1. Project title

Development and validation of a risk score for trauma patients with haemorrhage *The CRASH-2 score*

2. How the project has changed since the outline proposal was submitted (PR only)

Following feedback from the Board: 1) We have explained in detail how the CRASH-2 trial data are collected and justified why the use of these data are appropriate for developing a risk score. 2) We have described the quality of the CRASH-2 trial data which will be available and explained that there will be negligible missing data with a follow-up rate of about 99%. 3) We have described how we will tackle the problem of poor fit. Briefly, we will reduce the possibility of overfitting when developing the risk score because we will use a large sample size, with few key predictors, and large number of events. We will use a full model approach that minimises selection bias of predictors, and we will shrink the coefficients with bootstrapping if there is any evidence of overfitting. 4) We have explained that to overcome the potential problem of differences in care patterns we will update the estimates for the new setting (UK) following a Bayesian approach. 5) We have described in more detail the potential benefit to patients and impact on clinical practice. Briefly, failure to recognize the extent of haemorrhage is a leading cause of preventable deaths in trauma patients. A simple and accurate risk score, such as the proposed CRASH-2 trial score, will be useful to make triage decisions in the pre-hospital setting, the battlefield, and to initiate necessary diagnostic and therapeutic interventions at hospital admission. 6) We have described how we will involve three potential risk score users groups (ambulance crew, military personnel and A&E clinicians) to adapt the CRASH-2 trial score for each of these setting.7) We have added the Board recommendation that respiratory rate could not be practical, and 8) Included a more active public participation.

3. Planned investigation

Research objectives

To develop a practical risk score for use in the emergency setting to predict unfavourable outcomes in patients with trauma and haemorrhage.

Specifically:

(a) Develop a risk score for in-hospital mortality and disability in patients with trauma and significant haemorrhage using data from CRASH-2 trial patients;
(b) Validate the performance of the CRASH-2 trial score in a sample of patients with trauma and bleeding from the NHS (TARN dataset) and, if needed, re-calibrate and adjust the CRASH-2 trial score according to the validation results;
(c) Adapt the CRASH-2 trial score to the specific needs of the pre-hospital setting, battlefield, and A&E departments.

Existing research

Trauma

Trauma is a common cause of death and disability worldwide, causing 5 million deaths each year.(1) It is a leading cause of death in people younger than 35 years and causes approximately 10,000 deaths annually in England and Wales. Serious injuries result in 640,000 hospital admissions each year and more than 6 million attendances to accident and emergency (A&E) departments. It is estimated that trauma costs the NHS £1.2 billion annually.(2)

Traumatic haemorrhage

Haemorrhage is the second leading cause of death in trauma patients, exceeded only by traumatic brain injury. It is estimated that haemorrhage causes approximately 30% to 40% of trauma-related deaths.(3) Not only does haemorrhage itself contribute to mortality, but its associated hypotension is also a prognostic factor for poor outcome in patients with traumatic brain injury.(4) Much of the impact of haemorrhage occurs in the early hours after injury, when haemorrhage accounts for an even larger proportion of trauma deaths. Almost 50% of trauma deaths in the first 24 hours of medical care, and over 80% of deaths in the operating room, are estimated to be due to haemorrhage.(5)

The importance of early treatment in traumatic haemorrhage

The initial treatment of patients with haemorrhage has two objectives; to stop the haemorrhage and restore the volume.(6) Interventions should be implemented as soon as possible after the injury, as the probability of survival increases with shorter times between injury and the onset of medical care.(7) The recent European guidelines for the management of bleeding following major trauma recommend that the *"time elapsed between injury and operation be minimised for patients in need of urgent surgical bleeding control"*.(8) A joint report from the Royal College of Surgeons of England and the British Orthopaedic Association stresses the importance of early treatment and recommends that the time of on-scene care should not exceed ten minutes and that the start of the operation for visceral injuries must be within 60 minutes of admission.(9)

Traumatic haemorrhage is the leading cause of preventable death in trauma

The failure to initiate appropriate early management of trauma patients with haemorrhage is not unusual, and consequently uncontrolled haemorrhage is considered to be the leading cause of preventable death among trauma patients.(10) Most of these preventable deaths are associated with missed diagnosis or delayed interventions. For example, it has been shown that there were delays in treating the source of bleeding in 32% of the patients with blunt injuries, who later died from haemorrhage, and that 79% of patients whose deaths were considered preventable had received no, or delayed, operations for conditions that would normally require an operation.(11, 12) Similarly, another study showed that a delay in treatment or a misdiagnosis was reported in 75% of patients with preventable haemorrhage related deaths.(13)

Early assessment of traumatic haemorrhage

Estimation of blood loss is very challenging early after trauma. Different studies showed that medical personnel estimate of the amount of blood loss is generally inaccurate in the emergency situation.(14, 15) Furthermore the risk associated with the haemorrhage does not depend only on the amount of blood lost, but also on the speed of blood loss, and the patient's characteristics (e.g. previous clinical condition, age or weight). Therefore, for the early assessment of patients with trauma and haemorrhage what is really important is to evaluate the association of variables with poor outcome (i.e. their predictive ability).

Trauma patients with haemorrhage present a physiological response which is related with the extent of blood loss, and has been recognized as useful for predictive purposes. Part of this response, such as the reduction in blood pressure, the increase in capillary refill time, and the alteration of consciousness (Glasgow Coma Scale score), is a direct result of the loss of intravascular volume. Other variables are related with compensatory mechanisms, such as the increase of heart and respiratory rate as a

consequence of the sympathetic activation.(16) All these physiological variables have been considered as useful parameters for the initial assessment of patients with traumatic haemorrhage.(6, 17, 18)

Although these physiological variables have been shown to be useful, they have showed limitations when used as an isolated parameter. For example, hypotension has been shown to be a late marker of shock, which in this context can be defined as the inadequate tissue perfusion as a result of blood loss.(17, 19) Tachycardia, when used as an isolated predictor of shock, has shown low sensitivity and specificity.(20) To overcome the limitations of using isolated physiological parameters there have been many attempts to combine several variables into risk scores.

Risk scores, which can be defined as the mathematical combination of two or more patient or disease characteristics to predict outcome, have shown to be more accurate than clinical prediction.(21, 22) According to studies in cognitive psychology, the human brain is poorly prepared for making and updating precise quantitative prediction.(23) The difficulties in collecting and summarizing quantitative data to make predictions are even more extreme in emergency situations such as in the treatment of trauma patients.(24)

The potential use of risk scores

Most of the preventable deaths due to haemorrhage occur in the early hours after injury, during the pre-hospital period or in the initial hours after injury. It is therefore important to assess rapidly the extent of haemorrhage in order to identify those patients who require prompt referral to hospital and, at hospital admission, initiate the necessary diagnostic and therapeutic interventions. A simple and accurate method to assess the extent of bleeding in the early stages of trauma could guide doctors in their early evaluations of these patients and therefore reduce preventable deaths associated with delayed treatment in traumatic haemorrhage. This decision-making process is commonly called ‘triage’ and can be defined as the sorting of medical conditions into different categories to achieve a true priority of care.(25)

An accurate and simple risk score could be used as a triage tool in the pre-hospital setting. There is some evidence, from observational studies, that care provided to major trauma patients in specialized centres improves outcome.(26) Therefore, a simple risk score at the pre-hospital setting could stratify patients and be used for appropriate referral.

A risk score could be also used at hospital admission. As mentioned before, most of the preventable deaths are associated with missed or delayed diagnosis of traumatic bleeding, therefore an accurate risk score could rapidly trigger the appropriate diagnostic and therapeutic interventions, and ensure a fast and adequate response at hospital admission. Fisher and collaborators showed that the use of the Revised Trauma Score for triage at hospital admission reduced management errors in trauma patients.(27) However, this study had methodological limitations as it was a before after study from a single centre with several interventions introduced in the same period. Furthermore, as discussed below the Revised Trauma Score has some limitations.

An additional setting in which a simple risk score could be useful is for trauma in combat fields. Haemorrhage is also considered the leading cause of preventable death in the battlefield, and development of new triage methods is among the priorities of military medical research.(28) A further advantage of a simple risk score in this setting is that it could be used by non-medical personnel.

Finally, an important use of triage could be related with mass causalities in the context of terrorist incidents in urban settings, such as the bombing that occurred in London in 2005. In these situations large numbers of casualties may overwhelm existing medical resources and therefore prioritization of medical care according to risk becomes very relevant.(29)

Existing trauma scores

Trauma scores can include anatomical or physiological variables or a combination of the two types.(30) The physiological scores can be further divided into: simple, when only clinical data are included (e.g. heart rate), or complex, when laboratory test are added (e.g. lactic acid). Simple physiological scores are more useful in the early management of trauma patients when the extent and exact nature of the anatomical impact of the injury is still unclear, and data from more complex diagnostic tests are yet to be obtained. Although several trauma scores have been published, to date none of these have been widely accepted and none are without limitations.

The recent European Guideline for the Management of Bleeding following major trauma recommends the use of the '*American College of Surgeons Advanced Trauma Life Support classification of haemorrhage severity*' for initial assessment of the extent of traumatic haemorrhage.(8)

American College of Surgeons Advanced Trauma Life Support classification of haemorrhage severity

Haemorrhage severity according to ACS/ATLS classification[a]	Class I	Class II	Class III	Class IV
Blood loss (ml)	<750	750–1,500	1,500–2,000	>2,000
Pulse rate (per minute)	<100	>100	>120	>140
Blood pressure	Normal	Normal	Low	Low
Pulse pressure (mm Hg)	Normal	Low	Low	Low
Respiratory rate (per minute)	14–20	20–30	30–40	>40
Urine output (ml/hour)	>30	20–30	5–15	Negligible
Central nervous system (mental status)	Slightly anxious	Mildly anxious	Anxious, confused	Lethargic

a Values are estimated for a 70-kg adult. Table adapted from the American College of Surgeons. ACS/ATLS, American college of Surgeons/Advanced Trauma Life Support.

The development of this classification is unreferenced, and to the best of our knowledge there is no evidence to support the blood loss volumes used in each category of severity. In addition, some of its components, such as urine output measurement, require some time to evaluate, therefore it would not be practical for use in the pre-hospital setting or in the early stages of admission.

The Revised Trauma Score (RTS) is the most widely used physiologic score.(31) The RTS consists of the following variables: Glasgow Coma Scale (GCS) score, systolic blood pressure and respiratory rate. The RTS is calculated by adding the coded value for each variable.

Coding variables for the Revised Trauma Score

GCS score	SBP	RR	Coded value
13–15	>89	10–29	*4*
9–12	76–89	>29	*3*
6–8	50–75	6–9	*2*
4–5	1–49	1–5	*1*
3	0	0	*0*

For outcome prediction a weight for each individual component is added according to the following formula: 0.7326 SBP + 0.2908 RR + 0.9368 GCS score. Limitations of this score include the fact that the values for each of the variables is based on expert consensus and not empirical data, and that the weight for each component was derived from patients from a single hospital in the United States more than 20 years ago.(31) Furthermore, the weighted RTS is not presented in a simple way practical to use in the emergency setting. In addition, it has been shown that the RTS coded values do not accurately describe the relationship of the variables with mortality.(32)

A simple score, called shock index (SI) has also been proposed. The SI is calculated as the ratio of heart rate to systolic blood pressure. In some studies the SI has shown to have better discrimination than either systolic blood pressure or heart rate alone. Although this index has good specificity, its sensitivity is low. (33) Another limitation of this index is that it does not incorporate information from other important variables such as respiratory rate, capillary refill time or level of consciousness, as measured by the Glasgow Coma Scale.

Finally, there are other clinical aspects that have not been fully considered in the risk scores described above. It is plausible that some of the variables have different relationships with mortality in certain clinical subgroups. At least two subgroups should be considered when estimating the potential different prediction of the physiological variables, these are: type of injury (i.e. penetrating versus blunt), and presence of traumatic brain injury.

In blunt trauma there might be a different physiological response in blood pressure and heart rate in comparison with penetrating trauma due to greater nociceptive response.(34) In patients with traumatic brain injury, hypotension and GCS score have been shown to be strong predictors of poor outcome. (35, 36)

It is therefore plausible that risk prediction will differ according to the type of injury, or the presence of traumatic brain injury; therefore specific risk scores should be developed for these populations.

The CRASH-2 Trial

CRASH-2 is a large clinical trial evaluating the effect of tranexamic acid on mortality and the need for transfusion among trauma patients with significant haemorrhage.(37) The trial includes patients within eight hours of injury, collects clinical and demographic variables at entry (described below), shown to be predictors of poor outcome, and data on outcome at hospital discharge with a high follow-up rate (99%). Furthermore, approximately 30% of the recruited patients have a concomitant TBI, and patients with both types of injury (blunt or penetrating) are included. These data would allow us to explore the performance of a risk score in the relevant subgroup of patients. A total of 20,207 patients have been recruited in the CRASH-2 trial. The CRASH-2 cohort of patients represents a unique opportunity to develop a risk score (CRASH-2 score) for patients with traumatic bleeding. The large sample size will ensure precise predictions.

Trauma Audit & Research Network (TARN)

The CRASH-2 score will subsequently be validated in a large sample of trauma patients (12,358) included in TARN, which is the largest European trauma registry. TARN mainly includes patients from the UK. The evaluation of the CRASH-2 score on this sample will have practical implications for assessing its validity for NHS patients.

Research methods

This project will be divided into three phases

1. *Score development*: Development and internal validation of the CRASH-2 score using the CRASH-2 dataset

2. *Score validation*: External validation of the CRASH-2 score in the TARN database, recalibration and comparison with other trauma scores
3. *Score adaptation*: Adaptation of CRASH-2 score to pre-hospital setting, battlefield and A&E departments.

Phase 1: Score Development

Sample

The cohort of patients used to develop the model will be all patients recruited to the CRASH-2 trial. The sample includes 20,207 patients from 40 different countries. Patients eligible for inclusion in the trial are "adult trauma patients with ongoing significant haemorrhage, within 8 hours of injury."

Outcome

The primary outcome is death at 28 days. Patient outcome is recorded at either discharge, death in hospital or 28 days after injury, whichever occurred first. (Appendix A of the protocol) Information on the date of death is collected and will be used to create a binary outcome: dead or alive.

The secondary outcome will be death or severe disability at 28 days. In patients who survived, dependency status at 28 days or prior to discharge is recorded on the outcome form using the Modified Oxford Handicap Scale.(38) This consists of five categories: no symptoms, minor symptoms, some restriction in lifestyle but independent, dependent but not requiring constant attention, and fully dependent requiring attention day and night. (Appendix A of the protocol) This scale has been shown to be predictive of poor outcome as measured with the Glasgow Outcome Scale in traumatic brain injury patients.(39)

A binary variable will be created combining information on survival and dependency at 28 days post injury, where outcome will be either favourable (alive with no symptoms, minor symptoms or independent with some restriction in lifestyle) or unfavourable (dead or alive but dependent).

Predictors

Variables analysed as potential predictors will be taken from the patient entry form completed prior to randomisation. (Appendix B of the protocol) Variables included in the CRASH-2 trial entry form can be divided into

1. Patient demographic characteristics: age and gender
2. Injury characteristics: type of injury, traumatic brain injury, and time from injury to randomization
3. Physiological variables: Glasgow Coma Scale score, systolic blood pressure, heart rate, respiratory rate, and central capillary refill time

Variable definitions:

- Age is recorded as a continuous variable measured in years
- Type of injury is recorded as a categorical variable with 3 categories – blunt injury, penetrating injury, or blunt and penetrating injury
- Traumatic brain injury is recorded a binary variable, presence or absence of significant traumatic brain injury as defined by the clinical criteria of the CRASH-2 collaborator (This variable is recorded in the outcome form.)
- Time since injury is recorded as a continuous variable measured in hours
- The five physiological variables are recorded on the patient entry form according to usual clinical definitions. For each of these variables the value given on the entry form is the first measurement available taken after injury.
    - Glasgow Coma Scale is measured as a categorical variable (3 to 15)
    - Systolic blood pressure is measured in millimetres of mercury
    - Heart rate is measured in beats per minute
    - Respiratory rate is measured in breaths per minute

- Central capillary refill time is measured in seconds

Because central capillary refill time is not universally measured in clinical practice, further guidance on how to measure it was provided. Collaborators were advised to *"Apply firm pressure with your fingertips to the selected area, e.g. chest for about 5 seconds. Timing starts on release of pressure and is counted in seconds. Timing stops when the blanched area of the skin returns to its normal colour. If skin is dark or there is injury to the chest, CRT can be measured by applying pressure to another area such as the base of the thumb, nail bed or gums*".

Trial treatment (placebo or tranexamic acid) will be included as a separate predictor. Following the Board recommendation we will consider that respiratory rate might not be practical to consider as it is often not recorded in practice.

Why CRASH-2 data are appropriate for the development of a risk score

The characteristics of the CRASH-2 trial, a large pragmatic and simple trial, have many advantages for developing a risk score. It is a prospective cohort of patients with almost no missing data and high follow-up. The inclusion criteria are broad, there are not specific exclusion criteria and there are not additional tests required, so although it is a clinical trial it includes "real life" patients. Furthermore, the physiological variables are defined as usual practice so the definitions are fit for purpose; this means that the risk score will be used by physicians who will measure these variables in the usual way in the context of the emergency setting. A rigid and standard definition of variables (e.g. two readings of blood pressure with an automatic device) will not be practical to use in this context. Using data from the CRASH-1 trial, which has a similar design to the CRASH-2 trial, we have already shown that variables recorded in this way are useful for developing a risk score.(36) Finally, all the variables are measured at a similar time point: first measurement available after the injury. The outcomes are also measured at a pre-specified time.

Because of the characteristics of the CRASH-2 trial there is almost no missing data among the potential predictors. Age, type of injury, time since injury and Glasgow Coma Scale score are all mandatory variables and a patient cannot be included in the trial if any of these variables is not available in the entry form. The other physiological variables, except capillary refill time, are routinely measures in clinical practice. Furthermore, the practical design of the CRASH-2 trial and the minimum requirement of data will ensure very few missing data on these variables.

Analysis

Continuous variables

Continuous variables will be initially kept as continuous. This is to avoid loss of information and bias introduced by choosing cut points to group variables.(40) Continuous variables will be re-coded as categorical variables and plotted against log odds of each outcome variable to assess the relationship between variables and outcomes. Linearity and departure from linearity will be assessed by adding quadratic terms and cubic terms into the model and carrying out likelihood ratio tests. We will also explore more complex relationships using spline functions and fraction polynomial analysis.(41)

Correlation

In a multivariate prognostic model, variables which are highly correlated with each other provide little independent information. Several predictor variables, such as systolic blood pressure and heart rate, are likely to be correlated. The correlation between these variables will be assessed by drawing scatter plots of the relationship between each variable and calculating the correlation coefficient. If the correlation coefficient is less than 0.8, both variables will be included in the model.(41) If for any pair of variables it is greater than 0.8, a decision based on clinical importance will be made about which variable to keep as a predictor.

Interaction

Interactions will be considered between all the predictors and:

- Traumatic brain injury
- Type of injury

These two interactions will be considered because, a priori, it is possible that the effect of predictors of mortality may vary depending on the presence of traumatic brain injury and type of injury. Interactions will be assessed by likelihood ratio tests. If there is strong evidence of interaction between these variables and any of the predictors, additional models will be developed separately for the corresponding subgroup of patients.

Multivariable analysis

The variables considered for the risk score have been previously associated with prognosis in trauma patients, so all of them will be included in the multivariable logistic regression analysis. Analyses will be adjusted for trial treatment. We will include all the variables irrespective of their statistically significance, because selection of predictors according to their statistical significance has been shown to introduce selection bias and results in overfitting of models.(41) We will use random effect logistic regression models to take into account the variability among the different settings (hospitals). Random effect logistic regression model estimates random intercepts and coefficients. This implicitly assumes that the intercepts and estimates vary by centre and follow a normal distribution. With this approach we will establish the heterogeneity between settings, and this heterogeneity estimate will be used to update the model to the TARN setting.

Performance

Performance of the CRASH-2 score will be assessed in terms of calibration and discrimination. Discrimination will be assessed using the c statistic (an equivalent concept to area under the receiver operator characteristic curve). Calibration will be assessed graphically (plotting the observed versus expected probabilities of the outcomes by deciles of risk) and with the Hosmer-Lemeshow test.(42) We will also estimate the performance for each of the individual physiological variables, and their different combinations.

Internal validation and shrinkage of estimates

Internal validity of the final model will be assessed by using bootstrap re-sampling technique. Regression models will be estimated in 100 models. For each of the 100 bootstrap samples the model will be refitted and tested on the original sample to obtain an estimate of predictive accuracy corrected for overfitting. If there is evidence of overoptismism for the performance of the CRASH-2 score we will shrink the coefficients with bootstrapping methods.

Phase 2: Score Validation

Sample

For the external validation we will use the data from the Trauma Audit & Research Network (TARN). TARN was established in 1989 to benchmark and improve hospital trauma care (using case fatality measures). Membership is voluntary and includes 60% of hospitals receiving trauma patients in England and Wales and some hospitals in European centres. Data are collected on patients who arrive at hospital alive and meet any of the subsequent criteria:

- death from injury at any point during admission
- stay in hospital for longer than 3 days
- require intensive or high dependency care
- require inter-hospital transfer for specialist care.

Patients with isolated closed limb injuries are excluded, as are patients over 65 years old with isolated fractured neck of femur or pubic ramus fracture. All other isolated closed femoral injuries are included. Every TARN patient has each single injury described in terms of the abbreviated injury scale (AIS) dictionary where a descriptor and its corresponding numerical code is allocated. Hospitals submit data electronically to TARN via a secure website, data is held on the University of Manchester server. The physiological data available on TARN is identical to that on CRASH in that for every patient the HR, SBP, GCS score, RR and capillary refill on arrival is entered by the hospital data co-ordinators.

For each patient the volume of blood loss is estimated. This is done by allocating an estimated percentage of total volume of blood lost to each injury code in the AIS dictionary by blinded, then consensus, agreement from two emergency physicians. This estimation is based on previous work on blood loss in specific injuries.(43)

Adult (age >15 yrs at the time of injury) patients presenting between 2000 and 2008 to TARN participating hospitals will be selected if they had an estimated blood loss of at least 20%. A total of 12,358 patients fulfilling these criteria will be included in the validation. We will use this definition because the CRASH-2 definition is not available for the TARN dataset. We estimate that patients with blood loss of 20% or more would be comparable with the CRASH-2 patients. We will only include patients recruited from year 2000 onwards because trauma care in the UK has changed in terms of outcome significantly since then. (Fiona Lecky personal communication)

Outcome

We will validate the CRASH-2 score for in-hospital mortality at 28 days as this is the only outcome considered in this proposal for which TARN has data. TARN hospital patients are followed up for 93 days post admission or until the time the patient leaves hospital alive, whichever is first.

Predictors

TARN patients have data in all the predictors considered in the CRASH-2 score. Data are collated by trained staff in participating hospitals and submitted via the TARN Electronic Data Collection and Reporting (EDCR) system (ref www.tarn.ac.uk). Each submission is checked for consistency and accuracy by trained coders at the University of Manchester. The methods of measuring and recording the data within TARN are identical to those within CRASH 2 in that they reflect real measurements made by the clinical staff caring for patients on arrival in the Emergency Department.

Analysis

External validation

For the external validation process, we will apply the mean estimates from the random logistic regression model (obtained in the development phase with the CRASH-2 patients) to the validation sample (TARN dataset patients). If there are missing data in any of the predictors we will use multiple imputation to substitute the missing values.(41) We will estimate the performance (discrimination and calibration) in the new dataset.

Recalibration

If there is any evidence of poor performance in the validation set we will conduct an updating of the CRASH-2 score to improve the performance for the new setting. For this we will conduct a Bayesian updating approach.(41) For this analysis we need to know the estimate from the derivation sample (e_{ds}), the estimate from the validation sample (e_{vs}), the variance of the estimate in the validation sample (v_{vs}) and the variance between the different samples (v_{bs}). This latter estimate will be obtained with the random effect logistic regression model in phase 1. We will obtain the updated estimates ($\mathbf{e_u}$) with the following empirical Bayes formula.(41)

$$\mathbf{e_u} = e_{ds} + v_{bs}/(v_{bs} + v_{vs}) * (e_{vs} - e_{ds})$$

With this approach we will be able to obtain updated estimates for the new setting.

Comparison with other scores

We will compare the performance of the recalibrated CRASH-2 score with the Revised Trauma Score and with the Shock Index performance on the TARN data.

We will also estimate the performance for each of the individual physiological variables, and their different combinations. These results about the performance of individual predictors, their different combinations and the full model performance will inform the following phase of score adaptation in the different settings.

Phase 3: Score Adaptation

The previous two phases will ensure that we are following the necessary steps to obtain a valid risk score from a statistical perspective. But an important, and commonly neglected, aspect when developing a risk score is its clinical sensibility or acceptability.(44) The clinical acceptability of a risk score requires judgement, not statistical criteria, to select the predictors, and an adequate score presentation format for the specific setting where the score will be used. We identified three settings where CRASH-2 risk scores could be applied; the pre-hospital setting, the battlefield, and in A&E departments at hospital admission. Therefore, we will involve risk score users at these three levels: ambulance crew from the North West Ambulance Service, military personnel, and clinicians from A&E departments participating in TARN. We will work with these users to achieve two objectives: i) to identify the variables they consider important and practical for their respective setting, and ii) to obtain information on how to present the risk score in a practical way.

Selecting the variables appropriate for each setting

The first two phases will provide data about the performance of the full score, the individual predictors and different combinations of predictors. However the decision about which predictors should be included requires making a judgment about the trade off between the accuracy and practicality of the score. For example a score including Glasgow Coma Scale, respiratory rate, capillary refill time, and systolic blood pressure could be marginally more accurate than one excluding systolic blood pressure, but in the battlefield measurement of blood pressure might be complex and a risk score excluding that variable, at the expense of losing some accuracy, could be judged more convenient for that setting. On the other hand in the A&E department even if the increase of accuracy is marginal, clinicians could argue that a risk score for trauma patients and haemorrhage should always include systolic blood pressure.

Presentation of the risk score

A risk score allows the probability of the outcome for an individual patient to be estimated by combining the predictor values with the regression coefficients and obtaining the linear predictor for the model, which is then transformed to a predicted probability through the logistic transformation. However, even a valid risk score will not be used if the presentation to estimate the individual probability is inadequate or complicated. Methodological guidelines stress how important it is that prognostic models are easy and simple to use and well accepted by physicians.(45) Simplicity of presentation and ease of use is even more relevant in the context of the emergency situation when treating patients with trauma and bleeding. Risk score format presentation can be electronic or paper based. We have already developed an electronic calculator and a paper based risk score for patients with traumatic brain injury, using data from the CRASH-1 trial. The electronic calculator can be found at http://www.crash.lshtm.ac.uk.

We will conduct focus groups with all the relevant risk score users (ambulance crew, military personnel, and clinicians from A&E departments) at different stages of the study to inform us about their opinion regarding relevant predictors and to decide on the most suitable presentation for each setting.

For developing an appropriate presentation of the risk calculator we will work jointly with the *Winton programme for the public understanding of risk* based in the Statistical Laboratory in the University of

Cambridge. This programme aims to help improve the way that uncertainty and risk are presented, and they have experience in developing electronic risk calculators. (http://understandinguncertainty.org/) We contacted Professor David Spiegelhalter, leader of this programme, who confirmed his willingness to collaborate in this project.

Planned interventions (PR only)
NA

Planned inclusion/exclusion criteria
The CRASH-2 score will be developed using data from patients included in the CRASH-2 Trial. This trial recruits adult patients with trauma and significant haemorrhage.

Ethical arrangements
Ethics approval for this study and the use of the CRASH-2 trial data will be obtained from the London School of Hygiene and Tropical Medicine.

TARN already has ethical approval (PIAG section 60) for research on the anonymised data that is stored securely on the University of Manchester server.

Proposed sample size
We will include all the 20,207 patients recruited in the CRASH-2 Trial. It is recommended that for multivariable analyses there should be at least 10 events for each potential predictor evaluated.(46) The CRASH-2 trial has an overall mortality of approximately 15%. There were 3,076 events. As we are planning to consider 10 potential predictors, our study will have a ratio of 307 events for each predictor, so will have a very large sample for the multivariable analysis and therefore our estimates for predicting mortality will be very precise.

The validation will be conducted in the TARN database. We will include 12,358 adult trauma patients presenting after the year 2000 with an estimated blood loss of >20%.

Statistical analysis
The details of the statistical analysis have been included in the sections describing the phases of this study. In this section we explain why the statistical plan will minimize the potential poor fit.

There are two main causes of a poor fit of a risk score:

1. *Overfitting of the original score*: The possibility of overfitting will be low because i) We are using a large sample size with few predictors and high frequency of outcome; ii) We will follow a full model strategy for rmodel development which avoids selection bias of predictors; and iii) We will use bootstrapping to shrink the estimates if there is any evidence of overoptimism in the performance measures.
2. Differences between the derivation and validation sample (case mix and differences of the relationship between predictors and outcome): If there is any evidence of poor fit in the validation sample we will obtain updated estimates for this setting using a Bayesian approach.

Proposed outcome measures
We will develop risk scores for the most clinically relevant outcomes: in-hospital mortality and disability at discharge. The outcomes are defined as per the CRASH-2 trial protocol. No economic analysis is planned.

Research governance (for PR only)
The use of the CRASH-2 trial data for the development of the risk score has been approved by the Trial Management Group. Only fully anonymized data will be used.

The use of the TARN data has been agreed and approved by Fiona Lecky

This research will be monitored and supervised by the CRASH-2 Score Committee whose responsibility will be to monitor and supervise the progress of the project to ensure the milestones are achieved. Membership will consist of Pablo Perel (Chair), Haleema Shakur, Ian Roberts, Fiona Lecky, Tim Clayton and Ewout Steyerberg.

4. Project timetable and milestones

We propose to conduct this study in 12 months from the time the contract is signed: Month 1 (Preparation database and staff in post) Month 1 to 4 (Development and internal validation of risk scores) Month 5 to 7 (External validation and recalibration) Month 8 to 10 (Focus group with risk score users to develop practical and clinically acceptable risk scores) Month 11 to 12 (Preparation of final report) We will submit the final amended form taking into account the Board recommendation by May 24th. If the contract is signed in June 2010 we will be able to start in July 2010.

July 2010:	Study coordinator and statistician in post
	Start preparing databases
August 2010:	Start developing statistical program for CRASH-2 score development
September 2010:	CRASH-2 database ready for analysis
October 2010:	Complete CRASH-2 score development
	Complete internal validation
November 2010:	TARN database ready for analysis
December 2010:	Complete external validation
	Complete recalibration
February 2011:	Start evaluation of CRASH-2 scores by users
	Start electronic calculator development
April 2011:	Complete electronic and paper based presentation of CRASH-2 scores
June 2011:	Complete final report and paper for peer reviewed journal

5. Expertise

Pablo Perel is a clinical lecturer with expertise in clinical trials, prognosis research and emergency medicine. He has worked extensively on prognostic models in trauma. He led the project that developed and validated practical risk scores for traumatic brain injury.

Haleema Shakur is a senior lecturer in clinical trials with expertise in clinical trials and trial management. She has experience in research in emergency medicine and she is the trial manager of the CRASH-2 trial.

Ian Roberts is a professor of epidemiology with expertise in epidemiology, systematic reviews, clinical trials and emergency medicine. He is the principal investigator of the CRASH-2 Trial.

Fiona Lecky is a senior lecturer / honorary consultant in emergency medicine at the University of Manchester and Research Director of TARN. She has experience in trauma and has led the development of a prognostic model used to compare case fatality after major injury in NHS Trusts.

Tim Clayton is a senior lecturer in medical statistics. He has experience in statistical analysis of clinical trials and has been involved in the analysis of several risk scores in emergency medicine.

Ewout Steyerberg is professor of medical decision making. He has extensive experience in prognosis research in general and prognostic models in particular. He has recently published a book on this topic called "Clinical Prediction Models".

6. Service users

In the context of this project we considered as service users, the personnel who will potentially be using the CRASH-2 score. We have identified three types of potential service users: ambulance crew, military personnel, and medical staff from A&E departments; each of these groups will be involved in the focus groups described in phase 3 of this proposal.

Ambulance crew: Professor Kevin Mackway Jones, Medical Director for North West Ambulance Service NHS Trust, has confirmed the participation of ambulance crew from the North West Ambulance Service.

A&E doctors: Doctor Fiona Lecky, Research Director of TARN, has confirmed the participation of A&E departments'clinicians participating in TARN.

Military personnel: We have discussed this proposal with leading clinicians from the Defence Medical Services of the UK Ministry of Defence and they are keen to collaborate.

We will work with each of these groups to better understand their needs and to obtain feedback about how to tailor the risk score for their respective setting.

Brigitte Chaudry, President of the European Federation of the Victims of Road Traffic Crashes represents service users on the Trial Steering Committee of the CRASH-2 Trial. As this project involves a secondary analysis of the CRASH-2 trial, we will have input from the public through the participation of this patient organization. In addition, following the Board recommendation, we will ensure to have an active public participation conducting a series of focus groups meetings with relatives of road traffic crashes. In these meetings we will evaluate public's perspective of important outcomes to predict and preferences to present risk estimation. We have already contacted Amy-Aeron Thomas, who is Director of Road Peace (the UK charity providing support for victims of road traffic crashes) who has agreed to involve this organization in this research project. We will follow the "*Good practice in active public involvement in research*" published by INVOLVE.

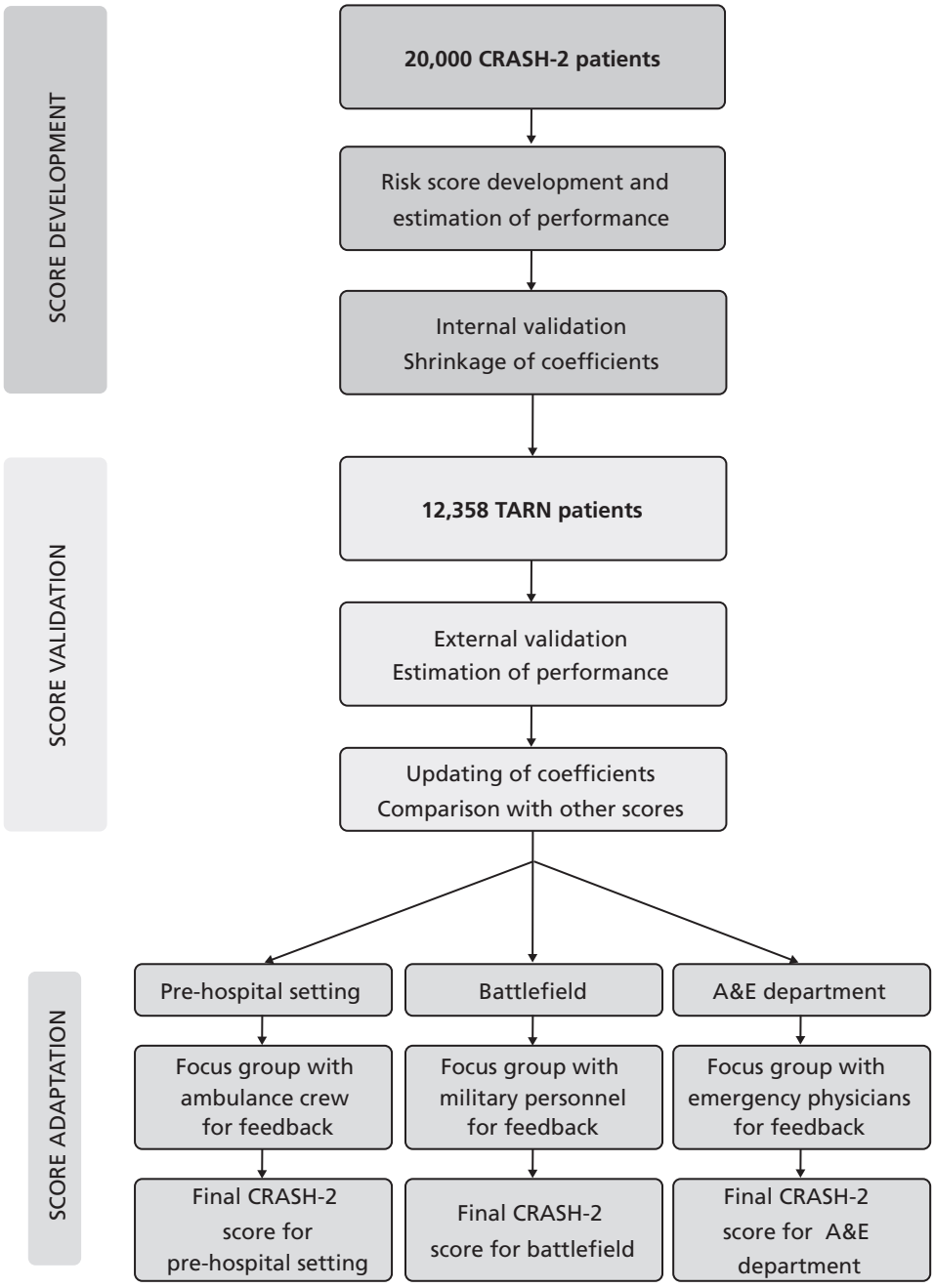
7. Justification of support required

LSHTM staff: A study coordinator (70%) is required to coordinate all the activities of the project to ensure a successful completion. A statistician (50%) is required to conduct the data cleaning and database development; he/she will also provide expertise in the statistical analysis of the study.

Other LSHTM costs: One new computer is needed plus the related departmental maintenance cost.

Other costs: Travel costs have been included to cover regular meetings in Manchester, Rotterdam, and for the welcome meeting in Southampton. It is anticipated that some focus group meetings will be held in London for a number of potential users of the score. TARN will provide the analysed patient data and the cost for obtaining this has been included as an FEC cost for University of Manchester. A consultancy fee will be paid to Ewout Steyerberg for his input as an expert in prognostic models. An electronic calculator will be provided by an external consultant. As suggested by the Board we will now ensure a more comprehensive participation of the public through focus group meetings. We included cost of the focus group meetings with the public.

8. Flow diagram (primary research only)



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Appendix A of the protocol: outcome form

CRASH-2
Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage

OUTCOME FORM

COMPLETE AT DISCHARGE FROM THE RANDOMISING HOSPITAL, DEATH IN HOSPITAL OR 28 DAYS AFTER INJURY, WHICHEVER OCCURS FIRST

Attach treatment pack sticker here

1. HOSPITAL

(Hospital name or code)

2. PATIENT

Patient Initials		Hospital ID Number		Sex	M	F
Date of Birth	YEAR / MONTH / DAY					

3. OUTCOME

3.1 DEATH IN HOSPITAL

Date of death YEAR / MONTH / DAY

Cause of death

- ☐ Bleeding
- ☐ Head injury
- ☐ Myocardial Infarction
- ☐ Stroke
- ☐ Pulmonary Embolism
- ☐ Multi organ failure
- ☐ Other – describe

3.2 PATIENT ALIVE

☐ **Discharged** – Date of discharge YEAR / MONTH / DAY

☐ **Still in this hospital now** *(28 days after injury)* – Date YEAR / MONTH / DAY

3.3 IF ALIVE TICK ONE BOX THAT BEST DESCRIBES THE PATIENT'S CONDITION *(at 28 days or prior discharge)*

- ☐ No symptoms
- ☐ Minor symptoms
- ☐ Some restriction in lifestyle but independent
- ☐ Dependent, but not requiring constant attention
- ☐ Fully dependent, requiring attention day and night

4. MANAGEMENT

a) **Days in Intensive Care Unit** *(if not admitted to ICU, write '0' here)*		
b) **Significant Head Injury**	YES	NO
c) **Operation site** - *Tick one box on every line*		
• Neurosurgical	YES	NO
• Chest	YES	NO
• Abdomen	YES	NO
• Pelvis	YES	NO

5. COMPLICATIONS

Tick one box on every line		
• Pulmonary Embolism	YES	NO
• Deep Vein Thrombosis	YES	NO
• Stroke	YES	NO
• Operation for bleeding	YES	NO
• Myocardial Infarction	YES	NO
• Gastrointestinal bleeding	YES	NO

6. TRIAL TREATMENT

a) Complete **loading dose** given	YES	NO
b) Complete **maintenance dose** given	YES	NO

7. TRANSFUSION

a) Blood products transfusion	YES	NO
b) Units transfused in 28 days		
• Red cell products	units	
• Fresh frozen plasma	units	
• Platelets	units	
• Cryoprecipitate	units	
• Recombinant Factor VIIa	YES	NO

8. PERSON COMPLETING FORM

NAME	
POSITION	
DATE	

NOW SEND THIS FORM TO THE CO-ORDINATING CENTRE IN ONE OF THE FOLLOWING WAYS:

- SECURE WEBSITE
- ELECTRONIC DATA FORMS / EMAIL
- FAX +44 (0)20 7299 4663

SEE INSTRUCTIONS IN YOUR SITE FILE

ISRCTN86750102

Appendix B of the protocol: patient entry form

CRASH-2 PATIENT ENTRY INTERNATIONAL

ALL QUESTIONS BELOW NEED TO BE ANSWERED
BEFORE CALLING THE RANDOMISATION SERVICE

INFORMATION ABOUT YOUR HOSPITAL

1. Country	
2. Name of hospital (or your hospital code)	
3. Name of caller	

INFORMATION ABOUT THE PATIENT

4. Patient sex (please circle)	**M**ale	**F**emale	**5.** Patient initials		
6. Patient hospital identification number					
7. Do you know patient's date of birth?					
a. **YES** – date of birth	YEAR	MONTH	DAY	b. **NO** – approximate age	

INFORMATION ABOUT THE INJURY

8.	Estimated number of hours since injury	hours		
9.	Type of injury (please circle)	**1** Blunt	**2** Penetrating	**3** Both

FIRST MEASUREMENT IN HOSPITAL OF THE FOLLOWING (IF UNKNOWN GIVE VALUE AT RANDOMISATION)

10.	Systolic BP (mmHg)		**11.**	Respiratory rate (per min)	
12.	Central capillary refill time (sec)		**13.**	Heart rate (per min)	
14.	Glasgow Coma Score (max 15)		EYE OPENING 4 Spontaneous 3 To sound 2 To pain 1 None	MOTOR RESPONSE 6 Obeys commands 5 Localising 4 Normal flexion 3 Abnormal flexion 2 Extending 1 None	VERBAL RESPONSE 5 Orientated 4 Confused speech 3 Words 2 Sounds 1 None

Now call **Randomisation Service** with these answers and write down the treatment pack number given at the end of the phone call

Box ☐☐☐☐ **Pack** ☐☐

Get this pack and follow the instructions on it carefully

Or paper randomise as per instructions in site file