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Abstract

The UK resuscitative endovascular balloon occlusion of the aorta in trauma patients with life-threatening torso haemorrhage: the (UK-REBOA) multicentre RCT

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Background: The most common cause of preventable death after injury is haemorrhage. Resuscitative endovascular balloon occlusion of the aorta is intended to provide earlier, temporary haemorrhage control, to facilitate transfer to an operating theatre or interventional radiology suite for definitive haemostasis.

Objective: To compare standard care plus resuscitative endovascular balloon occlusion of the aorta versus standard care in patients with exsanguinating haemorrhage in the emergency department.

Design: Pragmatic, multicentre, Bayesian, group-sequential, registry-enabled, open-label, parallel-group randomised controlled trial to determine the clinical and cost-effectiveness of standard care plus resuscitative endovascular balloon occlusion of the aorta, compared to standard care alone.

Setting: United Kingdom Major Trauma Centres.

Participants: Trauma patients aged 16 years or older with confirmed or suspected life-threatening torso haemorrhage deemed amenable to adjunctive treatment with resuscitative endovascular balloon occlusion of the aorta.

Interventions: Participants were randomly assigned 1 : 1 to:

- standard care, as expected in a major trauma centre
- standard care plus resuscitative endovascular balloon occlusion of the aorta.

Main outcome measures: *Primary:* Mortality at 90 days.

Secondary: Mortality at 6 months, while in hospital, and within 24, 6 and 3 hours; need for haemorrhage control procedures, time to commencement of haemorrhage procedure, complications, length of stay (hospital and intensive care unit-free days), blood product use.

Health economic: Expected United Kingdom National Health Service perspective costs, life-years and quality-adjusted life-years, modelled over a lifetime horizon.

Data sources: Case report forms, Trauma Audit and Research Network registry, NHS Digital (Hospital Episode Statistics and Office of National Statistics data).

Results: Ninety patients were enrolled: 46 were randomised to standard care plus resuscitative endovascular balloon occlusion of the aorta and 44 to standard care. Mortality at 90 days was higher in the standard care plus resuscitative endovascular balloon occlusion of the aorta group (54%) compared to the standard care group (42%). The odds ratio was 1.58 (95% credible interval 0.72 to 3.52). The posterior probability of an odds ratio > 1 (indicating increased odds of death with resuscitative endovascular balloon occlusion of the aorta) was 86.9%. The overall effect did not change when an enthusiastic prior was used or when the estimate was adjusted for baseline characteristics.

For the secondary outcomes (3, 6 and 24 hours mortality), the posterior probability that standard care plus resuscitative endovascular balloon occlusion of the aorta was harmful was higher than for the primary outcome. Additional analyses to account for intercurrent events did not change the direction of the estimate for mortality at any time point.

Death due to haemorrhage was more common in the standard care plus resuscitative endovascular balloon occlusion of the aorta group than in the standard care group.

There were no serious adverse device effects.

Resuscitative endovascular balloon occlusion of the aorta is less costly (probability 99%), due to the competing mortality risk but also substantially less effective in terms of lifetime quality-adjusted life-years (probability 91%).

Limitations: The size of the study reflects the relative infrequency of exsanguinating traumatic haemorrhage in the United Kingdom. There were some baseline imbalances between groups, but adjusted analyses had little effect on the estimates.

Conclusions: This is the first randomised trial of the addition of resuscitative endovascular balloon occlusion of the aorta to standard care in the management of exsanguinating haemorrhage. All the analyses suggest that a strategy of standard care plus resuscitative endovascular balloon occlusion of the aorta is potentially harmful.

Future work: The role (if any) of resuscitative endovascular balloon occlusion of the aorta in the pre-hospital setting remains unclear. Further research to clarify its potential (or not) may be required.

Trial registration: This trial is registered as ISRCTN16184981.

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List of abbreviations

A&E	accident and emergency	IRAS	integrated Research Application System
ACM	all-cause mortality	ISRCTN	International Standard Randomised Controlled Trial Number
ADE	adverse device effect	ISS	Injury Severity Score
AE	adverse event	ITT	intention to treat
AIS	Abbreviated Injury Scale	LYGs	life-year gains
APEASE	acceptability, practicability, effectiveness, affordability, side effects and equity	mmHg	millimetres of mercury
AUC	area under the curve	MTC	major trauma centre
BCT	behavioural change techniques	NIHR	National Institute for Health and Care Research
CACE	complier average causal effect	ONS	Office of National Statistics
CHaRT	Centre for Healthcare Randomised Trials	PHS	Public Health Scotland
CI/Co-CI	Chief Investigator/Co-Chief Investigator	PI	principal investigator
COVID-19	coronavirus disease discovered in 2019	PIL	participant information leaflet
CPR	cardiopulmonary resuscitation	PMG	Project Management Group
CRF	case report form	PSSRU	Personal Social Services Research Unit
CrI	credible interval	Q	quartile
DMC	Data Monitoring Committee	QALY	quality-adjusted life-year
eCRF	electronic case report form	R&D	research and development
ED	emergency department	RCT	randomised controlled trial
EQ-5D-5L	EuroQol Group's 5-dimension health status 5-level questionnaire	REBOA	resuscitative endovascular balloon occlusion of the aorta
EVPI	expected value of perfect information	REC	Research Ethics Committee
GBP	Great British pounds	SADE	serious adverse device effect
GOS-E	Glasgow Outcome Scale (Extended)	SAE	serious adverse event
HDU	high-dependency unit	SBP	systolic blood pressure
HEAP	health economics analysis plan	TARN	Trauma Audit and Research Network
HES	hospital Episode Statistics	TDF	Theoretical Domains Framework
HSRU	Health Services Research Unit	TSC	Trial Steering Committee
HTA	Health Technology Assessment	TTL	trauma team leader
ICER	incremental cost-effectiveness ratio	USADE	unanticipated serious adverse device effect
ICU	intensive care unit	USM	urgent safety measure

Plain language summary

Trauma (physical injury) is a major cause of death and disability. The most common cause of *preventable* death after injury is uncontrolled bleeding. Resuscitative endovascular balloon occlusion of the aorta is a technique whereby a small balloon is inflated in the aorta (main blood vessel) which aims to limit blood loss until an operation can be done to stop the bleeding.

In this study, which is the first randomised trial in the world of this technique, we investigated whether adding resuscitative endovascular balloon occlusion of the aorta to the standard care received in a major trauma centre reduced the risk of death in trauma patients who had life-threatening uncontrolled bleeding.

The study took place in 16 major trauma centres in the United Kingdom. Ninety adult trauma patients with confirmed or suspected uncontrolled bleeding took part and were randomly divided into two groups: (1) those who received standard care and (2) those who received standard care plus resuscitative endovascular balloon occlusion of the aorta. We followed participants for 6 months using routinely collected data from the National Health Service and from the Trauma Audit Research Network registry. We also contacted surviving patients at 6 months to ask about their quality of life.

In the standard care group, 42% of participants died within 90 days of their injury compared to 54% of participants in the standard care plus resuscitative endovascular balloon occlusion of the aorta group. Risk of death was also higher in the standard care plus resuscitative endovascular balloon occlusion of the aorta group at all other time points (3, 6 and 24 hours, in hospital and at 6 months). Overall, the study showed that the use of resuscitative endovascular balloon occlusion of the aorta in hospital increased the risk of death.

Scientific summary

Background

Trauma is a major cause of death and disability. Trauma (physical injury) disproportionately affects the young, killing those who might otherwise have lived long and productive lives. The most common cause of *preventable* death after injury is haemorrhage. The addition of resuscitative endovascular balloon occlusion of the aorta (REBOA) to current standard care is intended to provide earlier, temporary haemorrhage control, to facilitate transfer to an operating theatre or interventional radiology suite, for definitive haemostasis.

Objectives

The UK-REBOA trial was a pragmatic, multicentre, Bayesian, open-label, group-sequential, parallel-group randomised controlled trial comparing standard care plus REBOA versus standard care in patients with exsanguinating haemorrhage in the emergency room. The study included an elicitation exercise, an embedded mixed-methods process evaluation and a health economic evaluation.

The primary clinical outcome was 90-day mortality (defined as death within 90 days of injury, before or after discharge from hospital).

Secondary clinical outcomes included 3-, 6- and 24-hour mortality, in-hospital mortality, 6-month mortality, length of stay (in hospital and intensive care unit), 24-hour blood product use, need for haemorrhage control procedures (operation or angioembolisation), time to commencement of haemorrhage control procedure, complications/safety data and functional outcome [measured using the extended Glasgow Outcome Scale (GOS-E)] at discharge.

Economic outcomes were 6-month (within trial) and lifetime (modelled) UK NHS perspective costs, life-years and quality-adjusted life-years (QALYs) [calculated using EuroQol Group's 5-dimension health status 5-level questionnaire (EQ-5D-5L)], 6-month quality of life (measured using EQ-5D-5L).

Methods

Trauma patients were recruited in 16 UK major trauma centres. Trauma patients aged (or believed to be aged) 16 years or older, with confirmed or suspected life-threatening torso haemorrhage thought to be amenable to adjunctive treatment with REBOA were eligible. Women known (or thought to be) pregnant and those with injuries deemed unsurvivable were excluded.

The trauma team leader assessed the patients for eligibility. Patients who were eligible for inclusion in the trial were incapacitated and unable to give consent at the time of eligibility assessment and randomisation. There was also not sufficient time to consult a surrogate decision-maker, or even an independent medical practitioner, for advice about including the patient. Enrolment therefore took place without prior consent following Research Ethics Committee approval for this approach. Consent for continuing participation (i.e. data collection) was sought by a member of the UK-REBOA trial team once patients were no longer in a critical condition (defined as being cared for in a ward area rather than an intensive care unit or high-dependency unit) or from a personal (or nominated professional) consultee.

The trauma team leader enrolled the participant using a dedicated, secure website, available on a handheld device (smartphone, tablet) or desktop computer which is linked directly to the 24-hour

randomisation system at the Centre for Healthcare Randomised Trials, based in the Health Services Research Unit, University of Aberdeen. Patients were randomised into one of the two intervention arms, in a 1 : 1 allocation ratio, in randomly generated blocks of two or four.

Standard care: Patients allocated to the control group received 'standard care', as expected in a specialist major trauma centre. Such treatment typically included intubation, blood transfusion including blood products in a 1 : 1 : 1 ratio, interventions such as tourniquet application, and early operative or endovascular haemorrhage control. Treatment could also have included open aortic occlusion of the thoracic or abdominal aorta.

Standard care plus REBOA: Patients allocated to this arm of the trial additionally received the technique of endovascular aortic occlusion, for the purpose of resuscitation, as part of an overall treatment strategy. The addition of REBOA to current standard care was intended to provide earlier, temporary haemorrhage control, to facilitate transfer to an operating theatre or interventional radiology suite for definitive haemostasis. The trial sought to evaluate the *technique* of REBOA rather than a specific brand of device, and therefore permitted the use of any licensed occlusion balloon, and did not prescribe or mandate a particular product. The trial had an integrated training programme to ensure familiarity with the REBOA procedure.

In patients who had been randomised to the standard care plus REBOA arm of the trial, clinicians could decide not to insert the balloon occlusion device if: the patient's haemodynamic status improved (as a result of other resuscitative measures), if they were deemed to no longer have life-threatening torso haemorrhage requiring adjunctive treatment with REBOA; they deteriorated (to the point of imminent death); or there was technical difficulty in obtaining arterial access, and it was felt that operative control of haemorrhage could be obtained more quickly.

The data collection strategy for the UK-REBOA trial was designed to minimise the burden on participants and clinicians, and for the avoidance of duplication. The randomisation system collected balloon inflation/deflation times. The trial drew on routinely collected data, primarily from the Trauma Audit and Research Network (TARN) registry which includes demographic, injury, treatment and outcome data (including the GOS-E and EQ-5D-5L). Mortality and hospital resource use data were also sought from NHS Digital.

The main analysis was based on the intention-to-treat principle. There were two planned interim analyses of survival and a final analysis of all outcomes after follow-up was complete. Baseline and follow-up data were summarised using descriptive statistics and graphical summaries. Treatment effects are presented with 95% credible intervals for the primary and secondary outcomes.

Elicitation exercise

An elicitation exercise involving 20 subject matter experts (12 emergency medicine physicians, 3 pre-hospital care doctors, 4 surgeons and 1 intensivist) was undertaken to derive prior probability distributions to help contextualise the interpretation for the primary and secondary outcomes of the trial. Subject matter experts, on average, estimated in-hospital and 90-day mortality in this patient group, without the use of REBOA, to be in excess of 50%. Mortality at earlier time points (6 and 24 hours) was estimated to be closer to 25%. The elicited data, and the resulting prior probability distributions, indicate that the experts, on average, had a favourable opinion of REBOA, that is they expect the addition of REBOA to standard care to improve mortality at all time points.

Clinical results

Sixteen recruitment sites were opened in a staggered manner. Recruitment commenced in October 2017, was halted in March 2020 due to COVID-19, and restarted in July 2020. The second interim analysis (including 80 participants) triggered one of the pre-specified stopping rules, and recruitment closed in March 2022, by which time 90 participants had been recruited.

Forty-four participants were randomised to standard care (2 of whom did receive REBOA) and 46 were randomised to standard care plus REBOA (19 of whom had the catheter inserted and balloon inserted and the remaining 27 progressed to different time points along this pathway). The groups were well-matched in terms of age, gender, comorbidities, mechanism of injury and injury severity. In the standard care arm, the median age was 39 years (interquartile range 30–56 years) and 77% were male. In the standard care plus REBOA arm, the median age was 46 years (interquartile range 33–62) and 61% were male. The median Injury Severity Score in both arms was 41 (interquartile range 29–50), with the majority classed as having very severe injury.

Of the 46 patients allocated to standard care plus REBOA treatment, 25 (54%) died within 90 days. Of the 43 standard care patients for whom primary outcome data are available, 18 (42%) died within 90 days. Using the minimally informative prior, the odds of 90-day mortality were 1.58 for patients allocated to the standard care plus REBOA arm (95% credible interval 0.72 to 3.52). The posterior probability of an odds ratio > 1 (i.e. that REBOA was harmful) was 86.9%. The direction of the estimate did not change when an enthusiastic (the elicited) prior was used or when the estimate was adjusted for baseline characteristics. For the secondary outcomes (3-, 6- and 24-hour mortality), the posterior probability that REBOA was harmful was higher than for the primary outcome. Additional analyses to account for intercurrent events did not change the direction of the estimate for mortality at 3, 6 and 24 hours, at 90 days or 6 months, or in-hospital mortality.

Death due to haemorrhage was more common in the standard care plus REBOA group than in the standard care group. The mean number of days spent in intensive care and in hospital were lower in the standard care plus REBOA group compared to the standard care group, partly because of the higher number of earlier deaths in the standard care plus REBOA arm.

There were no serious adverse device effects.

Health economics

We costed individual components of resources and summed these to generate a total cost for the whole initial hospitalisation admission period. Total NHS resource use for the index hospitalisation was obtained from patient-level data in TARN and the key resource use variables for costing included time of arrival, time of emergency department departure, time of first operation, time of death/discharge, number and type of operative procedures and volume of blood transfusions that were required. Secondary care contacts and episodes of care that were commenced between the date of discharge from the index hospitalisation through 6 months post randomisation were sourced, where available, through linkage of patient records to the Hospital Episode Statistics database. All costs are reported from a UK NHS perspective in Great British pounds (GBP) (year 2020-1).

Quality of life was measured using the EQ-5D-5L prior to patient's discharge from their index hospitalisation and at 6 months post admission. EQ-5D-5L asks respondents to report any problems on a given day across five dimensions of mobility, self-care, usual activities, anxiety/depression and pain. The data were available from TARN and supplemented with data collected by the local trial teams. EQ-5D-5L data were cross-walked to the 3L version and valued using UK general population preference tariffs. Baseline utility was set equal to the unconscious state (-0.402) and utility following death was

set to 0. QALYs were calculated using an area under the curve approach assuming linear extrapolation between time points.

From the within-trial health economic analysis, participants in the standard care plus REBOA arm of the study incurred lower costs {index hospital admission: mean cost £57,384 [standard deviation (SD) £62,863]} compared to those in standard care [mean cost £116,064 (SD £128,957)]. Lower costs in the standard care plus REBOA arm of the study were mainly due to lower use of hospital resources (length of stay, etc.) due to the competing risk of death (i.e. a higher number of deaths in the REBOA plus standard care group). Similarly, life-years accrued and QALYs over 6 months post randomisation were also lower in standard care plus REBOA compared to standard care due to a greater proportion of trial participants dying, with mortality also occurring earlier in the follow-up period for the REBOA arm. The mean life-years gained in the standard care plus REBOA arm was 0.232 (SD 0.247) compared to 0.305 (SD 0.236) in the standard care arm.

When modelled over a full lifetime horizon, standard care plus REBOA is less costly (probability 99%), due to the competing risk of mortality but is also substantially less effective in terms of QALYs accrued over a lifetime horizon (probability 91%). The findings are robust to a range of scenario analyses undertaken, with the probability of standard care being the optimal treatment strategy ranging from 66% to 81% at a threshold value of a QALY = £50,000.

Process evaluation

The process evaluation was conducted in two phases; both phases involved interviews with clinical and research staff based at recruitment sites. Phase 1 was designed to identify barriers during trial initial and set-up; Phase 2 focused on exploring barriers and facilitators of recruitment into the trial and intervention delivery. A behavioural framework was used in Phase 2 to direct analysis and generate solutions designed to enhance trial practices, which included regular online meetings between the principal investigators from each site, updates to training materials and delivery, and e-mail/Twitter feedback on recruitment activity.

Conclusions

This is the first randomised trial ever to be conducted examining the potential clinical effectiveness of REBOA for the management of exsanguinating haemorrhage. All the analyses conducted suggest with high probability that a strategy of standard care plus REBOA is harmful.

Implications for health care: The continuing use of REBOA, at least in the UK in-hospital setting, should be re-evaluated.

Implications for research: The role (if any) of REBOA in the pre-hospital setting remains unclear. Further research to clarify its potential (or not) may be required.

Trial registration

This trial is registered as ISRCTN16184981.

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Chapter 1 Introduction

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Trauma is a major cause of death and disability. Trauma (physical injury) disproportionately affects the young, killing those who might otherwise have lived long and productive lives.² It is the leading cause of death for children and adults under the age of 46, accounting for nearly half of all deaths in this age group.³ Taken together, traumatic injuries account for more years of potential life lost before age 75 years than any other cause, including cancer or heart disease.^{2,4-6}

The most common cause of *preventable* death after injury is haemorrhage. The natural history of uncontrolled haemorrhage is of falling cardiac output and hypotension and ultimately failure of compensatory mechanisms with consequent cerebral and myocardial hypoperfusion, leading to death.⁷

Non-compressible torso haemorrhage (haemorrhage originating from within the torso) is particularly challenging, as bleeding generally cannot be controlled without surgery or angioembolisation.⁸⁻¹⁰ In patients in whom haemorrhage is either unrecognised or torrential, exsanguination (severe loss of blood) and death occur prior to definitive hemostasis.⁵ However, when haemorrhage is controlled expeditiously, patients often recover.¹¹

Temporary aortic occlusion can limit haemorrhage and help to maintain perfusion to the heart and brain, and is associated with improved survival.¹²⁻¹⁴ An adjunctive intervention to temporarily control haemorrhage is thus conceptually attractive, and could potentially reduce the number of haemorrhage-related deaths, and deaths overall.

Resuscitative endovascular balloon occlusion of the aorta (REBOA) is a novel technique whereby a percutaneously inserted balloon is inflated in the aorta (*Figure 1*), potentially providing a relatively quick means of temporarily controlling haemorrhage, by markedly reducing distal blood pressure and blood flow, and therefore blood loss, until definite control of haemorrhage (usually by means of an operation or sometime angioembolisation) can be obtained.

Resuscitative endovascular balloon occlusion of the aorta increases cardiac afterload and proximal aortic pressure, and thus improves perfusion of the heart and brain; and large animal models of uncontrolled haemorrhage have shown REBOA to be highly effective.¹⁵⁻¹⁸ However, REBOA is not without potential risks. Insertion of the device is technically challenging – arterial cannulation in patients with profound haemorrhagic shock is difficult. Failure to insert the device could waste valuable time that would

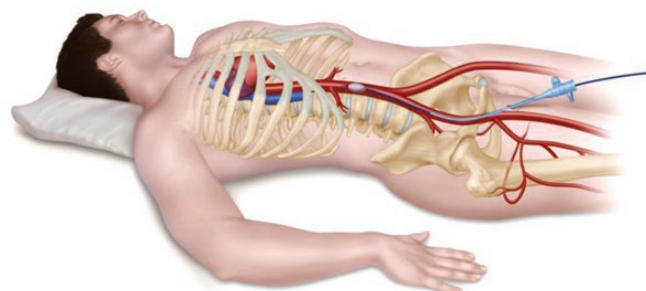


FIGURE 1 Resuscitative endovascular balloon occlusion of the aorta, deployed via the right common femoral artery. Reproduced from Jansen *et al.* (2022).¹

potentially be better spent taking the patient directly to an operating theatre, to obtain surgical control of bleeding. Insertions may also be associated with major damage to blood vessels. Even if the balloon is successfully deployed, the (intentional) severe reduction in distal blood pressure and blood flow, unless very short, can result in impaired tissue perfusion, ischaemic damage or thromboses, which may be irreversible.

The current evidence for REBOA in injured humans is limited and conflicting. There are a number of case series;¹⁹⁻²¹ cohort studies (retrospective and prospective),²²⁻²⁵ with divergent results; and several scoping reviews, systematic reviews and meta-analyses.²⁶⁻³⁰ There are also military clinical practice guidelines³¹ and a position statement from the American College of Emergency Physicians and the American College of Surgeons.³² However, there are no randomised clinical trials.

The objective of the UK-REBOA trial was to establish the clinical and cost-effectiveness of REBOA in addition to standard care (SC), as compared with SC alone, for the management of uncontrolled torso haemorrhage, in specialist major trauma centres (MTCs).

In [Chapter 2](#), we describe the trial design and methodology. [Chapters 3](#) and [4](#) describe the elicitation exercise (undertaken to inform the Bayesian analysis) and the mixed-methods trial process evaluation, respectively. In [Chapters 5](#) and [6](#), we present the baseline characteristics of the study population and the clinical results. In [Chapters 7](#) and [8](#), we describe the health economic evaluation and the health economic decision modelling, respectively. Finally, in [Chapter 9](#), we discuss the results of the trial and consider implications for practice and recommendations for research.

Chapter 2 Trial design and methods

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Overview

The UK-REBOA trial was a pragmatic, multicentre, Bayesian, group-sequential, open-label parallel-group, two-arm randomised controlled trial (RCT) comparing SC plus REBOA and SC. The aim was to recruit 120 adult patients with exsanguinating torso haemorrhage. The primary outcome was 90-day mortality.

We adopted a Bayesian approach to maximise the information that could be gathered with the relatively small sample size that was available. A Bayesian design is fundamentally different to the more traditional frequentist design in that it gives the probability of a specific treatment effect, given data from however many cases are available, rather than a p -value approach and a judgement that an effect is statistically significant (or not). It can also incorporate prior information about an intervention and effectively uses data from the trial patients to update what is known about an intervention. The Bayesian paradigm also fits well with clinical decision-making as it gives an estimate of the direct probability of a specific treatment effect given the data, rather than a more statistical p -value which can be harder to interpret directly. Additionally, the Bayesian framework is well suited to allowing interim analyses (it does not require the same level of inflation of the overall Type I error as in the frequentist approach). The trial design is summarised in [Figure 2](#). Participants were recruited to the trial and were followed up for 6 months post randomisation.

The trial protocol has been published in an open access journal¹ and is available on the project web page at <https://fundingawards.nihr.ac.uk/award/14/199/09>.

The University of Aberdeen and NHS Grampian co-sponsored the trial. The trial was approved by the Greater Manchester South Ethics Committee (REC), reference 17/NW/0352, Integrated Research Application System (IRAS) 226135. The study was prospectively registered on the International Standard Randomised Controlled Trial Number (ISRCTN) website (www.isrctn.com) on 23 August 2017 as ISRCTN16184981.

The study included an elicitation, described in [Chapter 3](#), an embedded mixed-methods process evaluation described in [Chapter 4](#), and a health economic evaluation described in [Chapters 7](#) and [8](#). The dedicated methods for these individual components are described in the respective chapters.

Eligibility criteria

The trial sought to enrol trauma patients with exsanguinating haemorrhage, in the emergency department (ED).

Inclusion criteria

Patients were eligible if they met the following criteria:

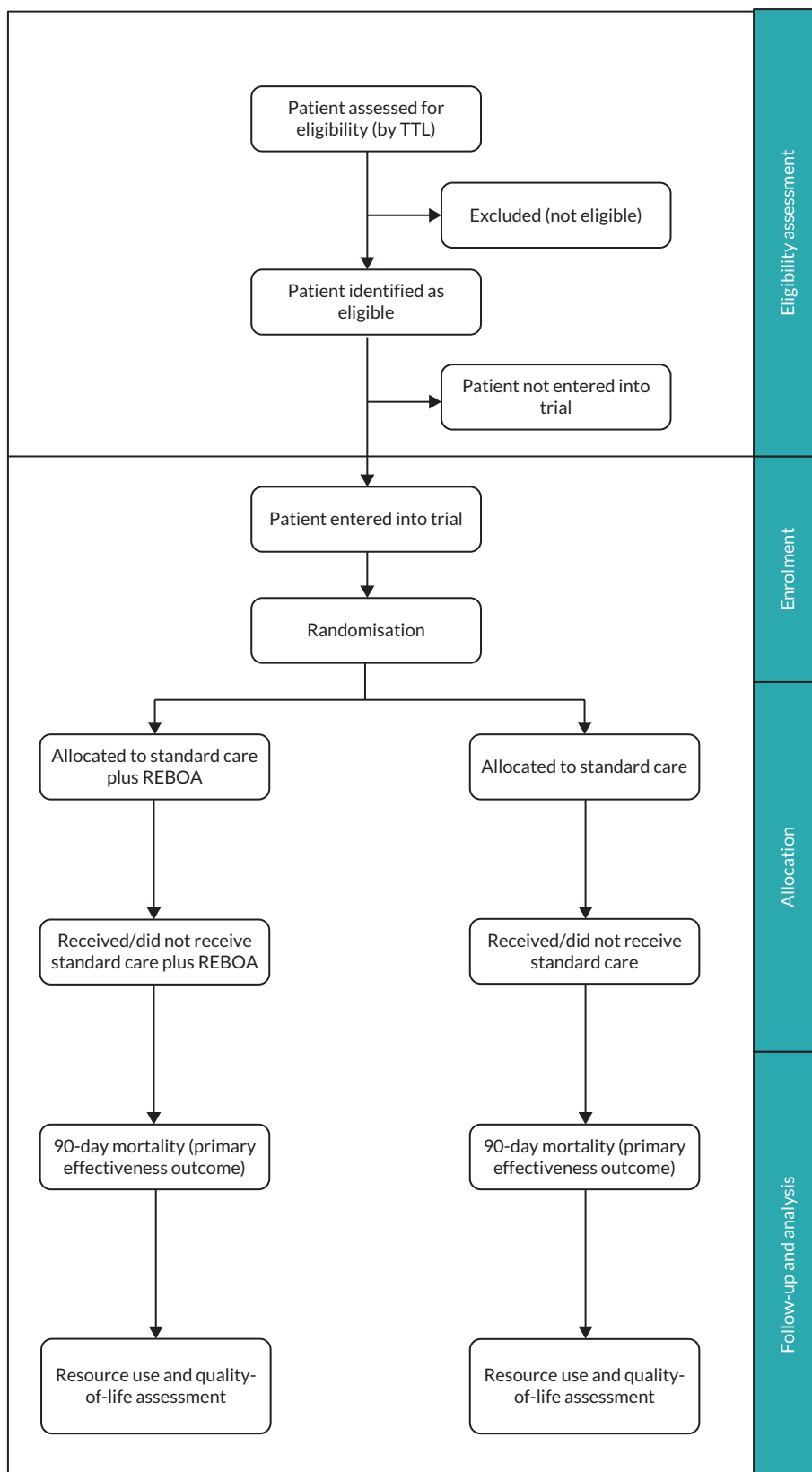


FIGURE 2 Trial design TTL, trauma team leader.

1. aged, or believed to be aged, 16 years or older
2. with confirmed or suspected life-threatening torso haemorrhage
3. which was thought to be amenable to adjunctive treatment with REBOA.

These criteria were chosen because they reflect the global assessment that expert clinicians intuitively perform when evaluating severely injured patients, and the pressured clinical setting in which this research has to be conducted.

Exclusion criteria

Women known or thought to be pregnant at presentation and patients with who that were deemed clinically unsurvivable were excluded.

Study setting

The trial was conducted in 16 MTCs in England (see [Appendix 2](#)). MTCs are specialist, tertiary centres designated to provide definitive care for seriously injured patients. Screening, recruitment and baseline data collection took place in the EDs of these MTCs. Patients were followed up to discharge from acute care, and by using data linkage after discharge.

Recruitment

Patients were deemed eligible for recruitment and appropriate for randomisation based on the assessment of the trauma team leader (TTL) – typically a consultant in emergency medicine, surgery or anaesthesia identified as the designated TTL – in the ED.

Assignment of interventions: sequence generation

Patients were enrolled by the TTL, or delegate, using a dedicated and secure website, accessible from handheld devices such as smartphones, tablets (one of which was provided to each centre) or a desktop computer in the resuscitation area. This mechanism took cognisance of the extreme acuity with which eligible patients would present and minimised distraction of the medical team. The website linked directly to the 24-hour randomisation system at the Centre for Healthcare Randomised Trials (CHaRT), based in the Health Services Research Unit (HSRU), University of Aberdeen. All TTLs and research staff were issued usernames and passwords for the randomisation website. The website was designed to require minimal data entry, so as not to distract clinicians from delivering life-saving care. Randomisation to SC or SC plus REBOA was in a 1 : 1 allocation ratio, by permuted blocks (in randomly generated blocks of two and four), in order to reduce predictability and selection bias.

Once a user had logged in, they saw image (a) shown in [Figure 3](#), with the 'Test Centre' field auto-populated with the user's hospital name. Users who worked in more than one MTC were able to select which site they were in.

In order to randomise a patient, a simple ID (such as the patient's 'trauma name' or record number) had to be entered. These data were used to subsequently link to patients' records, but was not included in the case report form (CRF).

The user then had to press 'Randomise'. The system then returned the patient's allocation status [images (b) and (c) in [Figure 3](#)].

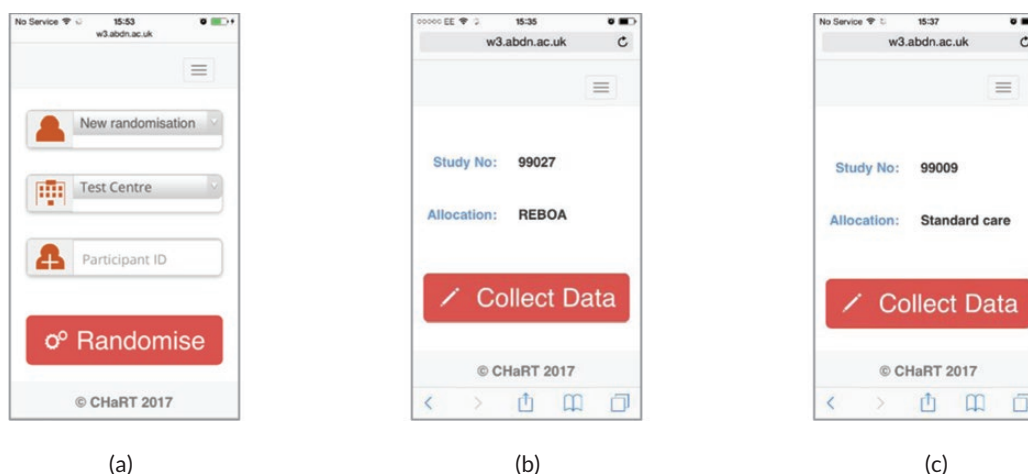


FIGURE 3 The randomisation system. (a) Randomisation screen; (b) Output of randomisation – randomised to SC + REBOA; and (c) Output of randomisation – randomised to SC.

Concealment

This was an open-label study. However, the allocation sequence was concealed from the TTL until they logged into the dedicated website and randomised the patient. They were then notified which intervention arm the patient had been randomised to (see [Figure 3](#)).

Consent

Patients who were eligible for inclusion in the trial were incapacitated and unable to give consent at the time of eligibility assessment and randomisation. Similarly, there was not sufficient time to consult a surrogate decision-maker or even an independent medical practitioner for advice about including the patient. Enrolment therefore took place without prior consent following appropriate ethics approval for this approach. There is a legal provision and precedent³³ for conducting research in these circumstances, in England, in the form of the Mental Capacity Act (2005) (for trials that are not Clinical Trials of Investigational Medicinal Products).

Consent for continuing participation (i.e. data collection) was sought from the patient by a member of the UK-REBOA trial team taking care of the patient at the hospital site once they were no longer in a critical condition or from a personal (or nominated professional) consultee. This was defined as being cared for in a ward area [rather than an intensive care unit (ICU) or high-dependency unit (HDU)]. We did not seek consent when patients died before consultees could be approached.

Intervention and comparator description

Patients were randomised to one of two treatment arms:

Standard care: Patients allocated to the control group received ‘SC’, as expected in a specialist MTC. Such treatment typically included intubation, blood transfusion including blood products in a 1 : 1 : 1 ratio, and early operative or endovascular haemorrhage control. Treatment could also have included open aortic occlusion of the thoracic or abdominal aorta.

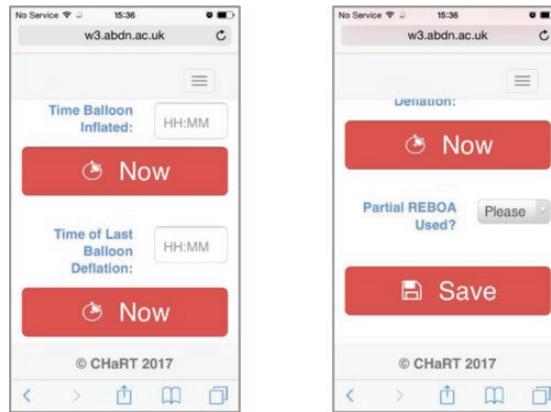


FIGURE 4 Data collection tool within the study website.

Standard care plus REBOA: Patients allocated to this arm would also receive the technique of endovascular aortic occlusion, in the ED for the purpose of resuscitation, as part of an overall treatment strategy. The addition of REBOA to current standard treatment was intended to provide earlier, temporary haemorrhage control to facilitate transfer to an operating theatre or interventional radiology suite for definitive haemostasis. The trial sought to evaluate the *technique* of REBOA rather than a specific brand of device, and therefore permitted the use of any licensed occlusion balloon, and did not prescribe or mandate a particular product.

In line with observed changes in the clinical condition of the patient following randomisation, in patients who had been randomised to the SC plus REBOA arm of the trial, clinicians were at liberty to not insert the balloon occlusion device if: the patient's haemodynamic status improved (either spontaneously or as a result of ongoing blood transfusions) as they were deemed to no longer have life-threatening torso haemorrhage amenable to adjunctive treatment with REBOA; they deteriorated (to the point of imminent death); or there was technical difficulty in obtaining arterial access, and it was felt that operative control of haemorrhage could be obtained more quickly. Patients were also free to withdraw from the study.

The duration of balloon inflation is important, as prolonged occlusion of the aorta leads to profound distal ischaemia and (if the balloon is deflated) reperfusion injury, which can be fatal. Balloon inflation and deflation times are often inaccurately recorded in clinical practice, and these data points were therefore included on the website used to enrol and randomise patients. Once a patient had been randomised to SC plus REBOA, a new screen appeared on which the time of balloon inflation and final deflation (if there were multiple attempts) could be recorded ([Figure 4](#)). In addition, if partial occlusion was used (to allow some blood flow to the lower part of the body), this could also be recorded.

Outcome

Primary outcome

The *primary clinical outcome* was 90-day mortality (defined as death within 90 days of injury, before or after discharge from hospital). This outcome was intended to capture any potential late harmful effects of REBOA.

The *primary economic outcome* was lifetime incremental cost per quality-adjusted life-year (QALY) gained, modelled over a lifetime horizon, from a health and personal social services perspective.

Secondary outcome

Secondary clinical outcomes included 3-, 6- and 24-hour mortality, in-hospital mortality, 6- month mortality, length of stay (in hospital and ICU), 24-hour blood product use, need for haemorrhage control

procedure (operation or angioembolisation), time to commencement of haemorrhage control procedure, complications/safety data and functional outcome [measured using the extended Glasgow Outcome Scale (GOS-E) at discharge].

Secondary economic outcomes included 6-month costs from a health service and personal social services perspective, as well as quality of life [measured using EuroQol Group's 5-dimension health status 5-level questionnaire (EQ-5D-5L)] at 6 months; and incremental cost per QALY gained at 6 months.

To note, the clinical outcomes were chosen prior to the publication of a core outcome set for patients undergoing REBOA,³⁴ and prior to the publication of recommendations regarding the choice of outcomes for haemorrhage control trials.³⁵

Sample size

The concept of an effect size and an associated sample size calculation does not figure per se in a Bayesian framework. Instead, a Bayesian trial gives the probability of a specific treatment effect, given data from a set number of cases. Therefore, we designed the trial around the available number of patients, rather than calculating a minimum sample size required, based on a retrospective study of national Trauma Audit and Research Network (TARN) data.¹⁶ 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, and further estimated that we would be able to enrol 120 patients over a period of 3 years, with a staggered start to recruitment across the sites. Actual enrolment rates in early sites were lower than our original estimates, and we therefore added a further six MTCs. (Trauma is less common in the UK than in, for example, the USA, and ballistic injuries caused by gunshot wounds in particular are rare.)

Data collection and management

The data collection strategy for the UK-REBOA trial was designed to minimise the burden on participants and clinicians and the avoidance of duplication. The trial drew on routinely collected data (all major trauma patients are audited), primarily from the TARN registry, and was effectively a registry-enabled RCT, although the case identification was not based on the registry, and the linkage occurred later. A summary of the within-trial data collection is shown in [Table 1](#).

TABLE 1 Schedule of data collection

	Up to 24 hours	ICU discharge	Hospital discharge	90 days	6 months
Mortality	✓		✓	✓	✓
Length of stay		✓	✓		
Blood product use	✓				
Need for haemorrhage control procedure	✓				
Time to commencement of haemorrhage control procedure	✓				
EQ-5D-5L			✓		✓
GOS-E			✓		
Resource use and costs	✓	✓	✓		✓
Complications			✓		

Trauma Audit and Research Network National Trauma Registry data

Data on the treatment of trauma patients are routinely collected by TARN, the national trauma registry for England, to which all MTCs are required to submit data. TARN collects demographic, injury, treatment and outcome data [including the GOS-E, and – through a third-party provider – patient-reported outcome measures, including EQ-5D-5L]. Data collected by TARN directly are reported to be very complete and of high quality.³⁶

NHS digital data

In addition to drawing on TARN data, the trial also linked to NHS England's Hospital Episode Statistics (HES) data to obtain information on hospital resource use and to Office of National Statistics (ONS) data for medium-term (6-month) mortality.

Mortality

Survival status and, where applicable, date and time of death were recorded in both the TARN and ONS data. However, in order to minimise delays in reporting, we also obtained death data directly from sites.

EuroQol Group's 5-dimension health status 5-level questionnaire

EuroQol Group's 5-dimension health status 5-level questionnaire data were also collected. These were initially to be collected directly from the TARN registry. Following the first TARN linkage, it became clear that the EQ-5D-5L results collected by the third-party provider contracted by TARN were incomplete. We therefore asked sites to collect EQ-5D-5L data prior to discharge, and subsequently, at approximately 6 months after randomisation, by telephone.

Data management

Data were entered directly into electronic case report forms (eCRFs) on the UK-REBOA trial website.

Confidentiality

Data collected during the course of the research were kept strictly confidential and only accessed by members of the UK-REBOA trial team (or individuals from the sponsor organisation or recruitment sites where relevant to the trial). Participants were allocated an individual study number upon randomisation. Participants' details were stored on a password-protected database and only accessible to the study team. Participant's data were fully anonymised for analysis and reporting.

Statistical methods

The statistical methods for the clinical outcomes are described below. The methods for the health economics analysis are described in [Chapters 7](#) and [8](#).

General rules for statistical analysis

The trial analysis followed a statistical analysis plan (see additional files www.fundingawards.nihr.ac.uk/award/14/199/09; accessed June 2024), which was agreed in advance by the Trial Steering Committee (TSC). The main analysis was based on the intention-to-treat (ITT) principle (i.e. analysed as randomised). There were two planned interim analyses for survival (see [Interim analyses](#)) and a final analysis on all outcomes after follow-up was complete. The interim analyses were timed to occur when one-third and then two-thirds of the expected number of patients had been recruited (in line with the recruitment projections) and completed the 90-day follow-up. We wanted to ensure that, should the intervention be deemed beneficial or indeed harmful at an early stage, the number of patients unnecessarily exposed in the trial would be minimised (especially given the concerns raised in one of the previous studies

of REBOA of potential for harm). Baseline and follow-up data were summarised using appropriate descriptive statistics and graphical summaries. Treatment effects are presented with 95% credible intervals (CrIs) for the primary and secondary outcomes. Unless stated, all analyses were carried out using Stata 17.³⁷

Analysis of primary clinical outcome

The number of eligible patients was known to be small, and we therefore adopted a Bayesian inferential framework for this trial, which has been described in detail in another publication.³⁸ The primary end point was the log odds ratio (OR) of 90-day mortality after MTC treatment with REBOA, compared to MTC treatment alone:

$$\log \left(\frac{\frac{p_R}{1-p_R}}{\frac{p_S}{1-p_S}} \right) = \log \left(\frac{p_R(1-p_S)}{p_S(1-p_R)} \right) = \log \left(\frac{p_R}{1-p_R} \right) - \log \left(\frac{p_S}{1-p_S} \right) = \delta$$

where p_R and p_S are the proportions of patients who died, to 90 days, after SC plus REBOA and SC, respectively.

Bayesian designs permit the inclusion of prior information about δ . The final analysis of the trial used a Bayesian logistic regression with 200,000 iterations allowing for 10,000 iteration burn-in and checking for convergence using autocorrelation and trace plots. We used a range of prior probability distributions, to contextualise the trial's findings. This approach has been used in a number of recent studies.^{39,40} A minimally informative prior was on the log OR of $N(0, 1.28^2)$ which rules out extreme ORs, and a non-informative prior on the intercept of $N(0, 10^2)$. The enthusiastic priors were obtained through elicitation and are described in [Chapter 3](#). We also present a Kaplan–Meier survival curve.

Analysis of secondary outcomes

Secondary outcomes were also analysed using a Bayesian approach with 200,000 iterations allowing for 10,000 iteration burn-in and checking for convergence using autocorrelation and trace plots. For 3-, 6- and 24-hour mortality, in-hospital mortality, 6-month mortality, need for haemorrhage control procedure and complications/safety, logistic regression was used using the same minimally informative prior as the primary outcome on the log OR and a non-informative prior on the intercept. For length of stay and time to commencement of haemorrhage control procedure, linear regression using non-informative priors was used. GOS-E was analysed using ordered logistic regression and 24-hour blood product use was analysed using negative binomial regression both with non-informative priors.

Sensitivity analysis

Adjusted analysis

The primary outcome, 90-day mortality and 3, 6, 24 hours, in-hospital, and 6 months mortality were unadjusted for any covariates; however, we also pre-specified covariates that might be important to adjust for. These were age, gender, Injury Severity Score (ISS), Abbreviated Injury Scales (AIS), pre-hospital cardiopulmonary resuscitation (CPR), systolic blood pressure (SBP) on arrival in the ED, CPR on arrival in ED and time from arrival to randomisation. We also did a post hoc analysis adjusting for centre as a random effect.

Learning curve effect

There is the possibility that there could have been a learning curve effect at the site level. The learning curve was undertaken at site level as the management of major trauma cases involves the whole team (and not just the REBOA operator). As such, the whole team were learning how to integrate REBOA into their management pathway. Therefore, a sensitivity analysis removing the first participant randomised to SC plus REBOA from each site was done with the same analysis as for the primary outcome analysis.

Competing risk

For length of stay, death is a competing event, therefore a competing risks analysis was done.

Interim analyses

We had planned two interim analyses, after 40 and 80 randomised participants, and a final analysis after the expected maximum of 120 randomised participants. This analysis was based on survival and not mortality.

The stopping rules included:

Harm: Defined by the probability that the 90-day survival OR fell below 1 (i.e. REBOA is harmful) at the first or second interim analysis, was 90% or greater. More formally, our Bayesian futility criterion at each stage was $P(\delta < 0 | \mathbf{y}) \geq 0.9$, where δ is the log OR and \mathbf{y} is the observed data.

Success: REBOA would be declared 'successful' if the probability that the 90-day survival OR exceeded 1 at the final analysis was 95% or greater, so our Bayesian success criterion was defined as $P(\delta > 0 | \mathbf{y}) \geq 0.95$. Our calculations are based on an estimated control group (standard MTC treatment alone) with a 90-day survival rate of 66.5%.¹⁶

In short, the trial would stop if the posterior probability for harm was 90% or greater, or the posterior probability for benefit was 95% or greater at either interim analysis.

Methods in analysis to handle classifying and analysing protocol non-adherence

We recognised that a number of patients who were randomised to REBOA might not proceed to have full balloon occlusion, for a variety of clinical reasons. These patients are not 'cross-overs', but sit on a spectrum of how far a patient progresses down a REBOA-strategy pathway, depending on intercurrent events. There are three main types of intercurrent events:

1. technical failure (inability to achieve arterial access/insert the device)
2. patients improved as a result of other resuscitative measures, and REBOA no longer indicated
3. patients deteriorated, and REBOA no longer possible.

We classified patients, in line with clinical scenarios encountered, as follows:

- R0 REBOA deemed inappropriate, decided against.
- R1/C1 Arterial access not attempted (patient improved).
- R1/C2 Arterial access not attempted (patient deteriorated).
- R2 Arterial access attempted, but unsuccessful.
- R3/C1 Arterial access achieved, no balloon insertion (patient improved).
- R4/C1 Catheter inserted, but balloon not inflated (patient improved).
- R5 Catheter inserted, balloon inflated.

Classifying patients in this way allowed us to consider the impact of these intercurrent events.⁴¹

We conducted three analyses to accommodate for the intercurrent events, which answered slightly different questions. The first (the main analysis) relates to effectiveness, whereas the second and third relate to efficacy and safety.

QUESTION 1: 'Does a strategy that includes REBOA (in addition to standard MTC care) reduce the mortality of exsanguinating trauma patients, ignoring all intercurrent events (such as REBOA not being deployed due to clinical improvement, deterioration, or technical failure)?'

This is the ITT analysis, and is relatively straightforward. It is the 'policy question' (that healthcare policy-makers want answered) and evaluated the effectiveness (the principal aim of the trial) in a pragmatic fashion. The problem is that, with many patients who were randomised to REBOA not progressing to full

occlusion given clinical changes in the patients, the estimate of the treatment effect was conservative (due to potential dilution of treatment effect).

The totality of the REBOA arm tells us what happens in real-life clinical practice, but the interpretation of the results is complex. In order to address the issue of these intercurrent events, we conducted two principal stratum/complier average causal effect (CACE) analyses. These analyses are preferable to a traditional per-protocol analysis, which wastes data and is subject to selection bias.⁴² The analysis used a two-staged residual inclusion estimator approach with non-informative priors. For safety, we also did an as-treated analysis using non-informative priors. CACE assumes that the patients in the SC 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 SC arm would be expected to improve/deteriorate or be difficult to cannulate.

We debated the use of the term 'compliance'. Although widely established in the statistical/methodological literature, it does not translate well to the circumstances observed in REBOA. Firstly, patients in the UK-REBOA trial were not 'non-compliant'. Decisions regarding whether REBOA was still indicated, or not, were made by doctors. However, doctors were also not 'non-compliant' since the decision not to proceed with insertion was not arbitrary but forced on the provider by intercurrent events.

We believe that better terms to indicate the extent of REBOA treatment received are 'strategy' or 'pathway'. However, since the term 'compliance' is established in the CACE analysis literature, we have retained it for the presentation of the CACE analyses.

QUESTION 2: *'Does a strategy that includes REBOA (in addition to standard MTC 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)?'*

Patients in the non-R5 categories were not excluded from the analysis. CACE analysis simply assumes that there would have been an equal proportion of these patients in the SC arm.

QUESTION 3: *'Does a strategy that includes REBOA (in addition to standard MTC care) reduce the mortality of exsanguinating trauma patients; when there is no technical failure?'*

For the purpose of this analysis, we defined 'compliance' (with the caveats regarding the terminology noted above) as patients who were classified as anything other than R2 and 'non-compliance' as all patients classified as R2 (arterial access attempted but unsuccessful).

Intervention implementation and training

Most of the participating sites had not used REBOA previously. The implementation strategy had three components.

Initial training

We designed a custom intervention 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 largely based on experience at the Royal London Hospital, as well as the Basic Endovascular Skills for Trauma and Endovascular Skills for Trauma and Resuscitative Surgery courses. Training was initially spread out over 2 days, but after delivering four of the courses, and following feedback from hospitals, we decided to compress the training into a single day. The training was delivered by two senior clinicians, and comprised a small number of didactic tutorials (indications, team organisation, imaging, ethics,

post-REBOA management), followed by small group work, focusing on equipment familiarisation, individual skills training and team training. The tutorials were intended to provide background, recognising the diverse clinical backgrounds of the participants. 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.

Development of a local service delivery and training framework, for ongoing skill development and training of new staff

Recognising the importance of ongoing and reminder training, we worked with sites to develop a sustainable, local service delivery and training framework. This involved the designation of 'super-users' and 'training leads' who organised regular refresher training, and initial training for new staff.

Reminder training sessions

The nature of the reminder training session was left to sites, but typically included discussion regarding clinical decision-making, application of the inclusion criteria, ethical considerations, post-REBOA management of patients, as well as simulations using a mannequin (provided by the trial).

Oversight and monitoring

Project Management Group

The study was led by CHaRT, a UK Clinical Research Collaboration registered Clinical Trials Unit in HSRU at the University of Aberdeen. The Project Management Group (PMG) consisted of the two co-Chief Investigators (co-CIs), a Senior Trial Manager, a Trial Manager and a Data Coordinator.

Trial Steering Committee

The trial was overseen by an independent TSC, which included a chairperson, a clinician, a statistician and two patient/public representatives. The TSC met at least annually. The TSC adhered to a charter that they agreed and signed at the start of the trial.

Data Monitoring Committee

The trial was monitored by an independent Data Monitoring Committee (DMC) who also oversaw the interim analyses. The DMC met at least annually, and reported to the TSC. The DMC adhered to a charter that they agreed and signed at the start of the trial.

Adverse event reporting and harms

As this study was recruiting trauma patients with life-threatening injuries and a high chance of dying, it was expected that many of the patients would experience events that are the consequence of the patient's life-threatening injuries, resulting critical illness and treatment. All adverse events (AEs)/device effects occurring between randomisation and discharge were recorded in the appropriate eCRF and closely monitored by the oversight committees.

Expected complications

Death and a number of expected complications (including some which result in life-threatening illness, permanent impairment of structure or function, additional medical or surgical intervention, or prolonged hospital stay) were pre-specified outcomes and therefore not reported as serious adverse events (SAEs) or serious adverse device effects (SADEs). Only unexpected SAEs/SADEs were to be reported to the sponsor.

Adverse events related to REBOA

The following AEs could be expected to occur as a result of using REBOA.

- Access-related adverse device effects (ADEs): External haemorrhage at insertion site requiring treatment other than simple pressure, pseudoaneurysm, arteriovenous fistula, dissection of artery, extremity ischaemia, stenosis of artery, distal embolism, air embolism, infection requiring surgical intervention, need for patch angioplasty (surgical repair), need for arterial bypass, need for amputation.
- Other ADEs: Balloon rupture, aortic rupture, side branch cannulation.

Adverse events related to standard treatment

The following AEs could be expected to occur as a result of standard aortic occlusion by means of a thoracotomy or laparotomy:

- AEs related to external thoracic aortic occlusion: Descending thoracic aortic injury, lung injury/bronchopleural fistula, cardiac injury, oesophageal injury, empyema, wound infection requiring surgical intervention, sternal non-union, rib fractures, extremity ischaemia, distal embolism, infection requiring antibiotics only, infection requiring surgical intervention.
- AEs related to external abdominal aortic occlusion: Abdominal aortic injury, wound infection requiring surgical intervention, extremity ischaemia, distal embolism, infection requiring antibiotics only, infection requiring surgical intervention.

Adverse events common to both treatments

- AEs related to impaired organ perfusion: Acute kidney injury requiring renal replacement therapy, mesenteric ischaemia requiring surgical intervention, paraplegia (permanent), paraplegia (temporary), acute respiratory distress syndrome, stroke (embolic or hypoperfusion-related), multiorgan failure.

Adverse event/device effect reporting

The principal investigator (PI) at each site, or their delegated investigator, was responsible for recording and reporting of AEs/ADEs observed during the study period on a trial-specific AE and SAE/SADE eCRF. The PI attempted, if possible, to establish a diagnosis based on the participant's signs and symptoms. When a diagnosis for the reported signs or symptoms was known, the PI reported the diagnosis as an AE/ADE, rather than reporting the individual symptoms.

Serious adverse event/device effect reporting

All events meeting the study definition of a SAE or SADE were to be entered onto the SAE/SADE eCRF and submitted to the central trial office within 24 hours of the PI becoming aware of the event. The PI at the site was instructed not to wait until all information about the event was available before notifying the trial office of an SAE/SADE. Information not available at the time of the initial report was documented on a follow-up SAE/SADE eCRF. Follow-up information was sought and submitted as it became available. The follow-up information described whether the event had resolved or persisted, if and how it was treated and whether the patient continued on the study or had been withdrawn from treatment. Once received, seriousness, causality and expectedness were confirmed by the Chief Investigator (CI or delegated clinical lead).

Unanticipated serious adverse device effects

Unanticipated serious adverse device effects (USADEs) were defined as SAEs that were deemed to be related to the study device or any of the research procedures and were unanticipated. USADEs were to be notified to the sponsor and Research Ethics Committee (REC) within 15 days of the trial office becoming aware of the event.

Assessment of seriousness

The PI or designee made an assessment of seriousness. As stated above, death and a number of expected complications (including some that result in life-threatening illness, permanent impairment

of structure or function, additional medical or surgical intervention, or prolonged hospital stay) were pre-specified outcomes and were therefore not reported as SAEs/SADEs.

Assessment of causality

The PI or designee was instructed to make an assessment of the causality (i.e. relationship to trial device). Events that were possibly, probably or definitely related to the device were defined and reported as related to the device. Events that were assessed as possibly related or unrelated were defined as not being related. This was determined as follows: (1) Definitely: There was clear evidence to suggest a causal relationship, and other possible contributing factors could be ruled out. (2) Probably: There was evidence to suggest a causal relationship, and the influence of other factors is unlikely. (3) Possibly: There was some evidence to suggest a causal relationship (e.g. the event occurred within a reasonable time after using the device). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant events). (4) Unlikely: There was little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial intervention). There was another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatments). (5) Not related: There was no evidence of any causal relationship. (6) Not assessable: Unable to assess the information available.

Assessment of expectedness

The PI or designee made an assessment of expectedness for each SAE/SADE regardless of the causal relationship to the trial device.

Follow-up procedures

All AEs/ADEs assessed by the PI or designee as possibly, probably or definitely related to the device and all SAEs/SADEs that occurred during this time were to be followed until they were resolved or were clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es). The CRF was updated with the date and time of resolution or confirmation that the event was due to the patient's illness as soon as this information became available.

Recording and reporting of urgent safety measures

If the PI, designee or a member of study staff became aware of information that necessitated an immediate change in study procedure to protect clinical trial participants from any immediate hazard, they were instructed to report the urgent safety measure (USM) immediately to the trial office. The trial office would then report any USM immediately to the sponsor, and liaise with the sponsor and site to implement immediate procedures to eliminate any hazard. The trial office would also report immediately by telephone to the REC that had approved the study and follow this up with an e-mail written notice within 3 days of becoming aware of the USM. The e-mail notice would state the reason for the USM and the plan for further action. The PI or designee was to respond to queries from the trial office immediately to ensure the adherence to these reporting requirements.

Protocol amendments

Protocol amendments were agreed among the PMG and then categorised by sponsor before being reported for approval to the REC. There were five protocol amendments which are summarised in [Table 2](#).

Study documentation

Documentation used in the UK-REBOA trial is available in the additional files www.fundingawards.nihr.ac.uk/award/14/199/09 (accessed June 2024).

TABLE 2 Summary of protocol amendments

Version number, date	Summary of amendment
Version 2, 20 July 2017	<p>Change of contact details for CI Clarifications within the safety section of the protocol</p> <ul style="list-style-type: none"> • Removal of reference to abnormal laboratory findings in the definition of an AE (recommendation of TSC) • Reorganisation of some text • Removal of inaccurate text defining events and effects • Removal of reference to Appendix E <p>Revision to text describing the length of training sessions</p>
Version 3, 14 September 2017	Clarification of secondary outcomes (24-hour in-hospital mortality; safety data); addition of new secondary outcome (procedural performance details)
Version 4, 18 April 2019	<p>Addition of within-study collection of EQ-5D-5L to supplement routine TARN data and confirmation of plans for imputation of missing EQ-5D-5L clarification that:</p> <ul style="list-style-type: none"> • Patients are only eligible on presentation to a MTC • Randomisation can be done on any networked computer • A letter to the GP will only be sent if consent is given for this
Version 5, 15 November 2020	To update timelines to reflect 24 months extension to the study
Version 6, 25 November 2021	Addition of 3- and 6-hour mortality as secondary clinical outcomes

GP, general practitioner.

Breaches

One non-serious breach was reported to the sponsor during the study. This is related to the use of the Clinician Topic Guide in the process evaluation before it had been approved by the REC. As part of the corrective action, this document was submitted and approved by REC.

Patient and public involvement

As noted above, the TSC included two patient/public representatives. In the early stages of study development, they had opportunity to input into the study design, and to review and comment on protocol and associated documentation.

Chapter 3 Elicitation of prior probability distributions

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Background

When a clinical trial is being planned, there is usually some existing knowledge regarding the effect of the intervention. A Bayesian approach to design and analysis of clinical trials can explicitly consider such data, which is referred to as a prior probability distribution, or 'prior' for short. Although the design and main analysis of the UK-REBOA trial rely on a non-informative prior, which 'lets the data speak for itself', additionally, we planned to elicit and use informative priors to help contextualise the interpretation of our results.

Informative priors can be derived from a number of data sources. One option is to conduct an 'expert elicitation', a formal data acquisition process where experts are assisted in converting their knowledge into mathematical format.⁴⁴⁻⁴⁷ This method is particularly helpful when the evidence originates from divergent sources, which are difficult to summarise mathematically.

This chapter describes the elicitation exercise conducted as part of the UK-REBOA trial, to derive prior probability distributions to help contextualise the interpretation for the primary and secondary outcomes of the trial.

Methods

The methodology for conducting expert elicitations is well described. These studies typically require an in-person meeting, lasting hours or days, where the participants are introduced to the subject matter and Bayesian methodology. Several rounds of elicitations are conducted, with intervening analyses, presentation of results and discussion.

In-person elicitation meetings are time-consuming and expensive, and – during a pandemic – difficult to organise and justify. We therefore conducted a remote, online elicitation exercise.

Videoconferencing platform

We used the Zoom platform (Zoom Video Communications, San Jose, CA, USA). The process and the group discussions were moderated by the CIs of the UK-REBOA trial.

Framework

We used the Sheffield Elicitation Framework methodology, as described by O'Hagan.⁴⁸ We adhered to good practice recommendations for eliciting expert opinion^{47,48} including preparation of the participants for the elicitation workshop, use of an elicitation protocol approved by a REC, provision of feedback to experts and an opportunity to revise elicited responses.⁴⁸

Participants

We invited 20 subject matter experts to participate. All participants were from the UK, to reflect the setting of the trial. Invitees included the grant holders (with the exception of those involved with the design and conduct of the elicitation itself), as well as site PIs. We reasoned that these individuals would have both knowledge of the published evidence for using REBOA, and personal experience. Participants included emergency medicine physicians ($n = 12$); pre-hospital care doctors ($n = 3$); surgeons ($n = 4$) and intensivists ($n = 1$).

Quantities of interest

The quantities of interest chosen to inform the analysis of the UK-REBOA trial were those specified by the protocol: 90-day mortality (the primary outcome of the trial), 6-hour mortality, in-hospital mortality and 24-hour mortality (secondary outcomes). For each of these time points, we elicited experts' opinions regarding treatment with REBOA (in addition to SC), and without REBOA (SC alone).

Information provided in preparation for the elicitation

We provided participants in advance with an overview of the elicitation process and the concept of subjective probabilities, as well as an evidence dossier which included reference to known studies of REBOA. We provided no commentary on the studies in the evidence dossier so as not to introduce any bias into the process. The list of included studies is included in the evidence dossier in [Appendix 3](#). We also asked participants to provide us with any other published studies or abstracts of which they were aware. The dossier was distributed by e-mail the week prior to the elicitation.

Phases

On the day, the elicitation exercise was split into seven phases:⁴³

1. Presentation of background information on the UK-REBOA trial. We did not present evidence relating to the intervention at this point to avoid bias by 'anchoring' the participants.
2. Introduction to Bayesian principles, focusing on the distinction between probability under frequentist and Bayesian paradigms, and emphasising that Bayesian probability represents the subjective level of uncertainty of an event happening and can vary among individuals.
3. Introduction to quantities of interest and their parameters: lower and upper bounds and most likely value of mortality, at different time points, in patients treated with REBOA (in addition to SC) or SC alone.
4. Elicitation training exercise. We worked an example with the participants, using the same online tool used for the actual elicitation, to increase familiarity with the process.
5. Elicitation, first round: Participants' beliefs for the quantities of interest were elicited using the online elicitation tool. We calculated prior distributions for each participant's elicited beliefs, and then graphed and presented deidentified individual responses.
6. Group discussion. Participants were then encouraged to discuss their choices. We emphasised that the purpose of the discussion was not to come to a consensus but rather to calibrate individual opinions, and to resolve any questions relating to process.
7. Elicitation, second round: The second round was designed to allow participants to revise and calibrate their beliefs, and therefore used the same questions as the first. Participants were provided with an individual code, to allow first- and second-round responses to be compared. The results were, once again, presented as deidentified individual responses.

The elicitation was supported by a biostatistician, who explained the concepts and was available throughout the day to answer questions.

Data collection

We created an interactive online graphical tool, based on previous work by Mason *et al.*,⁴⁹ and our own work,⁴³ using R software and the Shiny package.^{50,51} The purpose of the tool was to allow participants to

use it online, while also following instructions/conversation on Zoom. It was also designed to be user-friendly and intuitive.

Participants were provided with individual log-ins, so that responses could be tracked. For each quantity of interest, participants were first asked to provide their 'most likely' (median) estimate for a given quantity of interest, using a slider. Participants were then asked to quantify their certainty by selecting lower and upper plausible values, again using a slider. Once participants had selected their values, they clicked a button which then displayed their selection as a probability density graph. An example screenshot is included in [Appendix 4, Figure 17](#). The choices could then be amended, with corresponding changes to the graphical output.

Individual responses were electronically submitted, and analysed in real time. The results (individual as well as pooled) were then displayed, again using Zoom's screen-sharing function, for discussion.

Derivation of prior probability distributions

To obtain the expert-elicited prior distribution for the model, we adopted the following strategy. We aggregated individual expert-elicited beta distributions into a single pooled distribution (at each time point for each of the intervention and control groups) considering equal weight for each expert. We then sampled 500,000 observations for each pooled distribution and calculated the OR of the sampled data of the intervention to the control group at a given time point. The log-transformed OR of the distribution was incorporated as the prior distribution in analysis models (see [Chapter 2](#) for details).

Mathematical aggregation of experts' judgement and parameterising the prior distribution

The following section outlines the approaches used to combine the expert knowledge into a single prior distribution, parameterise the pooled prior distribution for incorporating in a logistic regression model with Bayesian inferential framework in the context of a randomised control trial setting.

We describe here the strategy to aggregate K experts' judgement of the intervention and control arms using equal pooling and implementation of the algorithm in an RCT setting.

1. Capture individual expert judgement as a *beta* distribution and obtain the parameters of individual *beta* distribution for a given scenario (say, 6-hour mortality), that is one each for the intervention (I) and control (C) groups at a given time point

$$f_{gk}; g = I, C; k = 1, 2, \dots, K$$

2. Obtain the linear pool of the beta distributions of all experts (f_g), considering equal weight for each expert, for each of the intervention and control group.
3. Sample ($n = 500,000$) from the corresponding linear pool of the distribution for each of the intervention and control arm.

$$y_{gi} \sim f_g; g = I, C; i = 1, \dots, 500,000$$

4. Calculate the OR of mortality for the intervention to control arms.

$$OR_i = \frac{y_{Ii}/(1 - y_{Ii})}{y_{Ci}/(1 - y_{Ci})}; i = 1, \dots, 500,000$$

5. Calculate the logarithm of OR.

$$\log OR_i = \log (OR_i); i = 1, \dots, 500,000$$

6. Summarise the parameters of the distribution of log OR assuming a normal distribution with mean (μ) and variance (σ^2). The derived distribution (with mean and variance as hyperparameters) represents the prior distribution of the regression coefficient (intervention vs. control) of the logistic regression model. The prior distribution is defined as:

$$\log OR \sim \text{Normal}(\mu, \sigma^2)$$

Results

Process

In total, the elicitation took 6 hours to complete. We encountered no significant technical difficulties with the videoconferencing platform (such as not having or being unable to use Zoom; disconnections; or loss of video or audio feeds).

Despite a relatively large number of participants and additional observers, we found that moderating the session was straightforward. Furthermore, we found that the group discussions resulted in meaningful deliberation and interaction, without being dominated by a small number of individuals.

We also encountered no major technical difficulties (crashes, inability to submit data, inability to enter data, etc.) with the app, and all participants were able to submit their data.

Prior probability distributions

As expected, there was a convergence of elicited distributions in round two. The derived prior probability distributions are summarised in [Table 3](#) and were used in the treatment effect estimation models in [Chapter 6](#). The prior distributions are presented visually in [Appendix 4, Figures 18–25](#).

Discussion

Subject matter experts, on average, estimated in-hospital and 90-day mortality in this patient group, without the use of REBOA, to be in excess of 50%. Mortality at earlier time points (6 and 24 hours) was estimated to be closer to 25%.

The elicited data and the resulting prior probability distributions indicate that the experts, on average, had a favourable opinion of REBOA, that is they expect the addition of REBOA to SC to improve mortality at all time points.

The process of conducting the elicitation online went smoothly and resulted in the participation of 20 experts from all over the UK to participate during the COVID-19 pandemic. Traditional elicitation exercises have been delivered in-person with classic methods, such as ‘chips and bins’ or ‘roulette’. However, an online elicitation, with appropriate software and support, can help to provide more contemporary results. We found that, after some instruction, participants were able to use the online tool without difficulty.

TABLE 3 Derived prior probability distributions of the log odds of mortality

Time	Mean	Variance	SD	Lower	Upper
6 hours	-0.3834	0.9282	0.9634	-2.2717	1.5048
24 hours	-0.3329	0.7765	0.8812	-2.0600	1.3943
90 days	-0.3025	0.6761	0.8223	-1.9141	1.3090
In-hospital	-0.3584	0.6454	0.8034	-1.9331	1.2162

Chapter 4 Embedded process evaluation

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Introduction

Clinical trials of complex interventions, of which REBOA would be considered one, face many challenges.⁵³ Understanding and intervening on challenges to the delivery of the UK-REBOA trial were deemed critical for trial success. An embedded process evaluation was incorporated at the design stage of the trial to identify challenges relating to trial design or conduct that could be addressed and modified to facilitate the delivery of the trial. The process evaluation consisted of two stages: a first stage (A) to explore and diagnose any core problems to the successful delivery of the trial and a second stage (B) to develop solutions to address the problems and identify enhancements (see [Figure 5](#) for an overview). Stage A was further composed of two phases. Phase 1 targeted staff at sites which were the early adopters of the trial and explored any initial difficulties associated with the set-up and activation of trial processes (focussing on recruitment and intervention delivery). Phase 2 focused on activity once the trial was established and sites had more experience of the trial, randomising participants and deploying the REBOA catheter. Both phases generated recommendations to improve trial delivery.

The process evaluation was designed to be responsive to the needs of the trial. As such, the original plans to interview trial participants and/or consultees were not progressed; largely due to only very small numbers of participants/consultees declining consent for further follow up, which suggested no significant issues that required investigation. In addition, the original analysis of participant recruitment, using the adapted screened, eligible, approached, randomised framework⁵⁴ was not applied within the process evaluation due to the low throughput of patients. Therefore, the process evaluation focused exclusively on key clinical site staff and included interviews as planned but also non-participant observation of site training.

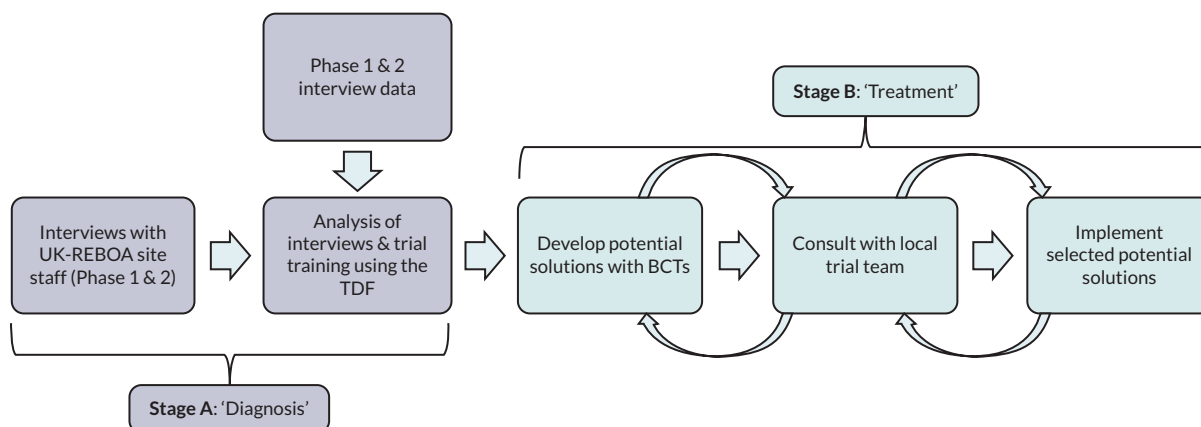


FIGURE 5 Steps involved in the 'diagnosis' (Stage A) and 'treatment' (Stage B) of issues related to trial recruitment and REBOA intervention delivery. BCT, behavioural change techniques; TDF, Theoretical Domains Framework.

Methods

This process evaluation was approved as part of the UK-REBOA trial by the Greater Manchester South Ethics Committee (17/NW/0352, IRAS project ID: 226135). Informed written consent was obtained from all participants. Documentation used in the process evaluation is available in the additional files www.fundingawards.nihr.ac.uk/award/14/199/09 (accessed June 2024).

Phase 1: Identifying initial difficulties associated with set-up and activation of trial processes

Sampling and recruitment

Recruitment in Phase 1 was purposive and targeted staff who had a role in the recruitment or randomisation of a patient in the first six sites to randomise a patient into the UK-REBOA trial. Site staff across active centres were sent an e-mail invitation (on behalf of the Clinical Co-CI) to participate in the interview study along with a participant information leaflet (PIL) and asked to contact the process evaluation team if interested. On contact with the process evaluation team, staff were provided with the opportunity to discuss the qualitative interview study further and book a mutually convenient time for a telephone interview. Two attempts were made to engage with potential participants. Sampling was informed by the key principles of information power, because the aim of the process evaluation was focused, the sample was specific (site staff involved in recruitment), rich narratives were provided during the interviews and no cross-case analysis was conducted.⁵⁵

Data collection

Qualitative data were collected through telephone interviews conducted with site staff who were recruiting patients to the UK-REBOA trial. A topic guide (developed by the process evaluation team and Co-CIs) was used to direct questions and aimed to elicit site staff's thoughts, comments, involvement and experience with the trial. Interviews took place between April and June 2018. Interviews were conducted by two members of the research team and were audio-recorded and transcribed verbatim.

Data analysis

The approach to analysis was systematic and interpretive, applying an inductive thematic analysis using the Framework approach.⁵⁶ One researcher re-read the interview transcripts and generated codes in NVivo (QSR International, Warrington, UK) (used to facilitate data management and initial coding)⁵⁷ which described relevant features of the data prior to collating into themes. Themes summarised the semantic content of interviewee responses and represented salient issues that were articulated by multiple participants.⁵⁸ Following review/refinement of themes, a thematic framework was developed by three members of the team which described the content of all themes and provided illustrative quotes to facilitate data analysis. The thematic coding framework was informed by both a priori questions and issues identified as emerging from the data. A double coder checked the themes and accurately described the content of participants' responses in a sample of interview transcripts. Any coding discrepancies identified during this process were discussed to reach consensus.

Solution development

Themes from the analysis were tabulated and identified as barriers and/or facilitators to trial delivery. The trial PMG met with the researchers who conducted the qualitative work to discuss potential solutions to the issues identified in the interviews. Proposed solutions were considered in relation to acceptability and deliverability.

Phase 2: Exploring barriers and facilitators for recruitment and intervention delivery in established trial sites

Design overview

As the process evaluation developed, it was recognised that many of the challenges within the trial were dependent on people's behaviour, that is clinicians performing actions (such as randomising a patient or delivering the intervention) that may not be part of their routine practice. There is now a growing body of evidence that suggests behavioural science has the potential to add value to exploring and providing solutions for challenges in the conduct of clinical trials.⁵⁹ Within Phase 2 of this process evaluation, we applied the Theoretical Domains Framework (TDF) as a method to help inform data collection and analysis. The TDF is an established framework that categorises behaviour into 14 domains that inhibit or enable behaviour (knowledge, skills, social/professional role and identity, beliefs about capabilities, beliefs about consequences, optimism, reinforcement, intentions, goals, memory/attention/decision processes, environmental context and resources, social influences, emotion and behavioural regulation).

Recent studies have highlighted the utility of the TDF to identify behavioural processes in clinical trials where the performance could be improved.⁶⁰⁻⁶³ The TDF was identified as an ideal framework to support components of this process evaluation as it provides an opportunity to examine behaviours which need to change in order to improve the conduct of a trial, and represents the first step in the process of developing behaviour change interventions.⁶⁴ Interventions can be developed to address trial process challenges through mapping barriers and facilitators onto behavioural change techniques (BCTs) via established methods in the behavioural science literature.⁶⁵ BCTs are defined as the smallest active ingredient of an intervention such as feedback on behaviour or goal setting, and they can be used alone or in combination with other BCTs.⁶⁴ We aimed to develop and implement potential solutions (containing BCTs) to minimise the barriers and maximise the facilitators to trial recruitment and intervention delivery identified from interviews with site staff.⁶⁴

Sampling and recruitment

Individuals invited to participate in Phase 2 were from sites which had either recruited a number of patients into the trial, experienced notable difficulties with recruitment, had recently randomised a patient to the trial and/or reported a missed opportunity to recruit an eligible patient. Staff in various roles who were involved in recruitment were invited to take part. E-mail invites were distributed as per previous description for Phase 1.

Data collection

Qualitative interviews were conducted via Microsoft Teams. Interviews were conducted by one member of the research team in October 2020. The topic guide was informed by the TDF, focused on recruitment and intervention delivery and the issues previously identified as important in Phase 1 – that is deployment and insertion of the REBOA catheter. The topic guide was developed and refined by two members of the process evaluation team.

Non-participant observation was conducted during the on-site training for a new recruiting centre at site setup. Detailed notes considering critical conduct problems and behaviours related to trial delivery were collected during this session and considered alongside training materials delivered and provided to sites. Trial training and support materials provided to site staff were compiled and coded using the TDF and BCT Taxonomy v1.⁶⁶ These were collected to identify areas where the process evaluation team could help to improve trial processes via adaptation of existing training and support materials (see Stage B subsection under *Data analysis*).

Data analysis

Stage A: Identification of salient theoretical domains framework domains relevant for recruitment and intervention-related behaviours

Data from Phase 1 interviews were transferred into NVivo alongside the data from Phase 2. This facilitated exploration of the factors that influence recruitment and intervention delivery across all cases, using the TDF, as opposed to using an inductive approach to analysis. We used a TDF coding guide to aid data interpretation, which was developed and iteratively updated during the coding process. One researcher coded transcribed data into the relevant TDF domains. Three of the 18 interview transcripts were independently double-coded and exhibited a large degree of agreement across the double-coding. Any disagreements were resolved by a third researcher and updates to the coding guide were added where appropriate.

After coding data into TDF domains, belief statements (representative descriptions of utterances across participants) were generated.⁶⁷ Belief statements were designed to present details on how each domain may be influencing the behaviours of interest, namely: (1) recruitment of patients to the trial and (2) delivery of the REBOA intervention. The research team collectively discussed the belief statements to agree they were an accurate representation of the quotes coded within each domain.

Established TDF analysis methods were used to identify the domains that were most likely to influence the target behaviours.⁶⁴ This included: (1) the frequency of belief statements across all domains (statements with a frequency of > 75% were considered most 'relevant' as per other TDF-based studies);⁶¹ (2) evidence of strong beliefs that influence the behaviours (i.e. the strength of conviction illustrated by participants during the interviews); (3) and the presence and prevalence of conflicting beliefs. This resulted in some domains that contained frequently reported belief statements not being identified as salient as there was no evidence of strong beliefs, from interviews, that influenced the target behaviours or conflicting beliefs within the domain.

Prior to the identification of potential solutions to mitigate trial challenges, we reviewed the barriers relevant to all domains that were amenable to change within the scope of this project. We omitted those that required wider infrastructure changes as delivering large-scale system changes was unlikely to be realised short term to aid the trial delivery (e.g. such as a lack of additional personnel to support recruitment) or were not amenable to change (i.e. low number of eligible patients). All criteria were evaluated concurrently (via group consensus) to judge the relevance of each domain.

Stage B: Identification of behavioural change techniques to inform the development of potential solutions to help improve trial processes

Following identification of the salient domains, components of potential solutions were determined using a standardised process that involved mapping the relevant theoretical domains to BCTs using the Theory and Techniques Tool.^{64,65} The BCTs identified as potentially relevant for selected TDF domains were collated, discussed by the research team, and adapted to the clinical context of the UK-REBOA trial. In addition, existing training and support materials provided to site staff were reviewed to examine the presence of BCTs that may already be delivered in the trial as an opportunity to enhance existing trial practices.

Behavioural change techniques proposed by the research team were presented at a meeting with the Trial Manager and Co-ClIs to discuss the applicability of selected BCTs to support specific trial behaviours (recruitment and intervention delivery). We applied the APEASE criteria (acceptability, practicability, effectiveness, affordability, side-effects and equity) to support the final selection of the content and mode of delivery for the potential solutions to improve trial processes.⁶⁴

During solution development, training materials were updated in response to the findings of the behavioural investigation and implemented in follow-on training for sites. Trainers were briefed on the purpose of the behavioural approach to the review of training materials and encouraged to embed BCTs

within the delivery. Training delivery with regard to BCT content was assessed by observation with feedback provided to the training team post session by the process evaluation lead. Training attendees (i.e. clinical staff tasked with trial delivery) were also asked in their feedback to consider the main message they had taken away from the training in order to determine the most salient aspects of the training content and whether updated content was received as intended.

Results

Sample characteristics

Forty-nine interview invitations were distributed to eligible site staff. Seventeen participants from eight sites were interviewed across both phases (Phase 1 $n = 13$, Phase 2 $n = 5$; one participant was interviewed in both phases), with the majority identifying their role as Trauma Consultants ($n = 9$, 53%) (Table 4). One of these participants was interviewed in both Phase 1 and 2 as they provided initial perspectives on early process problems and later experiences of more established trial process problems. Taken together, the interviews lasted an average of 37 minutes, ranging between approximately 22 minutes and 1 hour.

Phase 1 findings: Identifying initial difficulties associated with set-up and activation of trial processes

Seven primary themes were identified across the interviews, which could be further organised into barriers or facilitators of trial delivery. The seven primary themes and whether they were reported as a barrier or a facilitator, or both, are summarised in Table 5. Each of these identified themes will be presented in turn with examples.

TABLE 4 Participant demographics for both phases of the study

Characteristic	Phase 1	Phase 2	Total
Number of participants	13	5	18 ^a
Sites	5	4	8 ^a
Roles			
Consultant	8	2	10 ^a
Registrar	2	-	2
Research nurse	2	1	3
Radiologist	1	-	1
Trauma anaesthetist	-	2	2

a One participant was interviewed in both Phases 1 and 2.

TABLE 5 Overview of main themes identified from interview data

Theme	Barrier	Facilitator
1. Skills and competencies	✓	✓
2. Resource commitment	✓	✓
3. Individual and Community Equipoise	✓	✓
4. Working relationships	✓	✓
5. Interpretations of patient eligibility	✓	
6. Specifics of operationalising key aspects of the trial	✓	
7. Trial training: generic and site-specific		✓

Skills and competencies related to intervention delivery

Skills and competencies were identified as both a barrier and a facilitator by site staff. Findings within this theme largely reflected the specific skills, and associated expertise, required to deliver the intervention, that is insert the catheter and deploy the balloon. When discussed as a barrier, interviewees cited reasons such as making sure an appropriately qualified person was available to deliver the intervention.

I think most people who are in the game are concerned about or have nervousness around is actually once the app says, you know use REBOA, that's where people's blood vessels start to go up a bit! In terms of am I going to get it in right? Am I going to do it right, that sort of thing. I think, having never done it in anger before, but only as part of the training scenario.

Consultant 1

The need for staff experienced in delivering the intervention was also cited as a facilitator to successful trial delivery.

Any surgeon that is comfortable with personally being able to open a chest and put a clamp on. If they are happy doing that, I can't see them having a big issue with putting a REBOA balloon in. If the technical aspect of deploying a REBOA balloon is taken away from the trauma surgeon ... that may make it easier to integrate it into other trauma centres.

Consultant 2

Both barriers and facilitators in this theme cited the throughput of patients as a factor in influencing competencies and a site's ability to successfully deliver the trial.

So I think the urban centres are likely to find it easier purely because they're going to have larger numbers you know, obviously the more haemodynamically compromised patients that come through your system then the easier it tends to be to introduce new techniques because you're getting the numbers which people can gain technical experience in using those. So I imagine that most of the big cities will not struggle to do that.

Consultant 3

The numbers are likely to be such that I suspect most A&E [Accident and Emergency] doctors may not get enough experience to ever subsequently feel confident to do it themselves.

Radiologist 1

Resource commitment to successfully deliver the trial

With regard to resource commitment, the main facilitator cited by interviewees was dedicated staff members whose responsibility it is to deliver, or support delivery of, the trial. A lack of resource commitment in terms of monetary support to purchase the intervention, providing 24-hour cover for staff to help deliver the trial, and recognition for involvement with research projects were identified as barriers in the interviews.

Individual and community equipoise

Across the interviews, equipoise (or lack of equipoise) was evident as a complex issue that many interviewees highlighted. Many were not necessarily in individual equipoise but recognised that across the clinical community mixed views were held, and thus community equipoise rather than individual equipoise was more apparent.

At the moment they have to be really, really sick. And a little bit frustrating as a purely research side is when we go down there and say, 'What do you think about this patient? Can we put them into REBOA and the trial?' which happens probably once every 3 weeks I would say, probably a little more often

than once a month, and the usual answer is, 'No, they're not sick enough and, so I don't want to get the randomisation side that says REBOA and therefore I'm not going to do it'. And [name] really has said to us, 'If the clinicians are thinking REBOA, if they're thinking REBOA then randomise. But if they're not thinking REBOA then we're not going to randomise at all'. So yeah, I think that's what it's mainly makes it difficult to get them into the trial.

Registrar 1

For one of the sites involved, they already delivered in-hospital REBOA and identified this existing knowledge of application as potentially problematic for staff linked to the trial.

At our site, probably the only thing that hinders us is that we have already been delivering this procedure so there is some understanding about where it sits, and who needs it before we entered the trial. So, actually, the trial seems to muddle people up a little bit because some of our team are convinced they know when to use it and when not to, some of the team aren't. I just wonder if that probably makes it slightly more confusing at our centre than any other centre where it's completely new, they've never heard of it. They are more likely to feel that they have genuine equipoise.

Consultant 3

However, there were some who viewed community equipoise as the driver for delivering the trial. And indeed, the requirement for further evidence to support clinical decision-making was cited as a reason to promote the trial.

Well, and actually some of those other views stem from the lack of hard evidence, and, so, I mean I broadly find it slightly bizarre that you can be so polarised when the evidence is relatively weak, but some people aren't ... I think that their arguments could be won with better evidence.

Registrar 1

Responses from the interviews also highlighted that equipoise in an emergency care setting may be impacted by real-time events – staff perspectives regarding preferences for treatment (e.g. REBOA or standard major trauma care) reportedly changed often depending on the clinical presentation of the patient, and subsequent interpretations of patient eligibility.

Interpretations of patient eligibility

Closely linked to the viewpoints surrounding equipoise were interpretations of patient eligibility. In some instances, it was perceived as a barrier with interviewees stating there was ambiguity around who was eligible due to a lack of existing definition or assessment of exsanguination. This was also linked to variability in clinicians' interpretation of eligibility but was balanced against the pragmatic nature of the trial and its applicability to real-world practice.

I think the key word is exsanguination. The indication, if you read them verbatim, talk about exsanguination, the definition of exsanguination is bleeding to death, but the question is how does each individual clinician interpret that? How do we prove that, and how do we diagnose that? How do we do all that in a very short space of time, pre-hospital or ED environment. It's a very difficult question. I am not really sure how to answer it any better. I think [NAME] just is setting out to make a pragmatic trial. The point is, if the procedure is delivered on a broader scale, everybody will interpret it slightly differently, everybody will do it slightly differently, so actually what you are testing is probably the correct thing to be testing how clinicians across the country in different centres will perform this procedure.

Consultant 4

Working relationships

The need for teamwork, good communication and inclusion of a wide range of specialties to successfully deliver the trial was cited across interviews. For some sites, this was regarded as a facilitator, whereby

staff reported that the involvement of various people occupying different roles (such as anaesthetists and vascular surgeons) could enhance recruitment processes. Having a system in place that capitalised on the expertise of individuals from multiple specialties was perceived to be particularly important given the infrequency of REBOA eligible cases.

So, we've set up a system here where the operators are a mixed bag of ED [Emergency Department], vascular ... anaesthetic individuals involved as well ... set up, and to activate us, as and when ... the actual opportunities are few and far between, they are incredibly rare. So, we've elected to have a system whereby we get activated by the trauma team leader, a code red comes in and looks like it may or may not be suitable for REBOA.

Consultant 1

However, according to some staff, difficult working relationships or deferral to senior colleagues was raised as a potential barrier in randomising patients. This was intrinsically linked to perceptions of equipoise among the team or key members.

He's the PI for the centre, for the [hospital], but he was clinically involved in a case, and I think some of the team felt that they needed REBOA in and he really didn't, so ...

Registrar 1

Specifics to operationalising key aspects of the trial

Key barriers or problems relating directly to specifics of the UK-REBOA trial were identified. In a fast-paced and pressurised setting, it could be easy for some staff to forget where the randomisation app was stored on the electronic device, particularly when regular access to the app was not required (due to the low throughput of patients eligible for trial recruitment). During access to the app, other difficulties could also arise – such as non-technical errors related to signing into the device.

I think there are other things, because the randomisation process is on the app, which is a good thing, the only problem to me with that is because I'm about as technical as a sack of potatoes 'Where did I put the app?' Trying to find the [expletive] app, and heaven forbid if they ask the password! [laughter] For something that you would maybe only access once ever month...

Consultant 1

Trial training: generic and site-specific

Training, both the specific training received as part of the trial and research/clinical training more broadly, was perceived as a facilitator. The training provided during early phases of the trial was regarded as crucial in terms of ensuring all staff understood the parameters of the trial, the technicalities of the intervention as well as the non-technical skills involved in decision-making about randomisation and intervention delivery. Overall, training was perceived to facilitate enhanced (joint) decision-making, understanding and communication among team members with different levels of seniority, as well as creating institutional awareness of the trial across hospital sites.

Well so the other thing that's really important is having training in the technique and in the decision making. So we have a monthly training session for REBOA, so the aim is that we get all the senior nursing staff and all the senior EM [Emergency Medicine] staff and surgical staff and critical care staff trained to provide the ... to understand both the parameters of the trial and the things that REBOA may help with and may not help with, so then you've got a better informed joint decision making actually. And it [training] allows team members who are not the team leader also to make those prompts, 'Have we considered this patient for REBOA?' So I think having that better group understanding of the trials and the things that may help is very helpful.

Consultant 3

TABLE 6 Proposed solutions from Phase 1

Phase 1 theme	Potential solution(s)
1. Skills and competencies	Top-up training for sites.
2. Resource commitment	No direct solution due to funding but highlight opportunities to sites to draw on any existing research infrastructure or explore through Research and Development departments to support access to Research Nurses, for example.
3. Equipoise	An e-mail 'Update' on equipoise: reinforcing the need for the trial and incorporating findings from interviews to encourage equipoise will be drafted and disseminated to sites. Use as a prompt for discussion on PI teleconferences.
4. Eligibility	Develop clinical vignettes for PIs to work through on teleconferences which highlight different parameters of eligibility and aid discussion.
5. Specifics to REBOA	Solutions suggested for other barriers may help to address.
6. Working relationships	Intrinsically linked to equipoise – address equipoise to help address working relationships. In addition, shared learning calls, which are already implemented, could help to address skills and competencies and relational aspects through team building.

the people who actually run the trial at our site are [name] and [name], very proactive in terms of creating institutional awareness both of the procedure in general and of the trial in particular. So, they are ... there has been a lot of educational stuff, and all the consultants have full buy-in.

Registrar 2

Phase 1: Proposed solutions based on interview diagnostics from early adopter sites

Table 6 describes potential solutions, developed in collaboration with the PMG, some of which were implemented immediately, and others were combined into solutions within Phase 2 using a behavioural approach. In addition, findings from this Phase were also shared at an Investigators Meeting of recruiting centres in June 2019. Opportunities for discussion and suggestion of solutions was encouraged.

Phase 2 findings: Using a behavioural approach to explore the barriers and facilitators of REBOA recruitment and intervention delivery

Stage A: Identification of behaviourally focused recruitment challenges

Six of the 14 TDF domains, detailed in the [Design overview](#) section above, were considered relevant to both the processes of recruitment to the UK-REBOA trial (i.e. randomisation) and the processes of delivering the trial intervention (the deployment of the REBOA catheter), specifically: Skills; Environmental context and resources; Beliefs about capabilities; Beliefs about consequences; Social influences; and Memory, attention and decision processes. Thirty-eight belief statements were identified across these six TDF domains. The themes are presented below (with dominant TDF domains specified in brackets). Notably, some of the themes presented in this section overlapped with themes identified from Phase 1 of the process evaluation. However, categorising interview content (from both Phases 1 and 2) into the TDF, an established behavioural framework, allowed us to link identified factors to theory-informed potential solutions using established methods in the field of behavioural science.

Six themes were identified:

1. Skills required for successful recruitment and intervention delivery (TDF Domain: Skills): Recognising patients who may require REBOA was regarded as an essential skill which influenced both recruitment and intervention delivery, as well as the technical skills surrounding the deployment of REBOA. Staff reported concerns around maintaining these competencies due to the low frequency of eligible patients.

2. Environment, context and resources' impact on recruitment and intervention delivery (TDF Domain: Environmental Context and Resources). Some indicated that a lack of staff available (notably those who could deliver REBOA) on a 24/7 basis deterred recruitment and intervention delivery in some instances. Other site staff indicated that the presence of dedicated Research Nurses and Clinical Fellows facilitated recruitment. The clinical context of REBOA was also regarded as stressful and fast-paced, which could sometimes act as a barrier to both recruitment and intervention delivery.
3. Beliefs about clinicians' capabilities to deliver REBOA (TDF Domain: Beliefs about Capabilities): A lack of confidence was acknowledged by clinicians who were (or would have been) responsible for delivering REBOA. This was often related to the limited opportunities available to deliver REBOA outside of a simulated context.
4. Beliefs about the consequences of REBOA recruitment and intervention delivery (TDF Domain: Beliefs about Consequences): Many staff recognised the potential clinical benefits associated with the REBOA intervention as well as the institutional benefits associated with their involvement in the trial. However, most staff also acknowledged that the anticipated negative side effects of REBOA could intensify apprehension and inhibit staff from performing this high-risk procedure.
5. Social influences of REBOA recruitment and intervention delivery (TDF Domain: Social Influences): Mixed perspectives related to equipoise and trial patient eligibility among the team sometimes acted as barriers to recruitment and REBOA enactment. The content within this theme is also highlighted in the 'Working Relationships' and 'Individual and Community Equipoise' themes reported in Phase 1 findings.
6. Memory, attention and decision-making processes during the conduct of UK-REBOA trial delivery (TDF Domain: Memory, Attention and Decision-making Processes): Difficulties assessing patient eligibility resulted in observable discrepancies in decision-making across sites – namely the exact timing of randomisation. Dual acts of considering randomisation and intervention delivery within a stressful fast-paced setting also demanded significant mental resources.

An extended table containing the content and frequency of all TDF domains and associated belief statements is published in full elsewhere (Lawrie *et al.* 2022).⁵²

Stage B: Development and delivery of potential solutions to improve trial processes

The findings from Stage A provided diagnostic information relating to the core behavioural conduct challenges and informed the development of potential solutions that were designed to enhance recruitment and delivery of the REBOA intervention (Stage B). We identified 24 potential BCTs that could support UK-REBOA trial recruitment and clinical intervention delivery based on the barriers and facilitators highlighted in Stage A. Detailed descriptions of the solutions developed are described elsewhere.⁵² [Appendix 5](#) provides a thorough overview of the proposed solutions, first by the mode of delivery (i.e. via Training, Environmental Restructuring and/or Enablement), followed by the content of the proposed solutions, linked BCTs, beliefs statements to illustrate how the interview findings informed the solution development, and the APEASE assessment. While many of the identified barriers were actionable through development of targeted solutions, it is important to recognise that some barriers (such as the need for dedicated research nurses or clinical research fellows, or a 24/7 service to deliver the REBOA intervention) were not amenable to change within the bounds of the trial, and talk to wider infrastructure support costs for research more generally. Therefore, these challenges were not prioritised for solution development within the UK-REBOA trial.

The prioritised evidence-based potential solutions identified included a range of strategies designed to mitigate the barriers and maximise the facilitators identified from Stage A. Some of these strategies were already active within existing trial practices, such as prompt sheets that described recruitment and intervention delivery (targeting the TDF domain Memory, Attention and Decision-making processes). Findings also suggested staff could benefit from sharing existing mannequins across sites to facilitate rehearsal of the REBOA procedure and recruitment processes: this was proposed to mitigate issues related to maintaining the competencies to conduct randomisation and deliver REBOA (targeting the TDF domain Skills).

Other strategies developed from the evidence gathered during the process evaluation were also identified. These strategies were delivered within various settings – summarised below.

Trial meetings

The fortnightly, routine, PI conference calls were often structured to encourage discussion of issues related to randomisation, experiences of trial processes enacted (or not), anonymised case details about patient eligibility and procedural descriptions of recruitment/intervention delivery. As such, these meetings already incorporated strategies to improve recruitment and intervention delivery [BCTs such as social support (practical) and social comparison, targeting the TDF domain ‘Social Influences’]. The process evaluation team emphasised the value of these meetings to the local trial teams, and suggested methods to maximise BCTs within these PI meetings. This included encouraging PIs to prompt staff to proactively plan for any events that may occur unexpectedly on the basis of their past experiences (of randomisation and REBOA intervention delivery), as well as to consider solutions to overcome challenges that may arise in the future (incorporating the BCTs Action planning and Problem solving – targeting the TDF domain ‘Beliefs about capabilities’).

Findings from Phase 2 were also disseminated across three separate online meetings: two collaborative meetings held on 18 March 2021 and 26 October 2021, and a TSC meeting on 11 October 2021. The process evaluation team used these meetings as an opportunity to raise awareness of notable challenges related to trial recruitment and REBOA intervention delivery, as well as to gain feedback about the conduct/results of the evaluation. Meeting attendees were also encouraged to reflect on any improvements that could be made, based on the findings, to enhance recruitment and intervention delivery processes in the UK-REBOA trial.

Updates to training material and delivery

Training was adapted to incorporate a greater emphasis on staff contributions and the value of the research (i.e. the UK-REBOA trial) in potentially changing clinical practice. The content from the training slides and presentation scripts were reviewed to ensure they explicitly contained BCTs that would maximise recruitment and facilitate the delivery of REBOA.

E-mail/Twitter feedback on recruitment activity

Monthly recruitment updates which contained BCTs were distributed to site staff via e-mail. The process evaluation team worked with the local trial teams to ensure that the BCTs selected would support recruitment and intervention delivery at that site. These e-mail updates included information related to the number of patients that had been recruited at their site in relation to other sites, incorporating the BCTs ‘Social comparison’ and ‘Feedback on behaviour’. The support available to trial staff was also reinforced within the updates, by providing contact details of the Trial Manager, Co-PIs, and clinical training lead (including the BCT ‘Social Support, Practical’). This solution was modelled on audit and feedback interventions, which are a foundational component of quality improvement initiatives in clinical care and have been used in other large multicentre trials as a recruitment intervention targeting healthcare professionals.

The interview findings also supported the ongoing praising of staff for their efforts in the trial (applying the BCT ‘Social Reward’). Praise was communicated via Twitter/E-mail following a randomisation.

Development and implementation of an infographic

A bespoke infographic was produced that was designed to target mixed levels of equipoise among trauma teams (see [Appendix 6](#)). This was developed in liaison with the local trial staff, using the expertise from the process evaluation team to ensure it contained strategies that were primarily designed to mitigate the barriers around individual and community equipoise, but also more general views around the consequences of recruitment and intervention delivery (i.e. using BCTs that target the TDF domains ‘Beliefs about consequences’ and ‘Social influences’).

The infographic contained information that reinforced the purpose of the trial with information about the social and environmental consequences of trial recruitment/REBOA intervention delivery (incorporating the BCT 'Information about social and environmental consequences'), as well as contact details of the clinical Co-Cl and clinical training lead to indicate the support available [incorporating the BCTs social support (practical) and credible source]. The infographic was distributed by the trial office to all site staff involved in recruitment (via email) and was requested to be shared among other site staff involved in the trial (electronic and paper copies for sharing).

Discussion

The purpose of this process evaluation was to inform the delivery of the trial by investigating the barriers and facilitators of recruitment and REBOA intervention delivery. Phase 1 was designed to identify barriers promptly during trial initiation and set-up across the first active sites, whereas Phase 2 focused on exploring barriers and facilitators of REBOA recruitment and intervention delivery when sites were more established. We applied a behavioural framework in Phase 2 to direct analysis and generate solutions designed to enhance trial practices using established methods from the behavioural science literature.

Embedded process evaluations often provide an opportunity to evaluate the challenges that can threaten trial rigour during the conduct of the study. Notably, Phase 2 of this process evaluation provides an example of how a behavioural science approach can be used to proactively implement strategies to address challenges, extending previous studies that have largely focused on identifying problems for trial recruitment and retention.⁶⁰⁻⁶³ Our embedded process evaluation study therefore demonstrates that the incorporation of a behavioural approach to understanding trial processes provided practical advantages: understanding the underlying determinants that affected behaviour, attitudes and beliefs in the UK-REBOA trial provided an avenue to implement theoretically informed evidence-based solutions to potentially enhance trial practices.

Although elements of the trial were redesigned with the aim of enhancing recruitment and intervention delivery using techniques from behavioural science, it would have been useful to conduct a formal evaluation of the effectiveness of these techniques. Another potential limitation of this process evaluation was that we were unable to recruit more site staff to interview using a TDF-based topic guide. This was due to site staff capacity limitations during the COVID-19 pandemic. Therefore, data from Phase 2 (which combined interviewee responses from both phases of the evaluation) represented interview responses from questions within two separate topic guides. However, during the analysis, common TDF-based themes were identified throughout all of the interviews. This demonstrates the flexibility and relevance of applying the TDF within the analysis process when the interview questions may/may not be guided by the theoretical domains.⁶⁸ In addition, our sample comprised of individuals who were largely supportive of the REBOA intervention. It may have been insightful to target recruitment towards individuals who had reservations about their sites' participation in the UK-REBOA trial and/or the intervention.

Conclusion

Both phases of this process evaluation revealed several barriers and facilitators to trial recruitment and intervention delivery in the UK-REBOA trial. Phase 2 highlighted the value of using a behavioural approach to adapt elements of a trial to optimise processes, including theoretically informed solutions that had the potential to proactively address recruitment and intervention delivery challenges.

Chapter 5 Baseline characteristics and procedural details

Recruitment

The first recruitment site was opened to recruitment on 30 October 2017. The first participant was recruited in January 2018. In total, 16 sites opened to recruitment, and 12 of these recruited participants to the UK-REBOA trial. The second interim analysis (which commenced on 9 March 2022) and included 80 participants, triggered one of the pre-specified stopping rules and recruitment to the trial was suspended on 16 March 2022. Ninety participants had been recruited overall by this time [the final 10 had not yet reached the follow-up time for the primary outcome measure (90-day mortality) and thus were ineligible to be included in the interim analysis]. The trial had originally planned to randomise 120 patients.

Impact of COVID-19 on recruitment

Recruitment had also been previously paused by sponsor on 18 March 2020 due to COVID-19. Sites were able to reopen to recruitment from July 2020; however, not all sites were able to reopen. The number of patients recruited, by sites, is shown in [Appendix 7, Table 23](#) and [Figure 26](#) show recruitment over time. The three highest recruiting sites were Leeds, Royal London Hospital and Birmingham.

Group allocation

Of the 90 participants enrolled, 46 were randomly assigned to a strategy of SC plus REBOA (SC + REBOA) and 44 to SC alone. [Figure 6](#) shows the Consolidated Standards of Reporting Trials diagram for the UK-REBOA trial.

One of the participants allocated to the SC strategy chose not to continue to participate after 4 days, but data collected up until this point could be used. Outcome data for this participant are therefore available up to this time point (3-, 6- and 24-hour mortality) only.

Patient characteristics

Demographics, comorbidities, injury severity and injury pattern are shown in [Table 7](#). The groups were well-matched in terms of age, gender, comorbidities, mechanism of injury and injury severity. ISS scores (calculated once all injuries have been identified) ranged from 0 to 75. A score of 0 indicates no injury, and a score of 75 represents injuries which are not usually compatible with survival. A score of > 15 is accepted as indicative of severe injury and major trauma, and a score of > 25 indicates very severe injury. The median ISS for the UK-REBOA trial was 41 (25th percentile 29, 75th percentile 50); the majority of participants were very severely injured. There were some differences in injury pattern, with a high AIS for the head region in participants allocated to the SC + REBOA arm.

[Table 8](#) shows pre-hospital and ED vital signs and participant transport characteristics. Patients were profoundly hypotensive, but slightly more so in the SC + REBOA strategy group. This is attributable to the extreme urgency of the clinical presentation, highlighted by the fact that 10 (22%) in SC + REBOA and 11 (25%) in SC strategy experienced a traumatic cardiac arrest in the pre-hospital setting.

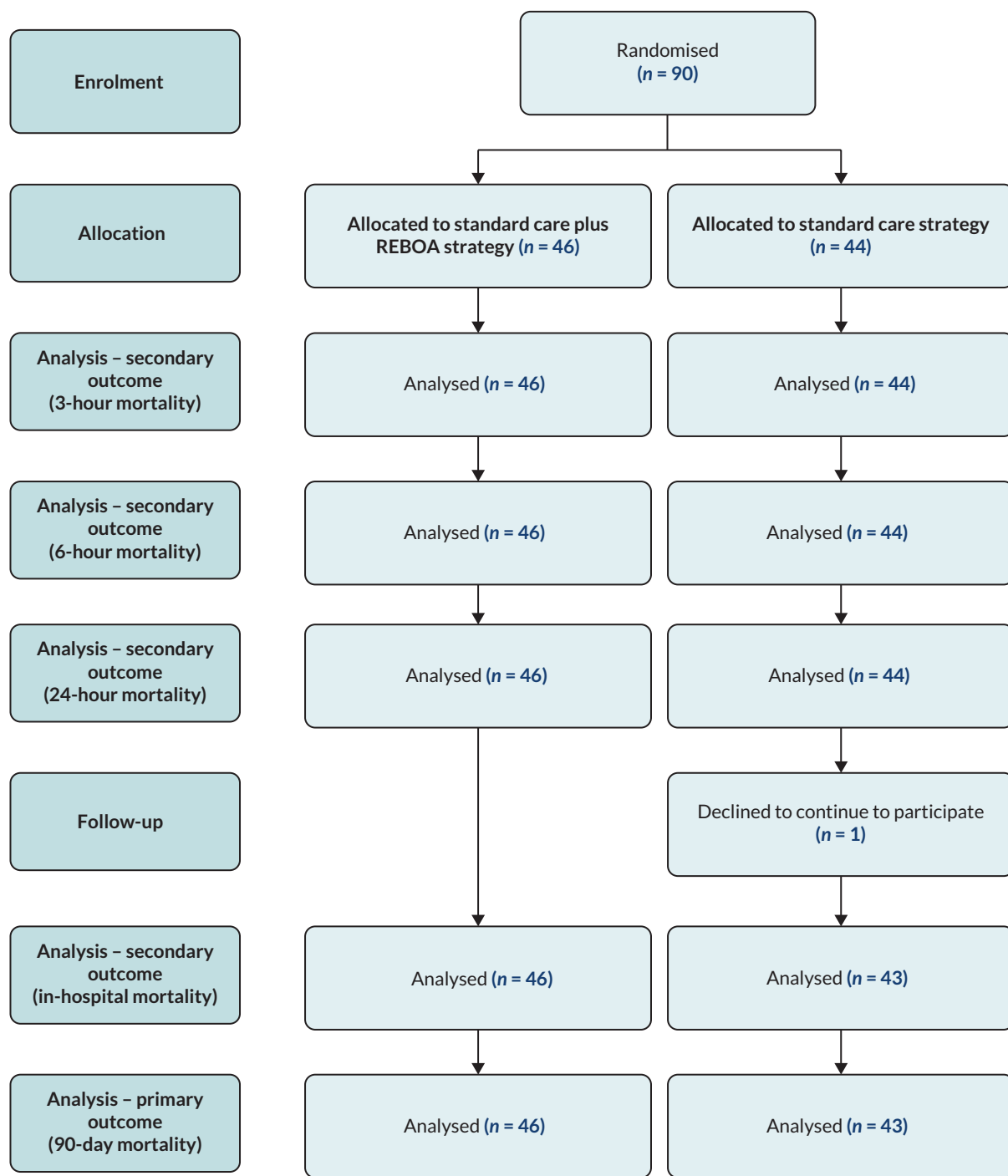


FIGURE 6 Consolidated Standards of Reporting Trials diagram.

For the ED arrival characteristics, participants were still hypotensive on arrival, although slightly more so in the SC + REBOA group. Otherwise, the groups were well matched.

Treatment received

Of the 46 participants allocated to the SC + REBOA strategy, 19 had the device inserted and inflated (Figure 7). The remaining 27 participants progressed to different time points along this pathway. In eight participants, arterial access was attempted but could not be established (R2); in three, arterial access

TABLE 7 Patient characteristics: demographics and injuries

	SC + REBOA N = 46	SC N = 44
Demographics		
Median age (Q1–Q3), years	46 (33–62)	39 (30–56)
Male sex, n (%)	28 (61)	34 (77)
Comorbidity		
Median Charlson Comorbidity Index (Q1–Q3); n	0 (0–1); 33	0 (0–1); 40
Mechanism of injury		
Blunt, n (%)	44 (96)	43 (98)
Penetrating, n (%)	2 (4)	1 (2)
Injury severity		
Median ISS (Q1–Q3)	41 (29–50)	41 (29–50)
ISS band		
Minor, n (%)	0	1 (2)
Moderate, n (%)	1 (2)	1 (2)
Severe, n (%)	7 (15)	4 (9)
Very severe, n (%)	38 (83)	38 (86)
Injury pattern		
ALS head, median (Q1–Q3)	3 (0–4)	0 (0–5)
ALS face, median (Q1–Q3)	0 (0–2)	0 (0–2)
ALS thorax, median (Q1–Q3)	4 (3–4)	4 (1–4)
ALS abdomen, median (Q1–Q3)	2 (0–3)	2 (0–4)
ALS spine, median (Q1–Q3)	2 (0–2)	2 (0–2)
ALS pelvis, median (Q1–Q3)	2 (0–5)	2 (0–5)
ALS limbs, median (Q1–Q3)	2 (2–3)	3 (2–3)
ALS other, median (Q1–Q3)	0 (0–1)	0 (0–1)
Q1, 25th percentile; Q3, 75th percentile.		

was not attempted, because the participant had improved with other resuscitative measures (R1/C1); in nine, arterial access was achieved, but the REBOA device was not inserted, because the participant had improved with other resuscitative measures (R3/C1); in five, arterial access was achieved, and the device inserted, but the balloon not inflated, because the participant had improved with other resuscitative measures (R4/C1); and in two, arterial access was not attempted because the participant rapidly deteriorated (R1/C2).

Of the 44 participants allocated to the SC strategy, 2 participants received SC + REBOA. In both participants, the device was inserted in the operating theatre.

TABLE 8 Pre-hospital and ED vital signs and participant transport characteristics

	SC + REBOA N = 46	SC N = 44
Pre-hospital		
Vital signs		
SBP, mmHg		
Median (Q1–Q3); n	85 (66–120); 34	97 (71–128); 37
≤ 90 mmHg, n (%)	18 (53)	17 (46)
≤ 70 mmHg, n (%)	11 (32)	9 (24)
Heart rate, bpm, median (Q1–Q3); n		
	113 (94–133); 42	109 (77–133); 40
Respiratory rate, b.r.p.m., median (Q1–Q3); n		
	21 (12–30); 38	22 (16–30); 42
Oxygen saturation, %, median (Q1–Q3); n		
	88 (90–95); 32	92 (81–98); 43
Glasgow Coma Scale, median (Q1–Q3); n		
	10 (3–14); 42	10 (3–14); 42
CPR		
Yes, n (%)	10 (22)	11 (25)
No, n (%)	33 (72)	33 (75)
Missing, n (%)	3 (7)	–
Method of transport		
Helicopter, n (%)	17 (37)	21 (48)
Ambulance, n (%)	22 (48)	19 (43)
Ambulance and helicopter, n (%)	6 (13)	3 (7)
Missing	1 (2)	1 (2)
Time from injury to ED arrival		
Minutes, median (Q1–Q3)	90 (70–125); 39	97 (78–119); 41
ED		
Pre-alert issued, ^a n (%)		
Yes	40 (87)	39 (89)
No	3 (7)	4 (9)
Missing	3 (7)	1 (2)
Massive haemorrhage protocol activated, n (%)		
Yes	40 (87)	39 (89)
No	6 (13)	4 (9)
Missing	–	1 (2)
Consultant present in ED, n (%)		
Yes	45 (98)	44 (100)
Missing	1 (2)	–

TABLE 8 Pre-hospital and ED vital signs and participant transport characteristics (*continued*)

	SC + REBOA N = 46	SC N = 44
ED vital signs		
SBP, mmHg		
Median (Q1–Q3)	84 (58–115); 44	99 (72–115); 42
≤ 90 mmHg, n (%)	26 (59)	19 (45)
≤ 70 mmHg, n (%)	18 (41)	9 (21)
Heart rate, bpm, median (Q1–Q3); n	105 (88–123); 45	120 (87–135); 43
Respiratory rate, b.r.p.m., median (Q1–Q3); n	20 (17–30); 38	20 (18–26); 40
Oxygen saturation, %, median (Q1–Q3); n	99 (90–100); 39	99 (95–100); 40
Glasgow Coma Scale, median (Q1–Q3); n	3 (3–11); 39	3 (3–15); 39
CPR on arrival, n (%)		
Yes	4 (9)	4 (9)
No	36 (78)	39 (89)
Missing	6 (13)	1 (2)

b.p.m., beats per minute; b.r.p.m., breaths per minute; mmHg, millimetres of mercury; Q1, 25th percentile; Q3, 75th percentile.

a 'Pre-alert' is a notification sent by ambulance services to alert trauma centres to the impending arrival of a seriously injured patient.

Procedural details

Table 9 describes the technical aspects of the 21 REBOA insertions, 19 in SC + REBOA and 2 in SC. The method of arterial access was percutaneous [17 (89%) in SC + REBOA and 2 (100%) in SC] and on the right [13 (68%) in SC + REBOA and 2 (100%) in SC]. The median duration of balloon inflation was 29 minutes in SC + REBOA and 71 minutes in SC.

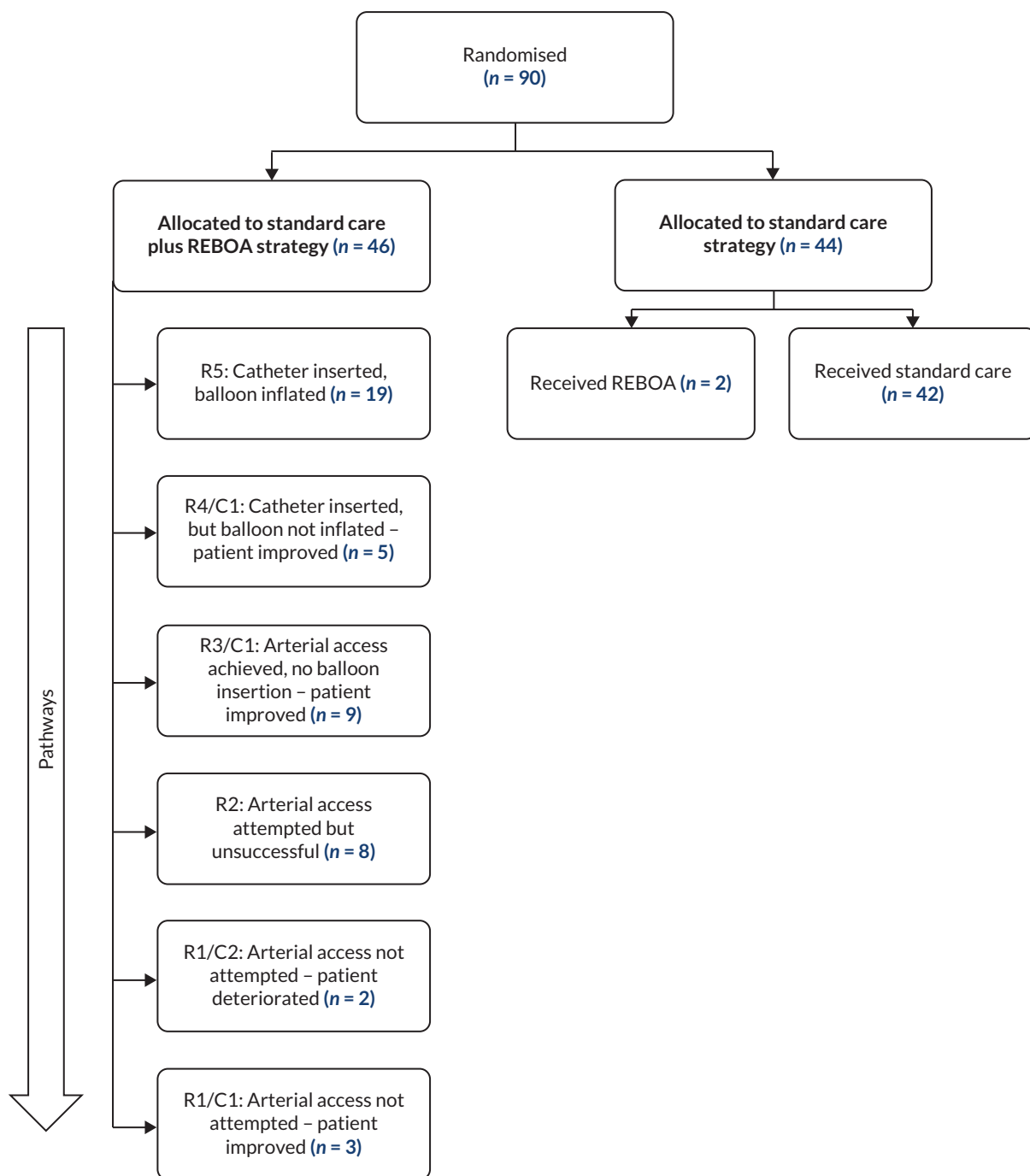


FIGURE 7 Treatment received.

TABLE 9 Resuscitative endovascular balloon occlusion of the aorta insertion – technical aspects

	SC + REBOA N = 46	SC N = 44
Received REBOA, <i>n</i>	19	2
Arterial access		
Prior femoral arterial line, <i>n</i> (%)	5 (26)	1 (50)
Method		
Percutaneous, <i>n</i> (%)	17 (89)	2 (100)
Percutaneous followed by cutdown, <i>n</i> (%)	2 (11)	–
Site		
Left, <i>n</i> (%)	5 (26)	–
Right, <i>n</i> (%)	13 (68)	2 (100)
Both, <i>n</i> (%)	1 (5)	–
REBOA operator		
Same as TTL, <i>n</i> (%)	18 (95)	2 (100)
Someone other than TTL, <i>n</i> (%)	1 (5)	–
Sheath size		
7F, <i>n</i> (%)	15 (79)	2 (100)
8F, <i>n</i> (%)	3 (16)	–
9F, <i>n</i> (%)	1 (5)	–
Occlusion		
Zone I, <i>n</i> (%)	10 (53)	–
Zone III, <i>n</i> (%)	9 (47)	2 (100)
Partial REBOA^a		
No, <i>n</i> (%)	11 (58)	1 (50)
Yes, <i>n</i> (%)	8 (42)	1 (50)
Location of balloon deflation		
ED, <i>n</i> (%)	10 (53)	–
Operating theatre, <i>n</i> (%)	5 (26)	2 (100)
Died with balloon inflated, <i>n</i> (%)	4 (21)	–
Time to balloon inflation (from ED arrival)		
Minutes, median (Q1–Q3)	32 (20–47)	124 (32–216)
Duration of balloon inflation		
Minutes, median (Q1–Q3)	29 (19–64)	71 (69–72)

Q1, 25th percentile; Q3, 75th percentile; TTL, Trauma Team Leader.
^a Partial REBOA denotes when clinicians partly deflated the balloon, to allow some distal blood flow.

Chapter 6 Clinical results

In this chapter, we present the clinical results for the trial. Discussion of the clinical results will be presented in [Chapter 9](#).

Primary outcome: 90-day mortality

The primary outcome of the trial was death within 90 days of injury.

Intention-to-treat-analysis

Of the 46 participants allocated to SC + REBOA strategy, 25 (54%) died within 90 days. Of the 43 SC participants for whom primary outcome data are available (1 participant decided against continued participation), 18 (42%) died ([Table 10](#)). Using the minimally informative prior, the OR for 90-day mortality was 1.58 (95% CrI 0.72 to 3.52). The posterior probability of an OR > 1 (i.e. that REBOA was harmful) was 86.9% ([Figure 8](#)).

When using the elicited enthusiastic prior, the OR for 90-day mortality was 1.40 (95% CrI 0.66 to 2.96) with a posterior probability of an OR > 1 of 81.0%. The adjusted analyses for covariates (see [Appendix 8, Table 24](#)) and centre (see [Appendix 8, Table 25](#)) showed similar results.

Survival curves

[Figure 9](#) shows the survival curves. There were more early deaths (within hours) in the SC + REBOA group, but deaths in this group also continued to 10 days.

Secondary outcomes

Mortality at other time points

Mortality at 3, 6, and 24 hours, in-hospital and at 6 months is also shown in [Table 10](#). For in-hospital and 6 months, the results were of the same order as 90-day mortality. For 3-, 6- and 24-hour mortality, however, there was an increased level of mortality in the SC + REBOA arm compared to SC with the greatest difference at 3 hours – 11 (24%) deaths in SC + REBOA compared with 2 (5%) deaths in SC, OR 4.25 95% CrI (1.33 to 15.99). For the adjusted analysis at other time points, the results were similar (see

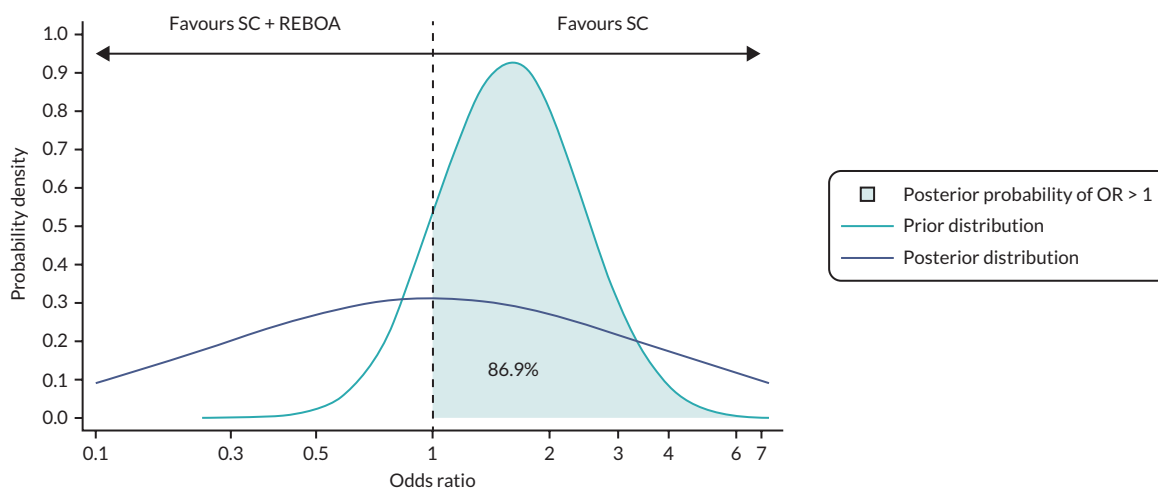


FIGURE 8 Posterior probability of mortality (OR > 1).

TABLE 10 Mortality

	SC + REBOA N = 46 n (%)	SC N = 44 n (%)	Minimally informative prior			Elicited enthusiastic prior		
			OR	95% CrI	Posterior probability (%) of OR > 1	OR	95% (CrI)	Posterior probability (%) of OR > 1
Primary outcome								
90-day mortality ^a								
Death within 90 days	25 (54)	18 (42)	1.58	(0.72 to 3.52)	86.9	1.40	(0.66 to 2.96)	81.0
Survived to 90 days	21 (46)	25 (58)						
Secondary outcomes								
3-hour mortality								
Death within 3 hours	11 (24)	2 (5)	4.25	(1.33 to 15.99)	99.3	3.01	(1.05 to 9.47)	97.7
Survived to 3 hours	35 (76)	42 (95)						
6-hour mortality								
Death within 6 hours	13 (28)	4 (9)	3.14	(1.13 to 9.76)	98.6	2.48	(0.95 to 6.82)	96.6
Survived to 6 hours	33 (72)	40 (91)						
24-hour mortality								
Death within 24 hours	17 (37)	10 (23)	1.85	(0.79 to 4.46)	91.8	1.61	(0.72 to 3.67)	87.2
Survived to 24 hours	29 (63)	34 (77)						
In-hospital mortality ^a								
Death while in hospital	25 (54)	18 (42)	1.58	(0.72 to 3.52)	86.9	1.40	(0.66 to 2.96)	81.0
Survived to discharge	21 (46)	25 (58)						
6-month mortality ^a								
Death within 6 months	25 (54)	18 (42)	1.58	(0.72 to 3.52)	86.9	1.40	(0.66 to 2.96)	81.0
Survived to 6 months	21 (46)	25 (58)						

a Number of patients in SC group at this time point was 43 due to one participant withdrawing on day 4.

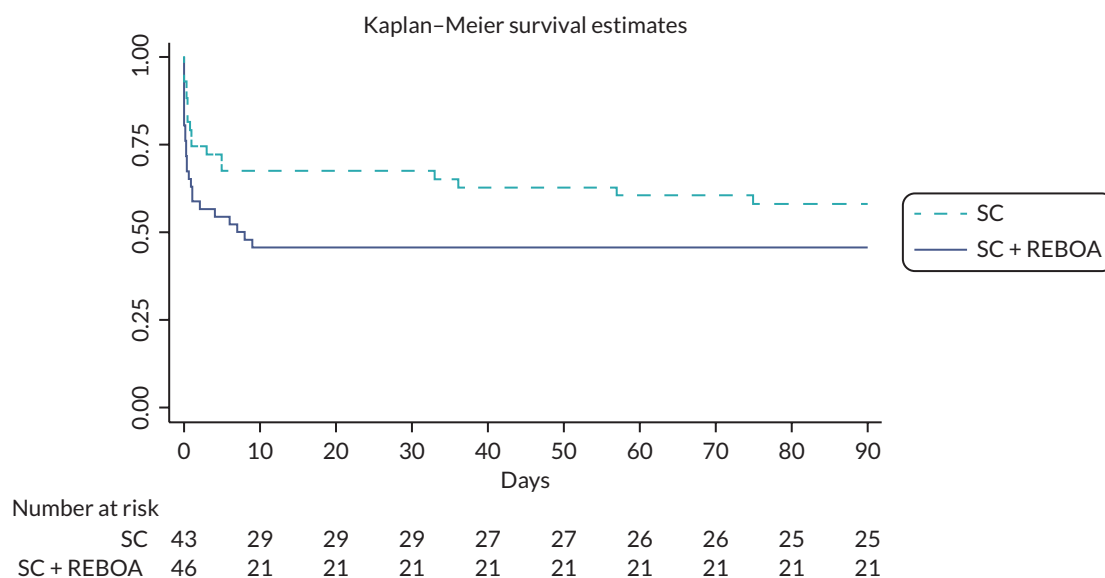


FIGURE 9 Survival curves.

[Appendix 8, Table 26–29](#)). [Appendix 8, Table 30](#) shows the learning curve analysis of excluding the first participant randomised to SC + REBOA from each site.

Cause of death

The causes of death, at different time points, are shown in [Table 11](#). The cause of death was listed as ‘unknown’ when a clinician could not determine the cause of death. Typically, this occurred when a patient died very early, before any imaging or operations could be performed, and/or if the patient had injuries that resulted in bleeding, as well as other major injuries, such as a traumatic brain injury. Furthermore, for some patients, a coroner’s report (and therefore cause of death) was still pending at the time of analysis. (These reports can take months to years to be returned to hospitals.)

[Table 11](#) shows that death due to haemorrhage was more common in the SC + REBOA strategy. This difference is apparent at all points, but is accounted for by deaths that occurred early (within 24 hours), after which time there were no further bleeding-related deaths in the SC + REBOA group. Although there were some early deaths due to traumatic brain injury, the overall number of deaths due to traumatic brain injury was similar in both groups.

Haemorrhage control procedures

[Table 12](#) shows the proportion of participants that underwent operations, operations that involved haemorrhage control and the time from randomisation to commencement of such procedures. There were 14 (30%) participants in SC + REBOA and 19 (43%) in SC that underwent a haemorrhage control procedure (OR 0.60, 95% CrI 0.26 to 1.37). The mean time from admission to haemorrhage control procedure (minutes) was 42 [standard deviation (SD) 121] in SC + REBOA and 28 (SD 41) in SC (MD 14.41 95% CrI –22.80 to 52.20). The majority of the participants had a haemorrhage control laparotomy [7/14 (50%) in SC + REBOA and 12/19 (63%) in SC], with one participant having two haemorrhage control procedures.

Length of stay

[Table 12](#) shows length of ICU and hospital stay for all patients. The table also shows length of stay for only those patients who survived to ICU (i.e. excluding early deaths). For ICU the median time (days) spent for SC + REBOA was 2 (25th percentile 0, 75th percentile 9) and 5 (25th percentile 1, 75th percentile 28) for SC. For length of stay in hospital (days), the median time was 8 (25th percentile 1, 75th percentile 34) in SC + REBOA and 19 (25th percentile 1, 75th percentile 63) in SC. Due to death being

TABLE 11 Cause of death

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

TABLE 12 Haemorrhage control procedures, length of stay and functional outcome

	SC + REBOA <i>n</i> = 46	SC <i>n</i> = 44	Effect size	95% CrI
Haemorrhage control procedures				
Need for haemorrhage control procedure for all participants				
Yes, <i>n</i> (%)	14 (30)	19 (43)	0.60	(0.26 to 1.37)
No, <i>n</i> (%)	32 (70)	25 (57)		
Time from randomisation to haemorrhage control procedure (minutes)				
Mean (SD); <i>n</i>	42 (121); 44	28 (41); 44	14.41	(-22.80 to 52.20)
Median (Q1-Q3)	0 (0-42)	0 (0-55)		
Had an operation, <i>n</i> (%)	31 (67)	35 (80)		
Haemorrhage control procedure for those that had operation, <i>n</i> (%)	14 (45)	19 (54)		
Time from randomisation to haemorrhage control procedure for those that had a procedure (minutes)				
Mean (SD); <i>n</i>	155 (197); 12	65 (40); 19		
Median (Q1-Q3)	83 (56-156)	64 (34-83)		
Type of haemorrhage control procedures for those who had a haemorrhage control procedure, <i>n</i> (%)				
Haemorrhage control laparotomy	7 (50)	12 (63)		
Extremity vascular ligation, shunting or repair	2 (14)	4 (21)		
Pelvic packing	4 (29)	1 (5)		
Angioembolisation ^a	2 (14)	2 (11)		
Haemorrhage control thoracotomy	1 (7)	-		
Length of stay				
ICU stay (days)				
All patients				
Mean (SD); <i>n</i>	7 (9); 45	15 (18); 44	-8.58	(-14.46 to -2.58)
Median (Q1-Q3)	2 (0-9)	5 (1-28)		
Removing those with a length of stay of 1 day				
Mean (SD); <i>n</i>	7 (10); 39	19 (18); 35	-11.40	(-17.88 to -4.77)
Median (Q1-Q3)	4 (0-10)	14 (3-33)		
Hospital stay (days)				
All patients				
Mean (SD); <i>n</i>	20 (26); 46	43 (54); 43	-22.16	(-39.53 to -4.71)
Median (Q1-Q3)	8 (1-34)	19 (1-63)		
Removing those with a length of stay of 1 day				
Mean (SD); <i>n</i>	34 (27); 27	61 (59); 33	-26.31	(-50.27 to -1.72)
Median (Q1-Q3)	29 (9-48)	38 (17-91)		

continued

TABLE 12 Haemorrhage control procedures, length of stay and functional outcome (*continued*)

	SC + REBOA n = 46	SC n = 44	Effect size	95% CrI
Hospital- and ICU-free days				
ICU-free days (base 90 days)				
Mean (SD); n	35 (40); 46	40 (37); 43	-4.79	(-20.75 to 11.31)
Median (Q1-Q3)	0 (0-80)	45 (0-78)		
ICU-free days (base 6 months)				
Mean (SD); n	78 (86); 46	94 (82); 43	-14.46	(-48.79 to 20.25)
Median (Q1-Q3)	0 (0-173)	138 (0-171)		
Hospital-free days (base 90 days)				
Mean (SD); n	22 (30); 46	41 (39); 43	-18.58	(-32.86 to -3.93)
Median (Q1-Q3)	0 (0-49)	41 (0-82)		
Hospital-free days (base 6 months)				
Mean (SD); n	64 (73); 46	69 (74); 43	-3.32	(-33.34 to 27.11)
Median (Q1-Q3)	0 (0-142)	23 (0-151)		
Blood product and tranexamic acid use				
Red cell concentrate, units				
Mean (SD); n	10 (9); 46	11 (9); 43	0.92	(0.66 to 1.29)
Median (Q1-Q3)	7 (4-12)	9 (4-17)		
Plasma, units				
Mean (SD); n	8 (8); 46	11 (10); 43	0.73	(0.49 to 1.08)
Median (Q1-Q3)	6 (3-10)	7 (4-18)		
Platelets, pools				
Mean (SD); n	1 (3); 46	2 (2); 43	0.87	(0.50 to 1.52)
Median (Q1-Q3)	1 (0-2)	1 (0-2)		
Cryoprecipitate, units				
Mean (SD); n	2 (3); 46	2 (3); 43	0.79	(0.41 to 1.53)
Median (Q1-Q3)	0 (0-2)	2 (0-3)		
Tranexamic acid, grams				
Mean (SD); n	1413 (580); 46	1568 (695); 44	0.90	(0.70 to 1.16)
Median (Q1-Q3)	1000 (1000-2000)	2000 (1000-2000)		
Extended GOS				
Mean (SD); n	2 (2); 44	3 (2); 43	0.58	(0.26 to 1.25)
Median (Q1-Q3)	1 (1-4)	3 (1-5)		
Categories, n (%)				
One (death)	24 (52)	17 (39)		
Two (persistent vegetative state)	-	-		
Three (severe disability)	5 (11)	8 (18)		
Four (moderate disability)	8 (17)	7 (16)		
Five (good recovery)	7 (15)	11 (25)		
Missing	2 (4)	1 (2)		

Q1, 25th percentile; Q3, 75th percentile.

a One participant had an additional angioembolisation procedure.

a competing event, the competing risk analysis showed, for those in the SC + REBOA arm, a reduced length of stay (subhazard ratio of 0.75, 95% confidence interval 0.42 to 1.34) (see [Appendix 8, Figure 27](#)). In order to better account for the competing risk of death, we also calculated hospital-free and ICU-free days, as shown in [Table 12](#).

Blood product use

[Table 12](#) shows blood product and tranexamic acid use in the first 24 hours following injury. Overall, there was little difference between SC + REBOA and SC. For red cell concentrate, the median number of units was 7 (25th percentile 4, 75th percentile 12) in SC + REBOA and 9 (25th percentile 4, 75th percentile 17) in SC.

Functional outcome

For the functional outcome, GOS-E, the mean score was 2 (SD 2) in SC + REBOA and 3 (SD 2) in SC (proportional OR 0.58 95% CrI 0.26 to 1.25) (see [Table 12](#)). The GOS-E ranges from one (death) to five (good recovery). [Table 12](#) also shows these categories with majority of participants being under category one [death; 24/46 (52%) in SC + REBOA and 17/43 (39%) in SC].

Complications

In the SC + REBOA group, the number of participants with a complication (excluding death) was 6 (13%) and 10 (23%) in SC group (OR 0.54 95% CrI 0.19 to 1.48) ([Table 13](#)). There were no device-related AEs.

Additional analyses

As discussed in the methods (see [Chapter 2](#)), a number of patients who were randomised to REBOA did not proceed to have full balloon occlusion, for a variety of clinical reasons (intercurrent events e.g. patients improved so REBOA no longer indicated; patient deteriorated so REBOA no longer possible). These patients are not 'cross-overs' or true non-compliers, but reside on a spectrum of how far a patient has progressed down the REBOA-strategy pathway. As previously discussed, we had identified two additional analyses to accommodate for these intercurrent events via CACE analysis:

Complier average causal effect analysis 1

Question: 'Does a strategy that includes REBOA (in addition to standard MTC 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)?*'

As noted in [Chapter 2](#), CACE 'compliance' (with the caveats regarding the terminology noted in [Chapter 2](#)) in the SC + REBOA arm was defined as patients who were classified as R5 (catheter inserted, balloon inflated) and 'non-compliance' as all others (i.e. any patient in whom the balloon was not inflated, whether due to technical failure or changes in the patient's condition). In the SC group, the two patients who had REBOA were classified as 'non-compliance' and all other patients were regarded as 'compliers'. [Appendix 8, Table 31](#) shows the baseline characteristics of these groups. As expected, there are differences between 'compliers' and 'non-compliers'. [Table 14](#) shows the results of the CACE analysis, for all mortality time points. This shows that, even when inability to cannulate and changes in patients' clinical condition are taken into consideration, the use of REBOA was associated with increased odds of mortality.

Complier average causal effect analysis 2

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

For the purpose of this analysis, in the SC + REBOA arm, we defined 'compliance' for the CACE analysis (with the caveats regarding the terminology noted in [Chapter 2](#)) as patients who were classified as anything other than R2 (arterial access attempted, but unsuccessful) and 'non-compliance' as all patients classified as R2. In the SC group, the two patients who had REBOA were classified as 'non-compliance' and all other patients were regarded as 'compliers'. [Appendix 8, Table 32](#) shows the baseline characteristics of these groups. As expected, there are differences between 'compliers' and 'non-compliers'. [Table 15](#) shows the results of the CACE analysis, for all mortality time points which showed that, even when the patients in whom cannulation was not possible is taken into account, the use of REBOA was associated with increased odds of mortality.

As-treated (safety) analysis

The results of the as-treated (safety) analysis are shown in [Appendix 8, Tables 33](#) and [34](#).

TABLE 13 Complications

	SC + REBOA N = 46	SC N = 43 ^a
Complications		
Yes	6 (13)	10 (23)
No	40 (87)	33 (76.7)
Number of complications		
One	3 (50)	5 (50)
Two	2 (33)	4 (40)
Three	1 (17)	1 (10)
Details		
Access-related		
Pseudoaneurysm	2 (33)	1 (10)
Distal embolism	1 (17)	1 (10)
External haemorrhage 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/bronchopleural fistula	-	1 (10)
Infection requiring antibiotics only	-	1 (10)
AEs related to impaired perfusion		
Acute kidney injury requiring renal replacement therapy	3 (50)	5 (50)
Multiorgan failure	1 (17)	5 (50)
Acute respiratory distress syndrome	-	1 (10)

^a One participant declined to continue to participate on day 4.

Note

Values are n (%).

TABLE 14 Odds ratio of mortality in 'compliers' (R5) vs. 'non-compliers' (all others), using CACE analysis

		SC + REBOA N = 46		SC N = 44		OR	95% CrI	Posterior probability (%) of OR > 1
		Complied N = 20	Did not comply N = 26	Complied N = 42	Did not comply N = 2			
		N = 19	N = 26	N = 41	N = 2			
Death within 90 days								
Yes	13 (68)	12 (44)	17 (41)	1 (50)	4.25	(0.41 to 45.07)	88.9	
No	6 (32)	15 (56)	24 (59)	1 (50)				
Death within 6 months								
Yes	13 (68)	12 (44)	17 (41)	1 (50)	4.25	(0.41 to 45.07)	88.9	
No	6 (32)	15 (56)	24 (59)	1 (50)				
Death while in hospital								
Yes	13 (68)	12 (44)	17 (41)	1 (50)	4.25	(0.41 to 45.07)	88.9	
No	6 (32)	15 (56)	24 (59)	1 (50)				
		N = 20	N = 26	N = 42	N = 2			
Death within 24 hours								
Yes	8 (42)	9 (33)	10 (24)	-	6.59	(0.53 to 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 to 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 to 72,295.55)	99.8	
No	14 (74)	21 (78)	40 (95)	2 (100)				

TABLE 15 Odds ratio of mortality 'compliers' (non-R2) versus 'non-compliers' (R2) using CACE analysis

	SC + REBOA N = 46		SC N = 44		OR	95% CrI	Posterior Probability (%) of OR > 1
	Complied N = 36	Did not comply N = 10	Complied N = 42	Did not comply N = 2			
	N = 36	N = 10	N = 41	N = 2			
Death within 90 days							
Yes	18 (50.0)	7 (70.0)	17 (41)	1 (50)	2.07	(0.64 to 6.72)	88.9
No	18 (50.0)	3 (30.0)	24 (59)	1 (50)			
Death within 6 months							
Yes	18 (50.0)	7 (70.0)	17 (41)	1 (50)	2.07	(0.64 to 6.72)	88.9
No	18 (50.0)	3 (30.0)	24 (59)	1 (50)			
Death while in hospital							
Yes	17 (47.2)	7 (70.0)	17 (41)	1 (50)	2.07	(0.64 to 6.72)	88.9
No	19 (52.8)	3 (30.0)	24 (59)	1 (50)			
	N = 37	N = 9	N = 42	N = 2			
Death within 24 hours							
Yes	24 (66.7)	5 (50.0)	10 (24)	-	2.59	(0.73 to 9.79)	93.1
No	12 (33.3)	5 (50.0)	32 (76)	2 (100)			
Death within 6 hours							
Yes	9 (25.0)	4 (40.0)	4 (10)	-	6.88	(1.37 to 45.11)	99.1
No	27 (75.0)	6 (60.0)	38 (90)	2 (100)			
Death within 3 hours							
Yes	7 (19.4)	4 (40.0)	2 (5)	-	14.78	(2.02 to 240.52)	99.7
No	29 (80.6)	6 (60.0)	40 (95)	2 (100)			

Chapter 7 Costs and quality-adjusted life-years over 6 months' follow-up

Background

The purpose of this chapter is to descriptively summarise the resource use, costs, life-years and QALYs for UK-REBOA trial participants. We report costs and economic outcomes for REBOA added to standard of care (SC + REBOA), compared to SC alone over a follow-up period of 6 months post randomisation from a UK NHS perspective. As with the trial clinical analyses, we adopted a Bayesian framework of analysis and the base-case results are presented from an ITT analysis.

Objectives

The primary economic objective of the UK-REBOA trial was to evaluate the lifetime incremental cost-effectiveness (cost-per-QALY) for the SC + REBOA versus SC alone from a UK NHS perspective. The secondary economic objectives were to measure the total healthcare cost, quality of life (using the EQ-5D-5L mapped to EQ-5D-3L), life-years, and incremental cost per QALY and per life-year at 6 months post randomisation. A health economics analysis plan (HEAP), v1.0, was developed prior to the analysis of the trial data (see additional files www.fundingawards.nihr.ac.uk/award/14/199/09; accessed June 2024).

Important amendments to the pre-specified health economics analysis plan

Given that the clinical results of the trial showed that REBOA leads to increased mortality (see [Chapter 6](#)), reporting incremental cost-effectiveness ratios (ICERs) as pre-specified in v1.0 of the HEAP will not provide any additional meaningful information for decision-makers. Results of cost-effectiveness conclusions or estimates of the ICER could never practically lead to the ethical adoption of REBOA in this setting, therefore presenting ratios would be non-informative regardless of the magnitude of cost savings that might be achieved through early mortality. We therefore have not reported ICERs and instead have focused reporting on the estimates of costs, life-years and QALYs separately. These estimates of resource use and utilities may be useful and informative for future economic evaluations in trauma care and are therefore reported in as much detail as possible to facilitate future use of the parameters. Other than the amendments to the analysis plan described here, the health economics analysis follows the pre-specified HEAP v1.0.

Methods

Resource use and costs – index hospitalisation

Resuscitative endovascular balloon occlusion of the aorta refers to the insertion of a balloon, usually through the femoral artery. REBOA intends to obstruct blood flow upon inflation. The pragmatic trial design allowed any REBOA device to be used. It is assumed that there are no additional staff resources required to administer REBOA and that the skills to deliver REBOA would already be available within the MTC team and would be incorporated into their workload.

Typically, in major trauma, a multidisciplinary trauma team will assemble prior to the patient's arrival and will meet with the ambulance crew. We have therefore developed an assumed staff mix of the trauma team which was combined with Personal Social Services Research Unit (PSSRU) cost per working hour to calculate the cost per hour of trauma team staff.⁶⁹ This was added to the cost of overheads of the ED

sourced from Public Health Scotland (PHS), based on data from Scottish MTCs.⁷⁰ We applied the cost of the trauma team and ED overheads from arrival (randomisation) through to the patient's transfer to an operating theatre, death or exit from the ED, whichever happens first. The volume of blood products required for transfusion was sourced from TARN data linkage for trial participants, and unit costs were obtained from the literature and uplifted to 2020–1 prices.⁷¹

The complexity of the treatment required for these injuries means that standard NHS reference costs may under estimate the true opportunity cost of treatment, particularly as such patients require the use of multidisciplinary trauma teams, large blood transfusions, multiple operative procedures and lengthy stays in critical care and on hospital wards. We therefore costed individual components of resource and summed these component costs to generate a total cost for the whole initial hospitalisation admission period. Total NHS resource use for the index hospitalisation was obtained from patient-level data in TARN and the key resource use variables for costing include time of arrival, time of ED departure, time of first operation, time of death/discharge, number and type of operative procedures and volume of blood transfusions that were required.

Hospital resource use was reported and costed per unit of activity (hour, minute, day) using national average unit costs reported by PHS.⁷⁰ Scottish unit costs were used because they provide a greater level of detail in costs than the published English costing sources and were therefore more appropriate for a component costing approach. These included the direct and indirect costs for the entirety of the participants' stay in hospital (in theatre, in the ward and ICU). For operative costs, we applied national average unit costs based on the primary specialty in which the procedure falls. Duration of each operative procedure was not available from TARN. We therefore categorised each procedure as likely to be short (up to 2 hours), medium (2–4 hours) or long (4–6 hours). This categorisation was based on clinical expert judgement of the trial CI. While there is inevitably variability in the duration of each operative procedure, the approach allows an allocation of costs that broadly reflects duration and specialty of different procedures.

The cost of time in types 1 (e.g. general ward), 2 (e.g. HDU) and 3 (ICU/critical care) wards were calculated using the duration of stay in each department and the average direct and allocated cost per day sourced from PHS.⁷⁰

Details of all unit costs applied for the index hospitalisation are summarised in [Table 16](#).

Resource use and costs – discharge to 6 months' follow-up

Secondary care contacts and episodes of care that were commenced between the date of discharge from the index hospitalisation through 6 months post randomisation were sourced, where available, through linkage of patient records to the HES database. The HES database provides information on a variety of secondary care contacts including inpatient admitted patient care, critical care admissions, outpatient consultations and use of accident and emergency (A&E) services and includes secondary care rehabilitation service usage. The database provides the Healthcare Resource Groups (HRGs) and speciality codes that enable mapping of each secondary care contact to the appropriate NHS unit cost. Unit costs are obtained from NHS reference costs for 2020–1.

We had pre-planned a sensitivity analysis that would apply NHS reference costs to the index hospitalisation stay based on HES data from NHS Digital. However, this analysis was not able to be conducted because data linkage, where it was possible to identify the index hospitalisation, was only possible for 39/90 (43%) patients randomised to the study. NHS Digital agreed to provide data linkage only for participants who provided patient or consultee consent (56/90) and of those 56 with consent, data linkage was only available for 39 participants. This was despite the process of obtaining consent being approved by ethics and being conducted in accordance with the trial protocol. Of the remaining 51 patients who were not linked, 37 died during their index hospitalisation and so zero costs were

TABLE 16 Summary of unit costs applied to index hospitalisation resource use

Resource use item	Units	Unit cost (GBP)	Year	Source and notes
Devices and diagnostics				
REBOA device	Per participant	£1825	2022	Personal communication with REBOA supplier, May 2022.
CT scan	Per scan	£84	2019–20	Uplifted to 2020–1 prices (£87) using PSSRU inflation indices. Data and intelligence. Expenditure and activity – radiology services, hospital cost breakdown (R120). PHS. ⁷⁰
Blood products				
Red blood cells	Per unit	£49	2014–5	Uplifted to 2020–1 prices (£54) using PSSRU inflation indices. ⁷¹
Platelets	Per unit	£58	2014–5	Uplifted to 2020–1 prices (£65) using PSSRU inflation indices. ⁷¹
Fresh-frozen plasma	Per unit	£38	2014–5	Uplifted to 2020–1 prices (£42) using PSSRU inflation indices. ⁷¹
Cryoprecipitate	Per unit	£49	2014–5	Uplifted to 2020–1 prices (£55) using PSSRU inflation indices. ⁷¹
Trauma team staff costs				
Consultant: medical	Per working hour	£123	2020–1	Jones and Burns, 2021 ⁶⁹
Consultant: surgical	Per working hour	£122	2020–1	Jones and Burns, 2021 ⁶⁹
Associate specialist	Per working hour	£120	2020–1	Jones and Burns, 2021 ⁶⁹
Nurse consultant (Band 8a)	Per working hour	£70	2020–1	Jones and Burns, 2021 ⁶⁹
Modern matron (Band 8a)	Per working hour	£70	2020–1	Jones and Burns, 2021 ⁶⁹
Nurse advanced–team manager (Band 7)	Per working hour	£62	2020–1	Jones and Burns, 2021 ⁶⁹
Nurse specialist–team leader (Band 6)	Per working hour	£51	2020–1	Jones and Burns, 2021 ⁶⁹
Nurse (Band 5)	Per working hour	£41	2020–1	Jones and Burns, 2021 ⁶⁹
Clinical support worker higher level nursing (Band 3)	Per working hour	£29	2020–1	NHS. Agenda for change – payrates. 2021. Jones and Burns, 2021 ⁶⁹
Total cost of trauma team per hour (13 staff)	Per working hour	£1784	2020–1	3× Consultant medical, 1× Consultant surgical, 2× Associate specialists, 1× Band 8a nurse, 1× Band 7 nurse, 3× Band 6 nurse, 1× Band 5 nurse, 1× Band 3 nurse.

continued

TABLE 16 Summary of unit costs applied to index hospitalisation resource use (continued)

Resource use item	Units	Unit cost (GBP)	Year	Source and notes	
Hospital department					
ED	Per hour	£21	2019–20	Uplifted to 2020–1 prices (£22) using PSSRU inflation indices. Includes allocated and laboratory costs. Weighted average by discharges of Scottish hospitals within the major trauma network. Data and intelligence. Specialty group costs – inpatients in all specialties (excluding long stay), A&E (R040). PHS. ⁷⁰	
ICU (level 3 ward) ^b	Per day	£3104	2019–20	Uplifted to 2020–1 prices (£3200, £1968, £1446, £1412, £966, £787 for ICU, neurosurgery, HDU, plastic surgery, general surgery and orthopaedic surgery, respectively) using PSSRU inflation indices. Includes: direct cost per case excluding theatre costs divided by the specialty average length of stay weighted by discharges of Scottish MTCs. ^a	
Neurosurgery ward (level 1) ^b	Per day	£1909	2019–20		
HDU (level 2 ward) ^b	Per day	£1403	2019–20		
Plastic surgery ward (level 1) ^b	Per day	£1370	2019–20		
General surgery ward (level 1) ^b	Per day	£937	2019–20		
Orthopaedic surgery ward (level 1) ^b	Per day	£763	2019–20		
Theatre					
Dental	Per hour	£1114	2019–20	Uplifted to 2020–1 prices (£1148, £1353, £1319, £1323, £2107, £1426, £1347, £1411, £1316, £1197, respectively) using PSSRU inflation indices. Includes: average direct cost per hour of theatre across Scotland plus allocated costs per hour of theatre (£241) weighted by activity of Scottish MTCs ^a	
General surgery (excluding vascular surgery)	Per hour	£1313	2019–20		
Gynaecology	Per hour	£1280	2019–20	Data and intelligence. Theatre – direct cost per hour, by specialty (R142X). PHS.	
Maxillofacial surgery	Per hour	£1283	2019–20		
Neurosurgery	Per hour	£2044	2019–20		
Orthopaedics	Per hour	£1383	2019–20		Data and intelligence. Theatre services (R140). PHS. ⁷⁰
Plastic surgery and burns	Per hour	£1307	2019–20		
Thoracic surgery	Per hour	£1369	2019–20		
Urology	Per hour	£1277	2019–20		
Vascular surgery	Per hour	£1161	2019–20		

GBP, Great British pounds.

a Allocated costs include: administration, catering, uniforms, laundry, portering, waste disposal, transport and travel, property maintenance, cleaning, utilities, rent and rates, furniture and other equipment purchase, rental and repairs, depreciation, notional interest and miscellaneous.

b Level 1: Ward-based care where the patient does not require organ support (e.g. they may need an IV or oxygen by face mask). Level 2: HDU. Patients needing single-organ support (excluding mechanical ventilation) such as renal haemofiltration or inotropes and invasive BP monitoring. They are staffed with one nurse to two patients. Level 3: Intensive care. Patients requiring two-or-more-organ support (or needing mechanical ventilation alone). Staffed with one nurse per patient and usually with a doctor present in the unit 24 hours per day.

imputed. In total, follow-up costs were available for 76 trial participants. Data availability following the NHS Digital data linkage process is summarised in [Figure 10](#).

All costs are reported from a UK NHS perspective in Great British pounds (GBP; year 2020–1). Healthcare resource use is reported descriptively for each arm of the study, as *n* (%) for categorical data such as number of procedures and mean (SD) for continuous data (such as length of stay). Total per-participant costs (resource use × unit costs) are reported as mean (SD) for each arm of the trial from index hospitalisation to 6-month follow-up. Incremental costs for SC + REBOA compared to SC alone are estimated using Bayesian generalised linear regression models, with non-informative priors. The most appropriate distributional family and link function for cost data was determined to be a gamma family based on a Parks test, with an identity link. The gamma model accounts for the non-normality of cost data (i.e. a small proportion of participants with lengthy hospital stays and very high NHS costs). Regression models were adjusted for age and gender covariates.

Life-year and quality-adjusted life-year outcomes

EuroQol Group's 5-dimension health status 5-level questionnaire data were available from the TARN data set at two follow-up points. The first is administered through TARN prior to the patient's discharge from their index hospitalisation for major trauma care. The second is administered as a postal questionnaire through a third-party provider at 6 months post admission. Given that there is no generally accepted valuation set for the EQ-5D-5L, we generated utilities by first cross-walking the raw EQ-5D-5L data to the 3L version and applying UK general population tariffs to generate health state utilities. Due to the severity of injury sustained by participants in this trial, it was assumed that all patients were unconscious at the point of randomisation and were therefore assigned an EQ-5D-3L utility value of -0.402 at baseline. Participants who died during the study follow-up period were assigned a utility value of 0 from the date of death until the end of follow-up. These utility scores were then used to calculate the participant's QALYs over the observed 6-month period using the area under the curve (AUC) approach. The AUC approach assumes a linear change in utility between the time points

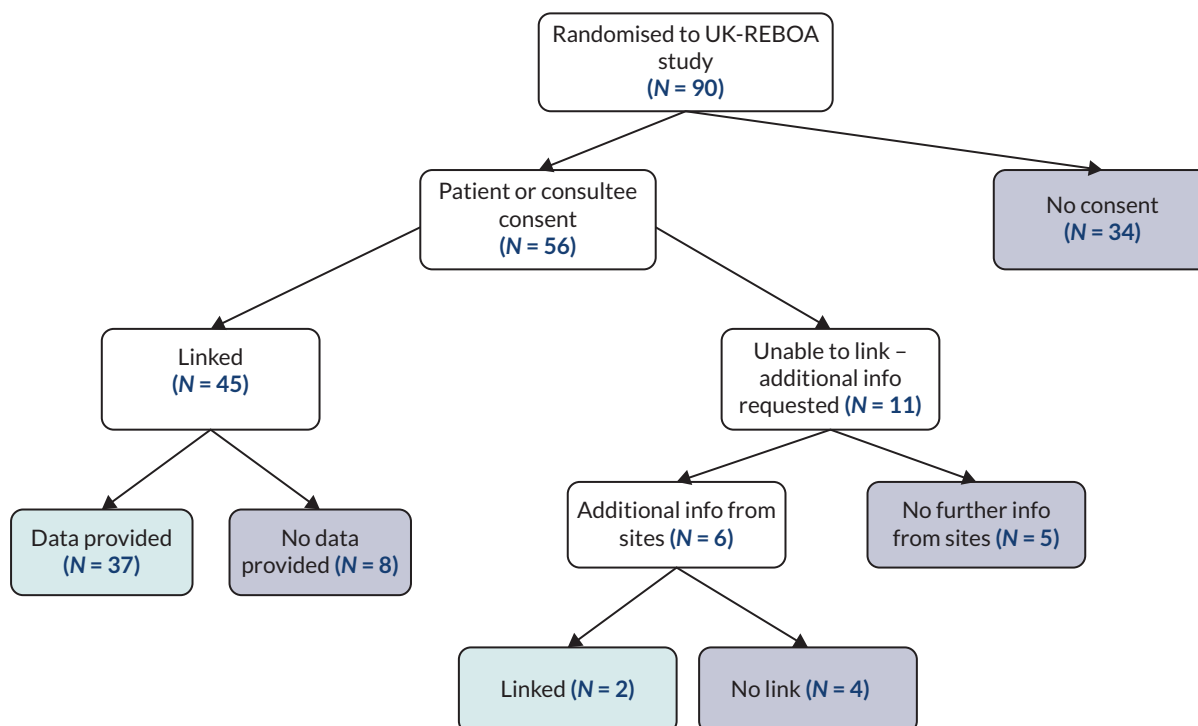


FIGURE 10 NHS Digital data linkage.

measured. Incremental life-years and incremental QALYs were estimated using Bayesian ordinary least squares regression models as the data appear to be normally distributed. Life-year and QALY regressions are adjusted for age and gender covariates.

Results

Costs

Tables 17 and 18 detail the results of the resource use and costs generated for the index hospitalisation using the component costing approach. The main driver of cost is the length of stay in hospital in general and particularly in critical care. Together, total hospital length of stay costs account for approximately 80% of the total index admission costs. Due to the larger number of earlier deaths in the SC + REBOA group, key cost drivers of critical care and hospital length of stay are substantially lower in the SC + REBOA group compared to SC.

TABLE 17 Resource use for index hospitalisation within TARN^a

Item	SC + REBOA			SC		
	N	Mean	SD	N	Mean	SD
Time in ED (minutes) ^b	45	263.02	307.67	43	261.40	295.52
Number of operations (n)	45	3.13	5.43	43	5.65	8.16
Length of stay in critical care (days)	45	6.60	9.32	43	14.72	17.53
Total length of stay (days)	45	18.42	24.80	43	41.52	53.78

a Index hospitalisation refers to the hospitalisation described within the TARN database. Therefore, the length of stay does not include cases where the patient was discharged to other hospitals. This is not consistent with the length of stay reported within Chapter 6, where the length of stay includes time in other hospitals within 6 months post injury. The episodes of care within other hospitals are captured within the HES costs (discharge to 6 months).

b Competing risk of death applies.

TABLE 18 Costs for the index hospitalisation

Item	SC + REBOA			SC		
	Mean (£)	SD (£)	N	Mean (£)	SD (£)	N
REBOA device costs	852	921	45	85	389	43
Trauma team	4761	5569	45	4731	5349	43
ED overheads	96	113	45	96	108	43
ED CT scan	87	49	45	103	44	43
ED Blood products	513	436	45	547	446	43
Operations	14,054	19,852	45	23,311	32,058	43
Level 3 ward (critical care)	21,262	34,077	45	53,767	62,836	43
Level 2 ward	8788	17,573	45	25,319	47,296	43
Level 1 ward	7067	16,730	45	8201	22,212	43
Total ward costs	37,117	50,505	45	87,287	102,884	43
Total index hospitalisation costs	57,384	62,863	45	116,064	128,957	43

TABLE 19 Costs of NHS resource use between discharge and 6 months

Item	SC + REBOA			SC			Unadjusted mean difference (95% CrI)
	Mean (£)	SD (£)	N	Mean (£)	SD (£)	N	
Index admission ^a	57,384	62,863	45	116,064	128,957	43	-£61,205 (-£106,881 to -£22,297)
Hospital costs for episodes of care commenced between index admission discharge and 6 months post injury							
Inpatient stay	10,647	32,157	40	4075	7090	36	+ £6800 (+ £3379 to + £11,222)
Outpatient attendance	954	1432	40	1309	1762	36	-£397 (-£1020 to + £123)
Critical care admission	0	-	40	0	-	36	--
Total costs discharge to 6 months	11,601	32,417	40	5385	7849	36	+ £6566 (+ £2707 to + £11,042)
Total NHS costs (non-adjusted)^b	59,049	70,983	40	91,980	100,403	36	-£35,470 (-£75,616 to + £424)
Total NHS costs (adjusted for age and gender)	-	-	-	-	-	-	-£21,997 (-£65,912 to + £13,193)
Total NHS costs (adjusted for age, gender and ISS)	-	-	-	-	-	-	-£20,949 (-£50,705 to + £11,206)

a Index hospitalisation costs, among those for whom follow-up costs could also be calculated were [mean (SD); N]: SC + REBOA: £47,448 (£54,292); 40 and SC only: £86,595 (£97,523); 36.

b Note that total cost results in this table are for complete-case analysis (i.e. patients for whom it was possible to derive a cost of index hospitalisation and a follow-up cost).

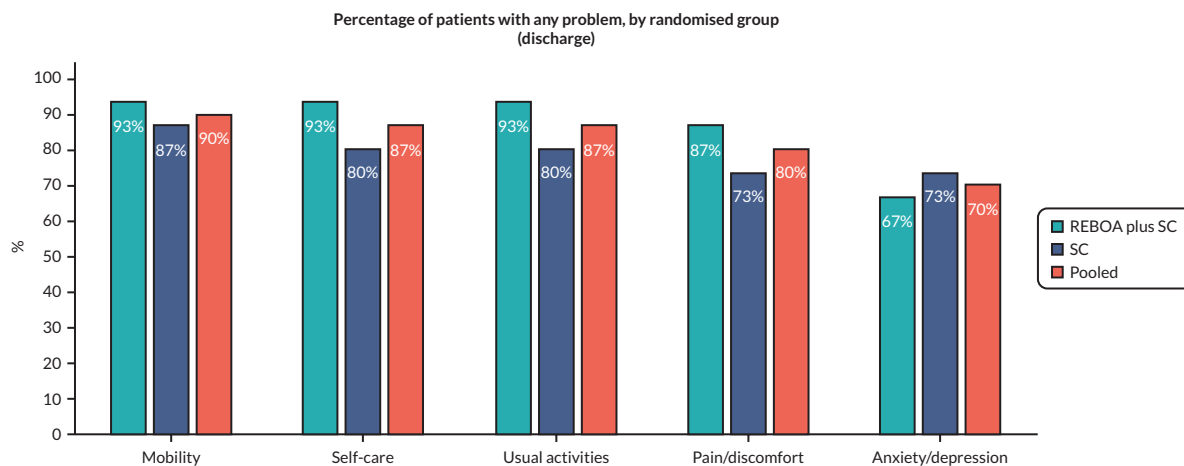


FIGURE 11 Proportion of respondents reporting any problems at hospital discharge.

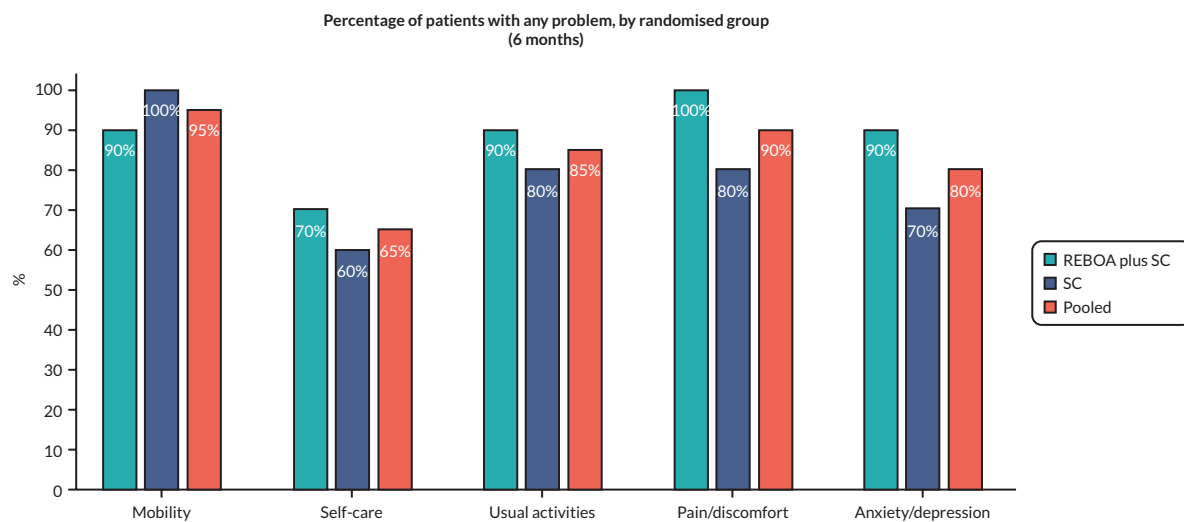


FIGURE 12 Proportion of respondents reporting any problems at 6 months.

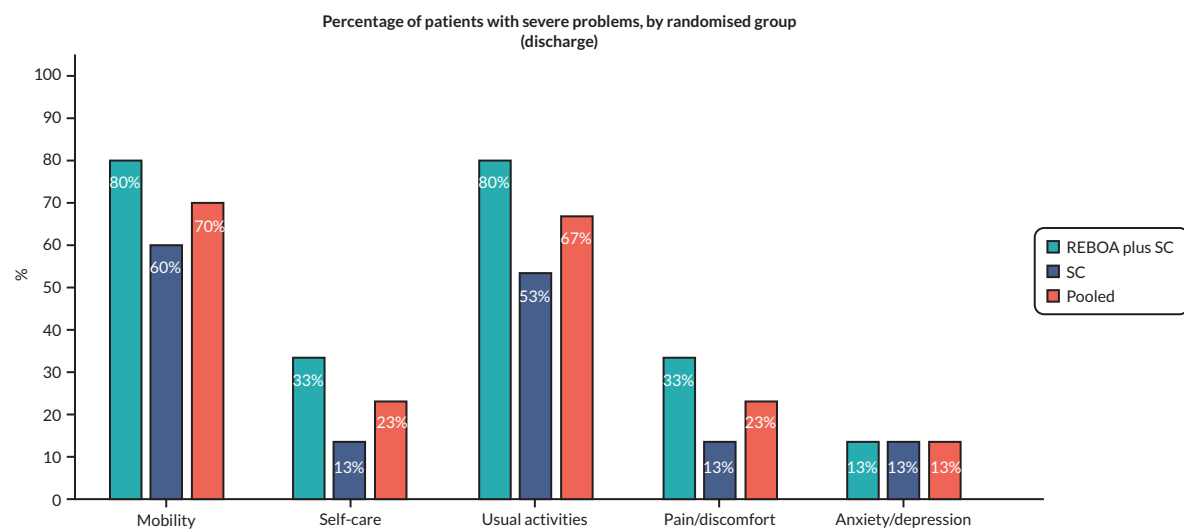


FIGURE 13 Proportion of respondents reporting severe problems at hospital discharge.

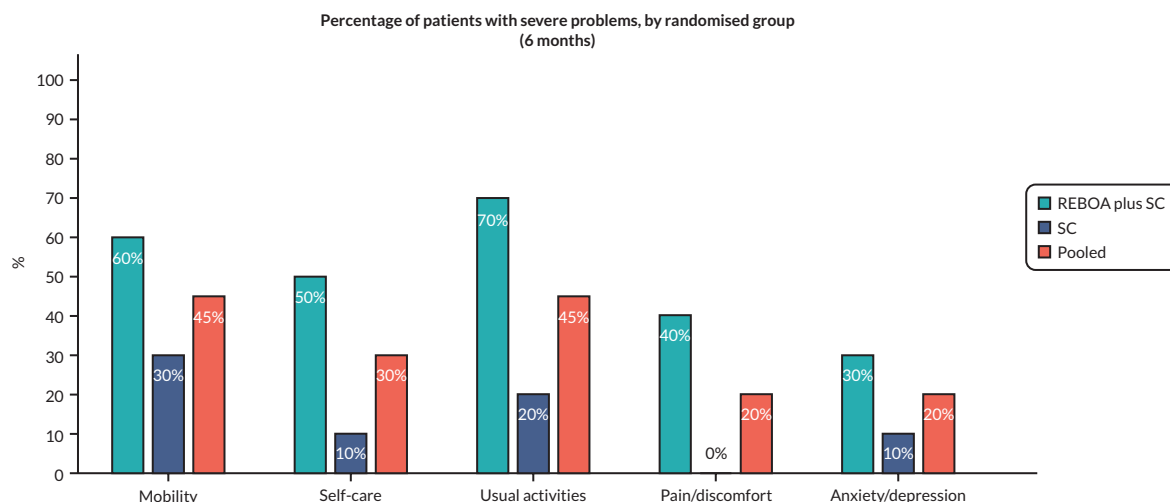


FIGURE 14 Proportion of respondents reporting severe problems at hospital 6 months.

[Table 19](#) shows that, over 6-month follow-up, SC + REBOA remains substantially less costly than SC alone, due to the competing risk of mortality. The overall finding was robust to whether models were adjusted for age, sex or ISS score.

Quality-adjusted life-years

EuroQol Group's 5-dimension data collected within the study are presented descriptively in [Figures 11-14](#), in accordance with EuroQol reporting recommendations.⁷² Data were available and are reported for $N = 29$ (SC + REBOA = 15; SC = 14) survivors at discharge and for $N = 20$ survivors at 6 months (SC + REBOA = 10; SC = 10). Given imputation of 0 utilities for participants who died, it was possible to derive QALYs for $N = 57/90$ (63%) participants. Data completeness for EQ-5D-5L was lower than expected. This was driven in part to a large proportion of missing data from TARN's partner provider at 6 months, but also missed TARN data collection prior to discharge. The available data from TARN were supplemented with additional efforts of the trial office to collect further EQ-5D-5L data through participating sites. Life-year gains (LYGs), utilities and QALYs calculated for each arm of the trial are reported in [Table 20](#).

Discussion

In summary, care for trauma patients included in this trial was expensive, with most costs incurred during the index hospitalisation, with less intense use of hospital resource over follow-up. On average, participants in the SC + REBOA arm of the study incurred lower costs than in SC, due to the competing risk of death. Similarly, life-years accrued and QALYs over 6 months post randomisation were also lower in the SC + REBOA arm compared to SC due to a greater proportion of trial participants dying in the SC + REBOA arm and with mortality also occurring earlier in the follow-up period for the SC + REBOA arm. Results for both costs and QALYs remain robust to adjustment age, gender and ISS score and whether baseline utility is set to the unconscious (-0.402) state or set to 0.

Given that REBOA was both less costly and less effective, an analysis of cost-effectiveness would place REBOA in the southwest quadrant of the cost-effectiveness plane, where decision-makers would normally consider the cost savings achieved for each QALY lost. While this is a perfectly valid consideration for decision-making when the magnitude of QALY loss is small, the large differences in mortality between the arms for this study mean that an assessment of cost-effectiveness in the SW

TABLE 20 Life-years and QALYs

Item	SC + REBOA			SC			Mean difference (95% CrI)
	Mean	SD	N	Mean	SD	N	
Life-years							
Life-years gained	0.232	0.247	45	0.305	0.236	43	-0.074 (-0.175 to + 0.030)
Quality of life (EQ-5D^a health state utilities) among survivors							
EQ-5D ^a utility at baseline	-0.402	-	-	-0.402	-	-	
EQ-5D ^a utility at discharge	0.147	0.339	15	0.388	0.349	14	
EQ-5D ^a utility at 6 months	0.188	0.399	10	0.538	0.296	10	
Quality of life (EQ-5D^a health state utilities) with 0s imputed for death							
EQ-5D ^a utility at discharge	0.057	0.218	39	0.181	0.305	30	
EQ-5D ^a utility at 6 months	0.055	0.226	34	0.192	0.313	28	
QALYs (baseline -0.402)							
Unadjusted	0.014	0.065	33	0.042	0.109	24	-0.029 (-0.075 to + 0.017)
Adjusted age and gender							-0.024 (-0.070 to + 0.025)
Adjusted age, gender and ISS							-0.027 (-0.071 to + 0.018)
QALYs (baseline 0)							
Unadjusted	0.022	0.068	33	0.056	0.110	24	-0.035 (-0.083 to + 0.011)
Adjusted age and gender							-0.030 (-0.080 to + 0.017)
Adjusted age, gender and ISS							-0.032 (-0.075 to + 0.015)

ISS, Injury Severity Score.

a EQ-5D utility scores based on EQ-5D-5L collected data cross-walked to EQ-5D-3L.

quadrant is not informative for decision-makers, regardless of the magnitude of cost-savings achieved. One limitation of the within-trial analyses is that the costs are all incurred up front, whereas the benefits of life-years saved and improvements in quality of life for survivors are likely to be accrued well beyond the 6-month trial follow-up. We therefore develop a simple decision analysis model to extrapolate life-year and QALY gains for survivors over a lifetime horizon (presented in [Chapter 8](#)).

Chapter 8 Decision analysis modelling

Background

In this chapter, we extrapolate the short-term costs and outcomes (mortality and utilities) from 6 months presented in [Chapter 7](#), over a full lifetime horizon. Considering costs and outcomes over a longer time horizon is particularly important in scenarios where substantial costs of saving a life in trauma care are incurred up-front, but the benefits in terms of extended length of life and recovery leading to improvements in quality of life among survivors are not fully realised until well beyond the 6-month period of data observation in the trial. Any statements on cost-effectiveness in this setting should therefore be made only on consideration of the lifetime economic modelling presented in this chapter.

Methods

A decision analysis model was created using TreeAge Pro 2021 software⁷³ to calculate expected costs, life-years and QALYs of SC + REBOA and standard major trauma care alone in adult patients with uncontrolled torso haemorrhage. The model extrapolated short-term (6-month) trial outcomes over a lifetime horizon from a UK NHS perspective. Development of the model structure, parameterisation and analysis methods are described in the following sections.

Model structure

A decision tree with a Markov cohort model was used to calculate expected costs, life-years and QALYs. The decision tree phase of the model captured 6-month mortality risks (and hence LYGs), costs and quality of life (utilities) among survivors as observed in the trial. The proportion of the cohort who were alive at 6 months post randomisation then entered a Markov cohort model, where costs and outcomes were accumulated over a lifetime horizon. As the primary outcome from the study was mortality, a simple two-state Markov model, with states for alive and dead is used to capture longer-term outcomes. The model was built flexibly to capture a range of different assumptions about the extent to which pre-injury quality of life is achievable among survivors, and the time taken to reach a steady state of quality of life. A simplistic model structure focussing on longer-term extrapolation of survival outcomes is consistent with other modelling work in trauma care, including the economic modelling approach taken for the Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage 2 (CRASH-2) study.⁷⁴ The model structure is illustrated in [Figure 15](#).

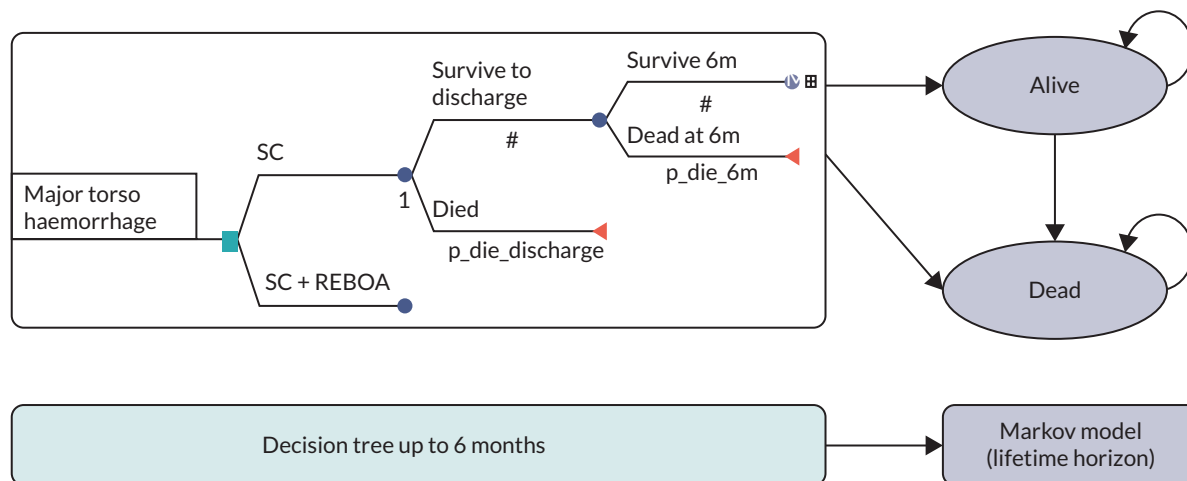


FIGURE 15 Economic model structure.

Model parameters

Patients enter the decision tree phase of the model at the point of randomisation to the trial (i.e. the point of arrival in the ED at hospital). The age and gender characteristics of the cohort were aligned with the baseline trial characteristics, where mean (SD) age was 45.35 (18.00) and the proportion of female was 28/88 (31.8%).

The trial data were used to inform the probability of survival to hospital discharge and further survival to 6 months post randomisation. Intervention costs (including the full-index hospital admission costs) were applied based on ITT costing, using the TARN data described in [Chapter 7](#), while follow-up use of resource usage to 6 months post randomisation was based on the available linked data for survivors from NHS Digital HES. Similarly, EQ-5D utility data collected during the trial, cross-walked from the 5L to 3L and valued using UK general population tariffs, were applied at hospital discharge and 6 months. For the 6-month follow-up data, mortality risk, costs and utilities were assumed to be treatment-specific, capturing any potential effect of REBOA.

The long-term trajectory of patient recovery is uncertain, and it is uncertain whether short-term differences in quality of life would be maintained over a lifetime horizon or converge to being equal among survivors at some future time point. We have therefore taken a conservative approach to modelling the longer-term trajectory of patient recovery. We assume that return to general population quality-of-life norms would converge to the pooled mean utility from the trial in the first model cycle. An alternative assumption, to assume that differences in utilities were accrued indefinitely, albeit based on a small sample are explored in scenario analysis. Scenario analysis also explored the impact of applying treatment pooled costs and utility data for the period between hospital discharge and 6 months, on the grounds that any resource use incurred post discharge would be related to initial injury rather than REBOA.

Long-term outcomes, including mortality, long-term recovery in quality of life (utilities) and ongoing costs related to initial injury were obtained from targeted literature searches with variation across studies tested extensively in scenario analyses. Longer-term utility data were available from two studies. The first study reported utility data for $N = 335$ trauma survivors in the Netherlands. Mean (SD) utility, based on the Dutch value set was 0.691 (0.299) for patients with an initial ISS ≥ 16 followed up for between 12 and 18 months.⁷⁵ These utilities were applied at the end of 18 months. A second, smaller study of $N = 56$ patients provided 15 years of EQ-5D-3L follow-up data for a cohort of major trauma patients in the Netherlands. Average utility (assumed to be mean), applying the Dutch value set at 15 years to a subgroup initially with ISS > 16 was 0.660.⁷⁶ A measure of uncertainty such as standard error (SE) or SD was not reported, so it was assumed that the SD of the sampling distribution was equal to 43% of the mean, applying the same ratio of mean : SD as observed from the 18-month study data.⁷⁵ The longer-term data from the literature were consistent with an assumption that most trauma survivors will reach their threshold of recovery by 1–2 years post injury. Beyond 15 years, the minimum of the 15-year utility or general population norms was applied, and general population utility was modelled to reduce over time as the surviving proportion of the cohort age.

For the base-case analysis, long-term mortality risk was assumed to be equal to the UK general population age- and sex-adjusted all-cause mortality (ACM) probability. The assumption is justified on the grounds that excess mortality among trauma patients is mostly expected to occur within the initial hospitalisation period. This is consistent with data observed from other trauma studies, including CRASH-2, where the hazard of mortality reduces dramatically over time.⁷⁴ However, it is still feasible to assume that survivors may experience an increased mortality risk later in life due to the long-term sequelae of their initial injury (e.g. due to compromised mobility or related chronic illness). To explore the impact of a potential excess mortality risk on model outcomes, scenario analysis applies an excess mortality risk of 1.5.

Patients who survive major trauma events may be at risk of longer-term disability, lower quality of life and thus would also be expected to consume more healthcare resources compared to the general population average. A prospective cohort study from the Netherlands, among 174 trauma patients with an ISS ≥ 16 found that post-hospital costs, including rehabilitation, were mean (SD), €7770 (€13,640) over 24 months of follow-up, with the highest post-hospital costs incurred for spinal injuries.⁷⁷ Inflating from 2017 values to 2021 values and converting to GBP, results in a 6-monthly cycle-specific cost of £1764 $[(€7770 * 1.06 * 0.86)/4]$ per 6-monthly cycle, up to 2 years.⁷⁸ Beyond 2 years, excess costs were assumed to be £0 for the remainder of the model time horizon. Scenario analysis explores the impact of assuming £0 excess cost for survivors beyond 6 months and applying the full cycle-specific cost for the duration of the model time horizon.

Time horizon and discounting

The Markov model was run over a lifetime horizon with a cycle length of 6 months. Costs and outcomes accruing beyond the first year of the model time frame (i.e. beyond cycle 1) were discounted at a rate of 3.5% per annum in line with NICE's guide for the methods of technology appraisal.⁷⁹ Costs and outcomes are half-cycle corrected to accommodate the assumption that costs are incurred, and outcomes accrued mid-way through each 6-monthly model cycle.

Model analyses

The model was fully probabilistic, with each model parameter sampled probabilistically from its underlying distribution as specified in [Table 21](#), using 10,000 Monte Carlo simulations. Results are expressed as mean expected lifetime costs, LYGs and QALYs per patient for SC + REBOA care and for SC alone. Calculations included both the 6-month costs and outcomes incurred in the decision tree phase of the model, summed with the lifetime costs and outcomes among 6-month survivors extrapolated over a lifetime from the Markov cohort model. As with the within-trial analysis, we do not report ICERs, but have sampled the probabilistic simulations of incremental costs and incremental QALYs on the cost-effectiveness plane, to illustrate the combined uncertainty surrounding costs and outcomes. QALYs are further adjusted by a multiplier in line with the NICE methods guide to account for QALY severity weightings. Using the QALY shortfall calculator, <https://shiny.york.ac.uk/shortfall/>, we apply the following parameters: average age of 45, proportion female = 32%, discount rate of 3.5% and remaining undiscounted QALYs = 0.01 if untreated. Remaining QALYs of 0.01 was an assumption for the calculation on the grounds that participants in the REBOA study were at immediate risk of death. Therefore, the maximum QALY weighing of 1.7 is applied.

While the HEAP had specified that an expected value of perfect information (EVPI) analysis would be undertaken, this was not undertaken because regardless of the EVPI results, it would not be deemed ethically justifiable to randomise patients to REBOA in this specific setting in a future study, given the clinical results of the trial. Additional scenario analyses (all applied probabilistically) were conducted to explore the impact of key modelling assumptions around the extent to which pre-injury quality of life is achieved among survivors and assumptions about the extent of ongoing long-term costs of rehabilitation of trauma patients on results.

Subgroup analyses

Given that the magnitude of available data for key model parameters, especially given utilities were small, we did not conduct any subgroup analyses using the economic model.

TABLE 21 Economic model parameters up to 6 months post randomisation

Utilities	Mean value	SD ^a	Distribution	Alpha	Beta	Source/notes
Utility baseline	-0.402	-	Fixed	-	-	Assumption
Utility discharge (treatment pooled)	0.263	0.067	Beta	11.09	31.09	UK-REBOA trial data
Utility discharge (treatment specific SC)	0.388	0.093	Beta	10.26	16.19	
Utility discharge (diff: SC + REBOA vs. SC)	-0.208	0.128	Normal	-0.208	0.128	
Utility 6 months (treatment pooled)	0.363	0.086	Beta	10.99	19.28	
Utility 6 months (treatment-specific SC)	0.538	0.094	Beta	14.60	12.53	
Utility 6 months (diff: SC + REBOA vs. SC)	-0.311	0.184	Normal	-0.311	0.184	
Utility general population	Calculated	Calculated	Fixed	-	-	Ara and Brazier 2010 ⁸⁰
Utility long-term – 2 years	0.691	0.016	Beta	575.64	257.42	Holtslag <i>et al.</i> , 2007 ⁷⁵
Utility long-term – 15 years	0.660	0.038	Beta	101.91	52.50	Wad <i>et al.</i> , 2018 ⁷⁶
Time parameters (days)	Mean value	SD^a	Distribution	Alpha	Lambda	Source/notes
Time to death (in hospital) SC (n = 16)	5.427	2.889	Gamma	3.53	0.650	UK-REBOA trial data
Time to death (in hospital) SC + REBOA (n = 24)	1.675	0.565	Gamma	8.79	5.247	
Time to discharge (survivors) SC ^b (n = 27)	62.282	11.120	Gamma	31.37	0.504	
Time to discharge (survivors) SC + REBOA ^b (n = 21)	37.556	5.463	Gamma	47.26	1.258	
Probabilities	n	N	Distribution	Alpha (n)	Beta (N-n)	
p die: discharge SC	16	43	Beta	16	27	UK-REBOA trial data
p die: discharge SC + REBOA	24	45	Beta	24	21	
p die: 6 months SC survive discharge	2	27	Beta	2	25	
p die: 6 months SC + REBOA survive discharge	1	21	beta	1	20	
p die: ACM	Calculated	Calculated	Fixed	-	-	ONS, 2021 ⁸¹

Utilities	Mean value	SD ^a	Distribution	Alpha	Beta	Source/notes
Excess mortality	Mean value	SD^a	Distribution	Alpha	Beta	
Excess mortality risk for survivors (base case)	1.0	-	Fixed	-	-	Assumption
Excess mortality risk for survivors ^c (scenario analysis)	1.5	0.30	Normal	1.5	0.30	Assumption
Costs	Mean value	SD^a	Distribution	Alpha	Lambda	
Index hospitalisation cost (SC + REBOA)	£57,384	£9371	Gamma	37.50	0.0007	UK-REBOA trial data
Index hospitalisation cost (SC)	£116,064	£19,666	Gamma	34.83	0.0003	
Index hospitalisation cost (pooled)	£80,062	£10,766	Gamma	55.30	0.0007	
Follow-up cost (SC + REBOA)	£11,601	£5126	Gamma	5.12	0.0004	
Follow-up cost (SC)	£5385	£1308	Gamma	16.95	0.0031	
Follow-up cost (pooled)	£8772	£2809	Gamma	9.75	0.0011	
Excess costs of survivors (6 months to 2 years)	£1764	£3087	Gamma	0.327	0.0002	

a Standard deviation of the distribution obtained as the SE of the data.

b Time to discharge capped at 6 months to allow alignment with 6-month time frame for decision tree phase of the model.

c Where SD is not available, it is assumed that the SD is equal to 20% of the mean.

Value of information analysis

Value of information analysis was not undertaken as planned again as a consequence of the clinical results of the trial. The analysis makes no statements about the value of research around the use of REBOA in other settings.

Model validation

The model was built by one health economist and independently checked against the Tappenden and Chilcott criteria by a second health economist on the study team.⁷⁹ Face validity was assessed through discussion of long-term extrapolations with the trial team, including clinical expert opinion.

Results

Base-case analysis (probabilistic)

[Table 22](#) shows the expected value of costs, LYGs and QALYs for each treatment strategy in the base case and for several scenario analyses undertaken. QALYs are reported with and without a 1.7 multiplier for severity weighting.

Substantial cost savings associated with SC + REBOA are due to the higher risk of mortality, occurring earlier in the patient journey compared to SC, meaning that there would be substantial life-year and QALY losses associated with the adoption of SC + REBOA in this setting. Despite the cost savings, the magnitude of QALY loss over a lifetime shows that SC + REBOA is both harmful (lost life-years and QALYs) and would be an inefficient use of scarce healthcare resources, when considering increased valuation of a QALY accrued at the end of life. Parameter uncertainty surrounding base-case results, with QALYs weighted at 1.7, is illustrated on the cost-effectiveness plane in [Figure 16](#).

Assuming a threshold value of a QALY = £30,000, but applying the maximum weighting for a QALY (multiplier = 1.7), turquoise dots indicate an inefficient use of resource (71% probability for base-case analysis), whereas dark blue dots indicate that REBOA is the most efficient use of resource (29% probability for the base-case analysis).

Iterations on the cost-effectiveness plane show that REBOA is definitively less costly (probability > 99%), due to the competing risk of mortality, but that it is also substantially less effective in terms of QALYs accrued over a lifetime horizon (probability 91%). The findings are robust to a range of scenario analyses undertaken. The results are also consistent with the findings of the clinical effectiveness.

TABLE 22 Probabilistic cost-effectiveness results^a

Strategy	Cost (£)	Inc. cost (£)	LY	Inc. LY	QALY	Inc. QALY	Severity weighted QALY (× 1.7)	Severity weighted inc. QALY (× 1.7)
Base-case analysis								
SC	122,603		11.84		7.18		12.20	
SC + REBOA	65,440	-57,163	9.05	-2.79	5.45	-1.72	9.27	-2.93
Scenario 1: Remove excess treatment costs for survivors beyond 6 months								
SC	120,117		11.84		7.18		12.20	
SC + REBOA	62,880	-57,237	9.04	-2.80	5.45	-1.73	9.26	-2.94
Scenario 2: Apply lifetime excess costs for survivors								
SC	160,575		11.84		7.17		12.19	
SC + REBOA	94,144	-66,431	9.04	-2.80	5.44	-1.73	9.25	-2.94
Scenario 3: Apply long-run SMR = 1.5								
SC	123,080		11.15		6.78		11.53	
SC + REBOA	65,499	-57,581	8.53	-2.62	5.15	-1.63	8.76	-2.77
Scenario 4: Undiscounted results								
SC	122,927		21.06		12.52		21.28	
SC + REBOA	65,629	-57,298	16.15	-4.91	9.56	-2.95	16.26	-5.02
Scenario 5: Return everyone to general population norms by 2 years								
SC	123,012		11.84		9.34		15.88	
SC + REBOA	65,543	-57,469	9.07	-2.77	7.12	-2.22	12.10	-3.78

SMR, Scottish Morbidity Records.

^a Note that all analyses are probabilistic and thus results are subject to variation across runs of the model due to Monte Carlo error.

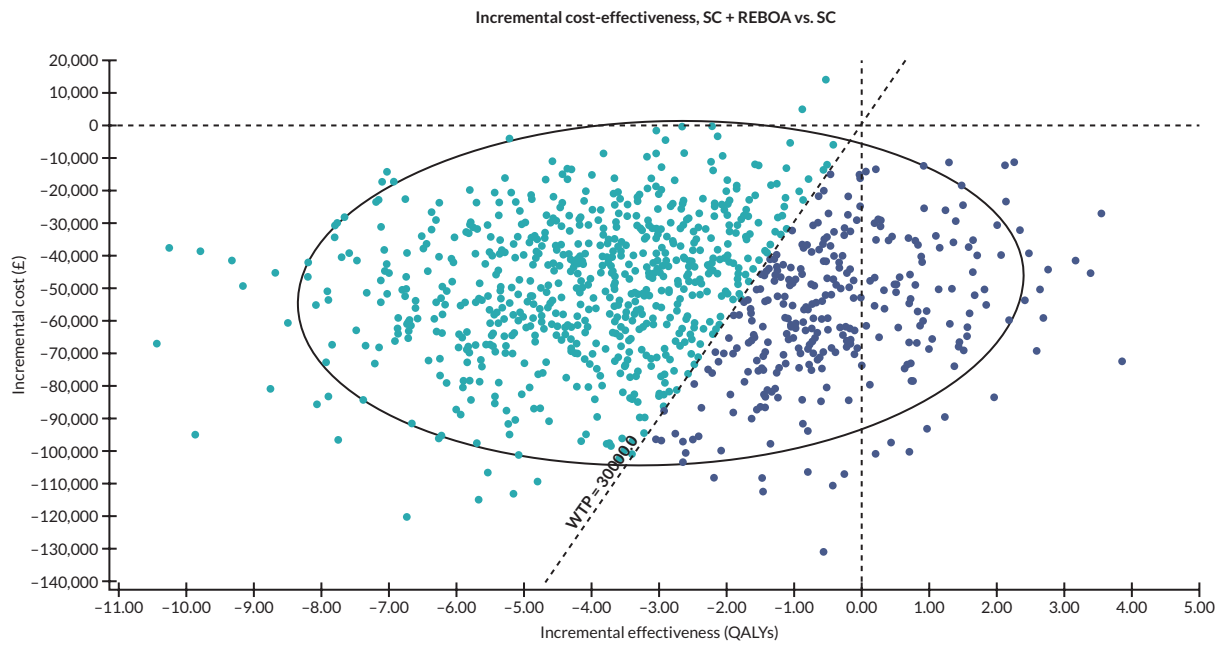


FIGURE 16 Scatterplot of the cost-effectiveness plane over a lifetime horizon (QALY weighting = 1.7).

Chapter 9 Discussion

This is the first randomised trial ever to be conducted examining the potential clinical effectiveness of the addition of REBOA to standard MTC care for the management of exsanguinating haemorrhage.

Summary of main findings

In this trial, the group that received care that included REBOA (SC + REBOA) was observed to have a high probability (above 80% in all analyses) of increased mortality at 90 days (the primary outcome) compared with the SC group.

This difference was apparent at all time points, and it was noted that the posterior probabilities of mortality increased with earlier time points. Given that more proximate mortality end points are now thought to better reflect the effect that haemorrhage control interventions – which, by definition, exert their effect early³⁵ – the progressively higher posterior probabilities at earlier time points add weight to the likelihood that REBOA is harmful.

The survival curves provide further evidence of the likely harmful early effects of REBOA. There was a sharp, early – within the first few hours – drop in survival, which likely represents failure to control haemorrhage. However, it is noteworthy that deaths in this group continued out to 10 days. This excess of early deaths was also apparent in the analysis of length of stay where patients who were allocated to the SC + REBOA strategy had fewer hospital-free and ICU-free days than those who received SC alone, suggesting that patients who did survive to ICU admission had sustained additional physiological insults that made them less likely to survive.

The findings from two additional sensitivity analyses, which adjusted for potential baseline imbalances between the groups, were consistent with the primary analysis. A principal stratification analysis, to account for intercurrent events, did not alter the findings. Furthermore, even when enthusiastic priors – derived during a formal expert elicitation exercise – were applied to the trial's results, the direction of the findings did not change. The addition of REBOA to SC, as delivered in MTCs in England, was observed to increase mortality, compared with the SC group.

A possible explanation for this finding of increased mortality was the observed delay in the SC + REBOA group in obtaining definitive haemorrhage control. This could be seen in the increased proportion of early deaths due to (uncontrolled) haemorrhage. Death due to haemorrhage 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 randomisation. Furthermore, in patients who survived to a definitive haemorrhage control procedure, it took, on average, an additional 26 minutes to commence these procedures.

Relevance to existing literature

The UK-REBOA trial is the only randomised clinical trial of the addition of REBOA to standard MTC care in trauma patients. Previously published observational studies, which are of variable quality, and at risk of bias, reported both positive and negative effects of REBOA. Three large, retrospective studies, from the USA and Japan, which had similar populations and similar treatment profiles to the UK-REBOA trial, reported results that would align with the findings of the UK-REBOA trial.

A retrospective study from the USA by Joseph *et al.*, using the 2015–6 national, multi-institutional American College of Surgeons Trauma Quality Improvement Program data set, propensity-score-matched 140 patients who received REBOA to 280 patients who did not.⁸² Among the REBOA group,

median ISS was 29 (Q1–Q3 18–38) – somewhat lower than in the UK-REBOA trial – and 129 patients (92.1%) had a blunt mechanism of injury. Patients were also less hypotensive than patients in our trial. The mean SBP was 108.8 millimetres of mercury (mmHg) (SD 32.7) for patients who underwent REBOA, and 106.5 mmHg (SD 28.7) for patients treated without REBOA. There was no significant difference between groups in 24-hour blood transfusion requirements. Patients in the REBOA group received a median of nine units of red blood cells (Q1–Q3 5–20), seven units of platelets (Q1–Q3 3–13) and nine units of plasma (Q1–Q3 6–20). In the no-REBOA group, patients received a median of 10 units of red blood cells (Q1–Q3 4–21), 8 units of platelets (Q1–Q3 3–12) and 10 units of plasma (Q1–Q3 7–20). These numbers are very similar to those in our trial. Median hospital length of stay was 8 days (Q1–Q3 1–20) for patients in the REBOA group and 10 days (Q1–Q3 5–22) in the no-REBOA group – shorter than in our trial, but this difference is explained by the fact that this was a study of patients in US trauma centres, which have shorter lengths of stay. Median ICU length of stay was 5 days (Q1–Q3 2–14) for REBOA patients and 6 days (Q1–Q3 3–15) for non-REBOA patients, which is more similar to the results in our trial. As in our trial, the in-hospital mortality rate was higher in the REBOA group (35.7%) than in the no-REBOA group (18.9%) ($p = 0.01$). Twenty-four-hour mortality was also higher in the REBOA group (26.4%) than in the non-REBOA group (11.8%) ($p = 0.01$). The authors concluded that placement of REBOA in severely injured trauma patients was associated with a higher mortality rate compared with a similar cohort of patients who were treated without REBOA. (The lower overall mortality rates reported may be a reflection of the lower injury severity or the less severe cardiovascular compromise.)

An earlier retrospective study by Norii *et al.*,²⁵ using 2004–11 data from the Japan Trauma Data Bank, propensity-score-matched 351 patients treated with REBOA to 1456 patients treated without REBOA. The median ISS in the REBOA group was 34 (Q1–Q3 22–45) and 29 (Q1–Q3 19–42) in the non-REBOA group, again slightly lower than in our trial. The probability of survival in the REBOA-treated group (26.2%) was significantly lower than the survival in the untreated (51.3%, $p < 0.0001$), for a crude conditional OR of survival by REBOA treatment of 0.30 (95% confidence interval, 0.23 to 0.40). The authors concluded that treatment with REBOA was associated with higher mortality compared with similarly ill trauma patients who did not receive REBOA.²⁵

A further retrospective study from Japan by Inoue *et al.*⁸³ also propensity-score-matched 625 patients who received REBOA, to 625 who did not. The in-hospital mortality was significantly higher in subjects who underwent REBOA (61.8% vs. 45.3%; absolute difference 16.5%; 95% confidence interval 10.9 to 22.0%). This study used the same data set as the Norii study.²⁵ The date range was not reported in the Inoue study, and there may thus be overlap.

In contrast, García *et al.*, in a propensity-score-matched study of 345 patients, 28 of whom received REBOA, from Columbia, found that patients treated with REBOA had lower risk-adjusted odds of mortality (OR 0.20, 95% confidence interval 0.05 to 0.77, $p = 0.01$).⁸⁴ Similarly, Yamamoto *et al.*,⁸⁵ in another propensity score-matched study of data from the national Japanese trauma registry, found that survival to discharge was higher among patients treated with REBOA than among those treated without REBOA (45.3% vs. 32.5%; OR 1.72; 95% CI 1.01 to 2.93; $p = 0.04$).

Health economic analysis

Care for trauma patients included in this trial was expensive, with most costs incurred during the index hospitalisation, with less intense use of hospital resource over follow-up. On average, participants in the SC + REBOA arm of the study incurred lower costs than in SC, due to the competing risk of death. Similarly, life-years accrued and QALYs over 6 months post randomisation were also lower in the SC + REBOA arm compared to SC due to a greater proportion of trial participants dying in the SC + REBOA arm and with mortality also occurring earlier in the follow-up period for the SC + REBOA arm. Results for both costs and QALYs remain robust to adjustment age, gender and ISS score and whether baseline utility is set to the unconscious (–0.402) state or set to 0.

Given that REBOA was both less costly and less effective, an analysis of cost-effectiveness would place REBOA in the southwest quadrant of the cost-effectiveness plane, where decision-makers would normally consider the cost savings achieved for each QALY lost. While this is a perfectly valid consideration for decision-making when the magnitude of QALY loss is small, the large differences in mortality between the arms for this study mean that an assessment of cost-effectiveness in the SW quadrant is not informative for decision-makers, regardless of the magnitude of cost-savings achieved. One limitation of the within-trial analyses is that the costs are all incurred up-front, whereas the benefits of life-years saved and improvements in quality of life for survivors are likely to be accrued well beyond the 6-month trial follow-up. We therefore developed a simple decision analysis model to extrapolate life-year and QALY gains for survivors over a lifetime horizon.

Substantial cost savings associated with SC + REBOA are due to the higher risk of mortality, occurring earlier in the patient journey compared to SC, meaning that there would be substantial life-year and QALY losses associated with the adoption of SC + REBOA in this setting. Despite the cost savings, the magnitude of QALY loss over a lifetime show that SC + REBOA is both harmful (lost life-years and QALYs) and would be an inefficient use of scarce healthcare resources, when considering increased valuation of a QALY accrued at the end of life.

Iterations on the cost-effectiveness plane show that UK-REBOA is definitively less costly (probability 99%), due to the competing risk of mortality but that it is also substantially less effective in terms of QALYs accrued over a lifetime horizon (probability 91%). The findings are robust to a range of scenario analyses undertaken, with the probability of SC being the optimal treatment strategy ranging from 66% to 81% at a threshold value of a QALY = £50,000. The results are consistent with the findings of the clinical effectiveness.

Strengths

The UK-REBOA trial has a number of strengths. Most importantly, it is the only RCT ever conducted of REBOA in trauma patients. This is in part a reflection of the difficulties inherent in evaluating a complex and technically challenging intervention in patients at imminent risk of dying, but the UK-REBOA trial showed that such a randomised trial could be done. It included an integrated training programme by design, recognising the challenges of evaluating a new technology that clinicians may not have been exposed to previously and thus mitigated against potential learning curve effects. The trial was pragmatic in design, with simple inclusion criteria that were based on the clinical judgement of experienced clinicians allowing clinicians to quickly evaluate suitability for the trial even in the somewhat chaotic environment of the ED. This study reflected the complex and dynamic situation faced by trauma teams when treating patients with severe haemorrhage with some patients responding rapidly to standard resuscitation during the time period that encompassed the decision-making, randomisation and preparation time to perform REBOA. The trial used routinely collected data extensively to minimise the burden on the clinical staff (although there were some issues with that approach – see below). It also adopted a Bayesian analytical framework and group sequential design, which allowed for robust interpretation even in a small population. The Bayesian group sequential design facilitated the interim analyses, and the interpretation of the findings.

Limitations

The UK-REBOA trial also has a number of limitations.

This was a small trial, reflecting the relative infrequency of exsanguinating traumatic haemorrhage in the UK. There were some imbalances between the groups, particularly with regards to SBP on arrival in the ED, which was found to be lower in patients allocated to the SC + REBOA strategy; and the presence

of traumatic brain injuries, which were possibly more severe in patients allocated to the SC + REBOA strategy. However, analyses adjusting for these found no material effect on the results. Furthermore, the proportion of deaths attributed to traumatic brain injury was broadly similar in the two groups.

There is a possibility that the results are in part due to inexperience with the REBOA technique, despite the extensive training programme instituted as part of the trial. Most (albeit not all) of the participating centres had never used REBOA before in the trauma setting, and as such most of the insertions were performed by clinicians who had never used the technique before. The technical skills required to perform arterial cannulation in severely shocked patients, under pressure, are considerable. In addition, clinical teams would have had little previous experience in managing patients once the device had been successfully inserted and inflated. Having said that, a post hoc sensitivity analysis, which excluded the first patient randomised to the SC + REBOA strategy at each site, showed marginally increased odds of mortality and posterior probabilities of harm compared to the main analysis. This analysis, however, could only account for institutional learning effects. The number of patients in the trial as a whole, and the number of patients enrolled by individual clinicians, were too small to allow for a similar analysis of individual learning effects.

Lastly, participating trauma centres' research infrastructure (only one had research staff available around the clock, to assist with recruitment and data collection) limited the collection of more granular procedural data, or mechanistic data, such as blood pressure readings. Our decision to rely on routinely collected audit data, for the baseline characteristics, resulted in some missing data, which then had to be queried later, although this did not impact on the results.

Context

The trial was conducted in the UK, where injury epidemiology and the trauma care delivery framework differ from other locations. The findings of the UK-REBOA trial should be interpreted in this context.

Pre-hospital care in the UK is of very high and uniform quality. Ambulance services are large organisations that adhere to nationally agreed clinical standards. Almost all trauma patients receive tranexamic acid on scene and blunt trauma patients have a pelvic binder applied before transport. In addition, ambulance services in the UK commonly provide pre-hospital transfusion support, and many patients receive treatment from a critical care paramedic or pre-hospital care doctor.

The reorganisation of in-hospital trauma care in England – which included the establishment of regional trauma networks and the designation of MTCs and trauma units; as well as the development of nationally agreed clinical standards for trauma care – has markedly improved mortality from injury over the past decade.⁸⁶ However, case volume (and operative case volume for haemorrhage control, in particular) in many MTCs is lower than in other countries, reflecting very high road safety standards and very low levels of interpersonal violence in the country. Furthermore, in most MTCs, the responsibility for the control of torso haemorrhage rests with surgeons who do not only provide trauma care. These surgeons are often on call from home, rather than resident in the hospital. The initial care of trauma patients is therefore usually the responsibility of senior emergency medicine doctors, but surgeons are called early (even before the arrival of a patient), on the basis of pre-alerts. Nevertheless, these organisational differences may have impacted on the speed with which trauma patients were treated and, in particular, operated on, if needed.

Intercurrent events

There were a number of pathways experienced by those who were allocated to the SC + REBOA strategy, due to intercurrent events. These findings demonstrated that obtaining arterial access in severely shocked patients; and that distinguishing between patients who are experiencing continuing,

severe haemorrhage from those in whom bleeding has stopped and only require transfusion is challenging. All clinicians working in the ED recognise the dynamic and unpredictable nature of severe trauma with haemorrhage. We considered these issues by means of a principal stratification analysis that did not alter our conclusions. However, perhaps most importantly, our experiences reflect 'real life' and shed light on the reality of the management of major trauma care where a patient's condition can change very rapidly. A trial where every patient randomised to REBOA receives full REBOA is never expected given the dynamic situation. The implementation and evaluation of any system incorporating REBOA must consider these challenges.

Methodological issues

The trial encountered a number of methodological issues, which are worth highlighting:

Registry-enabled design

We relied on data routinely collected by TARN, England's national trauma registry, to characterise the trial population (although most outcomes were collected directly, using a UK-REBOA trial-specific eCRF). Our intent was to make the trial as simple to run as possible, particularly given that many patients presented out of hours, and to avoid duplication of effort. However, there were a number of downstream effects. Firstly, the time from discharge to submission of data to TARN, by sites, was variable, and often prolonged for patients awaiting injury details from post-mortem examinations. This made the characterisation of the trial population more difficult, especially for interim analyses. There were also more missing data than anticipated, requiring queries to sites. (Fortunately, these data had actually been recorded in patients' health records, but not been transcribed into TARN.) Some of these issues may relate to the large proportion of patients who died, and sometimes died very early on. Lastly, we discovered that a small number of patients had opted out from all national health data collection (<https://digital.nhs.uk/services/national-data-opt-out>). These patients have all their TARN records deleted, without a record of such a deletion (which also comes under the opt-out). Fortunately, we were able to obtain the necessary data points directly from sites, under research-without-prior-consent rules.

Working with NHS Digital

The data obtained from NHS Digital (required for the health economic analysis) was of high quality, but it took almost the entire duration of the trial to secure the necessary permissions to use it. Data linkage was not agreed to for participants without either participant or consultee consent, limiting the usefulness of the data for the health economic analysis. This was largely related to the research-without-prior-consent framework, which NHS Digital had only limited familiarity with. Multiple changes in case workers, each requiring additional questions to be answered, further compounded the issue. Future research-without-prior-consent trials relying on NHS Digital data would benefit from early discussion.

Initial error in statistical design

Our initial design parameters contained an error in the formulation of the variance in calculations, resulting in an overestimation of the operating characteristics. Following extensive 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.³⁸ As it turns out, the design error – or the revised design – had no impact, given that REBOA turned out likely to be harmful, and the large size of the effect.

Streamlined framework with limited dataset

Executing clinical trials in patients at imminent risk of dying, particularly when they present out of hours, and with little notice, is extremely difficult. Although the UK's research delivery framework has many advantages, like all healthcare systems, it is not well suited to support such studies. Our reliance on clinicians to enrol patients and collect some data (albeit minimal) in real-time necessitated a limited dataset, focused on answering the trial's key question. If we had our time again, we would likely have

instigated more comprehensive data collection, to capture data such as changes in blood pressure in response to balloon inflation and other physiological data. However, this would have greatly increased the cost of the trial.

Choice of primary outcome

We have already alluded to the issue of choice of primary outcome, and the change in thinking that has taken place over the past 5 years. Our choice of 90-day mortality was based partly on the critical care literature, and concern that early benefit (prevention of early death) might be associated with late harm (increased mortality as a result of acute respiratory distress syndrome, acute kidney injury, etc.).

Experience with the ‘Pragmatic, Randomized Optimal Platelet and Plasma Ratios’ (PROPPR) trial, which compared two types of transfusion strategies in trauma patients,^{87,88} and several subsequent trials, has resulted in a better understanding of the impact of the time point at which mortality is evaluated. Deaths from haemorrhage occur early. Later deaths are typically due to causes such as traumatic brain injury or multiple organ failure. Although the latter may occur equally in both arms of the study, and the difference thus remains the same, the baseline mortality rate increases, which makes it more difficult to detect differences. A recent consensus statement – which was the product of a conference that involved the National Institute of Health, the Food and Drug Administration, the Department of Defense and researchers – has therefore advocated for using more proximate mortality endpoints in trauma haemorrhage control trials.³⁵

However, the above debate did not impact on the UK-REBOA trial, because the signal (of harm) is so strong – even at 90 days post injury. However, in keeping with the assertions above, the effect size is even greater at earlier time points.

Setting

The UK-REBOA trial was a study of the use of REBOA in-hospital. The use of REBOA in-hospital may, however, be ‘too late’, especially since patients can be delayed in arrival at the hospital and, when there, they can often be taken to an operating theatre, for definitive control of haemorrhage, very quickly. Potentially the result may have been different had REBOA been considered in the pre-hospital setting, which at the time of the trial design was not being considered in the UK. The pre-hospital environment differs from the in-hospital setting conceptually; it makes sense to obtain haemorrhage control as early as possible after injury, before large volumes of blood have been lost, and inflammatory sequelae are superimposed onto haemorrhagic shock. The findings of the trial should therefore not be extrapolated to the pre-hospital setting.

Equality, diversity and inclusion

We collected data on age and sex; the distribution in the UK-REBOA trial is broadly representative of the trauma patient population in the UK. We did not collect data on ethnicity, socioeconomic status, education or health literacy. Enrolment took place without consent, which may have removed some of the barriers to research participation (e.g. those related to English language and health literacy) that studies requiring consent may face.

Patient and public involvement

We have two PPI co-applicants (AP, NW) who were involved in the development of the study protocol and associated patient-facing paperwork, and contributed to meetings of the PMG throughout the lifespan of the study. The PPI representatives were invited to attend meetings where the initial results of the study were shared and have had the opportunity to comment on the plain language summary. The TSC included two independent PPI members who contributed to discussion at these meetings and were

available to comment on aspects of the trial throughout its lifespan. The trial manager supported the PPI representatives so that they were able to contribute fully.

Conclusions

The analyses of the primary and secondary endpoints in this trial of trauma patients with haemorrhagic shock show that a management strategy that includes REBOA, when used in-hospital, has a high probability of being associated with increased mortality, compared to SC alone.

Implications for practice

The continuing use of REBOA, at least in the UK in-hospital setting, should be re-evaluated.

Implications for research

This trial examined the role of in-hospital REBOA. Given the time from injury to hospital, and the aim of REBOA being to provide early temporary haemorrhage control, the role (if any) of treating patients earlier with REBOA (i.e. in the pre-hospital setting) remains unclear. Further research to clarify the potential (or not) of pre-hospital REBOA may be indicated.

This trial showed that while using routinely collected data was intrinsic to the trial and added to the streamlined nature of the data collection, use of routine data raised a number of issues (e.g. the time from discharge to submission of data to the registry; missing data; extensive permissions and delay in receiving data via NHS Digital). There is a need for further research into the development needs of registries and routine data to enable the routine support of clinical trials.

Additional information

Contributions of authors

Jan O Jansen (<https://orcid.org/0000-0001-8863-4398>) (Co-Chief Investigator) co-led the conception and design of the trial, the conduct of the trial, the interpretation of results and writing/editing the report.

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Patient data statement

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy and it's important that there are safeguards to make sure that they are stored and used responsibly. Everyone should be able to find out about how patient data are used #datasaveslives.

You can find out more about the background to this citation here: <https://understandingpatientdata.org.uk/data-citation>

Data-sharing statement

All data requests should be submitted to the corresponding author for consideration. Access to anonymised data may be granted following review.

Ethics statement

This trial was approved by the North West – Greater Manchester South Research Ethics Committee on 26 June 2017, REC reference: 17/NW/0352.

Information governance statement

The University of Aberdeen is committed to handling all personal information in line with the UK Data Protection Act (2018) and the General Data Protection Regulation (EU GDPR) 2016/679.

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Disclosure of interests

Full disclosure of interests: Completed ICMJE forms for all authors, including all related interests, are available in the toolkit on the NIHR Journals Library report publication page at <https://doi.org/10.3310/LTYV4082>.

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Appendix 1 Members of UK-REBOA Study Group

Chris Aylwin (<https://orcid.org/0000-0002-3212-1689>) (Consultant Vascular and Trauma Surgeon, St Mary's Hospital, London, UK) was principal investigator at a UK-REBOA trial recruitment site and contributed to the interpretation of results and writing/editing the report.

Duncan Bew (<https://orcid.org/0000-0003-2849-3567>) (Trauma and Acute Care Surgeon, King's College Hospital, London, UK) was principal investigator at a UK-REBOA trial recruitment site and contributed to the interpretation of results and writing/editing the report.

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Arun George (<https://orcid.org/0000-0003-4104-693X>) (Consultant in Emergency Medicine, University Hospital, Coventry, UK) was principal investigator at a UK-REBOA trial recruitment site and contributed to the interpretation of results and writing/editing the report.

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Phillip Johnstone (<https://orcid.org/0000-0002-9955-6425>) (Consultant in Emergency Medicine, Royal Victoria Infirmary, Newcastle, UK) was principal investigator at a UK-REBOA trial recruitment site and contributed to the interpretation of results and writing/editing the report.

Ansar Mahmood (<https://orcid.org/0000-0003-1359-6651>) (Consultant in Trauma and Orthopaedic Surgery, Queen Elizabeth Hospital, Birmingham, UK) was principal investigator at a UK-REBOA trial recruitment site and contributed to the interpretation of results and writing/editing the report.

Alex Novak (<https://orcid.org/0000-0002-5880-8235>) (Consultant in Emergency Medicine and Ambulatory Care, John Radcliffe Hospital, Oxford, UK) was principal investigator at a UK-REBOA trial recruitment site and contributed to the interpretation of results and writing/editing the report.

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Stuart Reid (<https://orcid.org/0000-0002-3129-7711>) (Consultant in Emergency Medicine and Major Trauma, Sheffield Teaching Hospital, Sheffield, UK) was principal investigator at a UK-REBOA trial recruitment site and contributed to the interpretation of results and writing/editing the report.

Abdo Sattout (<https://orcid.org/0000-0003-1848-9396>) (Consultant in Emergency Medicine, Aintree University Hospital, Liverpool, UK) was principal investigator at a UK-REBOA trial recruitment site and contributed to the interpretation of results and writing/editing the report.

Chris Smith (<https://orcid.org/0000-0002-7646-4122>) (Consultant in Emergency Medicine and Pre-hospital Emergency Medicine, James Cook University Hospital, Liverpool, UK) was principal investigator at a UK-REBOA trial recruitment site and contributed to the interpretation of results and writing/editing the report.

Tim Stansfield (<https://orcid.org/0000-0002-5875-6279>) (Consultant Vascular and Trauma Surgeon, Leeds General Infirmary, Leeds, UK) was principal investigator at a UK-REBOA trial recruitment site and contributed to the interpretation of results and writing/editing the report.

Julian Thompson (<https://orcid.org/0009-0003-8949-1220>) (Consultant in Intensive Care Medicine and Anaesthesia, Southmead Hospital, Bristol, UK) was principal investigator at a UK-REBOA trial recruitment site and contributed to the interpretation of results and writing/editing the report.

Appendix 2 United Kingdom-resuscitative endovascular balloon occlusion of the aorta trial recruitment sites

Aintree University Hospital, Liverpool

James Cook University Hospital, Middlesbrough

John Radcliffe Hospital, Oxford

King's College Hospital, London

Leeds General Infirmary, Leeds

Queen Elizabeth Hospital, Birmingham

Queen's Medical Centre, Nottingham

Royal Hull Infirmary, Hull

Royal Stoke University Hospital, Stoke

Royal Victoria Infirmary, Newcastle

Sheffield Teaching Hospital, Sheffield

Southmead Hospital Bristol, Bristol

St George's University Hospital, London

St Mary's Hospital, London

The Royal London Hospital, London

University Hospital, Coventry

Appendix 3 Evidence dossier used for elicitation exercise



Evidence for consideration

We have identified the following references as potentially relevant to the elicitation meeting. You may wish to review these or keep them for reference.

We do not expect you to read them all – this list is purely for your information. Please read as many or as few as you feel able to (although it would likely be helpful for you to dip into at least one or two of them if you have time).

We have only included studies that relate to the impact of REBOA on mortality, in humans, with a comparison group. The hyperlinks are clickable so that you can review the abstracts and/or full papers. There are two sections: Systematic reviews and meta-analyses, and comparative studies. Lastly, we have also included our epidemiological paper. The hyperlinks are clickable and will take you to abstracts in PubMed.

This is not a systematic review. If there are other studies that you are aware of, which we have failed to include, please let us know and we will add them.

Systematic reviews and meta-analyses

1. [A meta-analysis of resuscitative endovascular balloon occlusion of the aorta \(REBOA\) or open aortic cross-clamping by resuscitative thoracotomy in non-compressible torso hemorrhage patients.](#)

Manzano Nunez R, Naranjo MP, Foianini E, Ferrada P, Rincon E, García-Perdomo HA, *et al.* *World J Emerg Surg* 2017;**12**:30. <https://doi.org/10.1186/s13017-017-0142-5>

2. [Resuscitative endovascular balloon occlusion of the aorta \(REBOA\) in the management of trauma patients: a systematic literature review.](#)

Petrone P, Pérez-Jiménez A, Rodríguez-Perdomo M, Brathwaite CEM, Joseph DK. *Am Surg* 2019;**85**(6):654–62. PMID: 31267908.

3. [Resuscitative endovascular balloon occlusion of the aorta in trauma: a systematic review of the literature.](#)

Gamberini E, Coccolini F, Tamagnini B, Martino C, Albarello V, Benni M, *et al.* *World J Emerg Surg* 2017;**12**:42. <https://doi.org/10.1186/s13017-017-0153-2>. eCollection 2017. PMID: 28855960.

4. [Resuscitative Endovascular Balloon Occlusion of the Aorta for Control of Non-Compressible Truncal Hemorrhage: A Review of Clinical Effectiveness and Guidelines \[Internet\].](#)

- Richardson R, Adcock L. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 7 March 2018. PMID: 30325621.

5. A systematic review and meta-analysis of the use of resuscitative endovascular balloon occlusion of the aorta in the management of major exsanguination.

- Borger van der Burg BLS, van Dongen TTCF, Morrison JJ, Hedeman Joosten PPA, DuBose JJ, Hörer TM, Hoencamp R. *Eur J Trauma Emerg Surg* 2018;**44**:535–50. <https://doi.org/10.1007/s00068-018-0959-y>. Epub May 21 2018. PMID: 29785654.

6. A systematic review of the use of resuscitative endovascular balloon occlusion of the aorta in the management of hemorrhagic shock.

Morrison JJ, Galgon RE, Jansen JO, Cannon JW, Rasmussen TE, Eliason JL. *J Trauma Acute Care Surg* 2016;**80**:324–34. <https://doi.org/10.1097/TA.0000000000000913>. PMID: 26816219.

7. Resuscitative endovascular balloon occlusion of the aorta (REBOA) in the management of trauma patients: a systematic literature review.

Petrone P, Pérez-Jiménez A, Rodríguez-Perdomo M, Brathwaite CEM, Joseph DK. *Am Surg* 2019;**85**:654–62. PMID: 31267908.

Comparative studies

1. Resuscitative endovascular balloon occlusion of the aorta (REBOA) for severe torso trauma in Japan: a descriptive study.

Matsumoto S, Hayashida K, Akashi T, Jung K, Sekine K, Funabiki T, Moriya T. *World J Surg* 2019;**43**:1700–7. <https://doi.org/10.1007/s00268-019-04968-2>. PMID: 30824958.

9. Resuscitative endovascular balloon occlusion of the aorta (REBOA) is associated with improved survival in severely injured patients: A propensity score matching analysis.

Yamamoto R, Cestero RF, Suzuki M, Funabiki T, Sasaki J. *Am J Surg* 2019;**218**:1162–8. <https://doi.org/10.1016/j.amjsurg.2019.09.007>. Epub Sep 13 2019. PMID: 31540683.

10. Resuscitative endovascular balloon occlusion of the aorta or resuscitative thoracotomy with aortic clamping for noncompressible torso hemorrhage: a retrospective nationwide study.

Aso S, Matsui H, Fushimi K, Yasunaga H. *J Trauma Acute Care Surg* 2017;**82**:910–4. <https://doi.org/10.1097/TA.0000000000001345>. PMID: 28430760.

11. Nationwide analysis of resuscitative endovascular balloon occlusion of the aorta in civilian trauma.

Joseph B, Zeeshan M, Sakran JV, Hamidi M, Kulvatunyou N, Khan M, et al. *JAMA Surg.* 2019;**154**:500–8. <https://doi.org/10.1001/jamasurg.2019.0096>. PMID: 30892574.

12. Association of resuscitative endovascular balloon occlusion of the aorta (REBOA) and mortality in penetrating trauma patients.

García AF, Manzano-Nunez R, Orlas CP, Ruiz-Yucuma J, Londoño A, Salazar C, et al. *Eur J Trauma Emerg Surg* 2020. <https://doi.org/10.1007/s00068-020-01370-9>. Online ahead of print. PMID: 32300850.

13. Survival of severe blunt trauma patients treated with resuscitative endovascular balloon occlusion of the aorta compared with propensity score-adjusted untreated patients.

Norii T, Crandall C, Terasaka Y. *J Trauma Acute Care Surg* 2015;**78**:721–8. <https://doi.org/10.1097/TA.0000000000000578>. PMID: 25742248.

14. Resuscitative endovascular balloon occlusion of the aorta versus aortic cross clamping among patients with critical trauma: a nationwide cohort study in Japan.

Abe T, Uchida M, Nagata I, Saitoh D, Tamiya N. *Crit Care* 2016;**20**:400. <https://doi.org/10.1186/s13054-016-1577-x>. PMID: 27978846.

1. Resuscitative endovascular balloon occlusion of the aorta might be dangerous in patients with severe torso trauma: a propensity score analysis.

Inoue J, Shiraishi A, Yoshiyuki A, Haruta K, Matsui H, Otomo Y. *J Trauma Acute Care Surg* 2016;**80**:559–66; discussion 566–7. <https://doi.org/10.1097/TA.0000000000000968>. PMID: 26808039.

16. The AAST prospective Aortic Occlusion for Resuscitation in Trauma and Acute Care Surgery (AOR-TA) registry: data on contemporary utilization and outcomes of aortic occlusion and resuscitative balloon occlusion of the aorta (REBOA).

DuBose JJ, Scalea TM, Brenner M, Skiada D, Inaba K, Cannon J, *et al.*; AAST AORTA Study Group. *J Trauma Acute Care Surg* 2016;**81**:409–19. <https://doi.org/10.1097/TA.0000000000001079>. PMID: 27050883.

17. Temporal changes in REBOA utilization practices are associated with increased survival: an analysis of the aorta registry.

- Bukur M, Gorman E, DiMaggio C, Frangos S, Morrison JJ, Scalea TM, *et al.*; and the AAST AORTA Study Group. *Shock* 2020. <https://doi.org/10.1097/SHK.0000000000001586>. Online ahead of print. PMID: 32842023.

Epidemiological studies

18. Resuscitative endovascular balloon occlusion of the aorta (REBOA): a population based gap analysis of trauma patients in England and Wales.

Barnard EB, Morrison JJ, Madureira RM, Lendrum R, Fragoso-Iñiguez M, Edwards A, *et al.* *Emerg Med J* 2015;**32**:926–32. <https://doi.org/10.1136/emered-2015-205217>. PMID: 26598631.

Appendix 4 Elicitation exercise

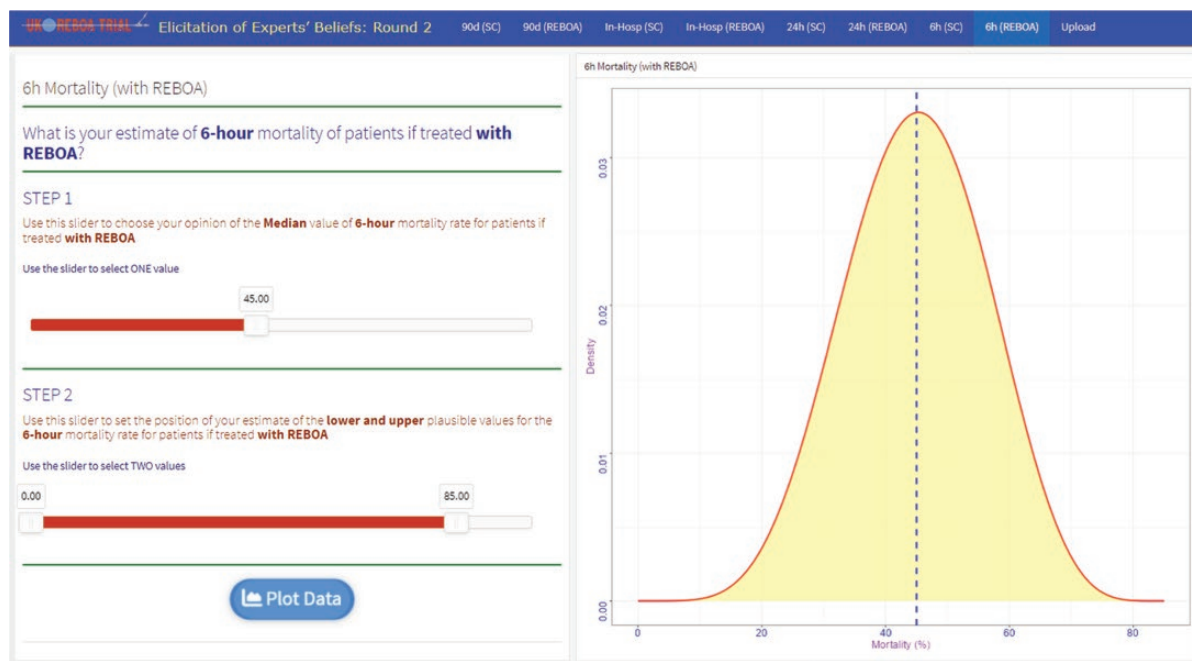


FIGURE 17 Screenshot showing the 'sliders' used to set the median and lower and upper plausible values, and the resulting graphical output as a probability density distribution.

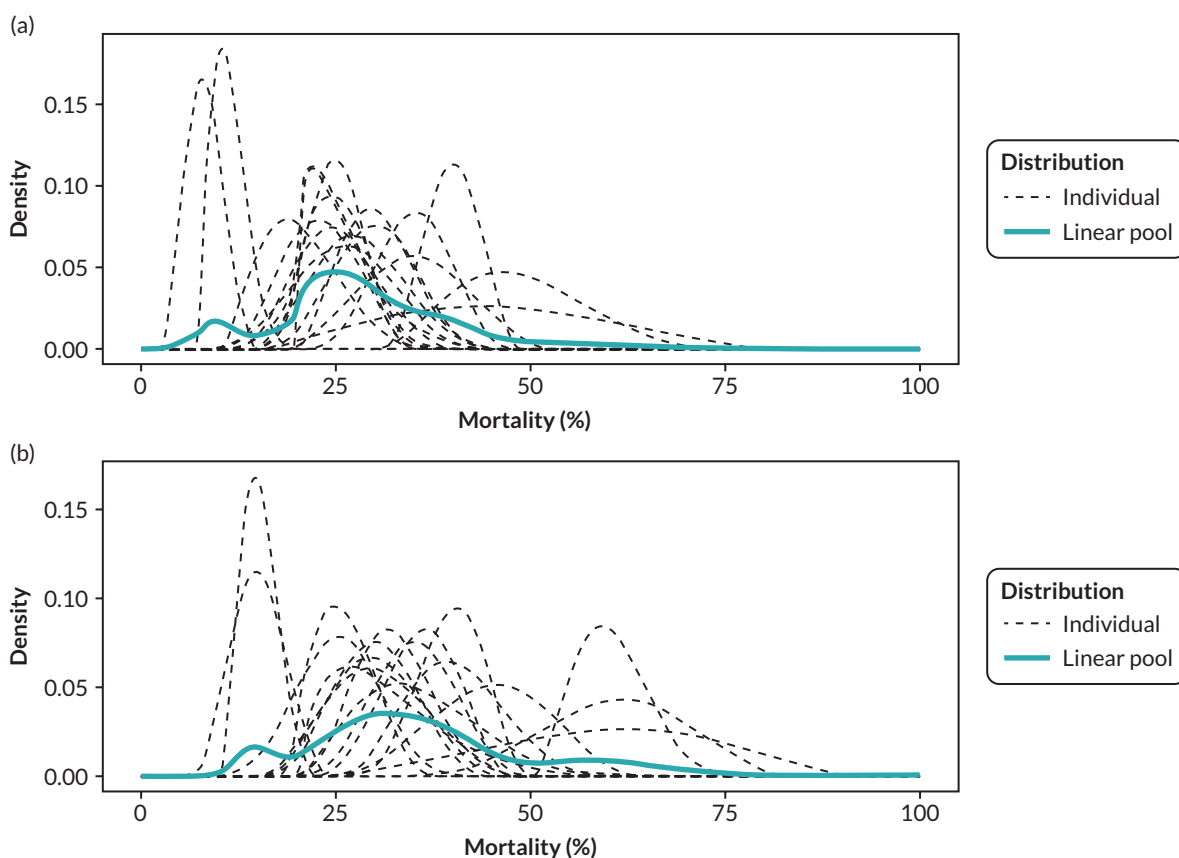


FIGURE 18 Plots of beta distribution of each individual expert (dashed line) and the plot of linear pool of the beta distributions of all experts (solid line) for (a) REBOA and (b) standard care for 6-hour mortality.

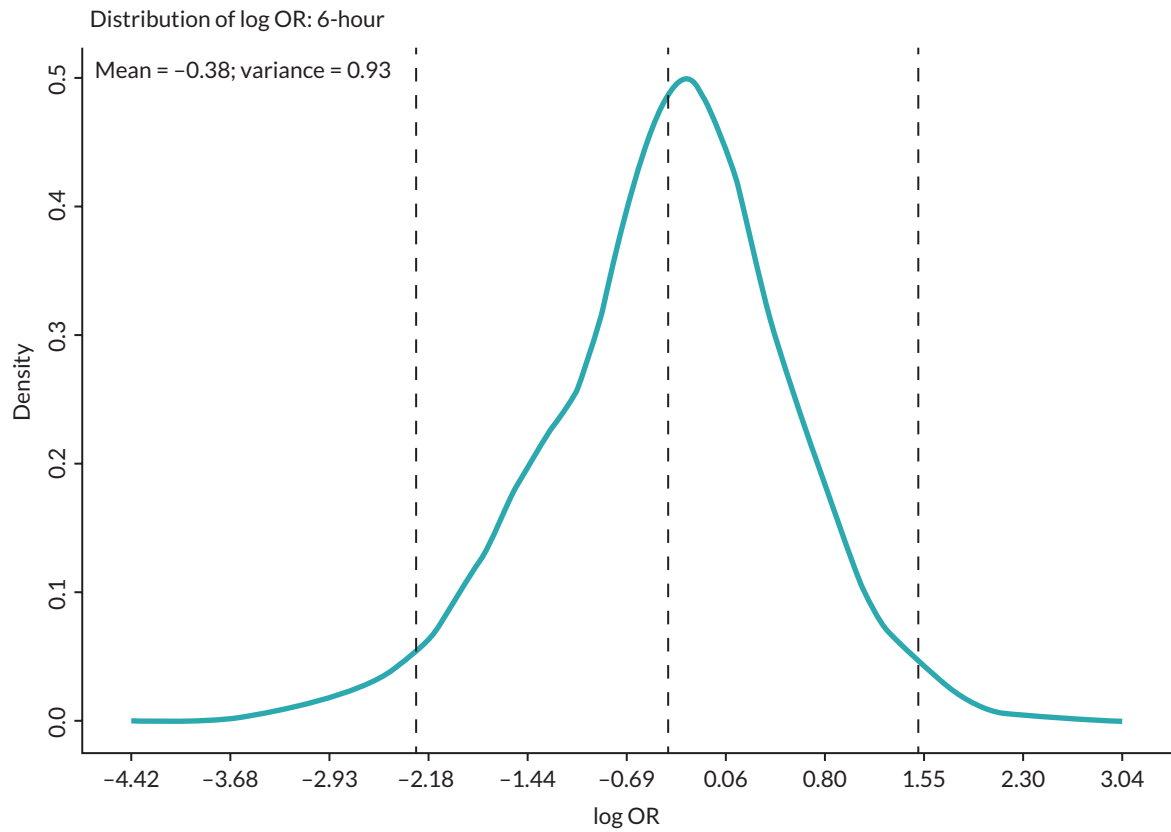


FIGURE 19 The prior distribution of logarithm of OR for REBOA for standard care based on 10,000 samples for 6-hour mortality.

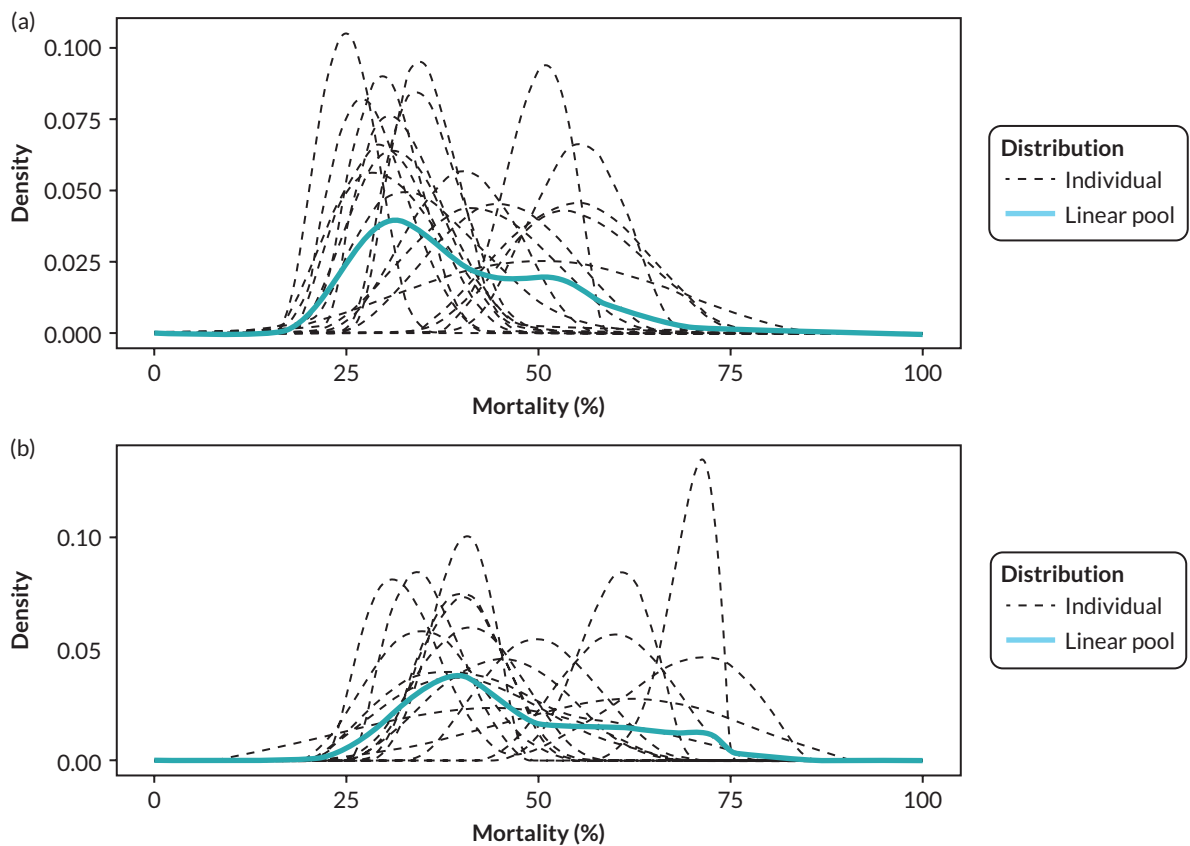


FIGURE 20 Plots of beta distribution of each individual expert (dashed line) and the plot of linear pool of the beta distributions of all experts (solid line) for (a) REBOA and (b) standard care for 24-hour mortality.

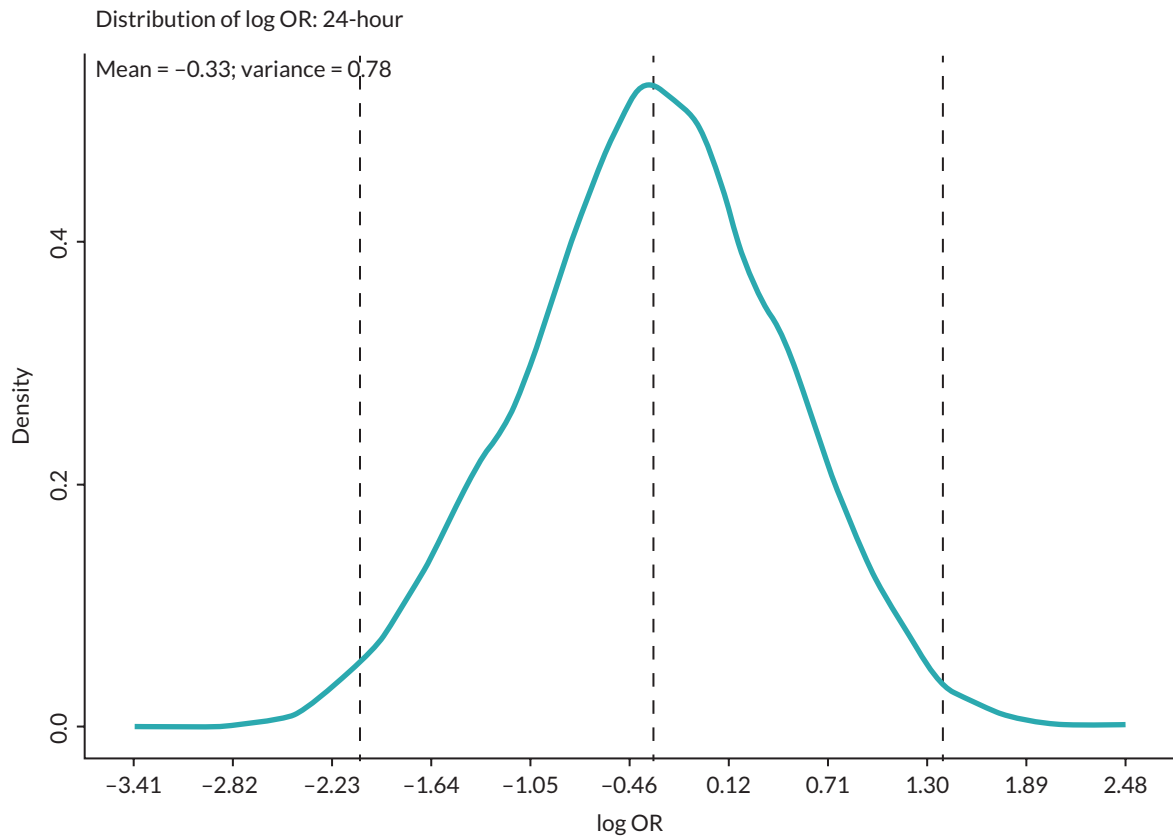


FIGURE 21 The prior distribution of logarithm of OR for REBOA to standard care based on 10,000 samples for 24-hour mortality.

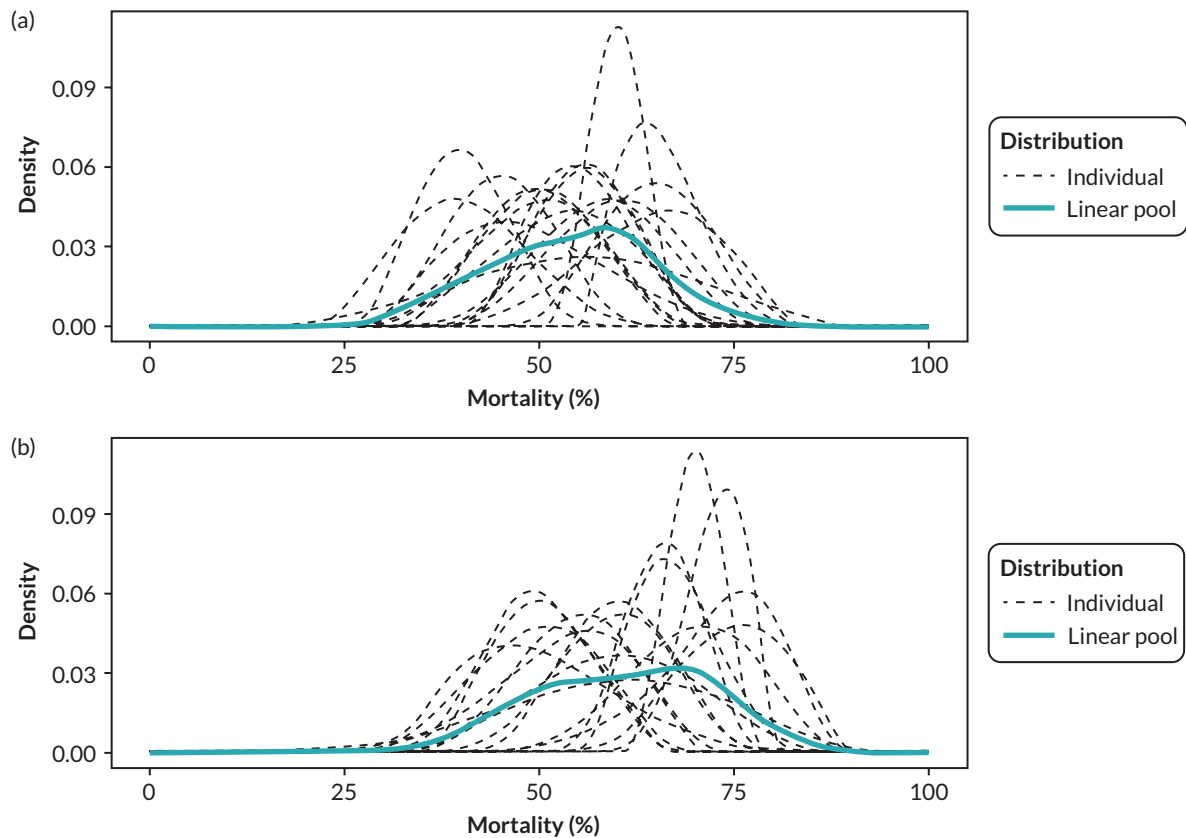


FIGURE 22 Plots of beta distribution of each individual expert (dashed line) and the plot of linear pool of the beta distributions of all experts (solid line) for (a) REBOA and (b) standard care for 90-day mortality.

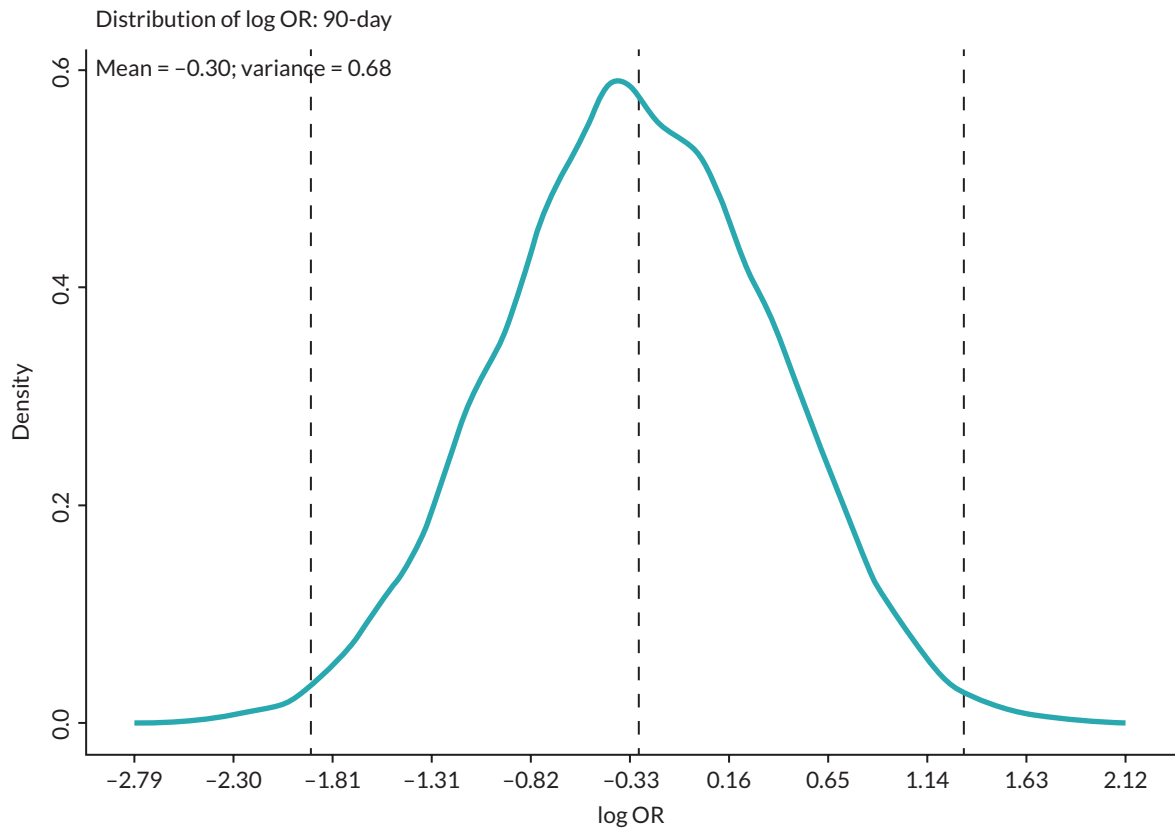


FIGURE 23 The prior distribution of logarithm of OR for REBOA to standard care based on 10,000 samples with 90-day mortality.

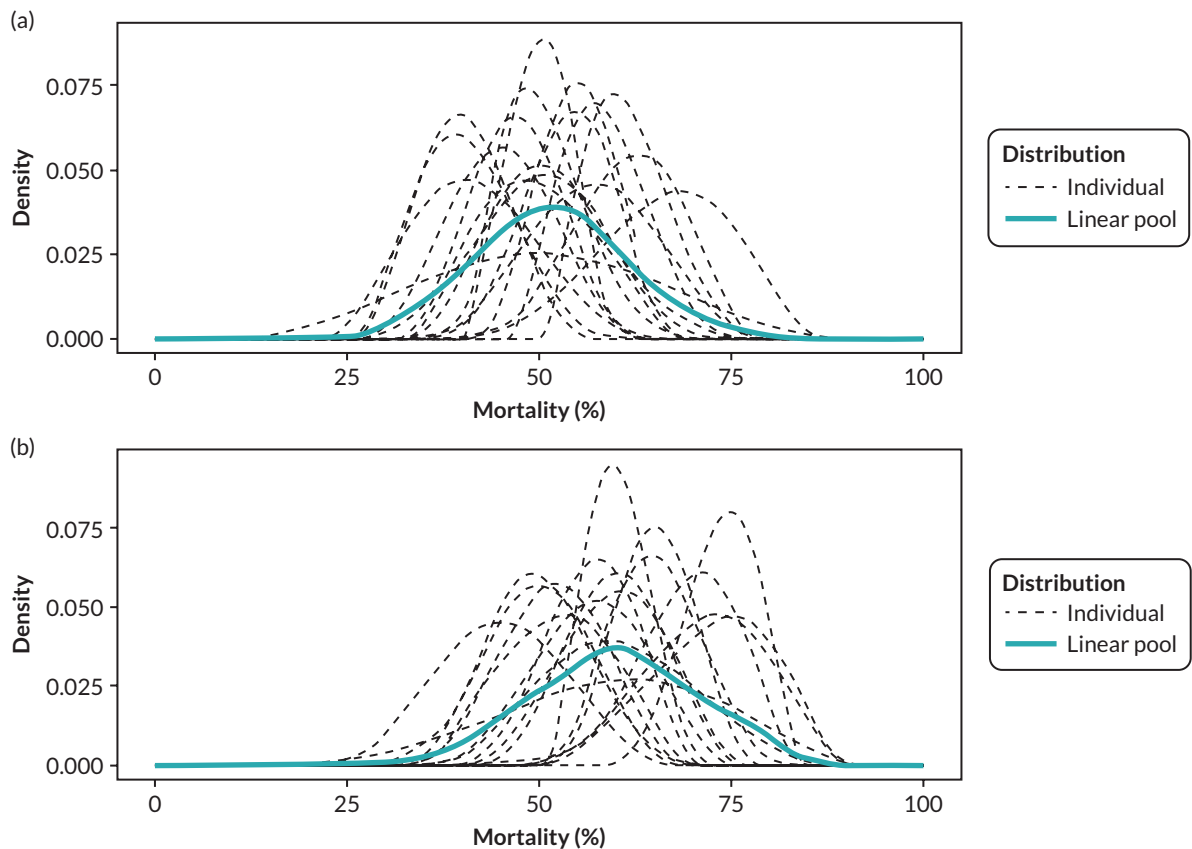


FIGURE 24 Plots of beta distribution of each individual expert (dashed line) and the plot of linear pool of the beta distributions of all experts (solid line) for (a) REBOA and (b) standard care for in-hospital mortality.

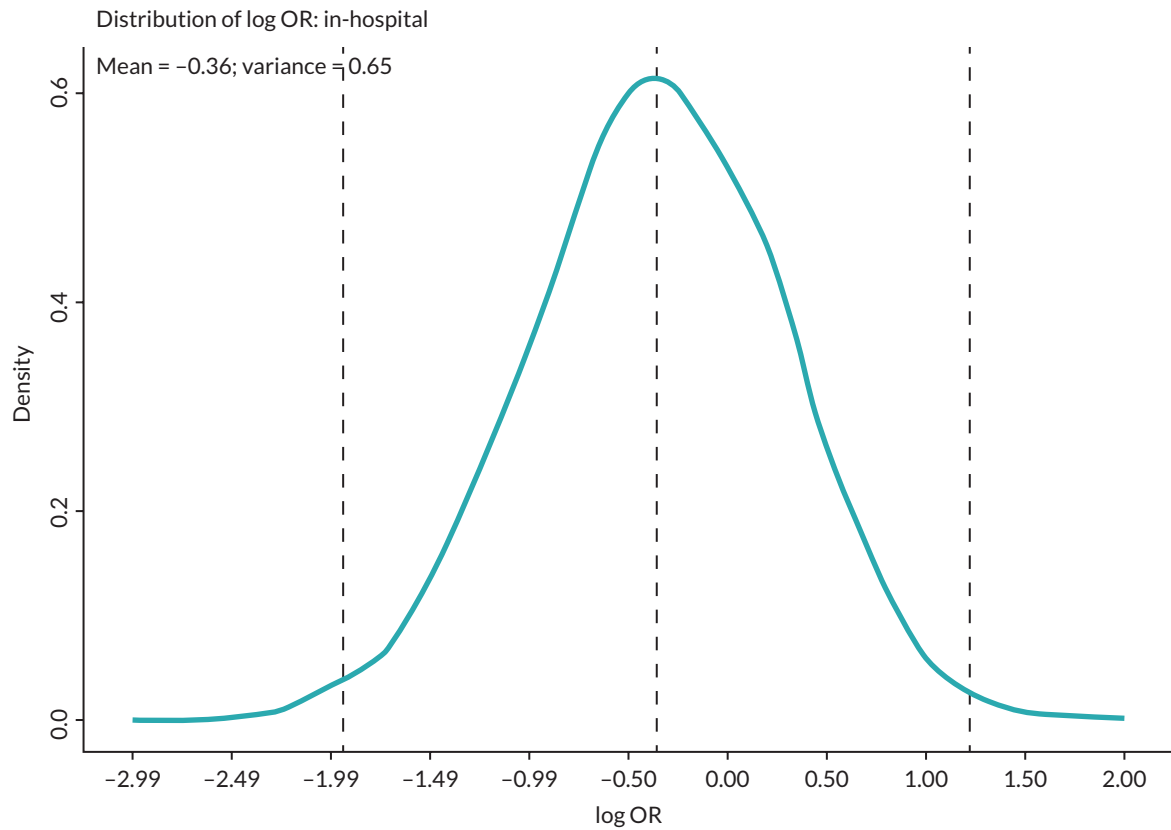


FIGURE 25 The prior distribution of logarithm of OR for REBOA to standard care based on 10,000 samples for in-hospital mortality.

Appendix 5 Process evaluation: overview of proposed solutions

Proposed solution (s)	Proposed content	Selected BCT(s) (domain-relevant/supplementary)	Belief statements (salient barriers/enablers, linked to TDF domains)	Inclusion record (including APEASE criteria)
Training	Target altruistic emotions – express satisfaction of being part of a trial which will influence clinical practice	5.6. Information about emotional consequences	'Reputational benefit for the institute associated with being able to recruit patients and deploy REBOA' (TDF Beliefs about consequences)	Include BCTs 5.6., 9.2., 3.2., 5.1., 5.2.: All APEASE criteria met
	Encourage reflection of the pros/cons to recruitment in the trial generally. Including advantages of knowing which clinical method is most effective. Highlight how the research will influence clinical practice	9.2. Pros and cons	'REBOA may be beneficial' (TDF Beliefs about consequences)	Exclude BCT 5.5: May not be acceptable. Many valid reasons for not recruiting eligible patients, external, out-with control. APEASE Acceptability, Equity and Side-Effects criteria not met
	Remind staff about the potential benefits of REBOA to patients with traumatic injury, despite the associated risks. Also benefits of not doing REBOA – SC. Purpose of the trial is to find out which method is best	5.1. Information about health consequences	'REBOA may cause complications' (TDF Beliefs about consequences)	
	Highlight that staff are contributing to valuable research which will also benefit the reputation of each institute	5.3. Information about social and environmental consequences	'It can be difficult to define exsanguinating haemorrhage' (TDF Beliefs about consequences)	
	Present case studies of real-life examples where patients have been treated with REBOA and SC, and highlight the valuable contribution of the trial	5.2. Salience of consequences		
	Link the benefit of taking part in the trial to anticipated regrets of failing to recruit eligible patients. Remind staff of the scarcity of cases. Highlight the requirement to address trial research question	5.5. Anticipated regret		
Training	Include step-by-step instructions on how to recognise eligibility and perform REBOA: provide a demonstration by presenting video clips. All sites have to agree on eligibility criteria. Provide case study examples	6.1. Demonstration of the behaviour	'Recognising an eligible patient requires expertise' (TDF Skills) 'Insertion of REBOA can be technical' (TDF Skills)	Include all BCTs (already delivered during on-site training): APEASE criteria met
	Set easy-to-achieve tasks (e.g. the areas which site staff find simple to complete, such as navigating the randomisation app) and progress to more complex steps, such as monitoring eligibility and performing REBOA	8.7. Graded tasks 8.1. Behavioural practice/rehearsal	'Concerns about competency due to low throughput of cases' (TDF Skills)	

Proposed solution (s)	Proposed content	Selected BCT(s) (domain-relevant/supplementary)	Belief statements (salient barriers/enablers, linked to TDF domains)	Inclusion record (including APEASE criteria)
Training	Incorporate advice on how to reduce the cognitive load of performing REBOA and randomising a patient. This can include assigning other tasks completed simultaneously to different members of the team	11.3. Conserving mental resources	'You need to remember technical aspects of REBOA' (TDF Memory Attention and Decision Processes) 'Our team is inclined to wait to see if our patient requires REBOA' (TDF Memory Attention and Decision Processes)	
Environmental restructuring	Social prompt: Assign an individual to prompt REBOA randomisation/delivery when a potentially eligible patient is flagged. This could include prompting eligibility assessment or technical aspects of REBOA. Remind healthcare professionals of protocol	7.1. Prompts/cues	The clinical context for REBOA is inherently stressful and fast-paced (TDF Environmental Context and Resources)	Include all BCTs: APEASE criteria met. While some BCTs were already incorporated in trial practices, it was recommended that delivery of all BCTs should be monitored to ensure continuous implementation
	Encourage the use of memory aid sheets to facilitate memory of REBOA recruitment and the procedure. Can include provision of cue cards to be slotted into staff lanyards. Sites could purchase a mannequin/ or recycle use of existing mannequin to practice REBOA on a weekly basis	12.5. Adding objects to the environment	'There are so few patients who require REBOA' (TDF Environmental Context and Resources)	
	Arrange for colleagues to provide practical help to recruitment and delivery of REBOA in each shift. This may include providing contact details of those who can help during out-of-hours	3.2. Social support (practical)	'The ability to recruit depends on staff availability' (TDF Environmental Context and Resources)	
	Assign REBOA champion roles at each site, highlight support available during team meetings	12.2. Restructuring the social environment		
	Ensure staff have a device with the app readily accessible for randomisation and gather essential equipment or prepare a REBOA trolley to assist in the delivery of the intervention	12.5. Adding objects to the environment		
	This could also include a diagram of the ideal positioning of staff during a code red call	12.6. Body changes 12.1. Restructuring the physical environment		
Enablement	Encourage staff to praise local efforts of recruitment and REBOA delivery when applicable. Praise can also be communicated via e-mail, as well as during local PI meetings	10.4. Social reward	'Our team is enthusiastic about the UK-REBOA trial' (TDF Social influences)	Include all APEASE criteria met

Proposed solution (s)	Proposed content	Selected BCT(s) (domain-relevant/supplementary)	Belief statements (salient barriers/enablers, linked to TDF domains)	Inclusion record (including APEASE criteria)
	Encourage sites to provide monthly updates on the progress of UK-REBOA trial recruitment and intervention delivery during trial meetings. Facilitate detailed discussion about recruitment procedures: ask staff to provide a description of latest recruitment cases including 'near misses' (when applicable). CIs to provide information about whether they approve of the procedures/decisions adopted	6.3. Information about others' approval	'People can hold different views about patient eligibility' (TDF Social influences) 'Our team has mixed levels of individual equipoise' (TDF Social influences, TDF Beliefs about Consequences)	While some BCTs were already incorporated in trial practices, it was recommended that delivery of all BCTs should be monitored to ensure continuous implementation
	Prompt discussion of what went well and what might have been done differently. Include action plans to tackle similar situations in the future	3.2. Social Support (Practical) 6.2. Social comparison 1.2. Problem solving 1.4. Action planning		
	Maintain the enthusiasm of REBOA by advising staff to encourage others to recruit and randomise eligible participants	3.1. Social support (unspecified, practical)		
	See examples listed above 5.3.: Designed to target mixed levels of team equipoise (beliefs about the consequences of REBOA intervention delivery). Delivered as bespoke infographic to be distributed to all site staff	5.3. Information about social and environmental consequences		
	Provide contact details of Clinical CI and Clinical Lead: Highlight support available	3.2. Social support (practical)		
Persuasion enablement	Remind staff that they have successfully performed REBOA and recruited participants in simulation and/or in real life. Enabled by PIs	15.3. Focus on past success Can also be incorporated into training	'Clinicians have to be confident to deliver REBOA; this can influence recruitment' (TDF Beliefs about capabilities) 'There is lots of nervousness around delivering REBOA related to personal abilities' (TDF Beliefs about capabilities)	Exclude: Difficult to implement. Depends on factors less amenable to change – for example PI personality and workplace culture. BCTs 15.3. and 15.1. can instead be incorporated via trial Training practices. APEASE Effectiveness criteria not met. APEASE Practicability criteria not met for BCT 15.4. Difficult to implement in a trauma care setting
	Local PIs can actively persuade relevant staff members that they are capable of performing the REBOA intervention during conversations/meetings. Highlight transferable skills of trial recruitment – include successful past experience of trial involvement	15.1. Verbal persuasion about capability		

Proposed solution (s)	Proposed content	Selected BCT(s) (domain-relevant/supplementary)	Belief statements (salient barriers/enablers, linked to TDF domains)	Inclusion record (including APEASE criteria)
	Encourage staff to practice positive self-talk as a team: this could include discussing one's own achievements/successes in a group setting. PIs to deliver	15.4. Self-talk		

Appendix 6 Process evaluation: infographic



- **Recruiting** to the UK REBOA Trial helps us compile **crucial, currently missing, clinical evidence on the effectiveness** (or not) of the treatment options available (for both **standard care and REBOA**) in this group of very sick and vulnerable patients.
- **Both** Standard Care alone and Standard Care plus REBOA **carry challenges and potential advantages**.
- Making the decision to **include eligible** patients in the UK REBOA Trial, **randomising** then swiftly **acting on the instruction** of that randomisation, means that we are **adding to the evidence base for both methods of management** that will help inform treatment decisions in the future.



- With the help of **you and your colleagues** at your hospital site providing this data, we can **generate this evidence base** and **positively impact** future policy and guidelines.
- Randomisation of patients within this trial is overseen by strong governance and ethics.
- **YOU** are making a **real difference** in this study.

For clinical questions or concerns please contact the **UK REBOA Trial CI**
Jan Jansen
jjansen@uabmc.edu
 or
UK Clinical Training Lead
Robbie Lendrum
robert.lendrum@nhs.net



Please keep up the good work, the trial would not be possible without **YOU!**



Appendix 7 Recruitment

TABLE 23 Recruitment by site

Site	SC + REBOA N = 46	SC N = 44	Total N = 90
Leeds General Infirmary	9 (20)	10 (23)	19 (21)
The Royal London Hospital	7 (15)	7 (16)	14 (16)
Queen Elizabeth Hospital, Birmingham	5 (11)	6 (14)	11 (12)
John Radcliffe Hospital, Oxford	4 (9)	3 (7)	7 (8)
Southmead Hospital Bristol	4 (9)	3 (7)	7 (8)
Queen's Medical Centre, Nottingham	3 (7)	4 (9)	7 (8)
University Hospital, Coventry	4 (9)	3 (7)	7 (8)
St George's University Hospital	3 (7)	3 (7)	6 (7)
Royal Victoria Infirmary, Newcastle	2 (4)	2 (5)	4 (4)
Aintree University Hospital	2 (4)	1 (2)	3 (3)
Sheffield Teaching Hospital	2 (4)	1 (2)	3 (3)
St Mary's Hospital, London	1 (2)	1 (2)	2 (2)

Note

King's College Hospital, London, James Cook University Hospital (Middlesbrough), Royal Stoke University Hospital, Royal Hull Infirmary did not recruit any participants.

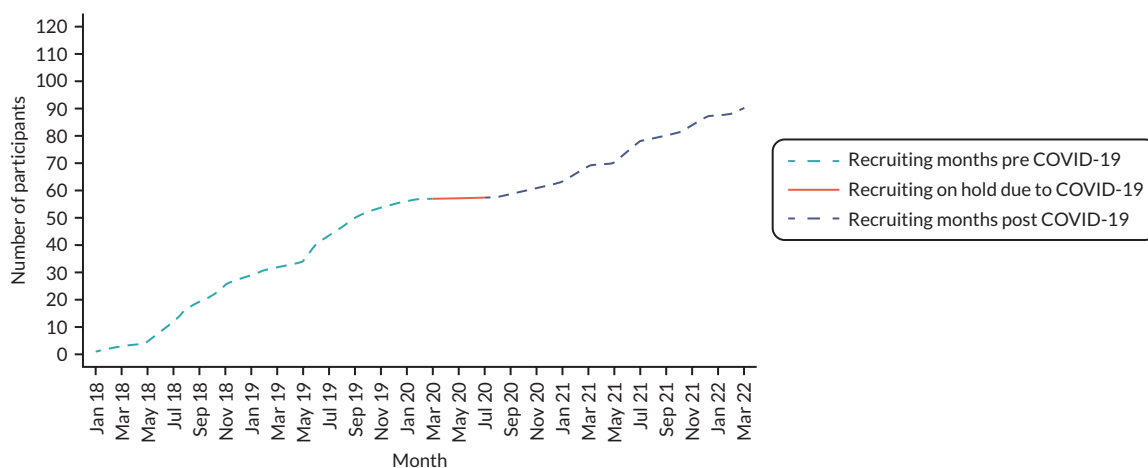


FIGURE 26 Recruitment over time.

Appendix 8 Additional clinical results

TABLE 24 Adjusted analysis for 90-day mortality

	OR	95% CrI	Posterior probability (%) of OR > 1 ^a
Age	1.39	(0.59 to 3.28)	77.3
Gender	1.53	(0.69 to 3.48)	85.1
ISS	1.63	(0.73 to 3.77)	88.1
AIS head	1.61	(0.72 to 3.79)	87.2
AIS face	1.65	(0.73 to 3.75)	88.5
AIS chest	1.68	(0.74 to 3.90)	89.5
AIS abdomen	1.50	(0.67 to 3.44)	83.6
AIS spine	1.72	(0.76 to 4.05)	89.9
AIS pelvic	1.61	(0.71 to 3.64)	87.2
AIS limbs	1.69	(0.73 to 3.99)	89.0
AIS other	1.60	(0.72 to 3.59)	87.4
Pre-hospital CPR ^b	1.69	(0.69 to 4.20)	87.4
ED SBP ^c	1.53	(0.69 to 3.52)	84.9
CPR on arrival ^b	1.62	(0.72 to 3.71)	87.9
Time from arrival to randomisation ^d	1.59	(0.71 to 3.61)	87.4
All ^e	1.80	(0.59 to 5.58)	84.9
All (removing ISS) ^f	1.67	(0.55 to 5.30)	81.6
AIS and ED SBP	1.53	(0.65 to 3.61)	84.0

a Probability of OR > 1.

b Missing values have been set to no.

c Mean SBP across group has been used to impute missing values.

d For those randomised before arrival, set to 0.

e Including all the covariates listed above.

f Including all covariates above but removing ISS.

TABLE 25 Mortality adjusted for centre

SC + REBOA	SC	Minimally informative prior			Elicitation prior		
		OR	95% CrI	Posterior probability (%) of OR > 1 ^a	OR	95% CrI	Posterior probability (%) of OR > 1 ^a
N = 46	N = 43						
Death within 90 days							
Yes 25 (54)	18 (42)	1.60	(0.71 to 3.66)	87.1	1.41	(0.67 to 2.98)	82.0
No 21 (46)	25 (58)						
Death within 6 months							
Yes 25 (54)	18 (42)	1.60	(0.71 to 3.66)	87.1	1.41	(0.67 to 2.98)	82.0
No 21 (46)	25 (58)						
Death while in hospital							
Yes 25 (54) Mortality at other time points	18 (42)	1.60	(0.71 to 3.66)	87.1	1.41	(0.67 to 2.98)	82.0
No 21 (46)	25 (58)						
N = 46	N = 44						
Death within 24 hours							
Yes 17 (37)	10 (23)	1.93	(0.80 to 4.84)	92.7	1.65	(0.73 to 3.79)	88.7
No 29 (63)	34 (77)						
Death within 6 hours							
Yes 13 (28)	4 (9)	3.24	(1.15 to 10.19)	98.7	2.52	(0.95 to 6.93)	96.7
No 33 (72)	40 (91)						
Death within 3 hours							
Yes 11 (24)	2 (5)	4.32	(1.34 to 16.39)	99.3	3.05	(1.05 to 9.43)	97.9
No 35 (76)	42 (95)						

^a Probability of OR > 1.

Note

Values are n (%).

TABLE 26 Adjusted analysis for 3-hour mortality

	OR	95% CrI	Posterior probability (%) of OR > 1 ^a
Age	3.89	(1.16 to 15.52)	98.6
Gender	4.24	(1.29 to 16.33)	99.2
ISS	5.20	(1.50 to 21.78)	99.6
AIS head	4.36	(1.36 to 16.85)	99.4
AIS face	4.32	(1.34 to 17.03)	99.3
AIS chest	5.80	(1.68 to 23.96)	99.8
AIS abdomen	4.12	(1.24 to 16.10)	99.0
AIS spine	5.80	(1.73 to 23.04)	99.8
AIS pelvic	4.40	(1.36 to 17.16)	99.4
AIS limbs	4.40	(1.36 to 17.04)	99.4
AIS other	4.48	(1.39 to 17.08)	99.4
Pre-hospital CPR ^b	4.63	(1.35 to 18.58)	99.3
ED SBP ^c	4.20	(1.31 to 16.71)	99.2
CPR on arrival ^b	6.20	(1.66 to 29.38)	99.7
Time from arrival to randomisation ^d	4.35	(1.36 to 16.82)	99.4
All ^e	9.80	(1.80 to 57.91)	99.6
All (removing ISS) ^f	8.77	(1.80 to 49.74)	99.6
AIS and ED SBP	4.25	(1.28 to 15.96)	99.1

a Probability of OR > 1.

b Missing values have been set to no.

c Mean SBP across group has been used to impute missing values.

d For those randomised before arrival, set to 0.

e Including all the covariates listed above.

f Including all covariates above but removing ISS.

TABLE 27 Adjusted analysis for 6-hour mortality

	OR	95% CrI	Posterior probability (%) of OR > 1 ^a
Age	2.88	(0.97 to 9.47)	97.1
Gender	3.05	(1.07 to 9.63)	98.1
ISS	3.41	(1.17 to 11.32)	98.8
AIS head	3.22	(1.14 to 10.18)	98.7
AIS face	3.20	(1.15 to 10.10)	98.7
AIS chest	4.32	(1.44 to 15.14)	99.6
AIS abdomen	3.03	(1.08 to 9.65)	98.2
AIS spine	4.18	(1.46 to 13.59)	99.6
AIS pelvic	3.22	(1.15 to 10.26)	98.8
AIS limbs	3.64	(1.25 to 11.79)	99.2

continued

TABLE 27 Adjusted analysis for 6-hour mortality (continued)

	OR	95% CrI	Posterior probability (%) of OR > 1 ^a
AIS other	3.20	(1.15 to 10.07)	98.7
Pre-hospital CPR ^b	3.60	(1.17 to 12.10)	98.8
ED SBP ^c	3.08	(1.09 to 9.83)	98.3
CPR on arrival ^b	4.42	(1.36 to 17.18)	99.3
Time from arrival to randomisation ^d	3.25	(1.16 to 10.11)	98.8
All ^e	9.75	(2.12 to 50.39)	99.9
All (removing ISS) ^f	10.44	(2.27 to 52.24)	99.8
AIS and ED SBP	3.08	(1.08 to 9.51)	98.2

a Probability of OR > 1.

b Missing values have been set to no.

c Mean SBP across group has been used to impute missing values.

d For those randomised before arrival, set to 0.

e Including all the covariates listed above.

f Including all covariates above but removing ISS.

TABLE 28 Adjusted analysis for 24-hour mortality

	OR	95% CrI	Posterior probability (%) of OR > 1 ^a
Age	1.66	(0.69 to 4.20)	86.7
Gender	1.80	(0.75 to 4.49)	90.4
ISS	1.88	(0.78 to 4.66)	91.9
AIS head	1.88	(0.77 to 4.75)	91.8
AIS face	1.92	(0.81 to 4.75)	93.1
AIS chest	2.10	(0.88 to 5.43)	95.1
AIS abdomen	1.72	(0.70 to 4.29)	87.9
AIS spine	2.34	(0.95 to 6.12)	96.7
AIS pelvic	1.87	(0.78 to 4.71)	92.1
AIS limbs	2.12	(0.86 to 5.46)	94.8
AIS other	1.94	(0.80 to 4.86)	93.0
Pre-hospital CPR ^b	2.20	(0.78 to 6.86)	93.1
ED SBP ^c	1.82	(0.75 to 4.47)	91.0
CPR on arrival ^b	2.01	(0.82 to 5.19)	93.5
Time from arrival to randomisation ^d	1.87	(0.79 to 4.65)	92.4
All ^e	4.22	(1.15 to 15.21)	98.5
All (removing ISS) ^f	4.53	(1.25 to 17.59)	98.9
AIS and ED SBP	1.81	(0.74 to 4.56)	90.4

a Probability of OR > 1.

b Missing values have been set to no.

c Mean SBP across group has been used to impute missing values.

d For those randomised before arrival, set to 0.

e Including all the covariates listed above.

f Including all covariates above but removing ISS.

TABLE 29 Adjusted analysis for in-hospital and 6-month mortality

	OR	95% CrI	Posterior probability (%) of OR > 1 ^a
Age	1.39	(0.59 to 3.28)	77.3
Gender	1.53	(0.69 to 3.48)	85.1
ISS	1.63	(0.73 to 3.77)	88.1
AIS head	1.61	(0.72 to 3.79)	87.2
AIS face	1.65	(0.73 to 3.75)	88.5
AIS chest	1.68	(0.74 to 3.90)	89.5
AIS abdomen	1.50	(0.67 to 3.44)	83.6
AIS spine	1.72	(0.76 to 4.05)	89.9
AIS pelvic	1.61	(0.71 to 3.64)	87.2
AIS limbs	1.69	(0.73 to 3.99)	89.0
AIS other	1.60	(0.72 to 3.59)	87.4
Pre-hospital CPR ^b	1.69	(0.69 to 4.20)	87.4
ED SBP ^c	1.53	(0.69 to 3.52)	84.9
CPR on arrival ^b	1.62	(0.72 to 3.71)	87.9
Time from arrival to randomisation ^d	1.59	(0.71 to 3.61)	87.4
All ^e	1.80	(0.59 to 5.58)	84.9
All (removing ISS) ^f	1.67	(0.55 to 5.30)	81.6
AIS and ED SBP	1.53	(0.65 to 3.61)	84.0

a Probability of OR > 1.

b Missing values have been set to no.

c Mean SBP across group has been used to impute missing values.

d For those randomised before arrival, set to 0.

e Including all the covariates listed above.

f Including all covariates above but removing ISS.

TABLE 30 Learning curve analysis

	SC + REBOA N = 34	SC 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 to 5.01)	95.1
No	13 (38)	25 (58)			
Death within 6 months					
Yes	21 (62)	18 (42)	2.06	(0.87 to 5.01)	95.1
No	13 (38)	25 (58)			
Death while in hospital					
Yes	21 (62)	18 (42)	2.06	(0.87 to 5.01)	95.1
No	13 (38)	25 (58)			

continued

TABLE 30 Learning curve analysis (continued)

	SC + REBOA N = 34	SC N = 44	OR	95% CrI	Posterior probability of OR > 1 (%)
	N = 34	N = 44			
Death within 24 hours					
Yes	13 (38)	10 (23)	1.92	(0.76 to 4.93)	91.5
No	21 (62)	34 (77)			
Death within 6 hours					
Yes	9 (26)	4 (9)	2.86	(0.94 to 9.25)	96.8
No	25 (74)	40 (91)			
Death within 3 hours					
Yes	9 (26)	2 (5)	4.58	(1.38 to 17.64)	99.4
No	25 (74)	42 (95)			

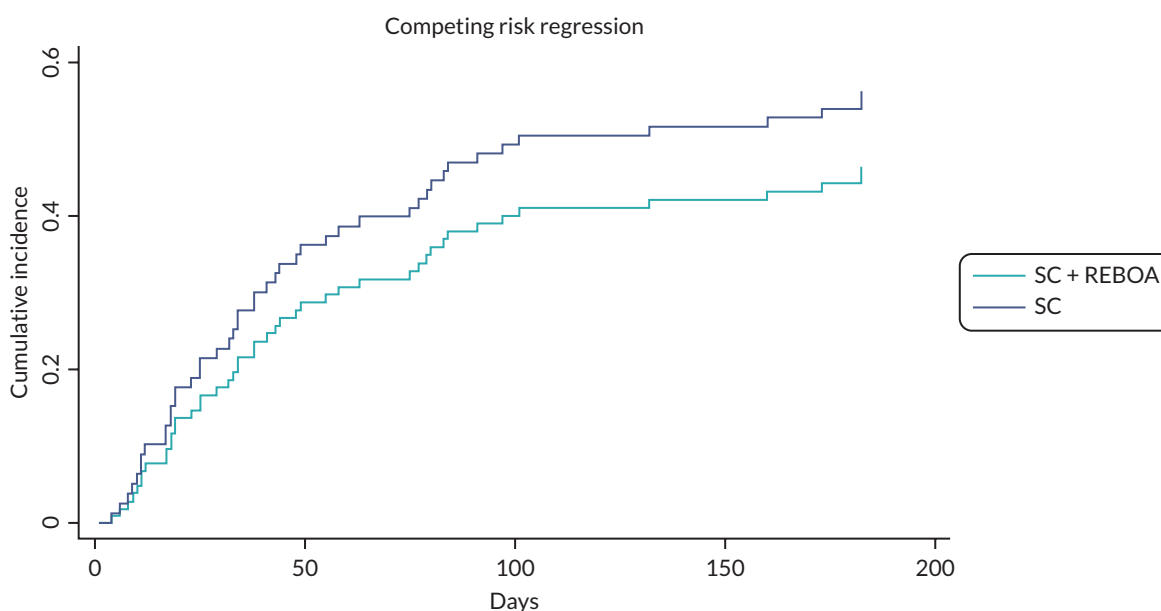


FIGURE 27 Competing risk regression.

TABLE 31 Baseline characteristics of 'compliers' (R5) vs. 'non-compliers' (all others)

	SC + REBOA		SC	
	Complied n = 19	Did not comply n = 27	Complied n = 42	Did not comply N = 2
Demographics				
Median age (Q1-Q3) (years)	57 (41-70)	38 (30-54)	38 (29-57)	52 (49-55)
Male sex, n (%)	10 (53)	18 (67)	33 (79)	1 (50)
Comorbidity				
Median CCI (Q1-Q3); n	1 (0-5); 14	0 (0-1); 19	0 (0-1); 38	2 (0-3); 2

TABLE 31 Baseline characteristics of 'compliers' (R5) versus 'non-compliers' (all others) (continued)

	SC + REBOA		SC	
	Complied	Did not comply	Complied	Did not comply
	n = 19	n = 27	n = 42	N = 2
Mechanism of injury				
Blunt, n (%)	19 (100)	25 (93)	41 (98)	2 (100)
Penetrating, n (%)	-	2 (7)	1 (2)	-
Injury severity				
Median ISS (Q1-Q3)	41 (35-54)	41 (25-48)	41 (29-50)	39 (27-50)
ISS band				
Minor	-	-	1 (2)	-
Moderate	-	1 (4)	1 (2)	-
Severe	2 (10)	5 (19)	4 (10)	-
Very severe	17 (90)	21 (78)	36 (86)	2 (100)
Injury pattern				
AIS head [median (Q1-Q3)]	3 (0-5)	0 (0-4)	2 (0-5)	0 (0-0)
AIS face [median (Q1-Q3)]	0 (0-2)	0 (0-2)	0 (0-2)	0 (0-0)
AIS thorax [median (Q1-Q3)]	3 (3-4)	4 (3-4)	4 (1-4)	4 (3-4)
AIS abdomen [median (Q1-Q3)]	2 (0-3)	2 (0-3)	2 (0-4)	4 (3-5)
AIS spine [median (Q1-Q3)]	2 (0-3)	2 (0-2)	0 (0-2)	0 (0-0)
AIS pelvis [median (Q1-Q3)]	4 (0-5)	2 (0-4)	2 (0-5)	1 (0-2)
AIS limbs [median (Q1-Q3)]	2 (2-3)	2 (2-3)	3 (1-3)	3 (3-3)
AIS other [median (Q1-Q3)]	0 (0-0)	0 (0-1)	0 (0-1)	0 (0-0)
Vital signs				
SBP (mmHg)	72 (50-109); 18	91 (68-123); 26	97 (72-114); 40	120 (115-124); 2
≤ 90 mmHg, n (%)	13 (72)	13 (50)	19 (48)	-
≤ 70 mmHg, n (%)	8 (44)	10 (39)	9 (23)	-
CPR on arrival				
Yes	3 (16)	1 (4)	4 (10)	-
No	14 (74)	22 (82)	37 (88)	2 (100)
Missing	2 (11)	4 (15)	1 (2)	-

CCI, Charlson Comorbidity Index; Q1, 25th percentile; Q3, 75th percentile.

TABLE 32 Baseline characteristics 'compliers' (non-R2) vs. 'non-compliers' (R2)

	SC + REBOA		SC	
	Complied <i>n</i> = 36	Did not comply <i>n</i> = 10	Complied <i>n</i> = 42	Did not comply <i>N</i> = 2
Demographics				
Median age (Q1–Q3) (years)	46 (33–63)	47 (31–62)	38 (29, 57)	52 (49, 55)
Male sex, <i>n</i> (%)	21 (58)	7 (70)	33 (79)	1 (50)
Comorbidity				
Median CCI (Q1–Q3); <i>n</i>	0 (0–2); 27	1 (0–1); 6	0 (0, 1)	2 (0, 3)
Mechanism of injury				
Blunt, <i>n</i> (%)	36 (100)	8 (80)	41 (98)	2 (100)
Penetrating, <i>n</i> (%)	–	2 (20)	1 (2)	–
Injury severity				
Median ISS (Q1–Q3)	41 (36–50)	33 (21–43)	41 (29–50)	39 (27–50)
ISS band				
Minor	–	–	1 (2)	
Moderate	–	1 (10)	1 (2)	
Severe	4 (11)	3 (30)	4 (10)	
Very severe	32 (89)	6 (60)	36 (86)	2 (100)
Injury pattern				
AIS head [median (Q1–Q3)]	3 (0–5)	0 (0–3)	2 (0–5)	0 (0–0)
AIS face [median (Q1–Q3)]	0 (0–2)	0 (0–2)	0 (0–2)	0 (0–0)
AIS thorax [median (Q1–Q3)]	4 (3–4)	3 (1–4)	4 (1–4)	4 (3–4)
AIS abdomen [median (Q1–Q3)]	2 (0–3)	0 (0–2)	2 (0–4)	4 (3–5)
AIS spine [median (Q1–Q3)]	2 (0–2)	1 (0–2)	0 (0–2)	0 (0–0)
AIS pelvis [median (Q1–Q3)]	2 (0–5)	1 (0–4)	2 (0–5)	1 (0–2)
AIS limbs [median (Q1–Q3)]	2 (2–3)	3 (2–3)	3 (1–3)	3 (3–3)
AIS other [median (Q1–Q3)]	0 (0–1)	0 (0–1)	0 (0–1)	0 (0–0)
Vital signs				
SBP (mmHg)	88 (58–115); 35	69 (50–83); 9	97 (72–114); 40	120 (115–124); 2
≤ 90 mmHg, <i>n</i> (%)	19 (54)	7 (78)	19 (48)	–
≤ 70 mmHg, <i>n</i> (%)	13 (37)	5 (56)	9 (23)	–
CPR on arrival				
Yes	4 (11)	–	4 (10)	–
No	29 (81)	7 (70)	37 (88)	2 (100)
Missing	3 (8)	3 (30)	1 (2)	–

CCI, Charlson Comorbidity Index; Q1, 25th percentile; Q3, 75th percentile.

TABLE 33 Odds ratio for mortality in SC + REBOA (R5) vs. SC (all others) using as-treated analysis A (R5) vs. SC (all others) using as-treated analysis

	SC + REBOA N = 21	SC N = 69	OR	95% CrI
Death within 90 days				
Yes	14 (67)	29 (43)	2.77	(1.01 to 8.20)
No	7 (33)	39 (57)		
Death within 6 months				
Yes	14 (67)	29 (43)	2.77	(1.01 to 8.20)
No	7 (33)	39 (57)		
Death while in hospital				
Yes	14 (67)	29 (43)	2.77	(1.01 to 8.20)
No	7 (33)	39 (57)		
Death within 24 hours				
Yes	8 (38)	19 (28)	1.60	(0.56 to 4.50)
No	13 (62)	50 (72)		
Death within 6 hours				
Yes	7 (33)	10 (14)	2.96	(0.91 to 9.37)
No	14 (67)	59 (86)		
Death within 3 hours				
Yes	5 (24)	8 (12)	2.33	(0.62 to 8.21)
No	16 (76)	61 (88)		

TABLE 34 Odds ratio for mortality in SC + REBOA (non-R2) vs. SC (everything else)

	SC + REBOA N = 38	SC N = 52	OR	95% CrI
Death within 90 days				
Yes	19 (50)	24 (47)	1.13	(0.49 to 2.63)
No	19 (50)	27 (53)		
Death within 6 months				
Yes	19 (50)	24 (47)	1.13	(0.49 to 2.63)
No	19 (50)	27 (53)		
Death while in hospital				
Yes	19 (50)	24 (47)	1.13	(0.49 to 2.63)
No	19 (50)	27 (53)		
Death within 24 hours				
Yes	12 (32)	15 (29)	1.13	(0.45 to 2.82)
No	26 (68)	37 (71)		

continued

TABLE 34 Odds ratio for mortality in SC + REBOA (non-R2) vs. SC (everything else) (*continued*)

	SC + REBOA N = 38	SC N = 52	OR	95% CrI
Death within 6 hours				
Yes	9 (24)	8 (15)	1.72	(0.58 to 5.14)
No	29 (76)	44 (85)		
Death within 3 hours				
Yes	7 (18)	6 (12)	1.75	(0.52 to 5.95)
No	31 (82)	46 (88)		

EME
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