PROTOCOL

Corticosteroid Randomisation After Significant Head Injury

A simple placebo controlled trial, among adults with head injury and impaired consciousness, of the effects of a 48-hour infusion of corticosteroids on death and neurological disability

April 2004

CONTENTS

A large simple placebo controlled trial, among adults with head injury and impaired consciousness, of the effects of a 48-hour infusion of corticosteroids on death and neurological disability

Worldwide, millions of people are treated each year for severe head injury. A substantial proportion die, and many more are permanently disabled. If short term corticosteroid infusion could be reliably shown to reduce these risks by just a few percent then this might affect the treatment of a few hundred thousand patients a year, protecting thousands from death or long term disability.

When all previous trials of steroids in head injury are combined, the risk of death in the corticosteroid treated group appears to be about 2% lower than in the control group, but the 95% confidence interval runs from 6% lower to 2% higher mortality. Thus, the overall result is compatible with there being no benefit, but is also easily compatible with a benefit of a few percent. The CRASH trial will determine reliably the effects on death and on disability of a short term corticosteroid infusion following significant head injury.

To detect or refute improvements of only a few percent in outcome, many thousands of acute head injury patients must be randomised between control and steroid infusions. Such large numbers will be possible only if hundreds of doctors and nurses can collaborate in the participating emergency departments. Since they are busy, and working in emergency situations, the trial involves them in almost no extra work: no special investigations or changes to usual management are required, and data collection is absolutely minimal. Patients participating in this trial are not precluded from enrolment in other trials. The trial design is summarised on page 20.

CRASH will determine reliably the effects of corticosteroids on death and on disability following significant head injury

1. Background

Corticosteroids in head injury

Worldwide, some millions of people are treated each year for serious head injury, of whom close to a million die, and a similar number are disabled,[1] often with profound effects on the subsequent quality of life of the affected individuals and their carers.[2] If a treatment as simple as short term corticosteroids produces just a moderate benefit, this could be worthwhile. For example, if corticosteroids reduced the risk of death by just 2% (e.g. from 15% to 13%), and reduced the risk of permanent disability by a similar amount, then treatment of 500,000 patients would avoid 10,000 deaths and prevent 10,000 permanent disabilities. But, such a benefit would be impossible to demonstrate reliably without large scale randomised evidence. If, for example, 10,000 patients were randomly allocated to receive a corticosteroid infusion and 10,000 a placebo infusion, then a reduction from 15% to 13% dead should be detectable - and a reduction from 15% to 12% would certainly be detectable. By contrast, a trial involving only 2,000 patients would probably miss such differences.

So far, all of the randomised trials of corticosteroids in head injury have been small: the largest included only a few hundred patients, and even in aggregate they have involved only about 2,000 patients (Figure 1).[3] When all previous trials are combined, the risk of death in the corticosteroid treated group appears to be about 2% lower than in the control group, but the 95% confidence interval runs from 6% lower to 2% higher mortality. (This overall reduction from 39% dead to 37% dead corresponds to an 'odds ratio' of 0.91, with 95% confidence interval 0.74 to 1.12; the corresponding odds ratio for death or disability in those trials is 0.90, with 95% confidence interval 0.72 to 1.11.) Hence, the overall result from the previous trials is compatible with there being no real benefit, but it is also easily compatible with a benefit of a few percent. However, the existing trials are too small to demonstrate or to refute either possibility.

Figure 1. *Aggregate mortality results from 13 randomised trials of steroids in head injury published before 1997*

	Steroid	Control
No. of patients	1,061	1,087
No. who died	396 (37%)	422 (39%)

Absolute benefit of steroids 2%, indicating 1 death prevented for every 50 patients treated: but these previous trial results are also statistically compatible with there being no real benefit at all (or even a small hazard).

Corticosteroids in spinal injury

Recent evidence of benefit from corticosteroids in acute spinal cord injury has renewed interest in their possible role in brain injury. The Second US National Acute Spinal Cord Injury Study (NASCIS 2) compared 24 hours of methylprednisolone (MP) vs placebo in 333 patients with acute spinal cord injury.[4] At six months, patients who had received steroids rather than placebo appeared to have greater improvement in motor function, and in sensation to pinprick and touch. Similar results were reported in a Japanese trial of the same regimen.[5] Recent trials of MP in acute spinal cord injury have indicated slightly more neurological recovery with 48 than with 24 hours of treatment.[6]

Dose selection

Post-traumatic neuronal degeneration can involve lipid peroxidation,[7] and in cats [8,9] and mice[10] this can be inhibited by methylprednisolone,[11] with 30 mg/kg needed for maximal effect. The dose of steroid used in previous head injury trials was, however, much lower than this,[3] and so a trial of the early administration of methylprednisolone in doses that are high enough to inhibit lipid peroxidation may produce slightly greater treatment effects than those in Figure 1. The CRASH trial has therefore been designed to determine reliably:

- the effects of high dose corticosteroid infusion on death and on disability following significant head injury, and
- the effects of such infusion on the risk of infection and of gastro-intestinal bleeding in this setting.

2. Study design

Summary

CRASH is a large simple, placebo controlled trial of the effects of a 48-hour infusion of corticosteroids on death and on neurological disability, among adults with head injury and some impairment of consciousness. The procedures are described in Figure 2, and on page 18. Head injured patients with impaired consciousness who are judged to be 16 years or older are eligible if the responsible doctor is, for any reason, substantially uncertain whether or not to use corticosteroids. Numbered drug or placebo packs will be available in each participating emergency department. Randomisation involves calling a 24-hour freephone service. The call should last only a minute or two, and at the end of it the service will specify to the caller which numbered treatment pack to use. The drug or placebo in the pack is made up in saline and, following a one-hour loading dose, is infused over 48 hours (or as close to 48 hours as possible). No extra tests are required, but a short form must be completed two weeks later (or after prior death or discharge). Long term recovery will be assessed at six months either by a simple postal questionnaire, sent directly to each trial participant from the CRASH co-ordinating centre, or by telephone interview. This does not involve any additional work for collaborating hospitals.

Number of patients needed

Two main factors determine the number of patients needed in a trial. These are the estimated event rate and the size of the treatment effect.

Estimated event rate: In a recent multi-centre randomised trial in head injury using inclusion criteria similar to those in the CRASH trial, the overall risk of death among controls was 15%, with the risk of unfavourable outcome (dead, unfit for work or needing rehabilitation) being 43%.[12] This trial is one of the most recent randomised trials of corticosteroids in head injury and it would be reasonable to expect a similar risk of unfavourable outcome in the CRASH trial.

Size of treatment effect that should be detectable: Because even a 2% survival advantage for an intervention as simple and widely practicable as corticosteroids would represent a worthwhile benefit, the current trial has been planned to be able to detect a benefit of this size.

Numbers needed: If the real mortality difference is 15% vs 13% then there is about a 65% chance that a trial involving 10,000 patients will achieve 2P<0.01, and a 95% chance that a trial involving 20,000 patients will do so. These calculations assess how well the trial is protected against an unfavourable play of chance. If however, as might well be the case, the actual results are not much distorted by the play of chance and involve 15% vs 13% mortality then a trial of 10,000 would yield 2P=0.004, and a trial of 20,000 would yield 2P=0.00004 (which is extreme enough to allow some exploratory sub-analyses of which types of patient seem most likely to benefit).

Eligibility

- *Head injured patients (judged to be 16 years or older) within 8 hours of injury who are not fully conscious (any abnormality on the Glasgow Coma Scale), except those for whom corticosteroids are thought to be clearly indicated or contra-indicated.*

All head injured patients who — in the absence of sedation — are observed whilst in hospital to have GCS of 14 or less, and are within 8 hours of the injury, are eligible for trial entry if they appear to be at least 16 years old. Although entry is allowed up to 8 hours from injury, the earlier that patients can be treated the better.

There are no other pre-specified exclusion criteria, as the fundamental eligibility criterion is the responsible doctor's "uncertainty" whether or not to use corticosteroids in a particular adult with head injury.[13] Patients for whom there is considered by the responsible doctor to be a clear indication for corticosteroids (such as, perhaps, those who also have an acute spinal cord injury) should **not** be randomised. Likewise, any for whom there is considered to be a clear contraindication to corticosteroids should **not** be randomised. But, all those for whom the responsible doctor is substantially uncertain as to whether or not to give corticosteroids are eligible for randomisation, and as many such patients as possible should be considered for the trial. Heterogeneity of the types of patients entering such a trial is a scientific strength, not a weakness. If a wide range of patients are randomised then it may be possible for a really big trial such as this one to help determine which (if any) particular types of patient are most likely to benefit from treatment.

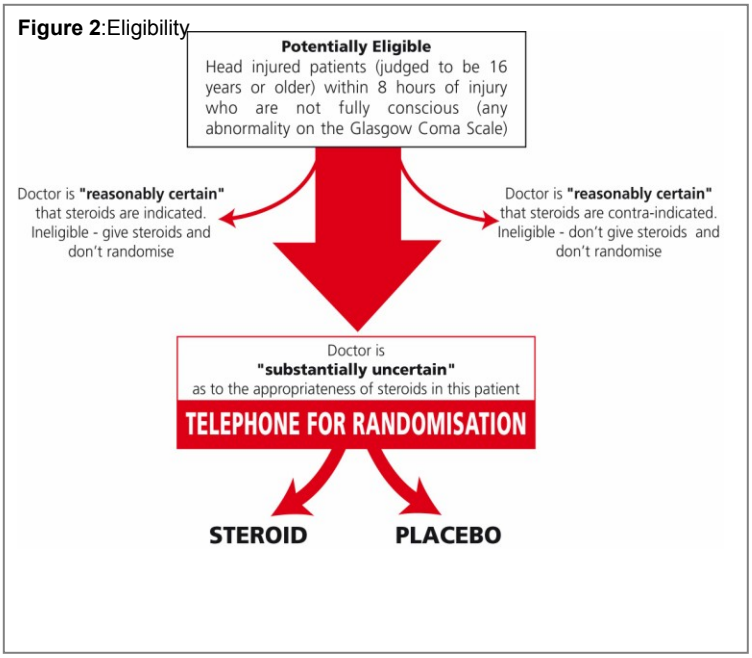
Special eligibility considerations: None. Routine exclusion of patients with gastrointestinal complaints or pregnancy is unnecessary, unless the responsible doctor considers these to be a definite contraindication.

Notes:

(1) This short term corticosteroid regimen should not cause serious gastrointestinal bleeding, nor should it cause a large increase in infection.

(2) Although prolonged use of corticosteroids in pregnancy may affect fetal adrenocortical development, this short term treatment should not do so.

Figure 2:Eligibility



Consent

Patients with head injury and impaired consciousness may be unable to give properly informed consent, and in this emergency situation it may not be medically appropriate to delay the start of treatment. The requirements of the relevant ethics committee will be adhered to at all times. An information leaflet on the study for patients will be available in all drug packs (Appendix 1).

Randomisation

Patients eligible for inclusion should be randomised, and the study treatment started, as soon as possible. Randomisation is done by telephoning a 24-hour toll-free service and takes only about two minutes. The patient entry form (Appendix 2) shows the questions that will be asked by the telephone operator prior to allocation of the treatment packs. The study computer will then randomly assign a treatment pack number that will identify one of the CRASH treatment packs stored in the emergency department. Once a patient has been randomised, we will definitely wish to learn the outcome in hospital, even if the trial treatment gets interrupted or is not actually given.

Study treatment

Each CRASH treatment pack contains:

- 11 x 2g vials of methylprednisolone (MP) or placebo
- 1 x 20mL sterile water for injection (for use with the loading dose)
- 1 x 100mL bag of 0.9% NaCl (for use with the loading dose)
- CRASH stickers (for attaching to infusion bags and patient notes)
- Patient information leaflet and early outcome forms

Treatment	Vials	Dose (MP or placebo)
Loading	1	2g over 1 hour
Day 1	5	0.4g/hour for ~24 hours
Day 2	5	0.4g/hour for ~24 hours

Loading

2g MP (or matching placebo) over 1 hour in 100 mL infusion:

1. Add 20mL water for injection to *one* 2g vial and mix well
2. Add contents of vial to the 100mL bag of 0.9% NaCl provided
3. Infuse over one hour

Daily Maintenance

0.4g/hour for about 24 hours in 20mL/hour infusion (MP or matching placebo):

1. Remove 100mL from a 500mL bag of 0.9% NaCl (to make room for the steroid)
2. Add 20mL water for injection to each of *five* 2g vials and mix well
3. Add all five (about 100mL) to the 500mL bag of 0.9% NaCl
4. Infuse at 20mL/hour for about 24 hours
5. Repeat for maintenance day 2

   N.B. As children under 16 are excluded, a simple fixed-dose treatment can be used. The dosing regimen is that used in the NASCIS-2 and NASCIS-3 trials of MP in acute spinal cord injury.

Unexpected adverse events

Anaphylactic reactions to intravenous corticosteroids are extremely rare, but should be treated in whatever way the responsible doctor prefers (one possibility being intra-muscular adrenaline 0.5mg, i.e. 0.5mL of 1 in 1,000 [1mg/mL] solution).[14] It would be expected that 24-hour anaesthetic cover would be available in all hospitals participating in CRASH. If a serious and unexpected adverse drug reaction occurs and is suspected to be related to the study medicine, this should be logged by calling the 24-hour randomisation service, who will inform the CRASH Co-ordinating Centre in London.

In general, gastro-intestinal bleeds and infections do not need to be reported in this way because some increase in their incidence might be expected with steroids. Likewise, the various medical events that are to be expected in head injured patients do not need to be reported by telephone. All such events are, however, routinely monitored among all patients on the Early Outcome Form (Appendix 3).

Unblinding

In general there should be no need to unblind the allocated treatment. If some contra-indication to corticosteroids develops after randomisation (e.g. severe gastro-intestinal bleeding), the trial treatment should simply be stopped. Unblinding was never found to be necessary in the NASCIS trial of MP in spinal cord injury,[4] and should be done only in those rare cases when the doctor believes that clinical management depends importantly upon knowledge of whether the patient received corticosteroid or placebo (e.g. suspected anaphylaxis). In those few cases when urgent unblinding is considered necessary, the randomisation service should be telephoned, giving the name of the doctor authorising unblinding and the CRASH treatment pack number (if available), and the caller will then be told whether the patient received corticosteroid or placebo.

Measures of outcome

The primary outcome measures are:

- Death from any cause within two weeks of injury
- Death or dependence at six months

In-hospital deaths, complications and short-term recovery are to be recorded on the Early Outcome Form which can be completed entirely from the hospital notes – no extra tests are needed.

Long term recovery will be assessed at six months using the Glasgow Outcome Scale (GOS), which assesses disability and handicap in major areas of life. The GOS will be administered by a postal questionnaire (Appendix 4), completed by the patient or a carer, or by telephone interview. (This does not involve any additional work for the collaborating hospitals.)

Analysis

Comparisons will be made of the primary outcome measures, comparing all those allocated methylprednisolone versus all those allocated placebo, on an 'intention to treat' basis. Analyses will be stratified on time from injury to the initiation of treatment, and on severity of head injury as assessed by the Glasgow Coma Scale. Comparisons will also be made of the risks of infection and gastrointestinal bleeding.

3. Organisation

Data Monitoring Committee

Professor Stephen MacMahon (Chair)
Professor Rory Collins
Professor Stephen Haines

The independent Data Monitoring Committee will conduct interim analyses of mortality and morbidity among all trial participants. It will advise the Steering Group if the randomised comparisons in the trial provide both (i) proof beyond reasonable doubt of a difference in outcome between the study and control groups, and (ii) evidence that would be expected to alter substantially the choice of treatment for patients whose doctors are, in the light of the evidence from other randomised trials, substantially uncertain whether to give corticosteroids to patients with head injury.[15]

Collaborators' responsibilities

Co-ordination within each participating hospital will be through a local collaborator who will:

- Discuss the trial with medical, neurosurgical and nursing staff who see trauma patients and ensure that they remain aware of the trial and its procedures (there are wall charts, pocket summaries and a set of slides to assist with this)
- Ensure that adults with acute head injuries are considered promptly for the trial
- Ensure that the early outcome forms are completed

Co-ordinating Centre responsibilities

- Provide study materials and a 24-hour randomisation (and unblinding) service
- Give collaborators regular information about the progress of the study
- Help ensure complete data collection at discharge and at six months
- Respond to any questions (e.g. from collaborators) about the trial

Publication

The success of CRASH will be entirely dependent upon the collaboration of nurses and doctors in the participating hospitals. Hence, the chief credit for the study will be assigned to them in the main publications, and the collaborators from each participating centre will be named personally in the main report.

Indemnity

The CRASH trial is funded by the Medical Research Council (MRC) and not the manufacturers of methylprednisolone. The London School of Hygiene and Tropical Medicine as the coordinating centre for the trial accepts responsibility attached to its sponsorship of the trial, and as such, would be responsible for claims for any non-negligent harm suffered by anyone as a result of participating in this trial.

Financial support

Medical Research Council funding covers meetings and central organisational costs only. Pfizer Inc. are donating drug and placebo, but the design, management and finance of the study are entirely independent of them. Methylprednisolone is not a new product. Really large trials of such drugs, involving many hospitals, are important for future patients but are practicable only if those collaborating in them do so without payment (except for recompense of any minor local costs that may arise).

4. References

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Appendix 1

Patient and Relative Information Sheet

International study of steroids after head injury

Information for patients, friends and relatives

Supported by the MRC Medical Research Council

This hospital is taking part in an international study to try to find ways to improve recovery after head injury

In this hospital, patients with head injury are given the usual emergency treatment for head injury. They are also given, by a drip into the arm, a treatment as part of a study that is trying to find ways to improve recovery after head injury.

The treatment in the drip is saline with either an active steroid (called *methylprednisolone*) or an inactive, dummy medicine included in it. The choice of what to give was made randomly by a computer in Oxford. The doctors looking after you do not know whether you got the active or the inactive medicine. This information is kept on a confidential list at another hospital.

All patients in the study, whether or not they got steroids, get the best care available.

The steroid may help recovery by slightly reducing the brain swelling that can occur after head injury. But steroids may make people slightly more prone to infection. We hope to find that steroids do a little more good than harm, but we don't yet know this. The study is being carried out in hospitals in Britain as well as overseas, and will include many hundreds of patients with head injury.

The study involves no extra tests, but we send brief details about how you have been in hospital to the trial centre in London, and about six months after your injury, we will contact you to ask how you are getting on. This information would be used in strict confidence by the people working on the study and would not be released under any circumstances.

If you have any questions about your care, please ask your doctor.

Thank you

Appendix 1a

Personal Legal Representative Consent Form

International study of steroids after head injury

Information for Personal Legal Representatives

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MRC
Medical Research Council

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If you have any questions about the patient's care, please ask their doctor.

Thank you

I hereby give permission for ……
to be entered into the CRASH Trial.

Name……

Relationship……

Address……

……

Signature…… Date / /

The trial has been explained to me by:……

……

Appendix 1b

Professional Legal Representative Consent Form

International study of steroids after head injury

Information for Professional Legal Representatives

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If you have any questions about the patient's care, please ask their doctor.

Thank you

I have read and understood the protocol and see no reason for not entering.....
in the CRASH Trial.

Name.....

Signature..... Date / /

Appendix 2

Patient Entry Form

CRASH

PATIENT ENTRY

QUESTIONS THAT WILL BE ASKED
WHEN YOU CALL THE RANDOMISATION SERVICE

[1] Country:

[2] Name of hospital where patient entered:
(or give your hospital code)

[3] Name of caller:

[4] Patient **sex:** Male Female

[5] Do you know patient's **name**? Yes No — if No, go to [8]

[6] Family name: | [7] Given name(s):

[8] Patient Hospital Identification Number:

[9] Do you know patient's **date of birth**? Yes No — if No, go to [11]

[10] Date of birth: / / — or, if not known: [11] Approximate age:

[12] Estimated number of hours since injury:

Current Glasgow Coma Scale: three questions will be asked — one or more replies must indicate an abnormality (if unable to assess, e.g. due to intubation, give most recent GCS)

(13) Eye opening:	[14] Motor response:	[15] Verbal response:
4 Spontaneous	**6** Obeys commands	**5** Orientated
3 To sound	**5** Localising	**4** Confused speech
2 To pain	**4** Normal flexion	**3** Words
1 None	**3** Abnormal flexion	**2** Sounds
	2 Extending	**1** None
	1 None	

[16] This GCS is: **1** Current **2** Most recent

Pupil reactiveness

[17] Left **1** Yes **2** No **3** Unable to assess

[18] Right **1** Yes **2** No **3** Unable to assess

Now call Randomisation Service with these answers and write down the treatment pack no. given at the end of the phone call

Treatment Pack ☐☐ **Box** ☐☐☐☐

Get this pack and follow the instructions on it carefully

Appendix 2

Patient Entry Form (reverse)

LOST OR DAMAGED TREATMENT PACK

1. Call Randomisation Service
2. Ask for *"Lost or damaged treatment pack"*
3. Give answers to questions 1 - 11 overleaf

REPORTING ADVERSE EVENTS

1. Call Randomisation Service
2. Ask for *"Adverse events"*
3. Give answers to questions 1 - 11 overleaf
4. Give **name** of person who has reported the adverse event:
   ……
5. Give **telephone number** of person who has reported the adverse event:
   ……

UNBLINDING

In general there should be no need to unblind the allocated treatment. Unblinding should only be done in those rare cases when management depends importantly upon knowledge of whether the patient received corticosteroid or placebo.

1. Call Randomisation Service
2. Ask for *"Unblinding"*
3. Give answers to questions 1 - 11 overleaf

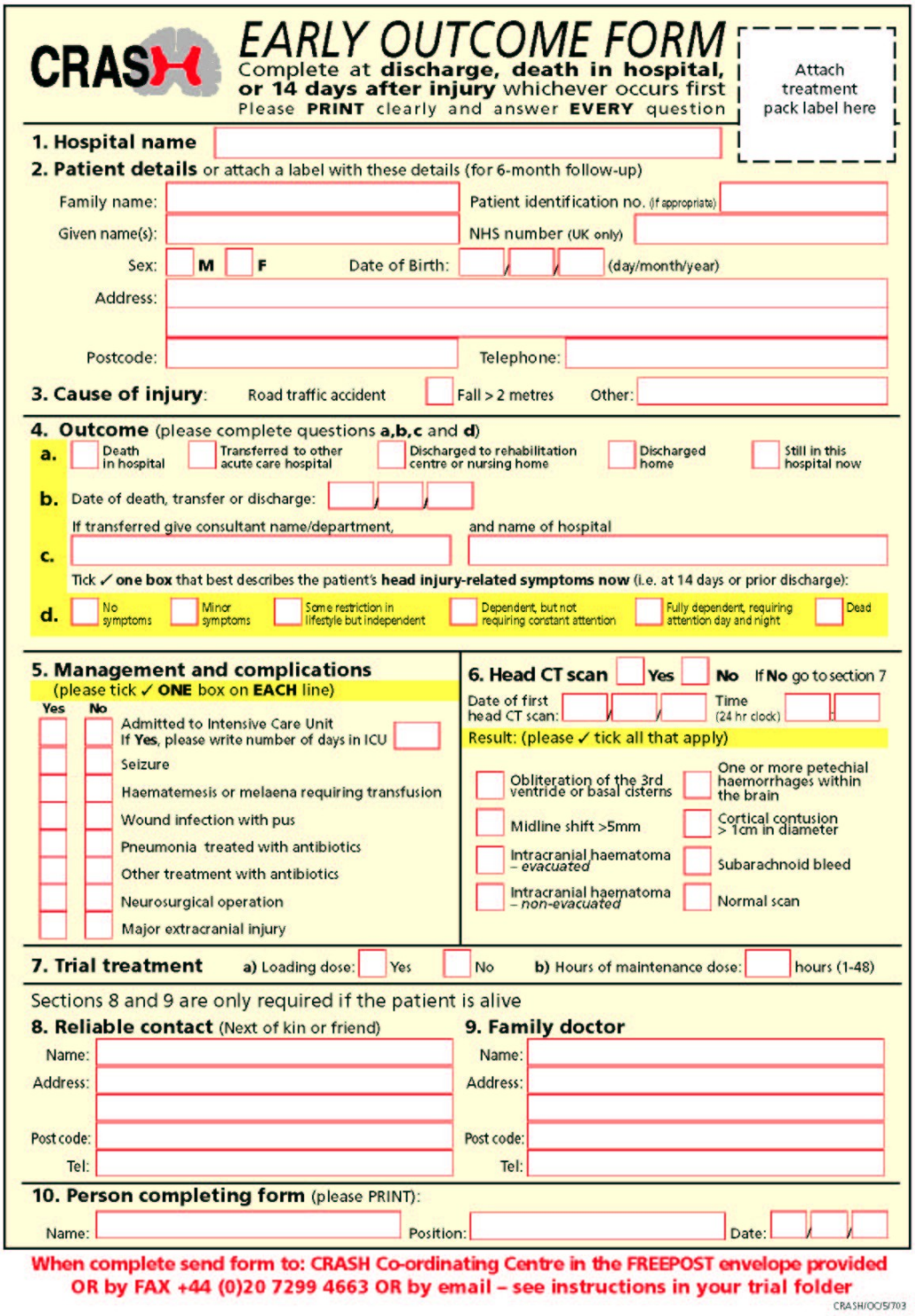
PLEASE COLLECT CONTACT DETAILS WHEN AVAILABLE TO AID FOLLOW-UP

PATIENT	
Name	
Address	
Tel home	
Tel work	
Mobile	

RELIABLE CONTACT 1		**RELIABLE CONTACT 2**	
Name / relationship		Name / relationship	
Address		Address	
Tel home		Tel home	
Tel work		Tel work	
Mobile		Mobile	

Appendix 3

Early Outcome Form



CRASH

EARLY OUTCOME FORM

Complete at **discharge, death in hospital, or 14 days after injury** whichever occurs first

Please **PRINT** clearly and answer **EVERY** question

Attach treatment pack label here

1. Hospital name

2. Patient details or attach a label with these details (for 6-month follow-up)

Family name:

Given name(s):

Patient identification no. (if appropriate)

NHS number (UK only)

Sex: M F Date of Birth: / / (day/month/year)

Address:

Postcode: Telephone:

3. Cause of injury: Road traffic accident Fall > 2 metres Other:

4. Outcome (please complete questions **a,b,c** and **d**)

a. Death in hospital | Transferred to other acute care hospital | Discharged to rehabilitation centre or nursing home | Discharged home | Still in this hospital now

b. Date of death, transfer or discharge: / /

c. If transferred give consultant name/department, and name of hospital

d. Tick ✓ **one box** that best describes the patient's **head injury-related symptoms now** (i.e. at 14 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 | Dead

5. Management and complications

(please tick ✓ **ONE** box on **EACH** line)

Yes	No	
		Admitted to Intensive Care Unit If **Yes**, please write number of days in ICU
		Seizure
		Haematemesis or melaena requiring transfusion
		Wound infection with pus
		Pneumonia treated with antibiotics
		Other treatment with antibiotics
		Neurosurgical operation
		Major extracranial injury

6. Head CT scan Yes No If **No** go to section 7

Date of first head CT scan: / / Time (24 hr clock) :

Result: (please ✓ tick all that apply)

- Obliteration of the 3rd ventricle or basal cisterns
- Midline shift >5mm
- Intracranial haematoma – *evacuated*
- Intracranial haematoma – *non-evacuated*
- One or more petechial haemorrhages within the brain
- Cortical contusion > 1cm in diameter
- Subarachnoid bleed
- Normal scan

7. Trial treatment a) Loading dose: Yes No b) Hours of maintenance dose: hours (1-48)

Sections 8 and 9 are only required if the patient is alive

8. Reliable contact (Next of kin or friend)

Name:

Address:

Post code:

Tel:

9. Family doctor

Name:

Address:

Post code:

Tel:

10. Person completing form (please PRINT):

Name: Position: Date: / /

When complete send form to: CRASH Co-ordinating Centre in the FREEPOST envelope provided OR by FAX +44 (0)20 7299 4663 OR by email – see instructions in your trial folder

CRASH/OC/5/703

Appendix 4

Six month Follow-up Questionnaire

INTERNATIONAL STUDY OF RECOVERY AFTER HEAD INJURY

These questions are about changes in your lifestyle since your injury. They can be answered by you, a relative or friend, or by you both together. If you have any questions about this form, please contact Phil Edwards on 020 7958 8112. Please answer each question below by ticking one box ☑ which is true for you.

Your answers will help us improve the care of people following a head injury.

Please say who filled out this form:

☐ Patient alone ☐ Relative, friend or carer alone ☐ Patient and relative, friend or carer together

1. At present, where do you live most of the time?

☐ In own home ☐ In hospital ☐ In residential care

2. As a result of your injury, do you now need help in the home?

☐ No ☐ Yes. I need some help in the home, but not every day. ☐ Yes. I need help in the home every day. ☐ I need help in the home, but not because of the injury.

3. As a result of your injury, do you now need help to shop?

☐ No ☐ Yes. I need some help, but can go to the local shops on my own. ☐ Yes. I need help to shop even locally, or cannot shop at all. ☐ I need help to shop, but not because of the injury.

4. As a result of your injury, do you now need help to travel?

☐ No ☐ Yes. I need some help, but can travel locally on my own (e.g. by arranging a taxi). ☐ Yes. I need help to travel even locally, or I cannot travel at all. ☐ I need help to travel, but not because of the injury.

5. As a result of your injury, has there been a change in your ability to work? (or to study if you were a student; or to look after your family)

☐ No ☐ Yes. I still work, but at a reduced level (e.g. a change from full-time to part-time, or a change in level of responsibility). ☐ Yes. I am unable to work at present. ☐ My ability to work is restricted, but not because of the injury, or I have retired.

6. As a result of your injury, has there been a change in your ability to take part in social and leisure activities outside home?

☐ No ☐ Yes. I take part a bit less, but at least half as often. ☐ Yes. I take part much less, or do not take part at all. ☐ My ability to take part is restricted for some other reason, not because of the injury.

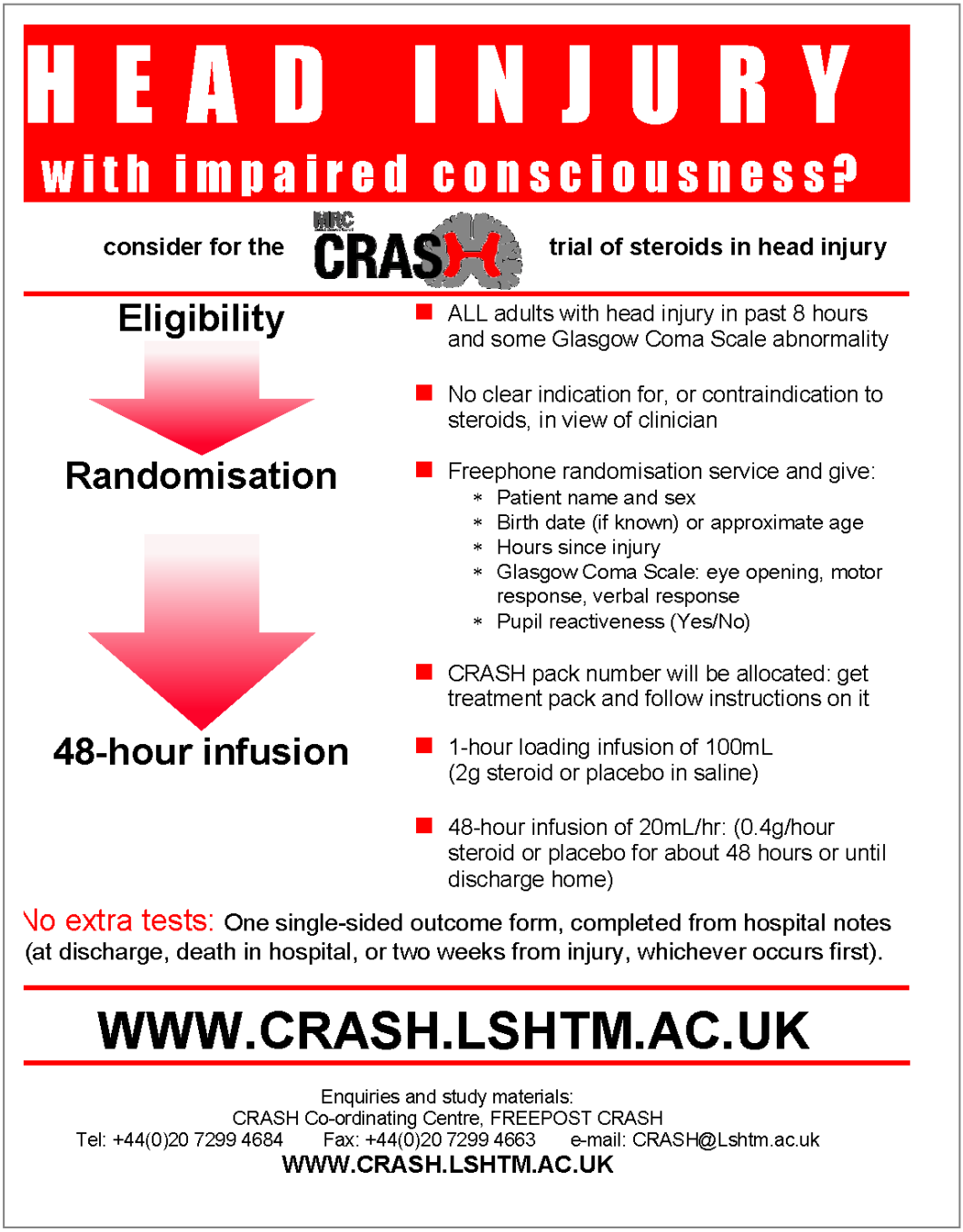
7. As a result of your injury, are there now problems in how you get on with friends or relatives?

☐ No ☐ Yes. There are occasional problems (less than once a week). ☐ Yes. There are frequent or constant problems. ☐ There are problems for some other reason, not because of the injury.

Thank you for your help. Please return this form in the envelope provided to: Dr Ian Roberts, International Study of Recovery after Head Injury, LSHTM, University of London, Keppel Street, London WC1E 7HT

Appendix 5

Protocol Summary



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