ORIGINAL ARTICLE

The MRC CRASH Trial: study design, baseline data, and outcome in 1000 randomised patients in the pilot phase

The CRASH Trial Pilot Study Collaborative Group

Emerg Med J 2002;**19**:510–514

Correspondence to:
Mr P Edwards, CRASH Trial Co-ordinating Centre, London School of Hygiene and Tropical Medicine, 49–51 Bedford Square, London WC1B 3DP, UK;
Phil.Edwards@LSHTM.ac.uk

Accepted for publication
14 June 2002

Objectives: To test the design and feasibility of a large scale multicentre randomised controlled trial evaluating the efficacy and safety of a high dose corticosteroid infusion after head injury. To assess whether large numbers of patients could be enrolled and treated within eight hours from injury and then followed up at six months.
Methods: Randomised placebo controlled multicentre trial of a 48 hour corticosteroid infusion after significant head injury. All head injured adults who were observed while in hospital to have GCS of 14 or less (out of a maximum score of 15), and who were within eight hours of the injury, were eligible for trial entry. Analysis of baseline and outcome data (for both treatment groups combined) for 1000 patients enrolled in the pilot phase of the MRC CRASH Trial.
Results: Fifty two hospitals in 14 countries participated in the pilot phase, recruiting an average of one patient per hospital per month. Of the 1000 randomised patients, 330 (33%) had mild head injury, 289 (29%) had moderate head injury, and 381 (38%) had severe head injury. Seven hundred and nine (71%) patients were randomised within three hours of injury. Outcome at two weeks from injury was known for 991 (99%) patients, of whom 170 (17%) patients died. At the time of writing, six month follow up for the first 500 patients was nearly complete. Vital status was known for 465 (93%) of the 500 patients, of whom 97 (21%) had died. Functional status based on the Glasgow Outcome Scale was known for 438 (88%) of the 500 patients: 21% were dead, 17% were severely disabled, 22% were moderately disabled, and 34% had made a good recovery.
Conclusions: The trial procedures proved practicable and a wide variety of patients were recruited in the emergency department within eight hours of injury. Using simple outcome measures, large numbers of patients can be successfully followed up.

Worldwide more than a million people die from head injuries each year and a similar number are disabled, often with profound effects on the quality of life of the affected individuals and their carers.[1] In 1990 over 5 500 000 intracranial injuries were caused by road traffic crashes alone. Road traffic crashes account for most of the deaths and serious head injuries and car use is rapidly increasing in many countries. The identification of effective treatments for head injury is of global health importance.

Corticosteroids have been used in the treatment of head injury for over 30 years, although recently their value has been questioned because of the failure to reliably demonstrate effectiveness in randomised trials.[2] For such a common problem, if a treatment as simple as short-term corticosteroids produced just a moderate benefit, this could be worthwhile. However, existing randomised trials of corticosteroids in head injury have been too small to demonstrate or refute the possibility of moderate but clinically important benefits or harm from corticosteroids.[3] To determine reliably the effects of a high dose corticosteroid infusion on death and on disability after significant head injury, many thousands of acute head injury patients must be randomised between corticosteroid and placebo infusions.[4 5]

Axonal disruption can continue for several hours after acute central nervous system trauma. In animal studies, it has been shown that early administration of corticosteroids is important for maximal effect.[6] Hence there may be an early phase when further neurological deterioration can be prevented. Timing of corticosteroid administration is also considered to be important in acute spinal cord injury.[7] The aim of the CRASH Trial pilot phase was to test the design and feasibility of a large scale multicentre trial to evaluate the effectiveness and safety of a short-term high dose corticosteroid infusion after significant head injury.[5] In particular, the pilot phase sought to assess whether the enrolment and follow up of large numbers of head injured patients would be possible, and whether treatment could be started within eight hours from the time of injury.

METHODS

Eligibility

All head injured patients (judged to be 16 years or older) who were observed while in hospital to have a score on the Glasgow Coma Scale of 14 or less (out of a maximum score of 15), and who were within eight hours of injury, were eligible for trial entry. There was no other pre-specified exclusion criterion, as the fundamental eligibility criterion was the responsible doctor's "uncertainty" whether or not to use corticosteroids in a particular adult with head injury.

Consent

Patients with head injury and impaired consciousness may be unable to give properly informed consent. In emergency situations it may not be medically appropriate to delay the start of treatment until proxy consent can be obtained, doctors therefore took responsibility for entering their patients, just as they would take responsibility for choosing other treatments. However, the specific requirements of local research ethics committees were strictly adhered to at all times. Information leaflets about the study were provided for patients and their friends and relatives.

Treatment regimen

The study treatment was a 48 hour infusion of methylprednisolone (MP) or placebo. The loading dose was 2 g MP (or matching placebo) over one hour in a 100 ml infusion. The maintenance dose was 0.4g/hour for 48 hours in a 20 ml per hour infusion (or matching placebo). If clinically appropriate,

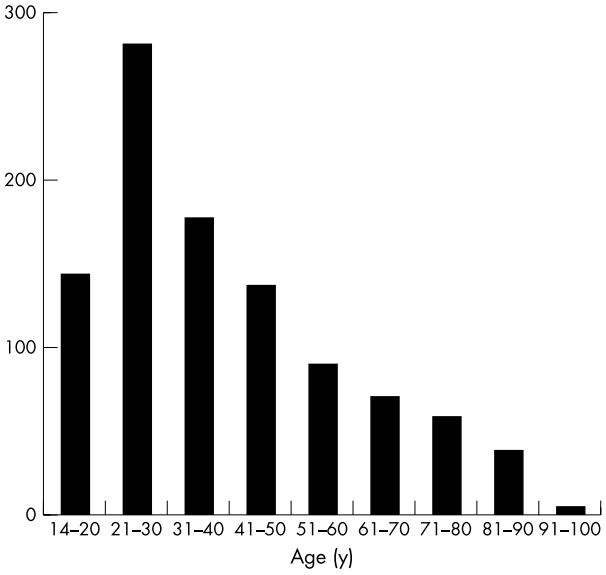

Figure 1 Age of patients at randomisation.

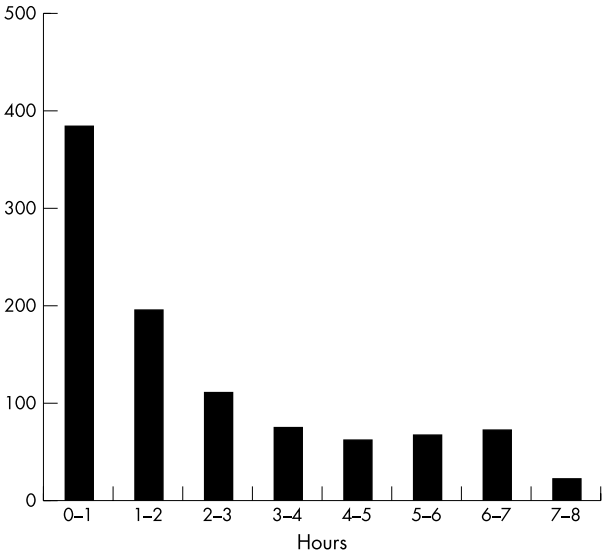

Figure 2 Time between injury and randomisation.

patients could be discharged from hospital before completing the trial treatment.

Randomisation, baseline data collection, and emergency unblinding

Patients were randomised in one of two ways. Central randomisation was by telephoning the 24 hour randomisation service at the Clinical Trial Service Unit (CTSU), Oxford, UK. During the telephone call, baseline data were requested and then entered into the CTSU database. The baseline data collected were—sex, age, hours since injury, Glasgow Coma Scale (GCS) including eye opening (scale 1–4), motor response (scale 1–6), and verbal response (scale 1–5), and localising signs as judged by the presence of one or more non-reactive pupils. A reasonable balance with respect to these, and with respect to hospital, was achieved using the method of treatment allocation known as "minimisation".[8] The minimisation factors were: sex, age (16–24 years, 25–34 years, 35 years and older), hours since injury (one hour or less, one to three hours, over three hours), GCS (3–8, 9–12, 13–14), localising signs, hospital and country. After recording the baseline data, the CTSU computer allocated a number identifying one of the treatment packs stored in the emergency department. Non-central randomisation was used in countries where telephone access is not reliable, or where hospital staff could not easily speak English. For these patients, blinded treatment packs were used sequentially and the baseline data were immediately sent by fax, or as encrypted email attachments to the Co-ordinating Centre. These data were entered into the CTSU database on the day of receipt. Only in special circumstances could treatment allocation be unblinded. Where emergency unblinding was necessary, for example when doctors believed that clinical management depended importantly on knowing whether corticosteroid or placebo had been given, unblinding was possible by telephoning the randomisation service, giving the patient details.

Outcome data collection

Inhospital deaths, complications, and short-term recovery were recorded on a single sided form completed by the responsible doctor at death, discharge, or two weeks after injury, whichever occurred first. Long term recovery was assessed at six months by a simple postal questionnaire, sent to patients or their carers, or by telephone interviews or by home visits (Sri Lanka and South Africa only). Before the start of the pilot, a simple postal questionnaire version of the Glasgow Outcome Scale (GOS) was developed and found to be both reliable and valid.[9] We also conducted a systematic review of randomised controlled trials of strategies to influence response to postal questionnaires in order to identify ways to maximise response to the follow up questionnaire.[10 11] The postal version of the GOS was translated into the relevant languages with back translation to ensure accuracy. Completed questionnaires were returned to the Co-ordinating Centre.

Data processing, analysis, and the data monitoring and ethics committee

Baseline data were transferred electronically each day from CTSU to the Co-ordinating Centre. Outcome data were entered twice and any differences resolved to eliminate data entry errors. Further extensive checks for data consistency were also undertaken. The pre-specified principal analyses were the effects of treatment on death from any cause within two weeks of injury, and on death or dependence at six months. The independent Data Monitoring and Ethics Committee periodically reviewed the accumulating trial data in strict confidence. In May 2000 the Committee reviewed the data and reported that the available data provided no cause to recommend any change to the study procedures or the plans for the expansion of patient recruitment in the main phase of the trial. As the treatment regimen and allocation remained unchanged in the main phase of the trial, the pilot phase results by treatment allocation will be combined with those of the main phase of the study, and will therefore remain confidential until the completion of the trial.

RESULTS

The first patient was enrolled on 13 April 1999, and by 21 December 2000 a total of 1000 patients had been enrolled, an average recruitment of 50 patients per month.

Fifty two hospitals in 14 countries participated in the pilot phase, recruiting an average of 1.0 (range 0.1–6.3) patient per hospital per month.

Baseline characteristics

Table 1 shows the baseline characteristics for the 1000 patients by treatment status. There were 781 (78%) men and 219 (22%) women. The average age was 39 years (SD=19, median = 35), with a range from 14 to 99 years. Four patients were aged under 16 years but were judged to have been aged 16 at the time of randomisation. Figure 1 shows the distribution of patient ages

Table 1 Baseline characteristics for 1000 patients by treatment status

	Corticosteroid n (%)	Placebo n (%)	Total
Age at randomisation (y)			
16–24	133 (27)	126 (25)	259
25–34	113 (23)	114 (23)	227
35–54	141 (28)	152 (30)	293
55+	109 (22)	112 (22)	221
Sex			
Male	393 (79)	388 (77)	781
Female	103 (21)	116 (23)	219
Glasgow Coma Scale			
Severe (GCS 3-8)	196 (40)	185 (37)	381
Moderate (GCS 9-12)	146 (29)	143 (28)	289
Mild (GCS 13-14)	154 (31)	176 (35)	330
Time since injury			
Less than or equal to 1h	211 (42)	193 (38)	404
Over 1 h, less than or equal to 3 h	143 (29)	162 (32)	305
Over 3 h, less than 8 h	142 (29)	149 (30)	291
Localising signs	69 (14)	87 (17)	156
No localising signs	427 (86)	417 (83)	844
All patients	496	504	1000

Table 2 Outcome at two weeks by baseline characteristics

	Outcome at 14 days (n = 991)	
	Number of patients randomised	Dead at two weeks n (%)
Age at randomisation (y)		
16–24	256	22 (8)
25–34	223	33 (14)
35–54	291	37 (23)
55+	221	78 (35)
Sex		
Male	773	122 (16)
Female	218	48 (22)
Glasgow Coma Scale		
Severe (GCS 3-8)	377	118 (31)
Moderate (GCS 9-12)	286	31 (11)
Mild (GCS 13-14)	328	21 (6)
Time since injury		
Less than or equal to 1 h	402	61 (15)
Over 1 h, less than or equal to 3 h	301	56 (19)
Over 3 h, less than 8 h	288	53 (18)
Localising signs		
Non-reactive pupil(s)	155	76 (49)
Pupils both reactive	836	94 (11)
All patients	991	170 (17)

at randomisation. The median time from injury to randomisation was two hours. Figure 2 shows the distribution of time from injury. Four hundred and four (40%) patients were randomised within one hour, 305 (30%) patients were randomised between one and three hours, and 291 (29%) patients were randomised between three and eight hours of injury. Severity of head injury was classified as mild (GCS 13 and 14) in 330 (33%) patients, moderate (GCS 9 to 12) in 289 (29%) patients, and severe (GCS 3 to 8) in 381 (38%) patients. Patients were classified as having localising signs only if one or both of their pupils were not reactive to light. One hundred and fifty six (16%) patients had localising signs before randomisation.

Principal measures of efficacy: deaths within 14 days, death or dependence at six months and proportion of patients with an unfavourable outcome

Table 2 shows the characteristics of the patients at the time of randomisation with their outcome at two weeks. Early outcome forms were received for 991 (99%) of the 1000 randomised patients. One hundred and seventy (17%) patients died within two weeks of randomisation. In assessing long term recovery, the follow up of some patients took over nine months to achieve. For this reason, we have presented the results for outcome at six months for the first 500 patients only. Table 3 shows the characteristics of these patients with their outcome at six months (we continue to seek the information for patients for whom long term recovery is still not known). Among the first 500 patients, vital status at six months was known for 465 (93%), of whom 97 (21%) had died. Functional status at six months based on the GOS was known for 438 (88%) of the 500 patients: 21% were dead, 17% were severely disabled, 22% were moderately disabled, and 34% had made a good recovery. Thus at six months 38% of patients had an unfavourable outcome (severely disabled, persistent vegetative state, or dead).

Other measures of efficacy and safety (fatal and non-fatal events within 14 days)

Table 4 shows the aspects of patient management and health events that were explicitly sought on the early outcome form (figures are for both treatment groups combined). Four

Table 3 Outcome at six months by baseline characteristics

	Outcome at six months (n = 465)					
	Vital status known (n)	Dead n (%)	Severely disabled n (%)	Moderately disabled n (%)	Good recovery n (%)	Alive, functional status not yet known* n (%)
Age at randomisation (y)						
16–24	107	7 (7)	17 (16)	26 (24)	48 (45)	9 (8)
25–34	106	19 (18)	13 (12)	20 (19)	45 (42)	9 (8)
35–54	134	24 (18)	28 (21)	36 (27)	39 (29)	7 (5)
55+	118	47 (40)	22 (19)	19 (16)	28 (24)	2 (2)
Sex						
Male	356	70 (20)	61 (17)	82 (23)	121 (34)	22 (6)
Female	109	27 (25)	19 (17)	19 (17)	39 (36)	5 (5)
Glasgow Coma Scale						
Severe (GCS 3-8)	155	69 (45)	32 (21)	31 (20)	19 (12)	4 (3)
Moderate (GCS 9-12)	147	16 (11)	20 (14)	37 (25)	63 (43)	11 (7)
Mild (GCS 13-14)	163	12 (7)	28 (17)	33 (20)	78 (48)	12 (7)
Time since injury						
Less than or equal to 1h	197	36 (18)	27 (14)	51 (26)	74 (38)	9 (5)
Over 1 h, less than or equal to 3 h	166	32 (19)	31 (19)	30 (18)	62 (37)	11 (7)
Over 3 h, less than 8 h	102	29 (28)	22 (22)	20 (20)	24 (24)	7 (7)
Localising signs						
Non-reactive pupil(s)	78	47 (60)	12 (15)	12 (15)	5 (6)	2 (3)
Pupils both reactive	387	50 (13)	68 (18)	89 (23)	155 (40)	25 (6)
All patients	465	97 (21)	80 (17)	101 (22)	160 (34)	27 (6)

Figures are based on followup of the first 500 patients. *Includes 12 patients flagged for over 18 months on the UK National Health Service Central Register, during which time no death was notified to the CRASH Trial Co-ordinating Centre. We continue to seek the information for every patient for whom long term recovery is still not known.

hundred and twenty four patients were admitted to ICU (43%), 241 (57%) of whom were admitted for four days or more. Seizure was recorded for 176 (18%) patients, haematemesis or melaena for four (0.4%) patients, wound infections for 31 (3%) patients, pneumonia treated with antibiotics for 90 (9%) patients, other treatment with antibiotics for 286 (29%) patients, neurosurgical operation for 195 (20%) patients, and major extracranial injury for 179 (18%) patients. Head CT scans were performed on 754 (76%) patients. The first head CT scan result was normal in 204 (27%) patients. Among the scans showing some abnormality, there were 76 (10%) with obliteration of the third ventricle or basal cisterns, 96 (13%) with midline shift over 5 mm, 163 (22%) with a subarachnoid bleed and 280 (37%) with a haematoma.

Compliance with trial treatment

Compliance with the trial treatment was known for 941 (94%) patients, of whom 918 (98%) received the full loading dose. When clinically appropriate, patients were discharged from hospital before completing the full maintenance dose. Two hundred and six patients (22%) were discharged before completing the maintenance dose and received less than 24 hours of treatment.

Emergency unblinding

Of the 1000 patients randomised, the treatment allocation was unblinded for seven (0.7%) patients. The most common reason for emergency unblinding, accounting for four instances, was that after randomisation the patient was found to have a spinal cord injury for which the responsible doctor considered that corticosteroids were indicated.

Table 4 Patient management and health events within14 days of randomisation

	n	(%)
Admitted to ICU	424	(43)
1–3 days	183	(19)
4 days or more	241	(24)
Seizure	176	(18)
Haematemesis or melaena	4	(0.4)
Wound infection	31	(3)
Pneumonia treated with antibiotics	90	(9)
Other treatment with antibiotics	286	(29)
Neurosurgical operation	195	(20)
Major extracranial injury	179	(18)
Head CT scan performed:	754	(76)
Head CT scan results (n=754)		
Normal scan	204	(27)
One or more petechial haemorrhages	249	(33)
Obliteration of the third ventricle or basal cisterns	76	(10)
Subarachnoid bleed	163	(22)
Midline shift over 5mm	96	(13)
Intracranial haematoma—non-evacuated	199	(26)
Intracranial haematoma—evacuated	81	(11)

Figures are for both treatment groups combined and are based on the data provided on 991 completed early outcome forms. For patients still in hospital 14 days after randomisation all management and health events recorded within 14 days are included. For patients discharged from hospital within 14 days, management and health events were recorded only for the period in hospital.

DISCUSSION

The CRASH Trial is the first very large scale randomised controlled trial in head injury, aiming to recruit and follow up 20 000 patients by 2005. The pilot phase confirmed that the study design was practicable in both university and general hospitals, and in high and middle income countries. Sample size calculations for the CRASH Trial were based on an estimated risk of death among controls of 15%. These data were obtained from a recent randomised controlled trial in head injury using similar but not identical inclusion criteria.[12] The pilot phase provides a more precise estimate of this parameter, using the uncertainty principle as the fundamental eligibility criterion, and confirms that the estimated event rate was appropriate (17% dead within two weeks of injury). The pilot study results at two weeks and at six months confirm that the limited data collected in the CRASH Trial can separate groups at high risk and low risk of a poor outcome. The main predictors of poor outcome were age and score on the GCS.

Among the first 1000 patients enrolled in the CRASH Trial, the median time from injury to randomisation was two hours. Over 70% of patients were randomised within three hours of

injury, confirming that the treatment of head injured patients within an appropriate therapeutic period is feasible.

In a recent survey of previous randomised controlled trials in head injury the average number of participants per trial was 82 and the average loss to follow up was 19%.[13] In the pilot phase of the CRASH Trial, short-term outcome was known for 99% of the 1000 randomised participants, and long term outcome was known for 93% of the first 500. This confirms that with simple outcome measures using postal strategies that have been shown to increase response, large numbers of patients can be successfully followed up. Tracing and contacting patients or their carers to assess long term recovery can take many months to achieve. However, we continue to be successful in tracing patients for whom long term recovery is not known, and continue to make efforts to collect this information.

The CRASH Trial is now the largest head injury trial ever conducted. Participation by more accident and emergency, intensive care, neurosurgical, and trauma departments is still needed worldwide. The Trial Co-ordinating Centre will supply the documentation needed to apply for ethical approval and all materials needed to take part, once approval is obtained. The full trial protocol is available from CRASH Co-ordinating Centre, London School of Hygiene and Tropical Medicine, 49–51 Bedford Square, London WC1B 3DP (email CRASH@LSHTM.ac.uk), or alternatively visit the CRASH web site (www.CRASH.LSHTM.ac.uk).

Contributors

The CRASH Trial Pilot Study Collaborative Group

Belgium (116 patients): A Z Kliena Hospital, Dr V Braet; Centre Hospitalier Regional de Namur, Dr G Mazairac; Hospital of Jolimont, Dr J Jacques. *Colombia* (8): Clinica Las Americas, Dr MF Arango. *Czech Republic* (181): Research Institute for Traumatology and Surgery of Brno, Professor P Svoboda, Dr J Ochmann, Dr I Kantorova, Dr P Scheer; Hospital Pribram, Dr J Bürger; Masaryk Hospital Usti n/L, Dr K Edelmann; Neurosurgical Clinic Charles University Hospital Prague, MUDr F Kramar. *Eire* (24): St James's University Hospital, Mr P Plunkett, Dr G MacMahon. *Germany* (1): Ernst Moritz Arndt University, Professor M Gaab, Dr W Kleist. *Greece* (3): KAT Hospital of Athens, Dr P Myrianthefs. *Malaysia* (4): Hospital University Science Malaysia, Dr J Abdullah, Dr G Ghazaime, Dr A Ariff, Dr M Abdullah, Dr I Zamzuri, Dr A Saufi, Dr A Ghani. *Singapore* (1): National Neuroscience Institute, Mr J Tan. *Slovakia* (20): Reimann Hospital, MD S Trenkler, Dr R Nachaj. *South Africa* (65): Tygerberg Academic Hospital, Professor B Hartzenberg; Wentworth Hospital, Dr N Nathoo, Mr S Khumalo. *Spain* (24): Trauma Centre - Virgen Del Rocio, Dr MA Muñoz-Sánchez, Dr JM Flores-Cordero, Dr F Murillo. *Sri Lanka* (62): Batticaloa General Hospital, Ms V Laloë (Médecins Sans Frontières); National Hospital of Sri Lanka, Dr S Perera. *Switzerland* (30): University Hospital of Zurich, Professor R Stocker, Miss S Ludwig, Miss A Sauerland. *United Kingdom* (461): Aberdeen Royal Infirmary, Mr J Richardson, Sr C Gallagher; Arrowe Park Hospital, Mr A Pennycook; Birmingham Heartlands Hospital, Mr A Bleetman, Sr S Pantrini; Blackburn Royal Infirmary, Dr C Clark, SN S Riding; Bromley Hospital, Dr I Stell; Bury General Hospital, Dr K Ali, CN S Greenwood; Cheltenham General Hospital, Mr P Wilson, Sr L Iddles; City Hospital, Dr D Moore, Dr K Murali; Colchester General Hospital, Mr N Brayley, Mr O Taha El-Amin, SN J Lynch; Countess of Chester Hospital, Mrs M Waters, Sr J Sampson; Doncaster Royal Infirmary, Mr C Chikhani; Eastbourne District General Hospital, Mr R Cottingham, Mr S Funnell; Furness General Hospital, Dr S Mardel, SN A Shaw, SN W Waddington; Harrogate District Hospital, Dr W Hulse, Sr J Crossley; Hope Hospital, Sister G Lomas, Professor D Yates; Leeds General Infirmary, Mr N Zoltie, Mr R Lewis; Medway Maritime Hospital, Dr A Morrice, Miss C Allonby-Neve; Ninewells Hospital and Medical School, Mr S Eljamel; North Manchester General Hospital, Mr J Stuart, SN T Roberts; Northern General Hospital, Dr S Mason, Mr I Loveday; Princess Alexandra Hospital, Mr A Saha, Mr A Pennell, CN D McPhee; Queen Elizabeth Hospital, Birmingham, Mr J Wasserberg, Sr H Shale; Queen Elizabeth Hospital, Gateshead, Mr B Dorani; Queen Elizabeth The Queen Mother Hospital, Mr A Jones, Sr R Perez; Royal Albert Edward Infirmary, Mr A Pinto, Sr D Lee; Royal Bolton Hospital, Dr B Flavin, Mrs B Fogg; Royal Liverpool University Hospital, Dr L Jaffey, Mr M Graves; Royal Oldham Hospital, Mr P Luthra, Sr G Dixon; Selly Oak Hospital, Mr M Green, Sr J Smith; Stepping Hill Hospital, Dr S Southworth, Dr J Butler, Mr M Young; Trafford General Hospital, Miss C Summers, Sr L Katiff; Whiston Hospital, Dr S Graham, Dr T Brown, Sr S Bathgate.

The CRASH Co-ordinating Centre (London)

Professor I Roberts (Clinical Co-ordinator); Miss N Ritchie (Trial Manager); Mr P Edwards (Senior Research Fellow); Ms R Mashru (Data Manager); Ms J Fernandes, Ms C Godward (Follow-up Co-ordinators); Mrs M Ramos (Trial Administrator); Mr A Ritchie (Trial Programmer).

The CRASH Trial Management Group

Professor D Yates; Professor G Teasdale, Ms B Farrell; Mr J Wasserberg; Professor I Roberts; Professor P Sandercock; Ms G Lomas; Miss N Ritchie; Mr P Edwards.

Clinical Trial Service Unit, Oxford University

Professor R Peto, Dr A Young, Mr P Dove.

Data Monitoring Committee

Professor R Collins, Professor S MacMahon (Chair), Professor S Haines, Professor C Warlow.

Writing Committee

Mr P Edwards, Ms B Farrell, Ms G Lomas, Ms R Mashru, Miss N Ritchie, Professor I Roberts, Professor P Sandercock, Mr J Wasserberg, Professor D Yates.

Guarantors

Mr P Edwards and Professor I Roberts.

REFERENCES

1 **Murray CJ**, Lopez AD. *Global health statistics: a compendium of incidence, prevalence and mortality estimates for over 200 conditions*. Harvard School of Public Health, Boston: Harvard University Press, 1996.
2 **Bullock R**, Chesnut RM, Clifton G, *et al*. Part 1: Guidelines for the management of severe traumatic brain injury. *J Neurotrauma* 2000;**17**:499–553.
3 **Alderson P**, Roberts I. Corticosteroids in acute traumatic brain injury: a systematic review of randomised trials. *BMJ* 1997;**314**:1855–9.
4 **Teasdale G**. The treatment of head trauma: implications for the future. *J Neurotrauma* 1991;**8** (suppl 1):53–60.
5 **Yates D**, Farrell B, Teasdale G, *et al*. Corticosteroids in head injury—the CRASH trial. *J Accid Emerg Med* 1999;**16**:83–4.
6 **Braughler JM**, Hall ED. Current application of "high-dose" steroid therapy for CNS injury—a pharmacological perspective. *J Neurosurg* 1985;**62**:806–10.
7 **Bracken MB**. Pharmacological interventions for acute spinal cord injury (Cochrane Review). In: *The Cochrane Library, Issue 4, 1999*. Oxford: Update Software.
8 **White S**, Freedman L. Allocation of patients to treatment groups in a controlled clinical study. *Br J Cancer* 1978;**37**:849–57.
9 **Wilson L**, Edwards P, Fiddes H, *et al*. Reliability of postal questionnaires for the Glasgow Outcome Scale. *J Neurotrauma* (In press).
10 **Edwards P**, Roberts I, Clarke M, *et al*. Methods to influence response to postal questionnaires (Cochrane Methodology Review). In: *The Cochrane Library, Issue 2, 2002*. Oxford: Update Software.
11 **Edwards P**, Roberts I, Clarke M, *et al*. Increasing response rates to postal questionnaires: systematic review. *BMJ* 2002;**324**:1183–5.
12 **Gaab MR**, Trost HA, Alcantara A, *et al*. Ultrahigh dexamethasone in acute brain injury. Results from a prospective randomised double-blind multi-centre trial. *Zentralbl Neurochir* 1994;**55**:135–43.
13 **Dickinson K**, Bunn F, Wentz R, *et al*. Size and quality of randomised controlled trials in head injury: review of published studies. *BMJ* 2000;**320**:1308–11.