Supplemental Online Content

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This supplemental material has been provided by the authors to give readers additional information about their work.

eTable 1. 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)

eTable 2. 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

eTable 3. 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

eTable 4. 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.

eTable 5. 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.

eTable 6. 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.

eMethods. Training information

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

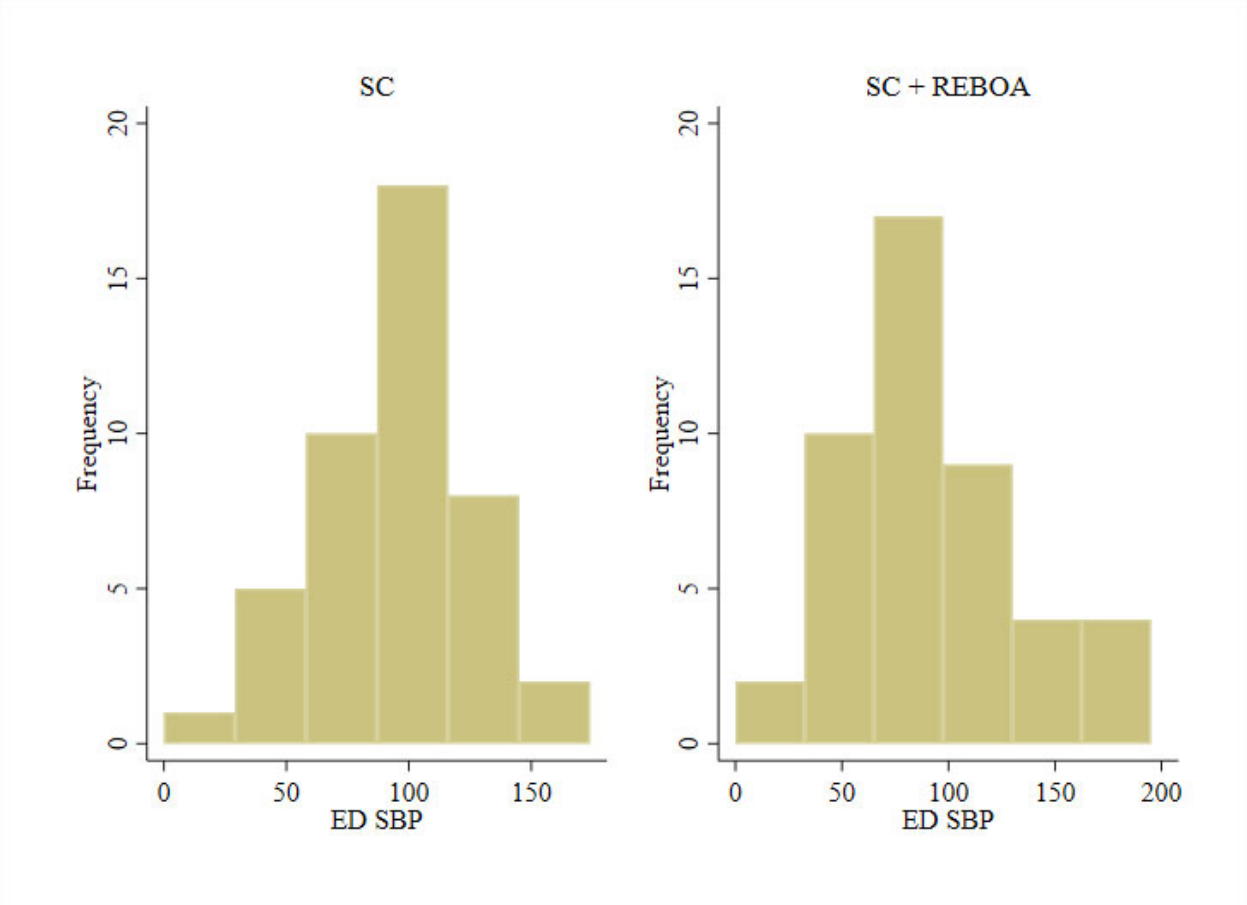
We also provided sites with an Implementation Guide document, which reiterated key aspects of setting up a REBOA service, and continuing training.

eFigure 1. Two-day course, sample program

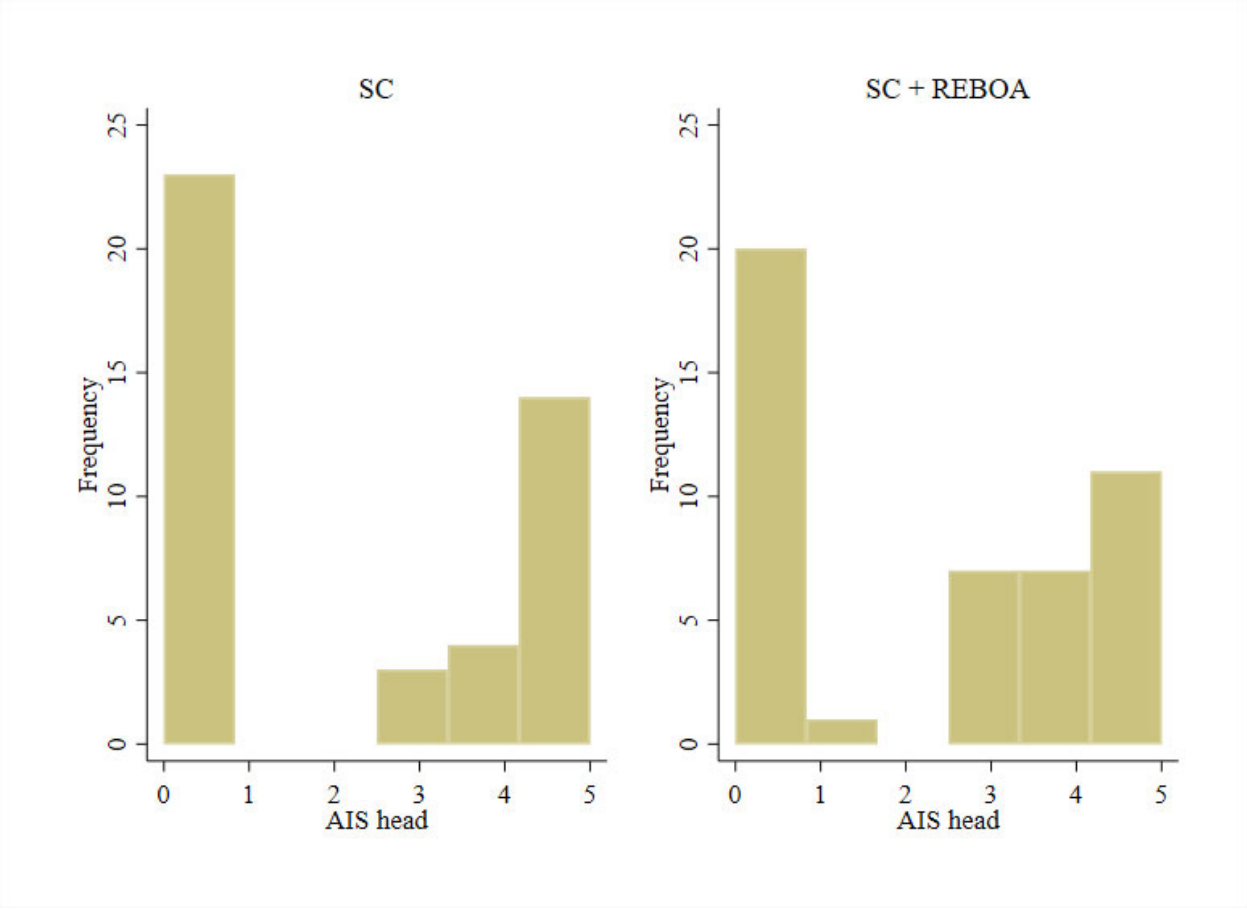
Day 1		
Time	**Activity**	**Additional details**
0900 - 0905	Welcome and Introduction to course	Aims of course: 1. Introduce the trial 2. Train and cement pathways
0905 - 0930	UK-REBOA Trial: Outline	Why we are here, the context of this training, trial outline
0930 - 1000	REBOA in context	History, current 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

eFigure 2. Distribution of ED systolic blood pressure (mmgHG) on arrival, by group

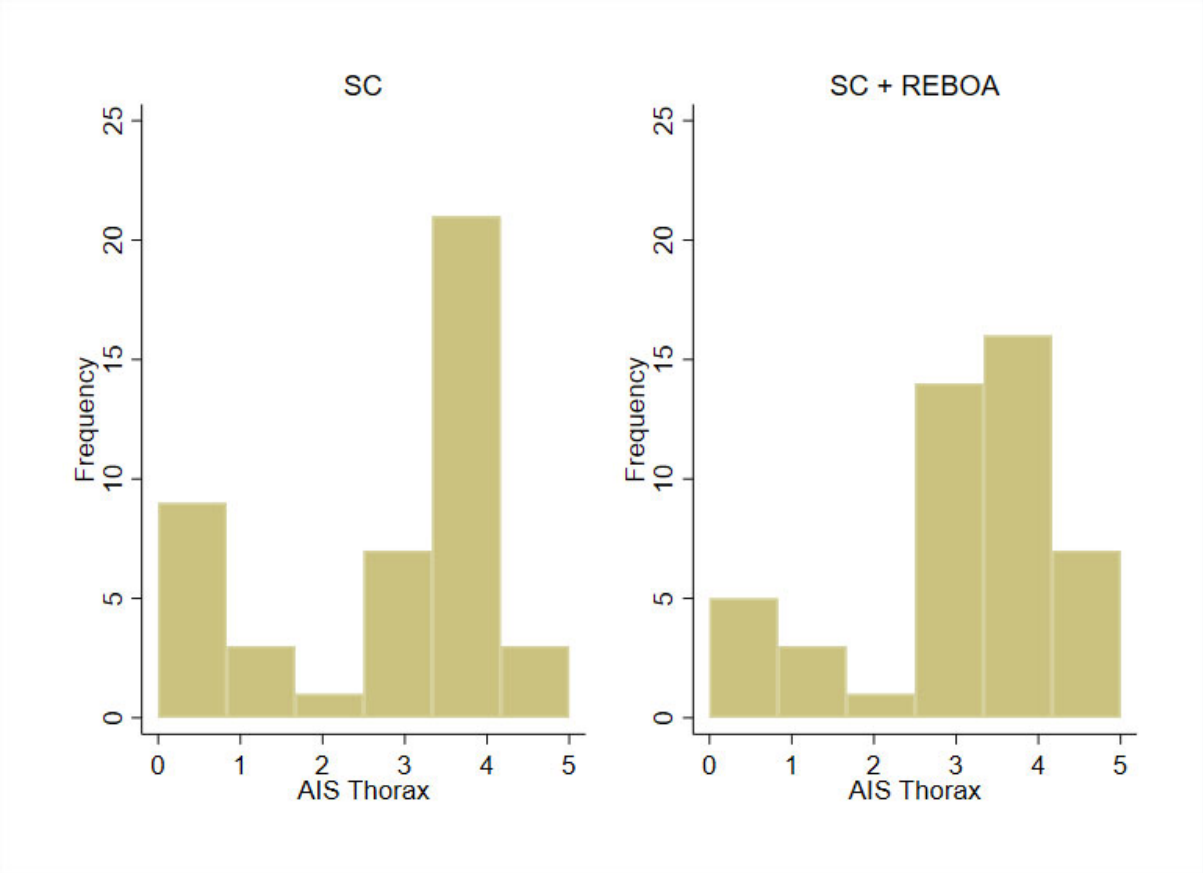


eFigure 3. Distribution of Head Abbreviated Injury Scales (AIS), by group



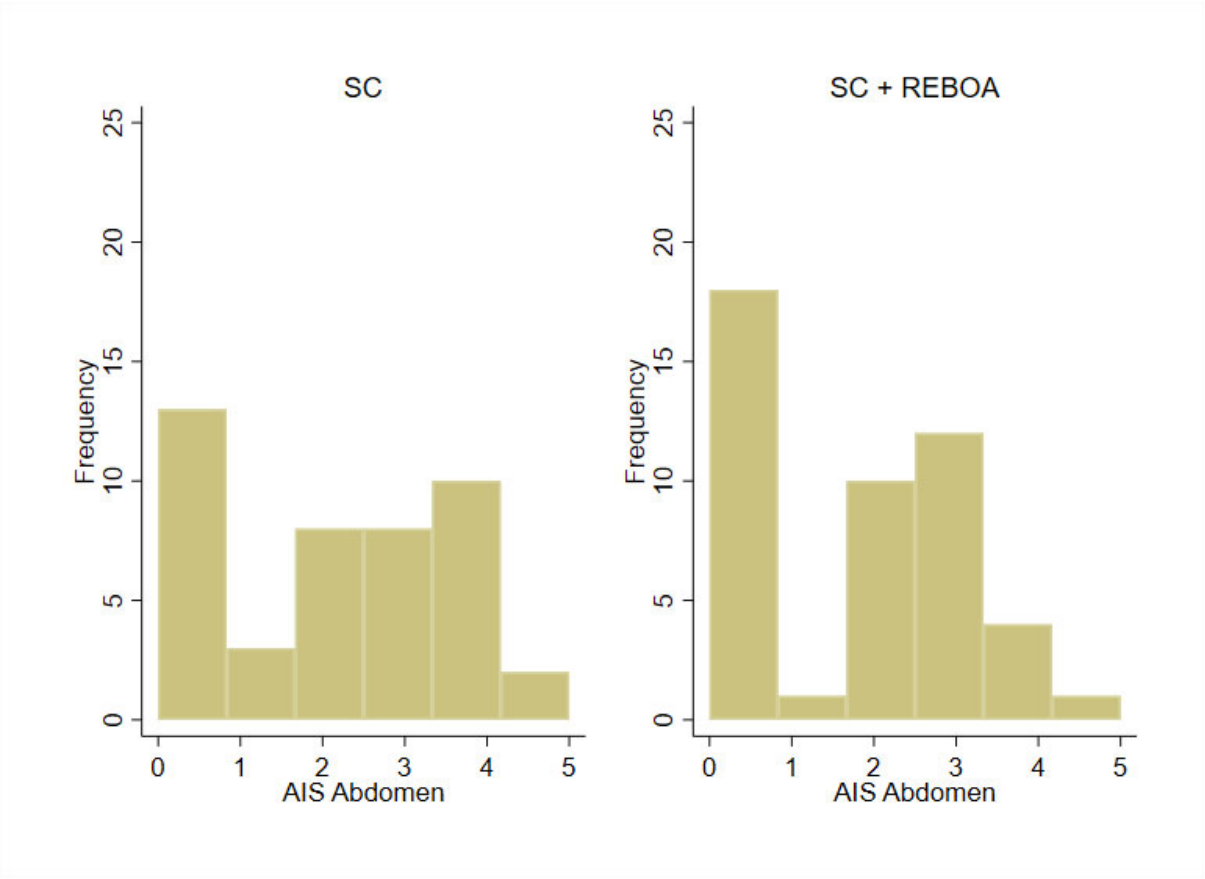
AIS, higher score indicates more severe injury

eFigure 4. Distribution of Thorax Abbreviated Injury Scales (AIS), by group



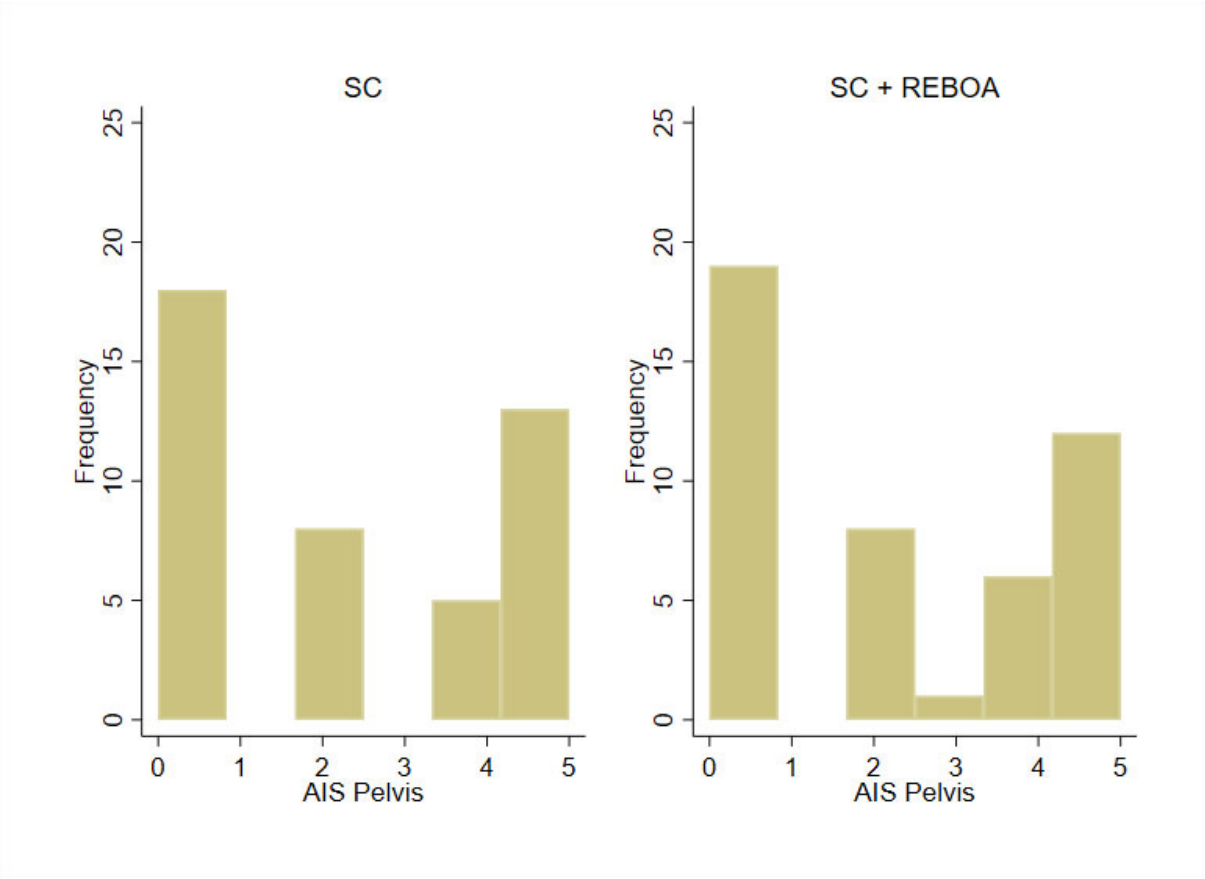
AIS, higher score indicates more severe injury

eFigure 5. Distribution of Abdomen Abbreviated Injury Scales (AIS), by group



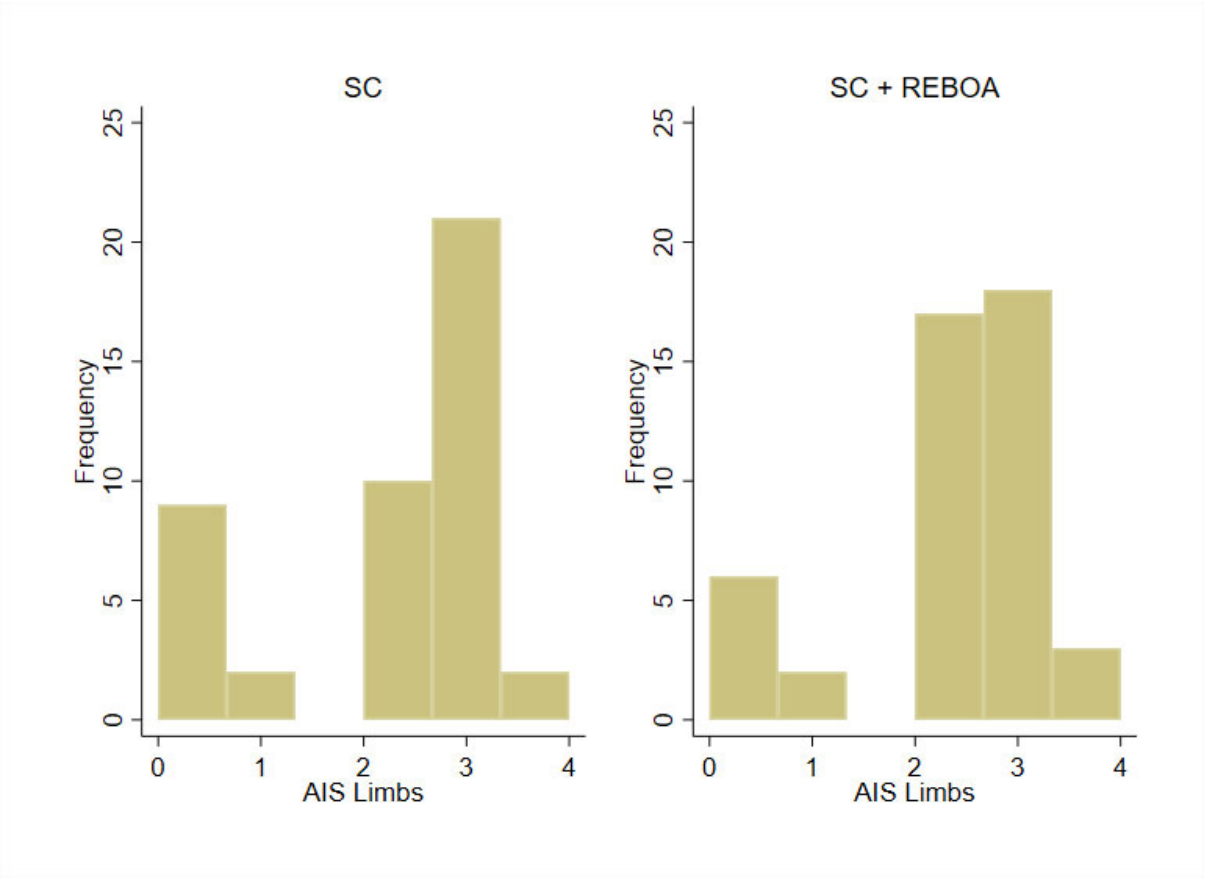
AIS, higher score indicates more severe injury

eFigure 6. Distribution of Pelvis Abbreviated Injury Scales (AIS), by group



AIS, higher score indicates more severe injury

eFigure 7. Distribution of Limbs Abbreviated Injury Scales (AIS), by group



AIS, higher score indicates more severe injury

eAppendix 1. Supplementary analysis: 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. Similarly, 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.

eAppendix 2. 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)			

eReference

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.