GUIDANCE FOR INVESTIGATORS FOR REPORTING ADVERSE EVENTS

The CRASH-2 Trial procedure for reporting adverse events will be carried out in accordance with the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) standards, National and International regulatory authorities' requirements, and the trial's Standard Operating Procedures.

THE FOLLOWING DEFINITIONS HAVE BEEN ADOPTED FOR THIS TRIAL:

Adverse event (AE)

Any untoward medical occurrence affecting a trial participant during the course of a clinical trial.

Serious Adverse Event (SAE)

An adverse event which resulted in the death or threatened the life of the participant; or where the participant required hospitalisation or prolonged hospital stay; or which resulted in persistent or significant disability or incapacity; or which was a congenital anomaly/birth defect. Note that investigators may also consider that other adverse events fall into the 'serious' category in that they were important medical events (other than the above) requiring medical investigation/intervention. These should be reported accordingly.

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. Note that 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.

WHAT SHOULD BE REPORTED IN CRASH-2?

- 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. The CRASH-2 trial is being conducted in a critical emergency condition using a drug (Tranexamic Acid) which in common use. It is important to consider the natural history of the critical medical event affecting each participant enrolled, the expected complications of this event and the relevance of the complications to Tranexamic Acid. Therefore, an SAE 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.
- In general, vascular events such as pulmonary embolism, deep vein thrombosis, stroke, myocardial infarction, and multi-organ failure, do not need to be reported as Serious Adverse Events because some increase in their incidence might be expected with antifibrinolytic agents. All such events are routinely monitored among all patients on the outcome form.
- Events that are part of the natural history of the primary event of traumatic injury or expected complications of traumatic injury should not be reported as serious adverse events.
- If a "SUSAR" occurs, this should be logged by calling the 24-hour randomisation service, which will inform the Trials Co-ordinating Centre (TCC) in London. The TCC will then contact the investigator within 24 hours so that a written SUSAR report can be completed.
- The 24-hour randomisation service number can be found on the Contact sheet in your Trial Site File Section 1 and on the trial posters sent to you.

In Section 8 of your Trial Site File you will find:

- A summary flow chart of the Adverse Event Reporting Procedure
- Forms for the written SAE/SUSAR report which must be made within 24 hours
- A pocket where the completed SAE/SUSAR reports must be filed

The TCC will coordinate the reporting to all relevant Ethics Committees, Regulatory Authorities and other Investigators.

If reporting required:

Clinical Trial Service Unit +44(0)1865 743743
or FREECALL number in your sitefile

TCC fax: +44(0)20 7299 4663

For other enquiries TCC tel: +44(0)20 7299 4684

ADVERSE EVENT

SERIOUS

1. Results in death
2. Is life-threatening
3. Requires hospitalisation or
4. Prolongation of existing hospitalisation
5. Results in persistent or significant disability or incapacity
6. Is a congenital anomaly or birth defect

NOT SERIOUS → Record in medical notes

EXPECTED SIDE EFFECTS LISTED IN PROTOCOL (page 8) DO NOT REQUIRE REPORTING (data collected on outcome form):

- Death – unless believed to be directly due to the trial treatment
- Pulmonary Embolism
- Deep Vein thrombosis
- Stroke
- Myocardial Infarction
- Gastro Intestinal Bleeding
- Multi-organ failure
- Result of trauma suffered by patient
- Medical events expected in severe injury

UNEXPECTED SIDE EFFECTS:

1. Complete a **Serious Adverse Event Form**
2. Telephone Randomisation Service (phone number as per Randomisation Poster or site file) to register Serious Adverse Reaction; give the information on the form
3. Fax/email completed form to the Co-ordinating Centre within 24 hours

CRASH TRIALS CO-ORDINATING CENTRE AND NATIONAL CO-ORDINATORS IN EACH COUNTRY MUST REPORT **SERIOUS ADVERSE REACTIONS** AS REQUIRED BY THAT COUNTRY'S RESEARCH ETHICS COMMITTEES AND NATIONAL REGULATORY BODIES