STATISTICAL ANALYSIS PLAN

CRASH-2
Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage

A LARGE RANDOMISED PLACEBO CONTROLLED TRIAL AMONG TRAUMA PATIENTS WITH OR AT RISK OF SIGNIFICANT HAEMORRHAGE, OF THE EFFECTS OF ANTIFIBRINOLYTIC TREATMENT ON DEATH AND TRANSFUSION REQUIREMENT

APPROVED BY:

Name	Signature	Date
Chief Investigator Ian Roberts		10/2/2010
Statistician Phil Edwards		10/2/2010

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1. INTRODUCTION

The outline statistical methods to be used for the analysis of trial data are included in the final trial Protocol. This analysis plan provides full details of the results to be presented. Shell data tables were created to provide an overview of the analysis to be conducted by the Data Monitoring and Ethics Committee (see Appendix 1).

2. STUDY SYNOPSIS

A Randomised Placebo Controlled Trial Among Trauma Patients with Significant Haemorrhage of the Effects of Tranexamic Acid on Death and Transfusion Requirement (CRASH-2).

3. STUDY OBJECTIVES

To quantify the effect on death, vascular events and transfusion requirements of the early administration of the antifibrinolytic agent tranexamic acid in patients with trauma and significant bleeding.

3.1. PRIMARY OBJECTIVE

The primary outcome measure is death in hospital within four weeks of injury.

3.2. SECONDARY OBJECTIVES

Secondary outcome measures are:

Blood Products

- Blood products transfusion given
- Number of units of blood products transfused (including the total number of units of red cells, platelets, fresh frozen plasma and cryoprecipitate)

Disability

- Death or dependency: this outcome will be measured using the five point Modified Oxford Handicap Scale. We will dichotomise the scale into 'independent' (no symptoms; minor symptoms; some restriction in lifestyle but independent) and 'dependent' (dependent, but not requiring constant attention; fully dependent; requiring attention day and night; death).

Surgery

- Neurosurgery, chest operation, abdominal operation and pelvis operation. We will analyse all surgery combined and separately.

Thromboembolic episodes

- Stroke, myocardial infarction, pulmonary embolism, clinical evidence of deep vein thrombosis. We will analyse thromboembolic episodes combined and separately.

Gastrointestinal bleeding

Days in intensive care unit

Causes of death will be described to assess whether deaths were due to bleeding, myocardial infarction, stroke, pulmonary embolism, vascular occlusion (bleeding or myocardial infarction or stroke or pulmonary embolism), multi-organ failure, head injury or other.

3.3. ASSESSMENT OF OBJECTIVES

All outcome variables are recorded on the outcome form which is completed entirely from the hospital notes – no extra tests are needed. The outcome form is completed at death, discharge or four weeks post randomisation, whichever occurs first.

3.4. CHANGE OF THE PRIMARY OBJECTIVE DURING THE CONDUCT OF THE STUDY

There has not been any change in the primary outcome of the study. The following secondary outcomes were included: death or dependency, gastrointestinal bleeding, days in intensive care unit, and type of surgical intervention.

4. STUDY DESIGN

4.1 GENERAL DESIGN AND PLAN

A randomised double blind placebo controlled trial. Adults with trauma who are within 8 hours of injury and have either significant haemorrhage, or who are considered to be at risk of significant haemorrhage, are eligible if the responsible doctor is for any reason substantially uncertain whether or not to use an antifibrinolytic agent. Numbered drug or placebo packs will be available in each participating emergency department. Randomisation will involve calling a 24-hour free-call randomisation service. The call should last only a minute or two and at the end of it the randomisation service will specify which numbered treatment pack to use. For hospitals where telephone randomisation is not feasible, randomisation will be by taking the next consecutively numbered treatment pack. No extra tests are required but a short form must be completed one month later or on discharge or on death (whichever occurs first).

4.2 SAMPLE SIZE

Since even a 2% survival advantage for an intervention as simple as TXA would represent a worthwhile benefit, the main trial has been planned to be able to detect a benefit of this size. If the real mortality difference is in fact 20% versus 18%, then there is about an 85% chance that a trial involving 20,000 patients will achieve $2P<0.01$ (and a 95% chance that it will achieve $2P<0.05$). With such large numbers, even moderate effects on the numbers needing transfusion or on the mean number of

units transfused will be determined accurately, as will any substantial effects on non-fatal vascular events (haemorrhagic or occlusive).

4.3 RANDOMISATION AND BLINDING

Patients are randomised in one of two ways: Hospitals with reliable telephone access, where the recruiting doctors are able to provide baseline data in English, will use the central telephone randomisation service provided by the Clinical Trial Service Unit (CTSU) in Oxford. During the call, which will last 2-3 minutes, baseline data are collected and recorded on the central computer. To achieve a reasonable balance on the key prognostic factors, the allocation uses a minimisation algorithm balancing for sex, age (16-24 years, 25-34 years, 35 years and older), hours since injury (1 hour or less, 1-3 hours, over 3 hours), type of injury (blunt or penetrating), Glasgow Coma Scale (3, 4-5, 6-8, 9-12, 13-15), Systolic Blood Pressure (>89, 76-89, 50-75, 1-49, 0), Respiratory Rate (>29, 10-29, 6-9, 1-5, 0), Central Capillary Refill Time (2 or less, 3-4, 5 or more) and country, bearing in mind what packs remain at that hospital. The allocated treatment pack number will be given and recorded on the trial entry form. Hospitals in which the doctors feel that central randomisation is not feasible will use a local pack system. At such hospitals, baseline information will be collected on the trial entry form and the next consecutively numbered treatment pack taken from a box of eight packs (with a random allocation sequence based on a block size of eight, also generated by CTSU). Once the pack number is recorded, the patient is included in the trial whether or not the pack was opened or the allocated treatment started.

4.3.1 Blinding

Blinding is achieved through the use of matching placebo. The blinding process is described in Appendix 1.

5. STUDY POPULATIONS

5.1 PARTICIPANT CHARACTERISTICS

A trial profile of participants will be presented as per the CONSORT recommendations (figure 1). The table of baseline characteristics will be as per Table 4 in DMEC shell tables but excluding the components of the GCS.

5.2 DEFINITION OF POPULATIONS FOR ANALYSIS

The analyses will be on an ‘intention-to-treat’ basis. All patients will be analysed on the basis of the group to which they were randomised, irrespective of whether the patients in the intervention group actually received the intervention.

5.3 MAJOR PROTOCOL DEVIATIONS

These will be described in the results section.

5.4 DEFINITION OF SUB-GROUP POPULATIONS

Analysis of the primary outcome will be stratified on:

- hours from injury to randomisation and the initiation of treatment (less than one hour, one to three hours, more than three hours)
- severity of haemorrhage as assessed by systolic blood pressure (≤75, 76-89, >89 mmHg)
- Glasgow Coma Scale (severe [GCS 3-8], moderate [GCS 9-12], mild [GCS 13-15])
- type of injury (blunt/blunt & penetrating, or penetrating only)

Subsequent analyses will include subgroup analyses according to baseline risk of mortality. We will develop a prognostic model including all the baseline variables (age, sex, systolic blood pressure, heart rate, respiratory rate, Glasgow Coma Score, number of hours since injury, central capillary refill time and type of injury). This model will be derived only from the control group. We will categorise the patients according to tertiles of risk and we will report the relative and absolute measures of effect for each category.

6. STATISTICAL ANALYSIS

6.1 GENERAL

For each binary outcome we will report relative risks with 95% confidence intervals and give a two-sided p-value for statistical significance. For analysis of the pre-specified subgroups (primary outcome only) we will report relative risks with 99% confidence intervals with two-sided p-value.

6.2 POOLING OF SITES

The data will be pooled across all participating sites.

6.3 INTERIM ANALYSES

Interim analyses were conducted by the independent DMEC as per the DMEC SOP.

6.4 TIME-POINTS FOR ANALYSIS

There will be one analysis at the end of the trial after the database has been locked.

6.5 METHODS FOR HANDLING MISSING DATA

A complete case analysis will be conducted (i.e. only including cases for which the relevant outcome data are available). There will be no imputation for missing data.

6.6 STATISTICAL ANALYTICAL ISSUES

6.6.1 Adjustments for covariate

There will be no covariate adjustment in the primary analysis.

6.6.2 Multiple Comparisons

There will be no adjustment for multiple comparisons. We will report 99% confidence intervals for subgroup analyses of the primary outcome.

6.6.3 Examination of Subgroups
We will report relative risks with 99% confidence intervals for the primary outcome by the following subgroups:

- hours from injury
- severity of haemorrhage systolic blood pressure (≤75, 76-89, >89 mmHg)
- Glasgow Coma Scale (severe, moderate, mild)
- type of injury (blunt, blunt & penetrating, or penetrating only)

We will conduct a test of homogeneity of effects across the subgroups and report a p-value. Unless there is strong evidence against the null hypothesis of homogeneity of effects (i.e. $p<0.001$) the overall relative risk will be considered as the most reliable guide to the approximate relative risks in all subgroups.

7. EVALUATION OF DEMOGRAPHICS AND BASELINE CHARACTERISTICS

7.1 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

As outlined above, a trial profile will be presented as per the CONSORT recommendations (figure 1). The baseline characteristics will be presented according to treatment (table 1).

8. EVALUATION OF TREATMENT COMPLIANCE AND EXPOSURE

8.1 COMPLIANCE TO STUDY DRUG AND TREATMENT

Compliance with study treatment will be defined as:

- Received allocated intervention (loading dose)
- Known not to have received allocated intervention (loading dose)
- Unknown whether received allocated intervention (loading dose)

- Continued allocated intervention (maintenance dose)
- Known not to have continued allocated intervention (maintenance dose)
- Unknown whether continued allocated intervention (maintenance dose)

This will be reported in figure 1.

9. EVALUATION OF PARAMETERS

9.1 ANALYSIS OF PRIMARY, SECONDARY AND OTHER EFFICACY ENDPOINTS

See section 6 above.

9.2 METHOD FOR ANALYSIS OF EFFICACY ENDPOINTS

9.2.1 Binary Data

For each binary outcome we will report relative risks with 95% confidence intervals and give a two-sided p-value for statistical significance. For analysis of the pre-specified subgroups (primary outcome only) we will report relative risks with 99% confidence intervals with two-sided p-value.

9.2.2 Count Data

Means and standard deviations will be estimated for count outcomes. We will report the two-sided p-value for statistical significance of the difference in means of logarithms of count outcomes.

9.2.3 Time-to-Event Data

There will be no analysis of time to event data.

9.2.4 Ordinal Scales and Non-Ordered Scales Data

For the analysis of the patients' condition at discharge, the five point scale will be dichotomised into independent (no symptoms, minor symptoms, and some restriction in lifestyle but independent) and dependent (including death) categories.

10. EVALUATION OF SAFETY PARAMETERS

10.1 ADVERSE EVENTS

Numbers and type will be described using MedDRA codes (Version 12.1).

FIGURE 1 – CONSORT FLOW OF PATIENTS

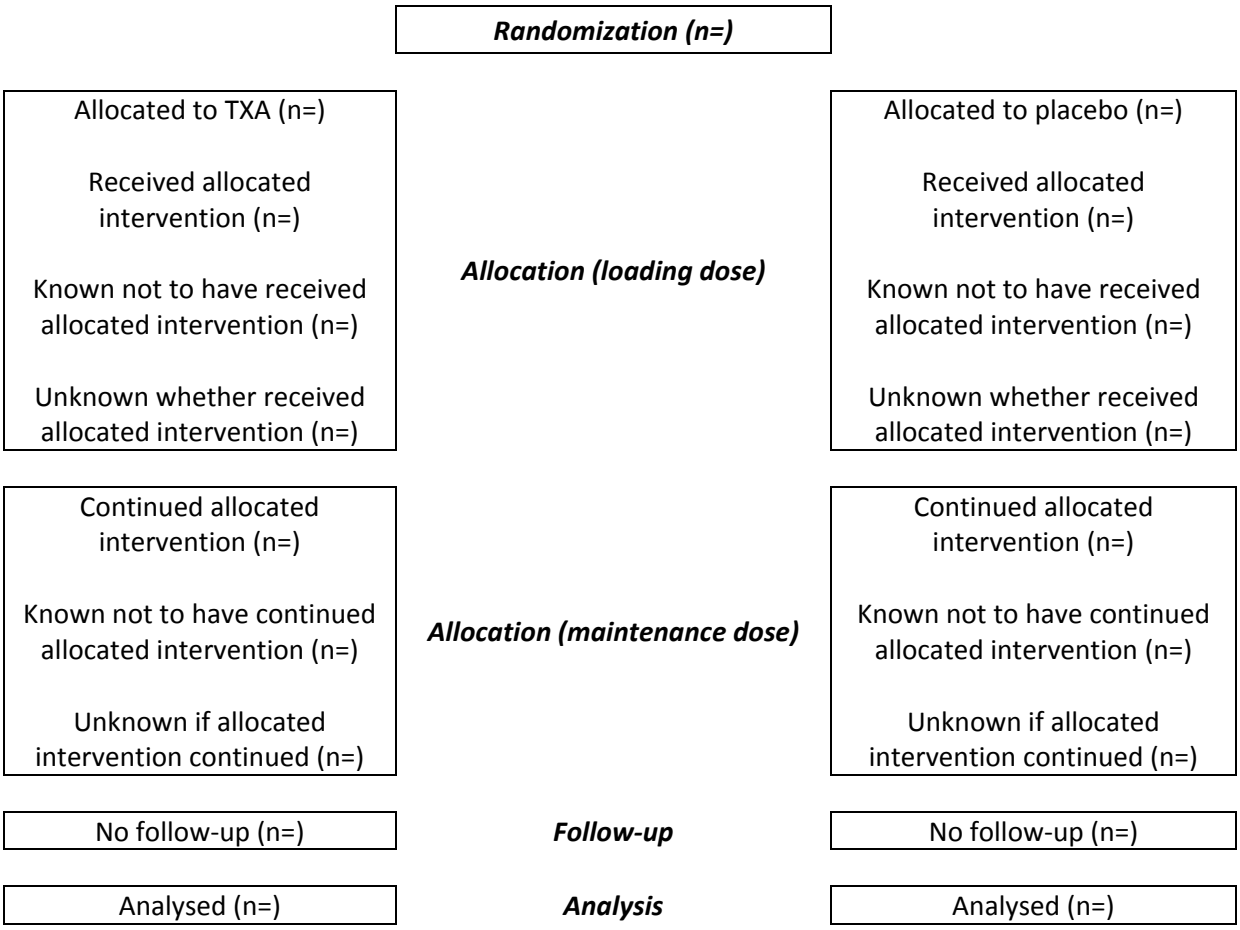

TABLE 1 – BASELINE DATA - ALL PATIENTS RANDOMIZED

Percentages are of group total unless specified		**TXA**	**Placebo**
Patients randomized as of <Date>			
Gender[2]	Male		
	Female		
Age[2]	Mean age in years (SD)		
	<25 years		
	25-34 years		
	35-44 years		
	≥45 years		
Hours since injury[2]	<1 hour		
	1-3 hours		
	>3 hours		
Type of injury[2]	Blunt†		
	Penetrating		
Systolic BP (mmHg)[2]	≥90 mmHg SBP		
	76-89 mmHg SBP		
	≤75 mmHg SBP		
Respiratory rate (per min)[2]	≥30		
	10-29		
	6-9		
	<6 [4]		
Central capillary refill time (secs)[2]	2 or less		
	3 to 4		
	5 or more		
Heart rate (per min)[2]	>107		
	92-107		
	77-91		
	<77		
Glasgow Coma Score[2]	Median [IQR]		
	Severe (GCS 3-8)		
	Moderate (GCS 9-12)		
	Mild (GCS 13-15)		

† *Blunt/ Blunt & penetrating*

TABLE 2. DEATH WITHIN 4 WEEKS - ALL PATIENTS RANDOMIZED

		TXA	Placebo	RR (95% CI)	p-value
All patients					
Pre-specified subgroups				**RR (99% CI)**	**p-value**
(i) Severity of haemorrhage	≥90 mmHg SBP				
	76-89 mmHg SBP				
	≤75 mmHg SBP				
(ii) Time since injury	<1 hour				
	1-3 hours				
	>3 hours				
(iii) Glasgow Coma Scale	Severe (GCS 3-8)				
	Moderate (GCS 9-12)				
	Mild (GCS 13-15)				
(iv) Type of injury	Blunt*				
	Penetrating only				

** Blunt/ Blunt & penetrating*
Analysis will include p-value from test of homogeneity of effects between subgroups

TABLE 3 BLOOD PRODUCTS† TRANSFUSION GIVEN

		TXA	Placebo	RR (95% CI)	p-value
All patients					

†All types of blood products (including red cells, fresh frozen plasma, platelets and cryoprecipitate)

TABLE 4 DISTRIBUTION OF NUMBER OF BLOOD UNITS

	TXA	Placebo	Mean difference (95% CI)‡	p-value
Mean units transfused [SD]				

‡Analysis will use logarithmic transformation of number of units transfused

TABLE 5. DEATH OR DEPENDENCY AT 4 WEEKS, DISCHARGE, OR TRANSFER

		TXA	Placebo	RR (95% CI)	p-value
All patients					

TABLE 6 MANAGEMENT AND COMPLICATIONS

		TXA	Placebo	RR (95% CI)	p-value
All surgery					
	NS operation				
	Chest operation				
	Abdominal operation				
	Pelvis operation				
Thromboembolic episodes					
	Pulmonary embolism				
	Deep vein thrombosis				
	Stroke				
	Myocardial infarction				
Gastrointestinal bleeding					
Days in intensive care unit				**Mean difference (95% CI)‡**	**p-value**
Mean days in ICU [SD]					

‡Analysis will use logarithmic transformation of number of days in ICU

TABLE 7. CAUSE OF DEATH

		TXA	Placebo	RR (95% CI)	p-value
Bleeding					
Vascular occlusion					
	Myocardial infarction				
	Stroke				
	Pulmonary embolism				
Multi organ failure					
Head injury					
Other					

Notes

1. All analyses include all patients randomized, on an intention-to-treat basis

2. Groups are pre-specified randomization strata

3. Includes patients for whom Systolic BP was not known

4. Includes patients for whom respiratory rate was not known

5. Denominators are of patients with management data received; numerators are number of patients non-compliant

6. Denominators are of patients with information on dose received

** indicates |z| > 3*

DHP pharma
Investigational Medicinal Products
Clinical Trial Supplies
Waller House, Elvicta Business Park, Crickhowell, Powys. NP8 1DF. UK.
Tel: +44 (0)1873 812182 Fax: +44 (0)1873 810836
info@dhpclin.com
http://www.dhpclin.com

Crash 2 : Blinding of placebo/active products

The study requires the test drug Tranexamic Acid and placebo (Sodium Chloride 0.9%) be supplied in ampoules and packaging which are blinded i.e. are of identical appearance whilst still permitting rapid identification in an emergency.

Tranexamic Acid (Cyklokapron brand) ampoules:

The product is supplied in clear glass 5ml ampoules with paper label and coloured neck rings of green and yellow. All label text is printed onto the paper label.

The blinding process is the complete removal of the original manufacturers label and its replacement with the clinical study label bearing patient/pack randomisation number and text in compliance with requirements for investigational medicinal products in the EU.

Placebo (Sodium Chloride 0.9%) ampoules

The placebo is supplied in identical clear glass ampoules with coloured neck rings of green and yellow. Car is taken during the production process to ensure that ampoules are filled to the same height and sealed to the same height as the Tranexamic acid.

Ampoules can be identified by using the unique randomisation code printed onto the label. This number enables access to the audit trail to trace the full history of the product

Ampoules are packed into patient treatment cartons which also contain an empty syringe, needle and 100ml saline for infusion. Quality assurance procedures ensure that cartons and other components used for both active and placebo containing packs are of similar appearance in order to preserve the blind. Pack identification is provided by the randomisation code printed onto labels fixed directly to the carton.

Patient packs containing Tranexamic acid and also those containing placebo are packed in balanced blocks of 8 (4 Tranexamic Acid: 4 placebo) into an Investigator Supply Box. The fixed numerical sequence of patient packs in the box is in random order of identity. The box is labelled with a unique box number that relates to the Patient Packs it contains.

All processes are carried with strict adherence to good manufacturing procedures for investigational medicinal products.

S D P Williams B.Pharm.,MRPharmS
Technical Director
EU Qualified Person
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