Statistical Analysis Plan

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Signatures

By signing this document, I am confirming that I have read, understood and approve the statistical analysis plan (SAP) for the UK-REBOA trial.

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Version History

SAP version	Protocol version*	Section number changed	Description of and reason for change	Date of change
Version 1.1	Version 6	Several	Minor edits to - Administrative information - Typos and layout changes to improve readability throughout - Clarity on analysis of secondary outcomes applied - Subgroup analysis section edited to reflect protocol (no pre-planned subgroups) - Text on sensitivity analysis confirmed (none pre-planned) - Compliance with allocated treatment edited for clarity - WinBUGS added to software section	30/03/2022
Version 1	Version 6		New document, based on SAP template Version 2	NA

* Please refer to 'Statistical Analysis Plan (SAP) review after Protocol updates' document that will be updated throughout the trial, documenting any amendments to the protocol and its relevance to the SAP.

Glossary of Abbreviations

AE	Adverse Event
CHaRT	Centre for Healthcare Randomised Trials
CI	Confidence Interval
CRF	Case Report Form
CONSORT	Consolidated Standards of Reporting Trials
DMC	Data Monitoring Committee
EQ-5D	EuroQol Group's 5-dimension health status questionnaire
HSRU	Health Services Research Unit
ITT	Intention-to-Treat

SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation

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1. Introduction

This statistical analysis plan (SAP) documents the analysis for the Resuscitative Endovascular Balloon Occlusion of the Aorta (REBOA) Trial. Trauma is the leading cause of death in those under forty. Bleeding is responsible for approximately one-third of trauma deaths, and between 16-29% of such deaths are thought to be preventable. Bleeding inside the torso is particularly challenging. For some patients this type of bleeding is either unrecognised or torrential, and results in death if it can't be controlled. However, if bleeding can be controlled patients often recover. Temporary aortic occlusion can limit bleeding and improve survival. This study is evaluating resuscitative endovascular balloon occlusion of the aorta, known as REBOA, to reduce haemorrhage-related deaths. Design elements of this trial have also come from Thomas Jaki and Philip Pallmann from the University of Lancaster MRC Adaptive Designs Working group. There are also elements of discussion with statisticians on the TSC and DMC, and input from a statistical review of the trial by an external statistician (requested by the HTA). The SAP is based on the protocol version 6 and any deviations from the plan will be described. This SAP focuses on the clinical outcomes of the trial, cost-effectiveness is described in a separate analysis plan. The SAP is based on the protocol version 6 and any deviations from the plan will be described.

2. Study Aim and question

The UK-REBOA trial aims to establish the clinical and cost-effectiveness of REBOA, as compared with standard treatment alone, for the management of uncontrolled torso haemorrhage caused by injury, in specialist trauma centres.

The ***question*** is does the use of REBOA, in addition to standard major trauma centre treatment, increase 90-day survival of trauma patients suffering from exsanguinating torso haemorrhage, and is it cost-effective?

3. General Study Design

Pragmatic, multicentre, Bayesian, group-sequential, randomised controlled trial (RCT), comparing standard major trauma centre treatment plus REBOA with standard major trauma centre treatment alone, for trauma patients with suspected life-threatening torso haemorrhage.

3.1. Design considerations

3.1.1. Original design

The original design is outlined in the technical document (Appendix 1). Briefly, we used a group-sequential design with three stages: an interim analysis after 40 randomised participants and again after 80 participants, and a final analysis after the expected maximum of 120 randomised participants. We planned that the trial be stopped early if the probability that the 90-day survival odds ratio (OR) falls below 1 (i.e. REBOA is harmful) at the first or second interim analysis, is 90% or greater. More formally, our Bayesian futility criterion at each stage is

$P(\delta < 0 \mid \mathbf{y}) \geq 0.9$

where δ is the log OR and $\mathbf{y}$ is the observed data. REBOA will be declared "successful" if the probability that the 90-day survival OR exceeds 1 at the final analysis is 95% or greater, so our Bayesian success criterion is defined as:

$P(\delta > 0 \mid \mathbf{y}) \geq 0.95$

Our calculations are based on an estimated control group (standard major trauma centre treatment alone) 90-day survival rate of 66.5%(ref). The design's properties in terms of the probabilities of stopping for futility and declaring success for potential effect sizes from an odds ratio of 0.7 (equating to a reduction in 90-day survival from 66.5% to 58.2%, ie. REBOA causing harm) through to 1.3 (equating to an increase in 90-day survival from 66.5% to 72.1%). The expected sample size requirement are shown in Appendix Table 1.

3.1.2. Error in original design

As is standard for this type of design, we assumed that δ was normally distributed with a known variance, allowing the use of a normal likelihood for the data, with a conjugate normal prior lead to a posterior distribution that is also normal. The software package used (gsbDesign in R) requires:

- the number of interim analyses (including final analysis),
- the standard deviation of individual observations per arm (σ_k)
- prior specification potentially per arm (n_{k0}),
- number of patients per arm and stage (n_{ki}),
- and success and futility criteria per stage ($s_{ir}, p_{ir}, f_{ir}, q_{ir}$).

It was in specifying the standard deviation where the error occurred. It was (incorrectly) assumed the standard approximate variance for log(OR) as

$$Var(\delta) = \frac{1}{n}\left(\frac{1}{p_r} + \frac{1}{p_s} + \frac{1}{1 - p_r} + \frac{1}{1 - p_s}\right)$$

where p_r and p_s are the survival probabilities in REBOA and standard care groups respectively. The correct form of the variance (and hence standard deviation) is at the individual observation, which should have been of the form

$$\frac{1}{p(1-p)}$$

Using the correct input had a non-trivial impact on the probability of declaring REBOA a success (holding all other design inputs as same) for example, if the true OR was 1.3 the probability of success dropped from 90% to 16%.

3.1.3. Revised specifications

There are several approaches to design and analysis of the trial that can help recover "power" or improve the probability of declaring success after 120 participants. These are broadly:

- increase sample size
- relax success criterion
- re-assess expected survival probabilities/effect size
- make use of informative priors

Sample size: The option to increase sample size has cost implications and is not considered further.

Success criterion: For "rare disease" it is more common to have a lower threshold for declaring success, reducing our criterion to 80% $P(\delta > 0 \mid \mathbf{y}) \geq 0.95$ increases the probability of declaring success to 43%.

Survival probabilities/effect size: The original maximum specified effect size was an OR of 1.3. Current evidence (with the caveats about risk of bias) suggests that this an under estimate and that an OR 1.5 would still be conservative. Considering the original design extended to an OR of 1.5 increases the probability of declaring success to 27%. Relaxing the criterion for success to 0.80 increases this to 57%. Better performance by REBOA would increase this further.

Informative priors: After consultation with our oversight committees we have several approaches to outline here. Firstly, we will construct prior distributions to use in analysis, broadly speaking these will take the form a sceptical, neutral, and enthusiastic. The distribution these take has yet to be decided and will be informed by separate pieces of work. New evidence has been published since 2016 on approximately 900 REBOA procedures in comparative studies. We plan to review the literature and synthesise the existing evidence. Furthermore, we plan to formally elicit expert opinion from trauma experts to construct prior distributions. Both of these pieces of work will have separate protocols (linked to this SAP), written, conducted, and analysed by statisticians and researchers with no knowledge of the emerging trend from UK-REBOA trial.

For example, a scoping review and crude meta-analysis of seven comparative studies (1846 events 4700 people) shows an OR approximately 2 in favour of REBOA. Using an enthusiastic prior of 1.5 weighted to be the equivalent of 40 patients in addition to the above revisions increases the probability of declaring success to 70%.

A summary of the original and draft revised design specifications are outlined in the Table 2

Table 1. Summary of the original and draft revised design specifications

Specification	Original	Revised
Sample size	120	120
1st interim look	40	40
2nd interim look	80	80
Control 90-day survival	0.665	0.665
Success criterion	0.95	0.80
Effect size (OR max)	1.3	1.5
Prior	Non-informative	Various
Futility criterion	0.90	0.90

4. Interventions to be evaluated

REBOA refers to the insertion – usually via the femoral artery – of a compliant balloon, which is advanced into the distal thoracic or abdominal aorta, and then inflated, thereby obstructing flow into the distal circulation, with the aim of reducing further blood loss, increasing cardiac afterload and proximal aortic pressure, and increasing myocardial and cerebral perfusion.
The trial seeks to evaluate the technique of REBOA rather than a specific brand of device.

Standard treatment of patients with life-threatening torso haemorrhage, in the setting of a major trauma centre, which includes a rapid, consultant-led assessment; as well as consultant-delivered anaesthesia and surgical care. Depending on the injuries, the receiving team includes emergency medicine physicians, anaesthetists, general and vascular surgeons, orthopaedic surgeons, radiologists, intensivists, as well as nursing and ancillary staff.

Life-saving interventions such as intubation of the airway, respiratory support, blood product transfusion, and imaging, are directed by protocols and guidelines, and aimed at minimising the time to control of haemorrhage, by surgical or endovascular means.

5. Randomisation, Allocation and Blinding

All participants who agree to enter the study will be logged with the central trial office and given a unique Study Number. Randomisation will utilise the existing proven remote automated computer randomisation application in the central trial office in the Centre for Healthcare Randomised Trials (CHaRT, a fully registered UK CRN clinical trials unit) in the Health Services Research Unit (HSRU), University of Aberdeen.

Randomisation is by permuted blocks of random size via a central randomisation service access through smartphone app. There is no blinding strategy for the trial statistician.

6. Outcome Measures

6.1. Primary Outcome

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

6.2. Secondary Outcomes

The secondary clinical outcomes include:

- 3-hour mortality
- 6-hour mortality
- In-hospital mortality ('24-hour)
- 6-month mortality
- Length of stay (in hospital and intensive care unit)
- 24h blood product use (from injury)
- Need for haemorrhage control procedure (operation or angioembolisation), defined as whether such a procedure was required (from time of injury)
- Time from admission to commencement of haemorrhage control procedure (REBOA, operation, or angioembolisation), defined as time to balloon inflation, incision, or first angiogram
- Complications/Safety Data
- Functional outcome (measured using the extended Glasgow Outcome Score) at 6 months
- Procedural performance details

7. Timing of Outcome Measurements

Table containing all outcome measures and the time points that they are measured at.

Table 2. Outcome measures and time point collection

	24h	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			✓		

8. Adverse Events

Adverse Event (AE): Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs in subjects, users or other persons whether or not related to the investigational medical device.

Adverse Device Effect (ADE): Adverse event related to the use of an investigational medical device.

Serious Adverse Event (SAE): Any adverse event that:

(a) Led to a death
(b) Led to a serious deterioration in health that either
  (i) resulted in a life-threatening illness or injury, or
  (ii) resulted in a permanent impairment of a body structure or a body function, or
  (iii) resulted in patient hospitalisation or prolongation of existing hospitalisation, or
  (iv) resulted in medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function.
(c) Led to fetal distress, fetal death, or a congenital abnormality of birth defect
(d)

Serious Adverse Device Effect (SADE): Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

Unanticipated Serious Adverse Device Effect (USADE): Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the independent risk assessment has been carried out by the sponsor.

Please see the study protocol for more details. The number of Adverse events (AEs) and serious adverse events (SAEs) and the proportion of participants with an event will be presented. These will be tabulated and not analysed and will be summarised by Intention-to-Treat (ITT) and as treated.

9. Sample Size and Power Calculation

The rationale for the sample size of 120 participants is detailed in the protocol. Briefly, 120 participants were considered the maximum number people with life-threatening torso haemorrhage that could be recruited over the duration of the trial. The operating characteristics of the design are detailed above.

10. Statistical Methods

10.1. General Methods

All the main analyses will be based on the Intention-to-Treat (ITT) principle. There are two planned interim analysis for the primary outcome (see section for details) and a final analysis on all outcomes after full recruitment and follow-up. The results of the trial will be presented following the standard CONSORT recommendations . Baseline and follow-up data will be summarised using the appropriate descriptive statistics and graphical summaries. Treatment effects will be presented with 95% credible intervals for the primary outcome and secondary outcomes. There will be no adjustment to secondary outcomes for multiple testing. All eligible participants will be included in the analysis and who provided consent.

10.2. Primary Outcome

The primary outcome will be analysed using Bayesian logistic regression. There are three planned analyses, two interim analyses for futility and a final analysis.

10.2.1. Interim Analysis

There are two planned interim analyses, after 40 and 80 randomisations, for futility. The interim analysis will be on the primary outcome only (although the DMC reserve the right to request additional data and/or analyses). The analysis method will be (Bayesian) logistic regression with a minimally informative prior on the logOR δ of $N(0, 1.28^2)$ which rules out extreme ORs, and a non-informative prior on the intercept $N(0, 10^2)$. If at either of these interim analyses we witness

$$P(\delta < 0 \mid \mathbf{y}) \geq 0.9$$

the DMC may consider recommending the trial stop due to futility. The minimally-informative prior used for interim futility analysis increases the probability of the trial stopping early should the data show harm.

10.2.2. Final analyses

The final analysis on all 120 participants will also use (Bayesian) logistic regression with informative priors, using a combination of the systematic review and synthesis of the literature of REBOA and from expert opinion. Prior distributions for sceptical, neutral and enthusiastic positions on the current evidence will be used. We'll summarise treatment effects as OR with 95% credible intervals and provide probability estimates of δ > $ (i.e an OR > 1) for each prior.

10.3. Secondary Outcomes

Secondary outcomes will be analysed in a similar manner using appropriate generalised linear models for the distribution of the outcome.

10.4. Subgroup Analyses

There is no pre-planned subgroup analysis.

10.5. Sensitivity analysis

There is no pre-planned sensitivity analysis other than assessing the impact of compliance (see below).

10.6. Compliance

We will explore the influence of compliance on the treatment effect for the primary outcome by doing a per-protocol analysis and complier adjusted causal estimation (CACE) using instrumental variable regression. The following classification has been developed to describe reasons for REBOA not being deployed as planned:

Classification	
R1/C1	Arterial access not attempted as patient had improved
R1/C2	Arterial access not attempted as patient had deteriorated
R2	Arterial access attempted but unsuccessful
R3/C1	Arterial access achieved, but catheter not inserted as patient had improved
R4/C1	Catheter inserted, but balloon not inflated as patient had improved

Technical stage
[R1] Arterial access not attempted
[R2] Arterial access attempted, but unsuccessful
[R3] Arterial access achieved, but catheter not inserted
[R4] Catheter inserted, but balloon not inflated
[R5] Catheter inserted, balloon inflated

Contributing Clinical Factors
[C1] Patient improved so REBOA no longer deemed appropriate
[C2] Patient deteriorated so REBOA no longer deemed appropriate

The primary CACE analysis will focus on defining non-compliance using the R2 classification above (all other classifications of REBOA not being deployed successfully are in line with the protocol).

10.7. Missing Data

10.7.1. Missing Outcome Data

We anticipate no missing outcome data for the primary outcome.

10.7.2. Missing Baseline Data

Data missing at baseline will be reported as such. If required secondary outcome data will be imputed with centre specific mean for continuous data and missing binary/categorical data will include a missing indicator.

10.8. Statistical software

All analysis will be carried out in Stata 16 and WinBUGS.

10.9. Derived variables – Patient reported outcome measures (PROMS)

There are several patient-reported outcomes collected using validated questionnaires which require scores to be calculated. Codes for these are developed in- house, checked and the code verified using dummy data by an independent statistician.

11. COVID-19

The effect of COVD-19 will be explored. In the first instance, periods before, during and after COVID-19 will be summarised using appropriate descriptive statistics and graphical summaries. If need be, formal analysis will be carried out to explore the effect of COVID-19.

12. Dummy Tables

13. Dummy Figures

14. References

Summary of revisions to SAP

SAP version	Protocol version*	Section number changed	Description of and reason for change	Date of change
Version 1.1	Version 6	Several	Minor edits to - Administrative information - Typos and layout changes to improve readability throughout - Clarity on analysis of secondary outcomes applied - Subgroup analysis section edited to reflect protocol (no pre-planned subgroups) - Text on sensitivity analysis confirmed (none pre-planned) - Compliance with allocated treatment edited for clarity - WinBUGS added to software section	30/03/2022
Version 1	Version 3		New document, based on SAP template Version 2	NA

Note: version 1 of the SAP was superseded by version 1.1 before it was signed.