

This Provisional PDF corresponds to the article as it appeared upon acceptance. Fully formatted PDF and full text (HTML) versions will be made available soon.

The International Stroke Trial database

Trials 2011, **12**:101 doi:10.1186/1745-6215-12-101

Peter A.G. Sandercock (Peter.Sandercock@ed.ac.uk)
Maciej Niewada (maciej.niewada@wum.edu.pl)
Anna Czlonkowska (czlonkow@ipin.edu.pl)

ISSN 1745-6215

Article type Research

Submission date 22 September 2010

Acceptance date 21 April 2011

Publication date 21 April 2011

Article URL <http://www.trialsjournal.com/content/12/1/101>

This peer-reviewed article was published immediately upon acceptance. It can be downloaded, printed and distributed freely for any purposes (see copyright notice below).

Articles in *Trials* are listed in PubMed and archived at PubMed Central.

For information about publishing your research in *Trials* or any BioMed Central journal, go to

<http://www.trialsjournal.com/info/instructions/>

For information about other BioMed Central publications go to

<http://www.biomedcentral.com/>

The International Stroke Trial database

Peter A.G. Sandercock^{1*}, Maciej Niewada^{2,3}, Anna Członkowska^{2,3}, on behalf of the International Stroke Trial Collaborative Group

¹ Department of Clinical Neurosciences, University of Edinburgh, Department of Clinical Neurosciences, Western General Hospital, Edinburgh EH4 2XU, UK

² Department of Clinical and Experimental Pharmacology, Warsaw Medical University, Poland, Krakowskie Przedmieście 26/28, 00-927 Warsaw, Poland

³ 2nd Department of Neurology, Institute of Psychiatry and Neurology, 9 Sobieskiego 02-957, Warsaw, Poland

Email addresses:

PS: Peter.Sandercock@ed.ac.uk

MN: maciej.niewada@wum.edu.pl

AC: czlonkow@ipin.edu.pl

*Corresponding author

Professor Peter Sandercock

Professor of Medical Neurology, Department of Clinical Neurosciences

Western General Hospital, Edinburgh, EH4 2XU, UK

Tel: +44 131 537 2928 (secretary), Fax +44 131 332 5150

Email. Peter.Sandercock@ed.ac.uk

Abstract

Background: We aimed to make individual patient data from the International Stroke Trial (IST), one of the largest randomised trials ever conducted in acute stroke, available for public use, to facilitate the planning of future trials and to permit additional secondary analyses.

Methods: For each randomised patient, we have extracted data on the variables assessed at randomisation, at the early outcome point (14-days after randomisation or prior discharge) and at 6-months and provide them as an analysable database.

Results: The IST dataset includes data on 19 435 patients with acute stroke, with 99% complete follow-up. Over 26.4% patients were aged over 80 years at study entry.

Background stroke care was limited and none of the patients received thrombolytic therapy.

Conclusions. The IST dataset provides a source of primary data which could be used for planning further trials, for sample size calculations and for novel secondary analyses. Given the age distribution and nature of the background treatment given, the data may be of value in planning trials in older patients and in resource-poor settings.

Background

The International Stroke Trial (IST) was conducted between 1991 and 1996 (including the pilot phase between 1991 and 1993). It was a large, prospective, randomised controlled trial, with 100% complete baseline data and over 99% complete follow-up data. The aim of the trial was to establish whether early administration of aspirin, heparin, both or neither influenced the clinical course of acute ischaemic stroke [1].

Methods

The study had a prospective, randomised, open treatment, blinded outcome (PROBE) design. The inclusion criteria were: clinical diagnosis of acute ischaemic stroke, with onset within the previous 48 hours and no clear indication for, or clear contraindication to, treatment with aspirin or subcutaneous heparin. Unlike many stroke trials of that era (and subsequently), the study did not set an upper age limit. Patients were to have a CT brain scan to confirm the diagnosis of stroke, and this was to be done before randomisation if at all possible. To enter a patient in the study, the clinician telephoned a central randomisation service (at the Clinical Trial Service Unit, Oxford) during this telephone call, the baseline variables were entered and checked, and once validated, the computer allocated the treatment and the telephonist then informed the clinician. The patients and treating clinicians were not blinded to the treatment given. Early outcome data were collected by the treating physician who completed a follow-up form at 14 days, death or hospital discharge (whichever

occurred first). This form recorded data on events in hospital within 14 days, and the doctor's opinion on the final diagnosis of the initial event that led to randomisation. These unblinded data, may therefore be subject to some degree of bias. The primary outcome was the proportion of patients who were either dead or dependent on other people for activities of daily living at six months after randomisation. This outcome was collected by postal questionnaire mailed directly to the patient, or (in Italy) by telephone interview of the patient by a trained researcher, blinded to treatment allocation. The primary outcome was therefore assessed – as far as practicable – blind to treatment allocation and hence should be free from bias. We re-checked the data set for inaccuracies and inconsistencies and extracted data on the variables assessed at randomisation, and at the two outcome assessment points: at 14-days after randomisation, death or prior hospital discharge (whichever occurred first) and at 6-months.

Results

Consent for publication of raw data was not obtained from participants. Consent for participation in the trial was obtained from all subjects or from an appropriate proxy, according to the procedures approved by relevant national and local hospital ethics committees (or Institutional Review Boards [IRB]). These patients were treated 15-20 years ago, and many have died. The dataset (see additional file 1 – IST_data.csv) is fully anonymous in a manner that can easily be verified by any user of the dataset. Patients and hospitals are identified only by an anonymous code; there are no identifying data such as name, address or social security numbers; patient age has

been rounded to the nearest whole number. In our view, publication of the dataset clearly presents no material risk to confidentiality of study participants.

The dataset includes the following baseline data: age, gender, time from onset to randomisation, presence or absence of atrial fibrillation (AF), aspirin administration within 3 days prior to randomisation, systolic blood pressure at randomisation, level of consciousness and neurological deficit. The deficits were classified as one of the Oxfordshire Community Stroke Project (OCSP) categories: total anterior circulation syndrome (TACS), partial anterior circulation syndrome (PACS), posterior circulation syndrome (POCS) and lacunar syndrome (LACS). We extracted events within 14 days on: the occurrence of recurrent stroke, pulmonary embolism, and death (date and cause of death). At 6 months we extracted: degree of recovery, place of residence and current use of antiplatelet or anticoagulant drugs and death (date and cause of death). The cause of death was classified as: due to initial stroke, recurrent ischaemic stroke, recurrent haemorrhagic stroke, pneumonia, coronary artery disease, pulmonary embolism, other vascular cause or a nonvascular cause. Patients were assigned to one of 6 categories according to the place of residence at 6 months following stroke: own home, relatives home, residential care, nursing home, other hospital departments or unknown. The variables extracted are listed with a brief description of each in Tables 1, 2 and 3. Nineteen thousand four hundred and thirty five patients from 467 hospitals in 36 countries were randomised within 48 hours of symptoms onset, of whom 13020 had a CT before randomisation, 5569 were first scanned after randomisation and 846 were not scanned at all. Five thousand one hundred thirty two (26.4%) were aged over 80 years at study entry. Given that 5569 patients were first scanned after randomisation, and 846 were not scanned at all, the 'final diagnosis' is somewhat imprecise. However, since the analysis was by intention to treat, all participants were

retained in the analysis, irrespective of the final diagnosis. The numbers of patients with each final diagnosis are given in Table 4. Whilst the 'final diagnosis variable' is of some interest, it may be influenced by events occurring after randomisation, so for any future analyses, the least biased assessment of the patient characteristics is that recorded at baseline, before randomisation.

To restrict analyses to cases of definite ischaemic stroke, confirmed at the time of trial entry, the variable denoting whether CT had been performed before entry (RCT) should = Y and the final diagnosis should also be ischaemic (DDIAGISC=Y).

Please note that, in the original 1997 Lancet report on the trial [1], figures two a and two b reported the effects of allocation to aspirin and to heparin on the primary outcome, subdivided by various baseline characteristics and by the final diagnosis. The numbers of patients with each pathological type of stroke are somewhat different to the numbers above, because they relate to the number of patients with complete 6 month follow-up data, whereas the numbers above relate to all randomised patients.

Anonymisation

As recommended by *Hrynaszkiewicz et al.* [2] we have removed all direct and indirect identifiers from the database. We therefore present patient's age rounded to the nearest whole number of years. Time of admission to hospital (a potential identifier) was not recorded. Dates of events occurring post randomisation have been converted to the number of days from randomisation. The time variables that were recorded (see below) referred to time of randomisation in the trial (i.e. the time at which the system generated the treatment allocation), not time of admission to hospital, a variable, that - in our view - would not help identify the patient.

Discussion

This large data set, with very complete follow-up, includes a very broad range of acute stroke patients with a uniquely large number of very elderly patients, and so may be useful to researchers planning future research studies. Users of the dataset should be aware that the study was conducted at a time when stroke unit care was not widely available and thrombolytic therapy was used rarely (and none of the included patients received it) [3]. Thus, the background stroke care for the included subjects, while not typical of present-day acute stroke care [4], is perhaps more typical of current stroke care in resource poor settings [5]. Given that the developing world faces a future epidemic of non-communicable diseases, including stroke [5], these data may therefore prove particularly valuable for planning future trials in resource-poor settings. In the developed world, the proportion of the general population who are ‘very elderly’ is rapidly increasing. Older people have been substantially under-represented in stroke trials to date [6], so we hope the large number of patients aged over 80 in this data set could also facilitate planning of trials in the ‘older old’.

The publication of raw datasets such as the IST’s may offer wholly unanticipated benefits to the wider research community. For example, the dataset was licensed to an independent statistical group who used the data to estimate the size and direction of biases introduced when non-randomised comparisons were made and the differences between direct and indirect comparisons. This empirical work led to two important publications on the topic [7,8]. Such additional benefits, realised long after the

original trial was completed, are a further clear indication of the value of opening access to such datasets.

Competing interests

The trial was designed, conducted, analyzed, and reported independently of all sponsors. P.S., M.N., A.C. have received honoraria and travel expenses to lecture at conferences and pharmaceutical advisory meetings, but neither holds any consultancy with, or financial interest in, a pharmaceutical company, nor are they aware of any other potential conflict of interest.

Note for users of the data set

The authors ask that any publications arising from the use of this dataset acknowledges the source of the dataset, its funding and the collaborative group that collected the data.

Authors' contributions

P.S. was the Chief Investigator of the IST responsible for the overall design, conduct and presentation of the study results. M.N. and A.C. were involved in preparation of database and data dictionary for publication and help to draft the manuscript. All authors read and approved the final manuscript.

Acknowledgements

The chief acknowledgement is to the thousands of stroke patients who joined the IST and to their doctors. The staff of the Neurosciences Trials Unit coordinated the study, and randomization was provided by staff at the Clinical Trial Service Unit in Oxford.

Sources of Funding

The study was principally funded by the UK Medical Research Council, the UK Stroke Association, and the European Union BIOMED-1 program. Limited support for collaborators' meetings and travel was provided by Eli Lilly, Sterling Winthrop (now Bayer USA), Sanofi, and Bayer UK. Follow-up in Australia was supported by a grant from the National Heart Foundation and in Canada by a Nova Scotia Heart and Stroke Foundation grant. Czech Republic IST was supported by a grant from the IGA Ministry of Health. India IST was supported by the McMaster INCLEN program and the All India Institute of Medical Sciences. The IST in New Zealand was funded by the Julius Brendel Trust and the Lottery Grants Board. In Norway, the IST was supported by the Norwegian Council on Cardiovascular Disease and Nycomed (for insurance).

References

1. Sandercock P, Collins R, Counsell C, Farrell B, Peto R, Slattery J, Warlow C, International Stroke Trial Collaborative Group. **The International Stroke Trial (IST): A randomised trial of aspirin, subcutaneous heparin, both, or neither among 19 435 patients with acute ischaemic stroke.** *Lancet* 1997, **349**:1569-1581.
2. Hrynaszkiwicz I, Norton ML, Vickers AJ, Altman DG. **Preparing raw clinical data for publication: guidance for journal editors, authors, and peer reviewers.** *Trials* 2010, **11**:9.
access: <http://www.trialsjournal.com/content/11/1/9>.
3. Weir NU, Sandercock P, Lewis SC, Signorini D, Warlow CP, on behalf of the IST Collaborative Group. **Variations between countries in outcome after stroke in the International Stroke Trial (IST).** *Stroke* 2001, **32**:1370-1377.
4. Irwin P, Hoffman A, Lowe D, Pearson M, Rudd AG. **Improving clinical practice in stroke through audit: results of three rounds of National Stroke Audit.** *J Eval Clin Pract* 2005, **11**:306-314.
5. Kengne AP, Anderson CS. **The neglected burden of stroke in Sub-Saharan Africa.** *International Journal of Stroke* 2006, **1**:180-190.
6. Sanossian N, Ovbiagele B. **Prevention and management of stroke in very elderly patients.** *Lancet Neurol* 2009, **8**:1031-1041.
7. Deeks JJ, Dinnes J, D'Amico RA, Sowden AJ, Sakarovitch C, Song F, Petticrew M, Altman DG. **Evaluating non-randomised intervention studies.** *Health Technology Assessment* 2003, **7**:1-173.

8. Glenny AM, Altman DG, Song F, Sakarovitch C, Deeks JJ, D'Amico R, Bradburn M, Eastwood AJ. **Indirect comparisons of competing interventions.** *Health Technology Assessment* 2005, **9**:1-148.

Tables

Table 1. Country codes used in International Stroke Trial.

Country	Code
Albania	43
Argentina	29
Australia	01
Belgium	03
Brazil	42
Bulgaria	04
Canada	05
Chile	06
Czech Republic	07
Denmark	08
Ireland	09
Finland	10
France	11
Georgia	32
Germany	12
Greece	31
Hong Kong	30
Hungary	36
India	37
Indonesia	41
Israel	13
Italy	14
Japan	38
Latvia	39
Malaysia	40
Netherlands	15

New Zealand	16
Norway	17
Poland	18
Portugal	19
Romania	33
Singapore	34
Slovak Republic	44
Slovenia	20
South Africa	21
Spain	22
Sri Lanka	23
Sweden	24
Switzerland	25
Thailand	26
Turkey	35
UK	27
USA	28

Table 2. Variables names and comments.

Randomisation data	
HOSPNUM	Hospital number
RDELAY	Delay between stroke and randomisation in hours
RCONSC	Conscious state at randomisation (F - fully alert, D - drowsy, U - unconscious)
SEX	M=male; F=female
AGE	Age in years
RSLEEP	Symptoms noted on waking (Y/N)
RATRIAL	Atrial fibrillation (Y/N); not coded for pilot phase - 984 patients
RCT	CT before randomisation (Y/N)
RVISINF	Infarct visible on CT (Y/N)
RHEP24	Heparin within 24 hours prior to randomisation (Y/N)
RASP3	Aspirin within 3 days prior to randomisation (Y/N)
RSBP	Systolic blood pressure at randomisation (mmHg)
RDEF1	Face deficit (Y/N/C=can't assess)
RDEF2	Arm/hand deficit (Y/N/C=can't assess)
RDEF3	Leg/foot deficit (Y/N/C=can't assess)
RDEF4	Dysphasia (Y/N/C=can't assess)
RDEF5	Hemianopia (Y/N/C=can't assess)
RDEF6	Visuospatial disorder (Y/N/C=can't assess)
RDEF7	Brainstem/cerebellar signs (Y/N/C=can't assess)
RDEF8	Other deficit (Y/N/C=can't assess)
STYPE	Stroke subtype (TACS/PACS/POCS/LACS/OTH=other)
RDATE	Year and month of randomisation (yyyy-mm)
HOURLOCAL	Local time – hours (99-missing data) of randomisation
MINLOCAL	Local time – minutes (99-missing data) of randomisation
DAYLOCAL	Estimate of local day of week; 1 – Sunday, 2- Monday, 3-Tuesday, 4- Wednesday, 5-Thursday, 6-Friday, 7-Saturday
RXASP	Trial aspirin allocated (Y/N)
RXHEP	Trial heparin allocated (M/L/N). The terminology for the allocated

dose of unfractionated heparin changed slightly from the pilot to the main study. Patients were allocated either 12500 units subcutaneously twice daily (coded as H in the pilot and M in the main trial), 5000 units twice daily (coded as L throughout) or to 'avoid heparin' (coded as N throughout).

Data collected on 14 day/discharge form about treatments given in hospital	
DASP14	Aspirin given for 14 days or till death or discharge (Y/N/U=unknown)
DASPLT	Discharged on long term aspirin (Y/N/U=unknown)
DLH14	Low dose heparin given for 14 days or till death/discharge (Y/N/U=unknown)
DMH14	Medium dose heparin given for 14 days or till death/discharge (Y/N/U=unknown)
DHH14	Medium dose heparin given for 14 days etc in pilot (combine with above; Y/N)
ONDRUG	Estimate of time in days on trial treatment
DSCH	Non trial subcutaneous heparin (Y/N/U=unknown)
DIVH	Non trial intravenous heparin (Y/N/U=unknown)
DAP	Non trial antiplatelet drug (Y/N/U=unknown)
DOAC	Other anticoagulants (Y/N/U=unknown)
DGORM	Glycerol or manitol (Y/N/U=unknown)
DSTER	Steroids (Y/N/U=unknown)
DCAA	Calcium antagonists (Y/N/U=unknown)
DHAEMD	Haemodilution (Y/N/U=unknown)
DCAREND	Carotid surgery (Y/N/U=unknown)
DTHROMB	Thrombolysis (Y/N/U=unknown)
DMAJNCH	Major non-cerebral haemorrhage (Y/N/U=unknown)
DMAJNCHD	Date of above (days elapsed from randomisation)
DMAJNCHX	Comment on above
DSIDE	Other side effect (Y/N/U=unknown)
DSIDED	Date of above (days elapsed from randomisation)
DSIDEX	Comment on above

Final diagnosis of initial event

DDIAGISC	Ischaemic stroke (Y/N/U=unknown)
DDIAGHA	Haemorrhagic stroke (Y/N/U=unknown)
DDIAGUN	Indeterminate stroke (Y/N/U=unknown)
DNOSTRKC	Not a stroke (Y/N/U=unknown)
DNOSTRXX	Comment on above

Recurrent stroke within 14 days

DRSISC	Ischaemic recurrent stroke (Y/N/U=unknown)
DRSISCD	Date of above (days elapsed from randomisation)
DRSH	Haemorrhagic stroke (Y/N/U=unknown)
DRSHD	Date of above (days elapsed from randomisation)
DRSUNK	Unknown type (Y/N/U=unknown)
DRSUNKD	Date of above (days elapsed from randomisation)

Other events within 14 days

DPE	Pulmonary embolism; (Y/N/U=unknown)
DPED	Date of above (days elapsed from randomisation)
DALIVE	Discharged alive from hospital (Y/N/U=unknown)
DALIVED	Date of above (days elapsed from randomisation)
DPLACE	Discharge destination (A-Home/B-Relatives home/C-Residential care/D-Nursing home/E-Other hospital departments/U-Unknown)
DDEAD	Dead on discharge form (Y/N/U=unknown)
DDEADD	Date of above (days elapsed from randomisation); NOTE: this death is not necessarily within 14 days of randomisation
DDEADC	Cause of death (1-Initial stroke/2-Recurrent stroke (ischaemic or unknown)/3-Recurrent stroke (haemorrhagic)/4-Pneumonia/5-Coronary heart disease/6-Pulmonary embolism/7-Other vascular or unknown/8-Non-vascular/0-unknown)
DDEADX	Comment on death

Data collected at 6 months

FDEAD	Dead at six month follow-up (Y/N/U=unknown)
FLASTD	Date of last contact (days elapsed from randomisation)
FDEADD	Date of death (days elapsed from randomisation); NOTE: this death is

	not necessarily within 6 months of randomisation
FDEADC	Cause of death (1-Initial stroke/2-Recurrent stroke (ischaemic or unknown)/3-Recurrent stroke (haemorrhagic)/4-Pneumonia/5-Coronary heart disease/6-Pulmonary embolism/7-Other vascular or unknown/8-Non-vascular/0-unknown)
FDEADX	Comment on death
FRECOVER	Fully recovered at 6 month follow-up (Y/N/U=unknown)
FDENNIS	Dependent at 6 month follow-up (Y/N/U=unknown)
FPLACE	Place of residence at 6 month follow-up (A-Home/B-Relatives home/C-Residential care/D-Nursing home/E-Other hospital departments/U-Unknown)
FAP	On antiplatelet drugs at six month follow-up (Y/N/U=unknown)
FOAC	On oral anticoagulants at six month follow-up (Y/N/U=unknown)
Other data and derived variables	
FU1_RECD	Date discharge form received (days elapsed from randomisation)
FU2_DONE	Date 6 month follow-up done (days elapsed from randomisation)
COUNTRY	Abbreviated country code
CNTRYNUM	Country code (see Table 1)
FU1_COMP	Date discharge form completed (days elapsed from randomisation)
NCCODE	Coding of compliance (see Table 3)
CMPLASP	Compliant for aspirin (N/Y)
CMPLHEP	Compliant for heparin (N/Y)
ID	Indicator variable for death (1=died; 0=did not die)
TD	Time of death or censoring in days
EXPDD	Predicted probability of death/dependence at 6 month
EXPD6	Predicted probability of death at 6 month
EXPD14	Predicted probability of death at 14 days
SET14D	Know to be dead or alive at 14 days (1=Yes, 0=No); this does not necessarily mean that we know outcome at 6 months – see OCCODE for this
ID14	Indicator of death at 14 days (1=Yes, 0=No)
OCCODE	Six month outcome (1-dead/2-dependent/3-not recovered/4-recovered/0 or 9 – missing status)

Indicator variables for specific causes of death

DEAD1	Initial stroke (1=Yes, 0=No)
DEAD2	Reccurent ischaemic/unknown stroke (1=Yes, 0=No)
DEAD3	Reccurent haemorrhagic stroke (1=Yes, 0=No)
DEAD4	Pneumonia (1=Yes, 0=No)
DEAD5	Coronary heart disease (1=Yes, 0=No)
DEAD6	Pulmonary embolism (1=Yes, 0=No)
DEAD7	Other vascular or unknown (1=Yes, 0=No)
DEAD8	Non vascular (1=Yes, 0=No)
H14	Cerebral bleed/heamorrhagic stroke within 14 days; this is slightly wider definition than DRSH and is used for analysis of cerebral bleeds; (1=Yes, 0=No)
ISC14	Indicator of ischaemic stroke within 14 days (1=Yes, 0=No)
NK14	Indicator of indeterminate stroke within 14 days (1=Yes, 0=No)
STRK14	Indicator of any stroke within 14 days (1=Yes, 0=No)
HTI14	Indicator of haemorrhagic transformation within 14 days (1=Yes, 0=No)
PE14	Indicator of pulmonary embolism within 14 days (1=Yes, 0=No)
DVT14	Indicator of deep vein thrombosis on discharge form (1=Yes, 0=No)
TRAN14	Indicator of major non-cerebral bleed within 14 days (1=Yes, 0=No)
NCB14	Indicator of any non-cerebral bleed within 14 days (1=Yes, 0=No)

Table 3. Provisional categories for non compliance (NCCODE).

1.	Should not have been randomised
2.	Refused treatment
3.	Initial event not a stroke
4.	Haemorrhagic stroke
5.	Non compliers
6.	Discharged after 14 days
7.	Discharged up to 14 days
8.	Died prior to receiving the study drug(s)
9.	Died after receiving the study drug(s)
10.	Recurrent stroke / pulmonary embolism
11.	Clinical decision
11a.	Suspected abnormality
11b.	Withdrawn as dying
11c.	Pre-existing condition
11d.	Stated abnormal PTT
11e.	Stated surgery
11f.	Stated atrial fibrillation
12.	Administration problem
13.	Missed out more than 3 doses
14.	Side effect
14a.	Refused treatment
14b.	Discharged
14c.	Administration problem
14d.	Clinical decision
14e.	Recurrent stroke
14f.	Haemorrhagic stroke

Table 4. Final diagnosis of initial event.

	Number
Ischaemic stroke	17398
Haemorrhagic stroke	599
Definite stroke, pathological type unknown	992
Not a stroke	420
Uncertain diagnosis	26
Total	19435

Additional files

Additional file 1 – IST_data.csv

File format: csv- comma separated values

Database with information completed in IST.

Additional files provided with this submission:

Additional file 1: IST_data.csv, 4714K

<http://www.trialsjournal.com/imedia/5187794705229895/supp1.csv>