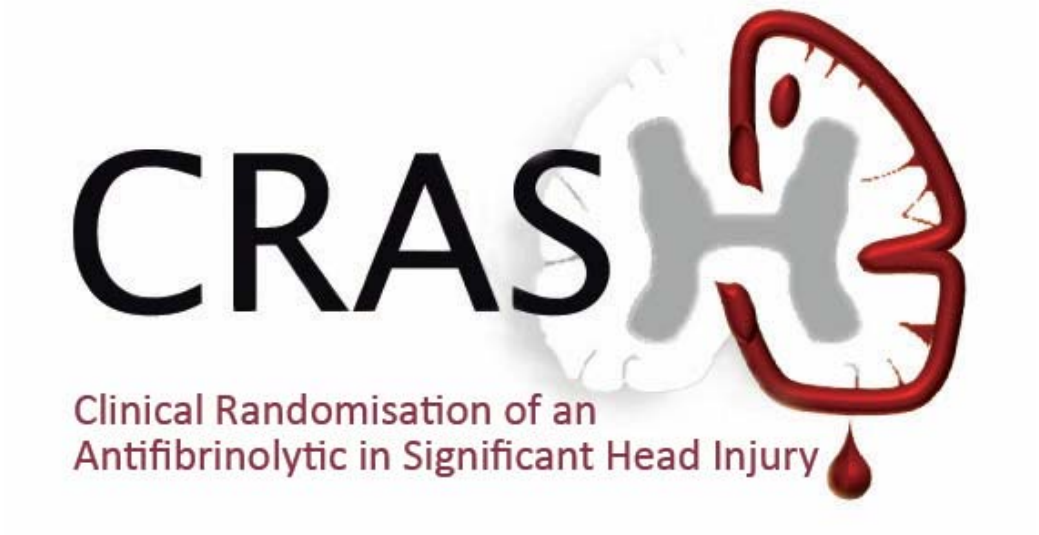
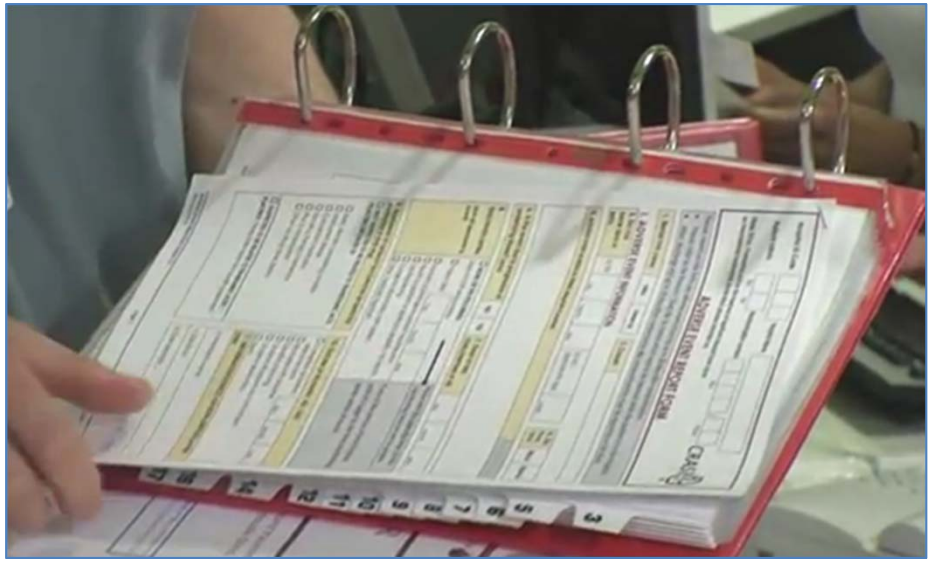


Reporting Adverse Events and Completing the Report Form

Protocol Code: ISRCTN15088122
V 1.1 date 27 Sep 2016

THIS PRESENTATION MUST BE USED WITH:

1. **THE PROTOCOL (Section 2.10) and**
2. **The guidance for investigators: ADVERSE EVENT REPORTING AND COMPLETING THE REPORT FORM (in Investigator Study File)**



Information about Adverse Events

- Death, life-threatening complications and prolonged hospital stay are pre-specified outcomes to be reported in this trial and also to the independent data monitoring committee. This clinical trial is being conducted in a critical emergency condition, using a drug in common use. It is important to consider the natural history of the critical medical event affecting each patient enrolled, the expected complications of this event and the relevance of the complications to TXA.

- Adverse events to be reported using an adverse event reporting form will be limited to those NOT already listed as primary or secondary outcomes, yet, which might reasonably occur as a consequence of the trial drug. Events that are part of the natural history of the primary event of traumatic brain injury or expected complications of traumatic brain injury should not be reported as adverse events (*see Protocol section 2.10*).

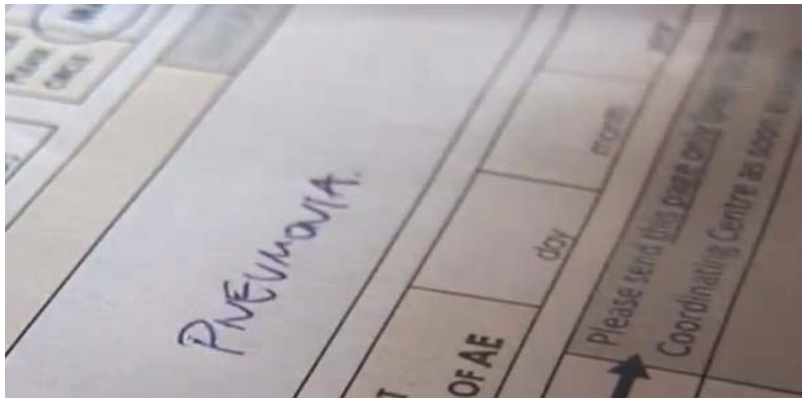
For example, event such as low blood pressure, increased heart rate, reduced urine output, altered level of consciousness, may be expected complications of traumatic brain injury and are not expected to be reported as Adverse Events.

Definitions

Adverse event (AE)	Any untoward medical occurrence affecting a trial participant during the course of a clinical trial
Serious Adverse Event (SAE)	A serious adverse event (experience) is any untoward medical occurrence that at any dose • results in death; • is life-threatening; • requires in-patient hospitalisation or prolongation of existing hospitalisation; • results in persistent or significant disability/incapacity; or • is a congenital anomaly/birth defect.
Adverse Reaction (AR)	An adverse event when there is at least a possibility that it is causally linked to a trial drug or intervention
Serious Adverse Reaction (SAR)	SAE that is thought to be causally linked to a trial drug or intervention
Suspected Unexpected Serious Adverse Reaction (SUSAR)	An ***unexpected*** occurrence of a SAR; there need only be an index of suspicion that the event is a previously unreported reaction to a trial drug or a previously reported but exaggerated or unexpectedly frequent adverse drug reaction.

Reporting Adverse Events

- The *Adverse Event Report form* should be used to report all adverse events in line with the Protocol
- Adverse Event Report forms can be found in your Study File Section 7 and on the CD in the front cover



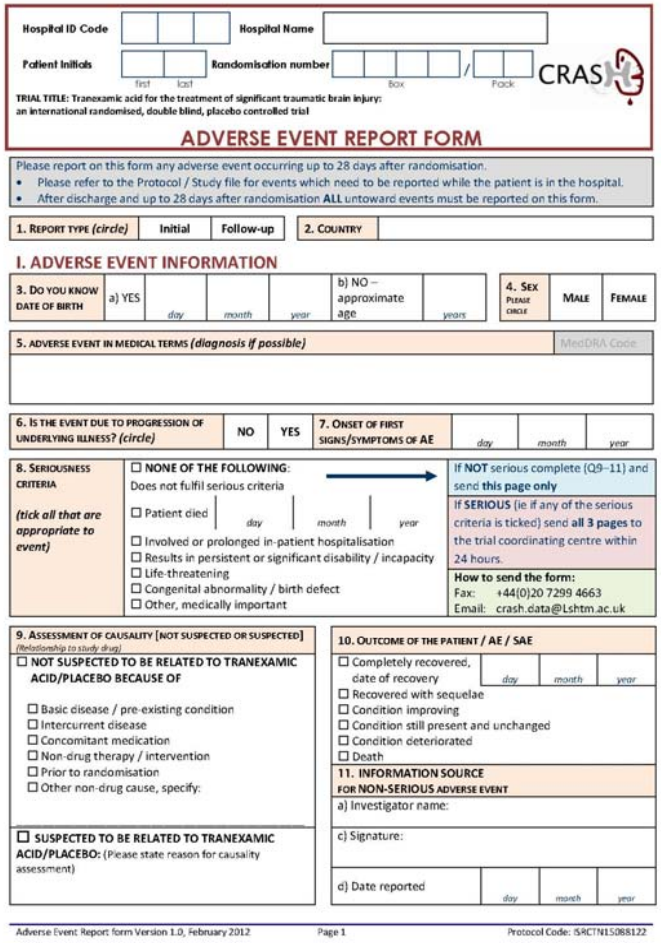
Reporting Adverse Events

- Any adverse event as defined in the Trial Protocol that occurs while the patient is in hospital **(up to Day 28)** should be reported

- The Adverse Event Report form must be completed manually, in English, Spanish or French
Please write clearly

- Adverse events that do NOT fulfil any of the seriousness criteria: only page 1 needs to be completed – this should be sent to the TCC as soon as possible even if all the information is not available

- **Adverse events that fulfil ANY of the seriousness criteria (Section 8 of the form): all 3 pages of the form must be completed and sent to the TCC WITHIN 24 HOURS of you becoming aware of the event.**



Hospital ID Code | Hospital Name | Patient Initials (first, last) | Randomisation number (Box / Pack) | CRASH-3

TRIAL TITLE: Tranexamic acid for the treatment of significant traumatic brain injury: an international randomised, double blind, placebo controlled trial

ADVERSE EVENT REPORT FORM

Please report on this form any adverse event occurring up to 28 days after randomisation.
- Please refer to the Protocol / Study file for events which need to be reported while the patient is in the hospital.
- After discharge and up to 28 days after randomisation **ALL** untoward events must be reported on this form.

1. REPORT TYPE *(circle)* | Initial | Follow-up | 2. COUNTRY

I. ADVERSE EVENT INFORMATION

3. DO YOU KNOW DATE OF BIRTH | a) YES (day, month, year) | b) NO – approximate age (years)

4. SEX (PLEASE CIRCLE) | MALE | FEMALE

5. ADVERSE EVENT IN MEDICAL TERMS *(diagnosis if possible)* | MedDRA Code

6. IS THE EVENT DUE TO PROGRESSION OF UNDERLYING ILLNESS? *(circle)* | NO | YES

7. ONSET OF FIRST SIGNS/SYMPTOMS OF AE (day, month, year)

8. SERIOUSNESS CRITERIA *(tick all that are appropriate to event)*

☐ NONE OF THE FOLLOWING: Does not fulfil serious criteria

☐ Patient died (day, month, year)
☐ Involved or prolonged in-patient hospitalisation
☐ Results in persistent or significant disability / incapacity
☐ Life-threatening
☐ Congenital abnormality / birth defect
☐ Other, medically important

If **NOT** serious complete [Q9–11] and send **this page only**

If **SERIOUS** (ie if any of the serious criteria is ticked) send **all 3 pages** to the trial coordinating centre within 24 hours.

How to send the form:
Fax: +44(0)20 7299 4663
Email: crash.data@lshtm.ac.uk

9. ASSESSMENT OF CAUSALITY [NOT SUSPECTED OR SUSPECTED] *(Relationship to study drug)*

☐ NOT SUSPECTED TO BE RELATED TO TRANEXAMIC ACID/PLACEBO BECAUSE OF

☐ Basic disease / pre-existing condition
☐ Intercurrent disease
☐ Concomitant medication
☐ Non-drug therapy / intervention
☐ Prior to randomisation
☐ Other non-drug cause, specify:

☐ SUSPECTED TO BE RELATED TO TRANEXAMIC ACID/PLACEBO: (Please state reason for causality assessment)

10. OUTCOME OF THE PATIENT / AE / SAE

☐ Completely recovered, date of recovery (day, month, year)
☐ Recovered with sequelae
☐ Condition improving
☐ Condition still present and uncharged
☐ Condition deteriorated
☐ Death

11. INFORMATION SOURCE FOR NON-SERIOUS ADVERSE EVENT

a) Investigator name:

c) Signature:

d) Date reported (day, month, year)

Adverse Event Report form Version 1.0, February 2012 | Page 1 | Protocol Code: ISRCTN15088122

If in doubt: Please report or call the 24-hour helpline for advice

Reporting Adverse Events

- All fields must be completed – do not leave blank fields. If the information is not known at the time of completing the form, write **NK** (not known) or **NA** (not applicable).

- The information supplied on the AE form must be consistent with the data recorded on the source data i.e. medical records and other data forms.

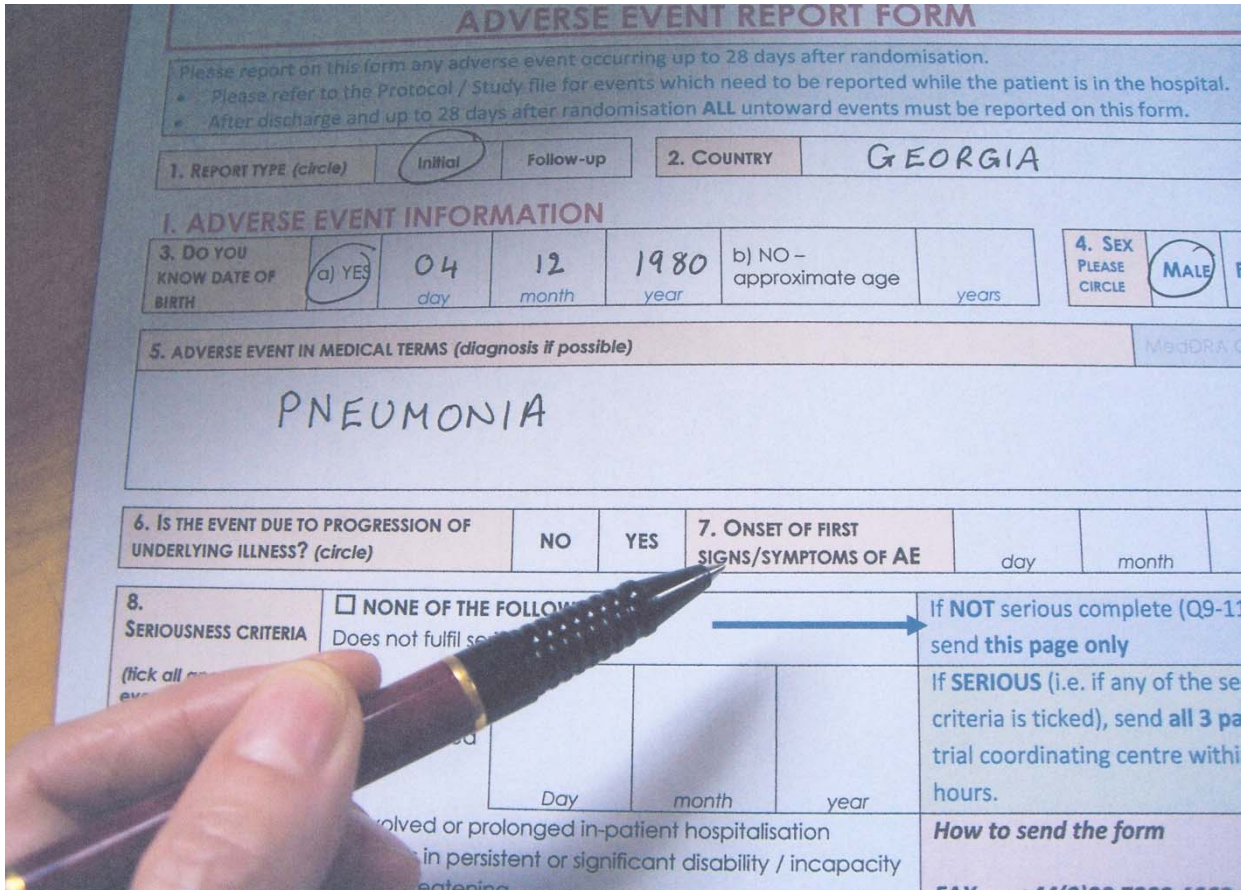
- The Initial adverse event report form should be submitted even if there is only limited information. When any additional or relevant information becomes available, it should be submitted on follow-up report forms – there may be more than one follow-up form. If the event is serious, then follow-up data must be sent to the TCC within 24 hours.

- In the follow-up report form, you must complete the header information (to identify the patient), the diagnosis must be written in (to identify the event) and only new or corrected information must be reported. Please note that the information provided in the Follow-up AE Report Form supersedes the information previously reported.

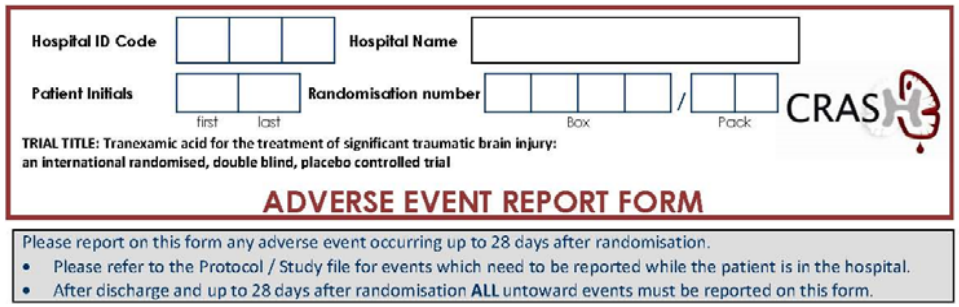
Completed forms can only be sent by FAX to +44(0)20 7299 4663
or as a scanned image/s attached to an email to crash.data@Lshtm.ac.uk

IF YOU NEED URGENT ADVICE ABOUT REPORTING AN ADVERSE EVENT PLEASE CALL +44(0)7768 707500

How to complete the Adverse Events reporting form



Header and Sections 1 to 5


Hospital ID Code | Hospital Name
Patient Initials (first, last) | Randomisation number (Box / Pack)
CRASH-3
TRIAL TITLE: Tranexamic acid for the treatment of significant traumatic brain injury: an international randomised, double blind, placebo controlled trial
ADVERSE EVENT REPORT FORM
Please report on this form any adverse event occurring up to 28 days after randomisation.
- Please refer to the Protocol / Study file for events which need to be reported while the patient is in the hospital.
- After discharge and up to 28 days after randomisation **ALL** untoward events must be reported on this form.

All fields MUST be completed in the header.

If the Adverse Event is SERIOUS, the header on all 3 pages must be filled in.

1. REPORT TYPE *(circle)*	Initial	Follow-up

Circle INITIAL if this is the first data being submitted for this AE.
Circle FOLLOW-UP for any subsequent information.

2. COUNTRY	

Write clearly the name of the country where the event occurred. This is most likely to be the country you are located in.

3. DO YOU KNOW DATE OF BIRTH	a) YES	*day*	*month*	*year*	b) NO – approximate age	*years*

If known enter the exact date of birth.
If not known put the estimated age in years.
Enter one field only, NOT both date of birth and age

4. SEX PLEASE CIRCLE	MALE	FEMALE

Circle either male OR female

5. ADVERSE EVENT IN MEDICAL TERMS *(diagnosis if possible)*	MedDRA Code

Enter the diagnosis if known, otherwise the sign(s) / symptom(s) relating to the event

Sections 6 to 8

6. IS THE EVENT DUE TO PROGRESSION OF UNDERLYING ILLNESS? *(circle)*	NO	YES

Please indicate if this event is due to TBI or any other pre-existing illness

7. ONSET OF FIRST SIGNS/SYMPTOMS OF AE	*day*	*month*	*year*

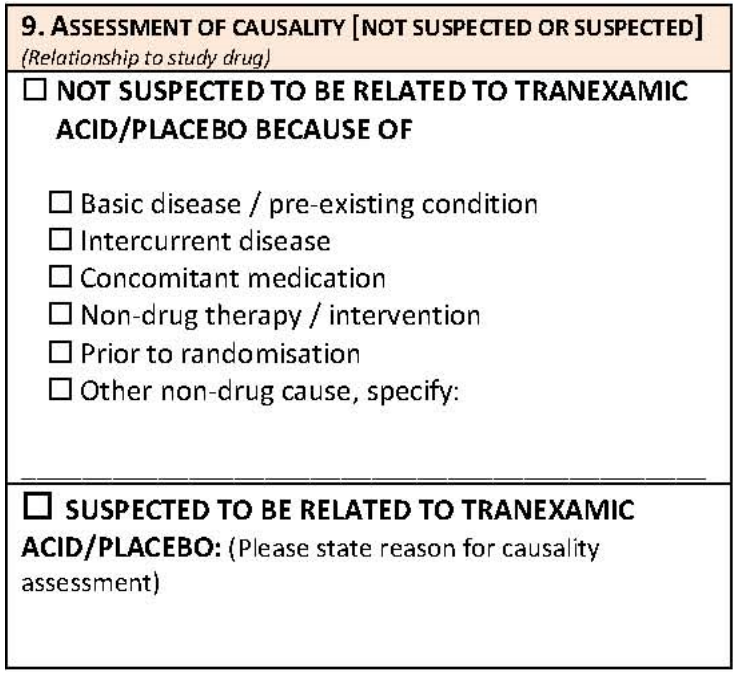
Insert the date when the first signs of the event were noted

- If the event does not fulfil any of the serious criteria tick box **NONE OF THE FOLLOWING**
- Complete sections 9 to 11 and send to the TCC as soon as possible
- If the event fufils ANY of the serious criteria tick **ALL** that apply
- Date is only required if the patient died
- If the event:
  - caused death
  - required in-patient hospitalisation, or prolonged existing hospitalisation
  - resulted in persistent or significant disability/incapacity
  - is life-threatening
  - is a congenital anomaly/birth defect
  - is medically important

  then this is a **SERIOUS ADVERSE EVENT**
- All serious adverse events **must be reported to the TCC WITHIN 24 HOURS**

8. SERIOUSNESS CRITERIA *(tick all that are appropriate to event)*	☐ NONE OF THE FOLLOWING: Does not fulfil serious criteria
	☐ Patient died — *day* | *month* | *year*
	☐ Involved or prolonged in-patient hospitalisation
	☐ Results in persistent or significant disability / incapacity
	☐ Life-threatening
	☐ Congenital abnormality / birth defect
	☐ Other, medically important

Section 9



9. ASSESSMENT OF CAUSALITY [NOT SUSPECTED OR SUSPECTED]
(Relationship to study drug)

☐ **NOT SUSPECTED TO BE RELATED TO TRANEXAMIC ACID/PLACEBO BECAUSE OF**

- ☐ Basic disease / pre-existing condition
- ☐ Intercurrent disease
- ☐ Concomitant medication
- ☐ Non-drug therapy / intervention
- ☐ Prior to randomisation
- ☐ Other non-drug cause, specify:

_____

☐ **SUSPECTED TO BE RELATED TO TRANEXAMIC ACID/PLACEBO:** (Please state reason for causality assessment)

Please indicate whether or not you suspect the event is related to tranexamic acid or placebo

If you suspect the event is related to the trial intervention you must enter a reason for causality, eg *rapid onset of symptoms*

NOT SUSPECTED: This is when a causal relationship between the event and administration of the trial treatment is considered unlikely. This may be because other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the observed event.

SUSPECTED: The temporal relationship of the event to trial treatment administration makes a causal relationship possible – and other drugs, therapeutic interventions or underlying conditions do not provide a sufficient explanation for the observed event.

Sections 10 to 11

10. OUTCOME OF THE PATIENT / AE / SAE			
☐ Completely recovered, date of recovery	*day*	*month*	*year*
☐ Recovered with sequelae			
☐ Condition improving			
☐ Condition still present and unchanged			
☐ Condition deteriorated			
☐ Death			
11. INFORMATION SOURCE FOR NON-SERIOUS ADVERSE EVENT			
a) Investigator name:			
c) Signature:			
d) Date reported	*day*	*month*	*year*

Tick as appropriate

If the patient made a complete recovery please enter the date of recovery, **otherwise** do not enter a date

Complete this section ONLY if the event is not serious.

If the event is serious continue to page 2

Sections 12 to 13

12A. START OF TRIAL TREATMENT	day	month	year	12B. END OF TRIAL TREATMENT	day	month	year

Please insert the date (DD MM YYYY) when the trial treatment **started**

Please insert the date (DD MM YYYY) when the trial treatment **ended**

13. TIME ELAPSED BETWEEN LAST DRUG ADMINISTRATION AND ONSET OF FIRST SIGNS / SYMPTOMS OF SAE	minutes	hours	days	months

Enter the time between last administration of the trial treatment and onset of the first signs or symptoms

Sections 14 to 17

14. ROUTE OF ADMINISTRATION		15. RANDOM CODE BROKEN *(circle)*	NO	YES

Please state the route of administration of the trial treatment

Please circle as appropriate – refer to the Protocol page 13 UNBLINDING

16. HEIGHT	*cm*	17. WEIGHT	*kg*	Estimated if actual values not available

If the exact height and weight are not known, please enter an estimate

The exact height and weight may become available later and the estimates can be overwritten

Sections 18 to 20

18. PATIENT'S PAST MEDICAL HISTORY *(eg co-existing medical conditions such as disease, allergies, similar experiences)*

List here any other medical conditions, allergies or similar experiences in the patient's past medical history

19. CONCOMITANT TREATMENT *(list all below)*

List all concomitant drugs/medications
If you need more space use a separate sheet

20. COMMENTS *(if adverse event is considered to be caused by a concomitant treatment, please note it here)*

Please make a note here if the AE is considered to be caused by any concomitant medication and state which medication is suspected

Sections 21 to 23

21. ACTION TAKEN *(tick all that apply)*

- ☐ No action taken
- ☐ Trial drug dosage adjusted / temporarily interrupted*
- ☐ Trial drug permanently discontinued due to this adverse event
- ☐ Non-drug therapy given**
- ☐ Drug therapy taken**
- ☐ Hospitalisation / prolonged hospitalisation

** if ticked, enter new dosage information in field 23* *** if ticked, provide therapeutic measure in field 23*

Please tick ALL that apply. Details about adjusted dosage and drug and non-drug therapies can be noted in field 23

22. TEST / LABORATORY FINDINGS *(relevant for SAE diagnosis or description)*

List all tests/laboratory findings relevant to the diagnosis of the SAE

23. ADDITIONAL INFORMATION:
Case description of the above SAE (include related signs/symptoms/lab results, treatment, outcome and suspected cause of the SAE)

In this section fully describe the nature, severity, cause and any other information that helps an understanding of the SAE. Describe therapeutic measures taken and, if available, outcome details. Please use precise medical terminology

Sections 24 to 25

24. INVESTIGATOR DETAILS	a) Full Name	b) Telephone number	c) Signature

- Please state full name and provide a direct telephone number where you may be contacted urgently
- Remember to sign the form
- If you are not the Principal Investigator, please make sure that s/he is informed of this SAE

25. DATE REPORTED	*day*	*month*	*year*

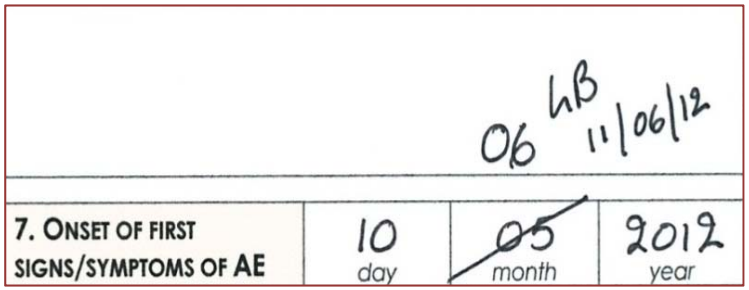
Please enter a full date of when this form was completed in format DD MM YYYY eg 25 | 06 | 2012

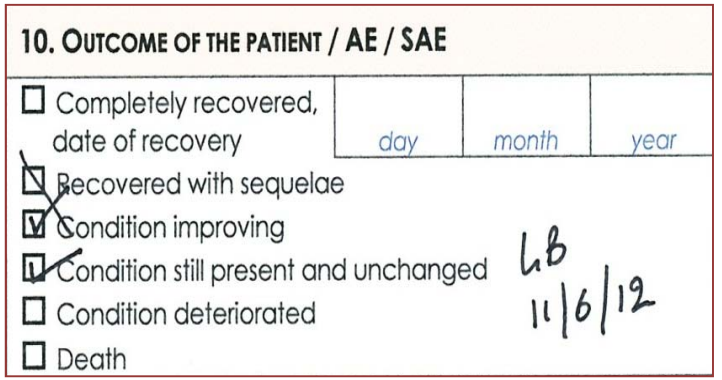
Corrections

If you enter an incorrect value on the form:

a) Cross out the incorrect value **so it is still visible**
b) Enter the correct value alongside
c) Enter the date and your initials alongside each change

EXAMPLES





How to send the Adverse Events reporting form

The form must be

Faxed to +44(0)20 7299 4663

or emailed to crash.data@Lshtm.ac.uk

PLEASE NOTE: if you would like access for the online data entry facility for Adverse Event reporting please email ctu.data@Lshtm.ac.uk

Please store original forms in

Study file Folder 2 Section 17

CRASH

Clinical Randomisation of an Antifibrinolytic in Significant Head Injury

Trial Coordinating Centre
London School of Hygiene & Tropical Medicine
Room 180, Keppel Street, London WC1E 7HT
Tel +44(0)20 7299 4684 | Fax +44(0)20 7299 4663
crash@Lshtm.ac.uk

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UKCRC Registered Clinical Trials Units