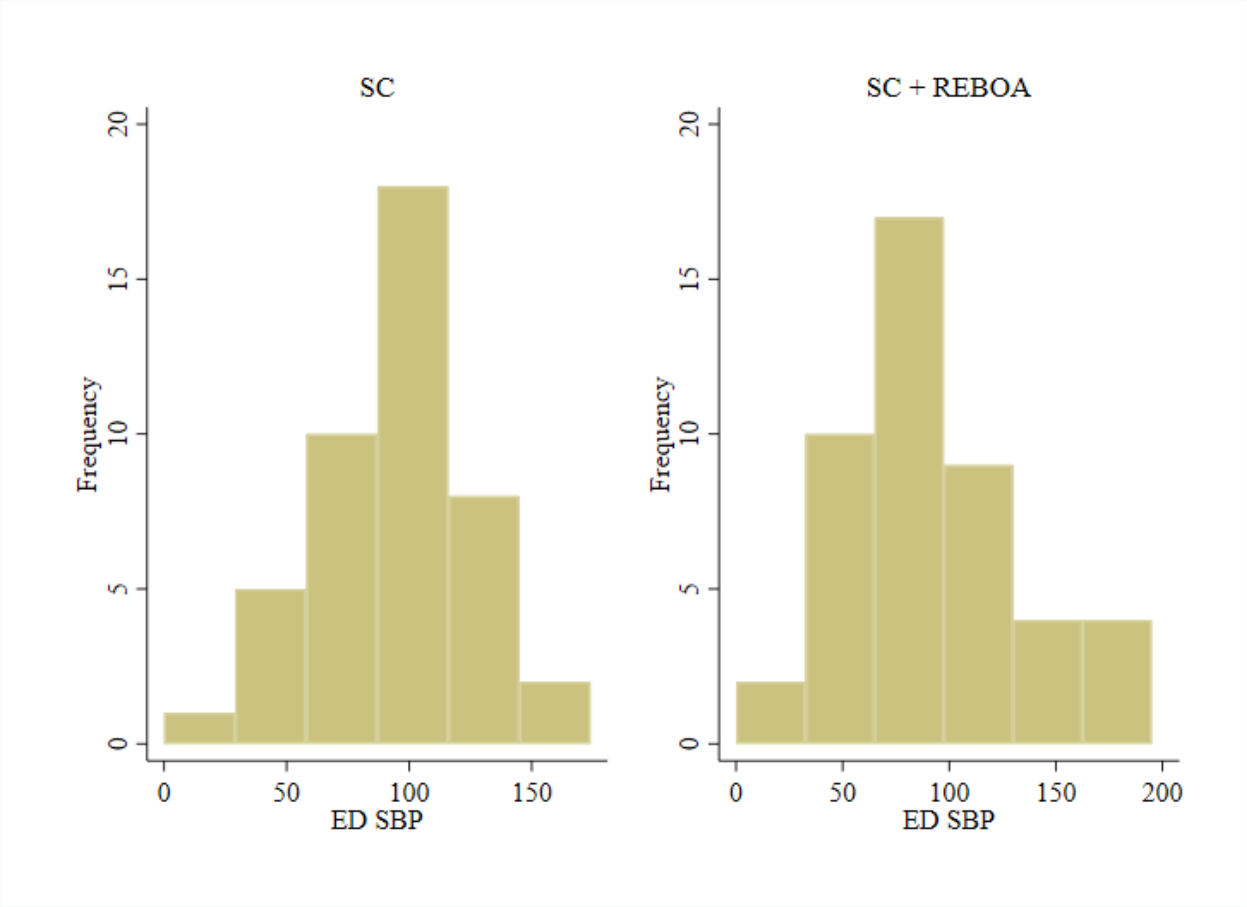
eTable6: Complications

	SC+REBOA N=46	SC N=43	OR	95% CrI
	n (%)	n (%)		
Overall				
Complications				
Yes	6 (13)	10 (23)	0.54	(0.19, 1.48)
No	40 (87)	33 (77)		
Number of complications				
One	3 (50)	5 (50)		
Two	2 (33)	4 (40)		
Three	1 (17)	1 (10)		
Specific complications				
Access-related				
Pseudoaneurysm	2 (33)	1 (10)[a]		
Distal embolism	1 (17)	1 (10)		
Hemorrhage at insertion site	1 (17)	-		
Arteriovenous fistula	-	1 (10)		
Extremity ischaemia	1 (17)	-		
Need for patch angioplasty (surgical repair)	1 (17)	-		
AEs related to external thoracic/abdominal aortic occlusion				
Lung injury/BP fistula	-	1 (10)		
Infection req. antibiotics only	-	1 (10)		
AEs related to impaired perfusion				
Acute kidney injury requiring renal replacement therapy	3 (50)	5 (50)		
Multi-organ failure	1 (17)	5 (50)		
Acute respiratory distress syndrome	-	1 (10)		

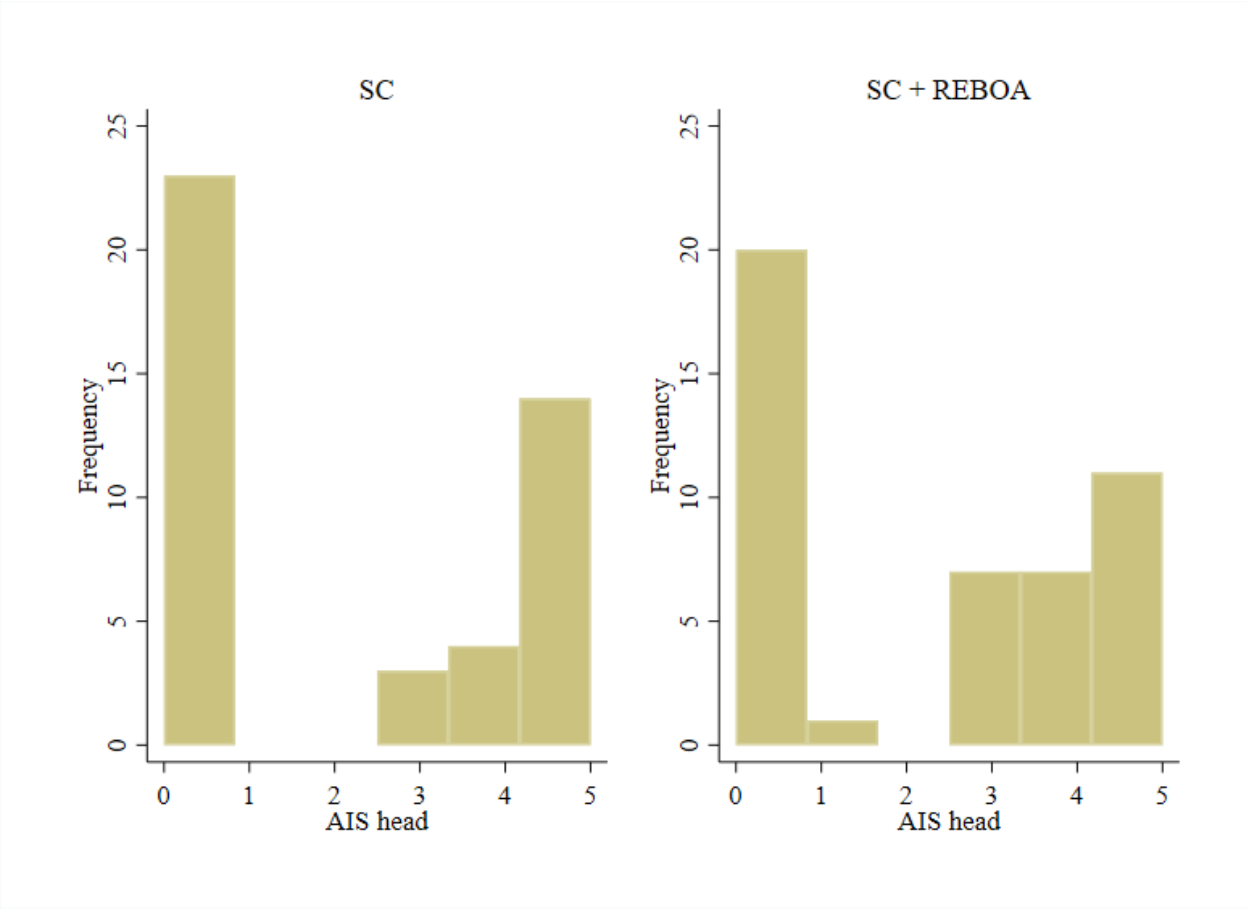
[a] this participant did not undergo REBOA procedure.

SUPPLEMENTARY FIGURES

eFigure1: Distribution of ED systolic blood pressure (mmgHG) on arrival, by group

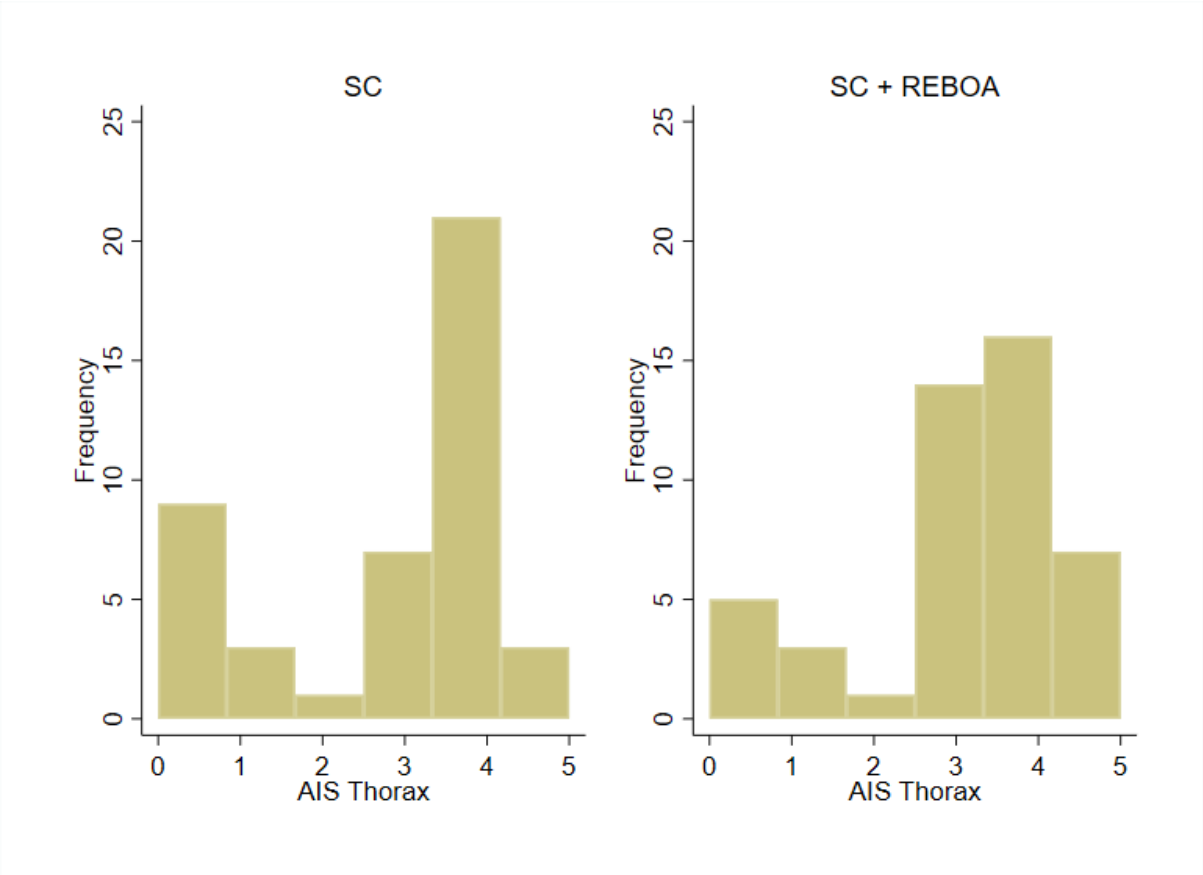


eFigure2: Distribution of Head Abbreviated Injury Scales (AIS), by group



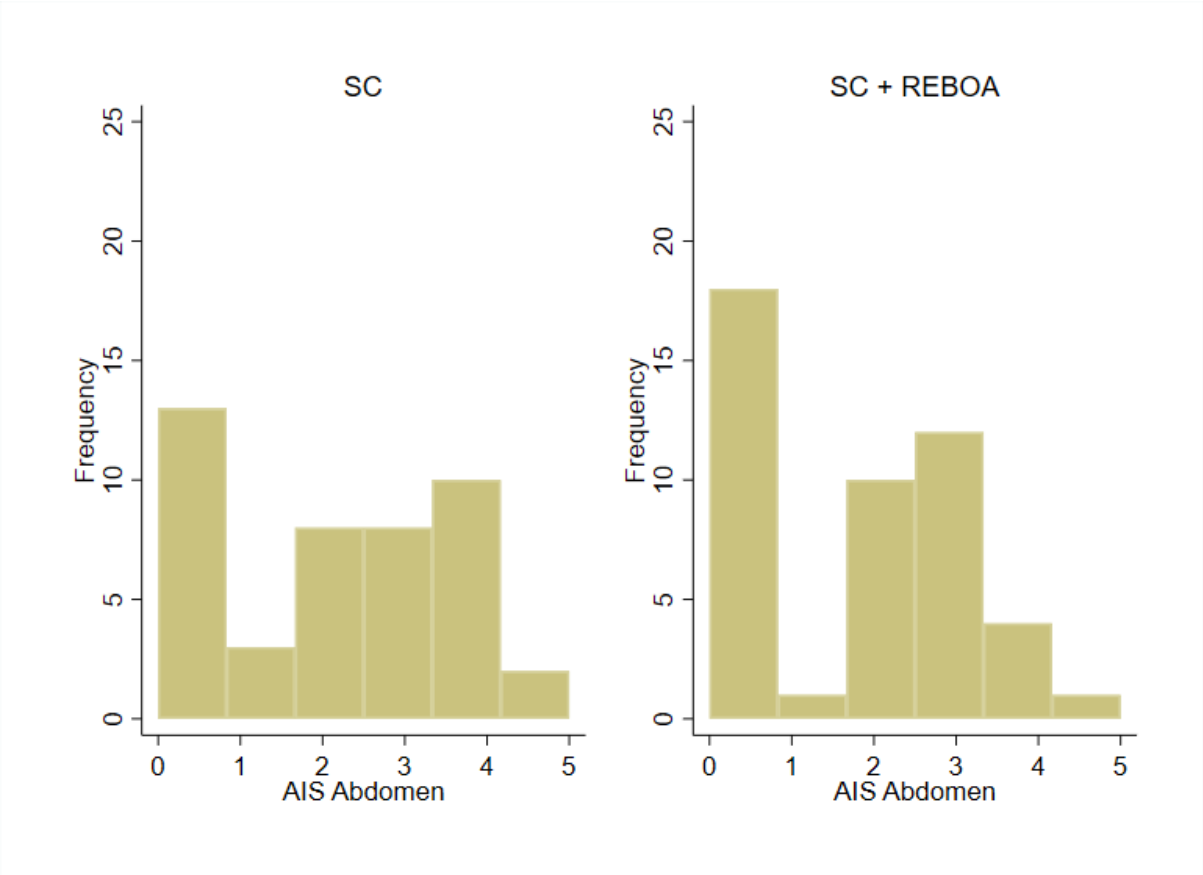
AIS, higher score indicates more severe injury

eFigure 3: Distribution of Thorax Abbreviated Injury Scales (AIS), by group



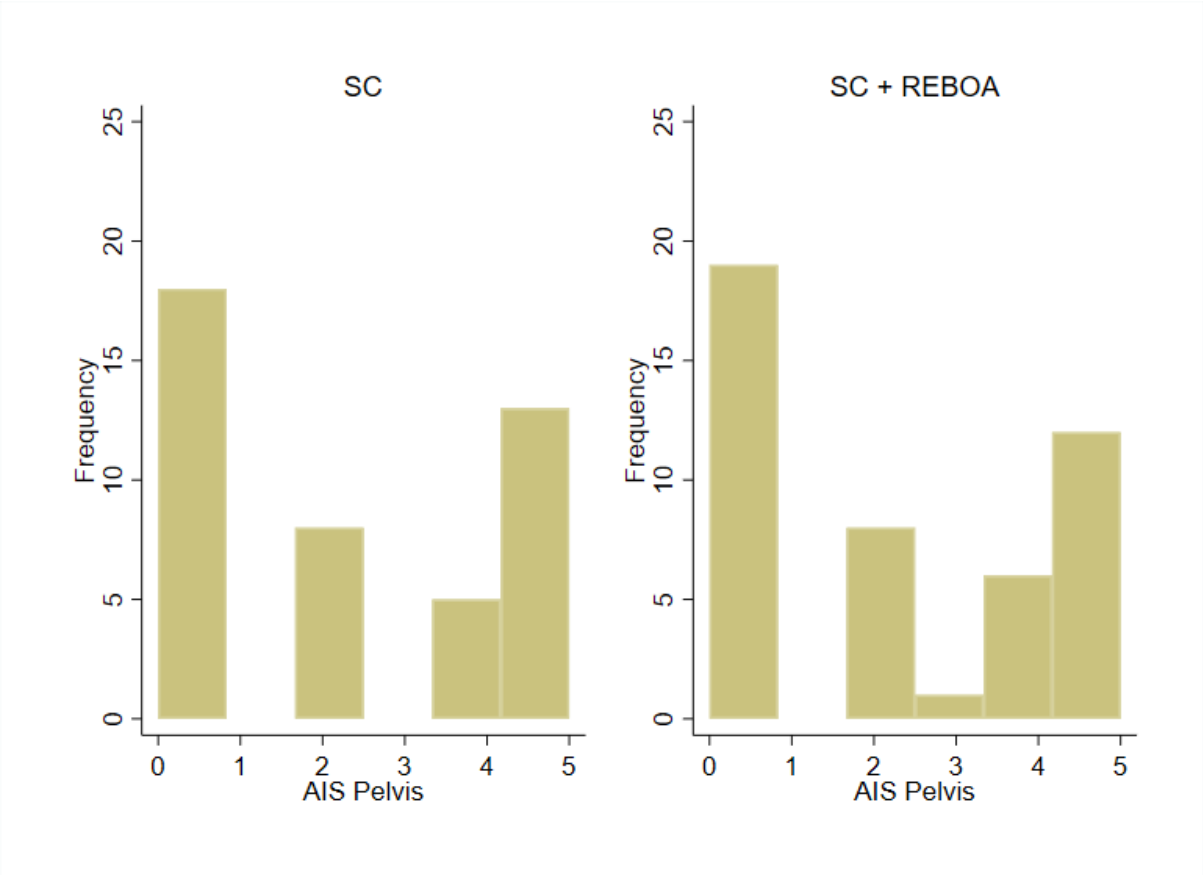
AIS, higher score indicates more severe injury

eFigure 4: Distribution of Abdomen Abbreviated Injury Scales (AIS), by group



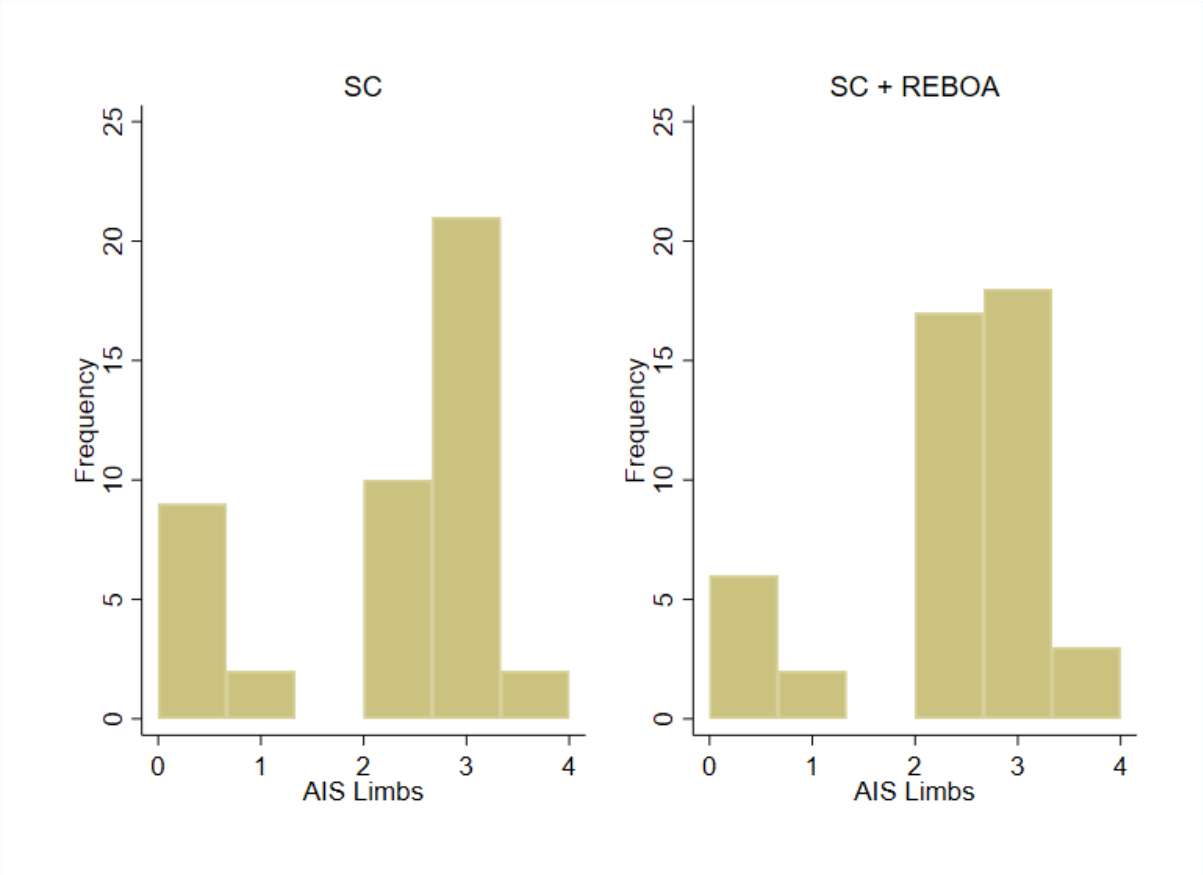
AIS, higher score indicates more severe injury

eFigure 5: Distribution of Pelvis Abbreviated Injury Scales (AIS), by group



AIS, higher score indicates more severe injury

eFigure 6: Distribution of Limbs Abbreviated Injury Scales (AIS), by group



AIS, higher score indicates more severe injury

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1. Holcomb JB, Moore EE, Sperry JL, Jansen JO, Schreiber MA, Del Junco DJ, et al. Evidence-Based and Clinically Relevant Outcomes for Hemorrhage Control Trauma Trials. Ann Surg. 2021 Mar 1;273(3):395–401.

TRAINING

Initial implementation and training package

We designed a custom implementation and training package, which was delivered as part of the trial site set-up, to facilitate the introduction of REBOA. The aim of the training package was two-fold: firstly, to teach REBOA, and secondly, to introduce clinicians to the trial.

The instruction was based on experience at the Royal London Hospital, as well as the Basic Endovascular Skills for Trauma (BEST) and Endovascular Skills for Trauma and Resuscitative Surgery (E-STARS) courses.

Training was initially spread out over two days, but after delivering four of the courses, and following feedback from participants, we decided to compress the training into a single, long day. The training was delivered by two senior clinicians, who had extensive experience of REBOA, and comprised a small number of didactic tutorials, followed by small group work, focusing on equipment familiarization, individual skills training, and subsequently whole-team training. Scenario based team training in a simulated resuscitation room was utilised to develop decision making regarding the incorporation of REBOA into standard resuscitative care, as well as the practical process of trial randomisation. A sample program for the two-day course is shown in eFigure 7.

The tutorials were intended to provide background, recognizing the diverse clinical backgrounds of the participants. Equipment familiarization sessions were tailored to sites' preferred devices. Individual skills training was aimed at giving individuals the opportunity to practice using the REBOA catheters, in "slow time", as well as revising ultrasound-guided femoral arterial access techniques, and was facilitated through the use of two perfused REBOA simulators. Team training involved complex scenarios, which integrated technical skills and decision making.

Follow-on training

A key part of the initial training was to facilitate the development of a local REBOA service, which sites then took ownership of. Having delivered the initial training, sites were encouraged and supported in developing a recurring training program, both to provide refresher training, and initial training for new staff members. Such training sessions were logged by trial staff. In addition, equipment manufacturers also provided device-specific support.

Implementation guide

We also provided sites with an Implementation Guide document, which reiterated key aspects of setting up a REBOA service, and continuing training.

eFigure 7. Two-day course, sample program

Day 1		
Time	**Activity**	**Additional details**
0900 - 0905	Welcome and Introduction to course	Aims of course: 1. Introduce the trial 2. Train and cement pathways
0905 - 0930	UK-REBOA Trial: Outline	Why we are here, the context of this training, trial outline
0930 - 1000	REBOA in context	History, current practice and future
1000 - 1030	REBOA background	Theory, evidence, procedure (current vs new), evolution
1030 - 1100	BREAK	
1100 - 1130	Diagnosis of catastrophic hemorrhage	Seminal REBOA cases
1130 - 1200	Clinical anatomy	As relevant to access
1200 - 1300	Case Demonstration	Real-time case and decision making
1300 - 1400	LUNCH	Meeting with PI and local leads during lunch
1400 - 1530	Equipment and procedure demonstration	Equipment; cannulation practice, p-REBOA, splints, trouble shooting
1530 - 1545	Break	
1600 - 1645	Post REBOA management and dilemmas	With “downstream” clinicians
1645 - 1700	Question and close	Summary and questions

Day 2		
Time	**Activity**	**Additional details**
0900 - 0930	Welcome and Introduction to day 2	Recap from yesterday. Plan for today.
0930 - 1015	Case simulation 1	Trauma team
1015 - 1100	Case simulation 2	Trauma team
1100 - 1130	BREAK	
1130 - 1215	Case simulation 3	Trauma team
1215 - 1300	Case simulation 4	Trauma team
1300 - 1345	LUNCH	
1345 - 1430	Case simulation 5	Trauma team
1430 - 1515	Coffee and cases	Selection of cases and conundrums
1515 - 1545	Developing your service	Discussion re local arrangements/SOPs, reminder training
1545 - 1615	Practical aspects of trial and GCP	Randomization, website, consent, GCP
1615 - 1630	Questions and close	
1630 - 1700	Final meeting with PI/local leads	Wash-up

SUPPLEMENTARY ANALYSIS 1: PRINCIPAL STRATUM/COMPLIER AVERAGE CAUSAL EFFECT (PS/CACE) ANALYSES

REBOA is a complex intervention, and can be technically challenging to perform. We recognized shortly after commencing the trial that not all participants who had been allocated to the SC+REBOA strategy progressed to full REBOA balloon occlusion. These participants did not "cross-over" to standard care, but resided on a spectrum of how far a patient had progressed down the REBOA-strategy pathway. Similar, these participants (or the treating clinicians) were not "non-compliant", or violating the protocol. Instead, there were three types of intercurrent events that impacted on how "much" of the intervention was delivered: Technical failure (inability to achieve arterial access), patients improving as a result of other resuscitative measures (typically blood transfusion) during REBOA deployment, and patient deterioration (where patients died before the device could be inserted) during REBOA deployment.

The trial's original intention-to-treat analysis, which relates to clinical effectiveness, was designed to answer the question of whether a strategy that includes REBOA reduced the mortality of exsanguinating trauma patients; under real-world conditions, ignoring all intercurrent events, such as REBOA not being deployed due to clinical improvement, deterioration, or technical failure. This question has been answered in the main body of this article.

We also undertook two supplementary post-hoc analyses to address intercurrent events answering the following questions: First, whether a strategy that includes REBOA reduces the mortality of exsanguinating trauma patients, when there was no technical failure, and when patients' clinical condition did not change; and second, whether a strategy that includes REBOA reduced the mortality of exsanguinating trauma patients, when there was no technical failure (irrespective of changes in clinical condition).

Methods

PS/CACE assumes that the patients in the Standard Care arm, had they been offered REBOA, would have had the same proportion of patients who would not have received REBOA (because of intercurrent events). This is a reasonable assumption, since an equal number of patients in the Standard Care arm would be expected to improve/deteriorate, or be difficult to cannulate.

Although as indicated above, while these intercurrent events did not lead to issues with compliance, since the term "compliance" is established in the PS/CACE analysis literature, we have retained it for the presentation of the PS/CACE analyses in this analysis.

For the first PS/CACE we considered R5 participants (those who had the device inserted, and the balloon inflated) as "compliers", and all other participants (in whom the device could not be inserted, and/or in whom there was a change in clinical condition) as "non-compliers".

For the second analysis, we considered patients in whom the device was inserted and inflated (R5), and those in whom there was a change in their clinical condition, for better (R4/C1, R3/C1, R1/C1) or worse (R1/C2), as "compliers", and R2 participants (arterial access attempted, but unsuccessful) as "non-compliers".

Type	Description	Q1	Q2
R5	Catheter inserted, balloon inflated	"Complier"	"Complier"
R4/C1	Catheter inserted, but balloon not inflated (patient improved)	"Non-complier"	"Complier"
R3/C1	Arterial access achieved, no balloon insertion (patient improved)	"Non-complier"	"Complier"
R2	Arterial access attempted, but unsuccessful	"Non-complier"	"Non-complier"
R1/C1	Arterial access not attempted (patient improved)	"Non-complier"	"Complier"
R1/C2	Arterial access not attempted (patient deteriorated)	"Non-complier"	"Complier"

Most reports of PS/CACE analyses rely on frequentist methods, but in order to keep with the original Bayesian philosophy of the trial, and allow comparison with the results of the intention-to-treat analysis, we conducted a Bayesian analysis using the two-staged residual inclusion estimator approach with non-informative priors. The output of the analysis comprises of Odds Ratios (ORs) as well as 95% credible intervals.

Results

Question 1: "Does a strategy that includes REBOA (in addition to standard major trauma center care) reduce the mortality of exsanguinating trauma patients; when there is no technical failure, and when patients' clinical condition did not change (improve or deteriorate)?"

The results are shown in the table below:

	Standard care + REBOA N=46		Standard care N=44		OR	95% Crl	
	Complied N=19	Did not comply N=27	Complied N=42	Did not comply N=2			Posterior Probability (%) of OR>1
Death within 90 days[a]							
Yes	13 (68)	12 (44)	17 (41)	1 (50)	4.25	(0.41, 45.07)	88.9
No	6 (32)	15 (56)	24 (59)	1 (50)			
Death within 6 months[a]							
Yes	13 (68)	12 (44)	17 (41)	1 (50)	4.25	(0.41, 45.07)	88.9
No	6 (32)	15 (56)	24 (59)	1 (50)			
Death while in hospital[a]							
Yes	13 (68)	12 (44)		1 (50)	4.25	(0.41, 45.07)	88.9
No	6 (32)	15 (56)	24 (59)	1 (50)			
Death within 24 hours							
Yes	8 (42)	9 (33)	10 (24)	-	6.59	(0.53, 91.96)	92.8
No	11 (58)	18 (67)	32 (76)	2 (100)			
Death within 6 hours							
Yes	7 (37)	6 (22)	4 (10)	-	48.28	(1.88, 2009.68)	99.1
No	12 (63)	21 (78)	38 (90)	2 (100)			
Death within 3 hours							
Yes	5 (26)	6 (22)	2 (5)	-	234.20	(4.32, 72295.55)	99.8
No	14 (74)	21 (78)	40 (95)	2 (100)			

[a] One participant in the SC arm withdrew from follow-up at day 4 so is not included in analysis of death while in hospital, within 90 days or within 6 months

For the primary outcome of 90-day mortality, the death rate was 68% for compliers (those in whom the device was successfully inserted and inflated), compared to 44% in non-compliers (those in whom the device could not be inserted, or whose condition changed), and 41% in patients allocated to standard care. The OR of dying within 90 days amongst patients in whom the device was successfully inserted and inflated (when there was no technical failure, and no change in patients' physiological condition); was 4.25 (95% Crl 0.41, 45.07). The effect became more pronounced at earlier mortality timepoints. A treatment strategy that includes REBOA does not reduce the mortality of exsanguinating trauma patients, even when there is no technical failure, and when patients' clinical condition does not change.

Question 2: "Does a strategy that includes REBOA (in addition to standard major trauma center care) reduce the mortality of exsanguinating trauma patients; when there is no technical failure?"

The results are shown in the table below:

	Standard care + REBOA N=46		Standard care N=44		OR	95% Crl	
	Complied N=36	Did not comply N=10	Complied N=42	Did not comply N=2			Posterior Probability (%) of OR>1
Death within 90 days[a]							
Yes	18 (50)	7 (70)	17 (41)	1 (50)	2.07	(0.64, 6.72)	88.9
No	18 (50)	3 (30)	24 (59)	1 (50)			
Death within 6 months[a]							
Yes	18 (50)	7 (70)	17 (41)	1 (50)	2.07	(0.64, 6.72)	88.9
No	18 (50)	3 (30)	24 (59)	1 (50)			
Death while in hospital[a]							
Yes	17 (47)	7 (70)		1 (50)	2.07	(0.64, 6.72)	88.9
No	19 (53)	3 (30)	24 (59)	1 (50)			
Death within 24 hours							
Yes	24 (67)	5 (50)	10 (24)	-	2.59	(0.73, 9.79)	93.1
No	12 (33)	5 (50)	32 (76)	2 (100)			
Death within 6 hours							
Yes	9 (25)	4 (40)	4 (10)	-	6.88	(1.37, 45.11)	99.1
No	27 (75)	6 (60)	38 (90)	2 (100)			
Death within 3 hours							
Yes	7 (19)	4 (40)	2 (5)	-	14.78	(2.02, 240.52)	99.7
No	29 (81)	6 (60)	40 (95)	2 (100)			

[a] One participant in the SC arm withdrew from follow-up at day 4 so is not included in analysis of death while in hospital, within 90 days or within 6 months

For the primary outcome of 90-day mortality, the death rate was 50% for those in whom the device was successfully inserted and inflated, or in whom there was a change in clinical condition (compliers), compared to 70% in those in whom the device could not be inserted, for technical reasons (non-compliers), and 41% in patients allocated to standard care. The OR of dying within 90 days amongst patients in whom the device was either successfully inserted, or in whom there was a change in clinical condition; was 2.07 (95% Crl 0.64, 6.72). Again, the effect became more pronounced at earlier mortality timepoints. A strategy that includes REBOA does not reduce the mortality of exsanguinating trauma patients, even when is no technical failure.

SUPPLEMENTARY ANALYSIS 2: LEARNING CURVE ANALYSIS

We conducted an additional post-hoc analysis, with the first participant randomised to SC+REBOA from each site removed. This analysis was conducted using the minimally informative prior, to account for possible learning curve effects.

	Standard care + REBOA N=34	**Standard care N=44**	**OR**	**95% CrI**	**Posterior Probability of OR>1 (%)**
	N=34	N=43			
Death within 90 days					
Yes	21 (62)	18 (42)	2.06	(0.87, 5.01)	95.1
No	13 (38)	25 (58)			
Death within 6 months					
Yes	21 (62)	18 (42)	2.06	(0.87, 5.01)	95.1
No	13 (38)	25 (58)			
Death while in hospital					
Yes	21 (62)	18 (42)	2.06	(0.87, 5.01)	95.1
No	13 (38)	25 (58)			
	N=34	N=44			
Death within 24 hours					
Yes	13 (38)	10 (23)	1.92	(0.76, 4.93)	91.5
No	21 (62)	34 (77)			
Death within 6 hours					
Yes	9 (26)	4 (9)	2.86	(0.94, 9.25)	96.8
No	25 (74)	40 (91)			
Death within 3 hours					
Yes	9 (26)	2 (5)	4.58	(1.38, 17.64)	99.4
No	25 (74)	42 (95)			