Description of IST3 Shared Dataset

Contents

1. Demographics, Treatment, Mortality

1.1 Introduction

Data collection in IST3 was principally based on the following forms:

- Randomisation form
- Expert scan reading forms (separate forms completed for pre-randomisation R scan and post-treatment P scan, which was taken within 48 hours of randomisation)
- Treatment form (alternatively called Infusion form)
- Hospital form, recording information for first 7 days post stroke (alternatively called 7 day form)
- Six month follow-up form
- Eighteen month follow-up form

In addition a very important part of IST3 concerned the adjudication of all fatal and non-fatal cerebral events recorded in the first seven days. For patients who had any such events the adjudication committee considered all relevant clinical and scan data and agreed an adjudicated final status in one of 11 categories. This constituted the principal indicator of early outcomes at up to 7 days; see Appendix 2.

The IST3 data management team also maintained a patient table which contained a lot of important housekeeping data, eg death data and records of receipt of completed forms. Relevant variables from this table have been added to the archived dataset.

A small number of derived variables have been added to the archived dataset, for example the predicted probability of good outcome based on the Konig model (Appendix 3).

There were changes to most forms over the 11.6 years of the trial. Where new questions were added the year that they were first asked did not necessarily apply uniformly in all countries, as countries or centres may have renewed their stock of forms at different times.

1.2 Patient IDs

There are 3035 patients in the database. ID numbers were allocated consecutively, but as such the original IDs would provide information on a patient's date of recruitment. To ensure anonymity we have therefore applied a random permutation to the IDs : **`randpat_ID`**.

1.3 Demographics

In order to ensure anonymity exact dates of birth or death are not given. Age is given as an integer - whole years between date of birth and day of randomisation. However there were some years of age with only a single individual. So ages under 40 and ages over 95 have been grouped. The 31 patients aged under 40 have each been given the mean **`age`** of 31.935; and the 26 patients aged over 95 have each been given the mean **`age`** of 97.846. Variable **`age_true`** takes a missing value for ages < 40 or > 95, and the correct integer value in all other case. There is also a variable **`agecat`** which just represents the three groups < 40, 40-95 and > 95.

Gender is coded numerically (*1='F' 2='M' contrary to what is on randomisation form).*

1.4 Centres and Countries

In the original dataset the list of 156 contributing hospitals (centres) were coded numerically. Although there was no obvious way of identifying a centre by its study ID, since there were some centres with very few patients we have assured anonymity by randomising the hospital IDs : **randhosp_id**.

Country is a text variable. Because there some countries with very few participants, or containing particular centres with very few participants, Austria, Canada, Mexico and Switzerland have been grouped together as 'Other'. The remaining 8 countries had sufficiently large numbers of participants that there was no prospect of identifying individuals.

1.5 Treatment allocation

Variable **treatment** is a text field (rtPA or Placebo). All our analyses have been by intention to treat. Protocol violations in which patients did not actually receive the full intended treatment are documented in Webtable 1 of the Lancet paper. They can be identified using variables from the treatment form (see below). The numeric variable **itt_treat** is equivalent to **treatment**

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(0='rt-PA' 1='Placebo').
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1.6 Trial phases

Variable **trialphase** is a text field (Blinded' or 'Open'). There were 276 patients in the blinded phase and 2759 in the Open phase. Between 1/8/2003 and 5/9/2005 both blinded and open phases were running.

1.7 Randomisation date and time and delay between stroke and randomisation

Randomisation dates and times are in local time for the country concerned. Although we are unable to provide exact dates because of privacy restrictions the database provides the year, month, hour and minute of randomisation. Thus analysis of trends over the years of the trial, or of differences between seasons or between times of day are possible.

The dataset does not contain the exact date and time of stroke because of privacy restrictions. The delay from stroke to randomisation is given in hours by variable **randdelay**. According to protocol only patients with a delay of less than 6 hours could be randomised. There were two violations of this aspect of the protocol. Patient **randpat_id**= '02406' was found to have advanced ischaemic change on the R scan, such that the stroke must have occurred well before randomisation. This patient was given a putative delay time of 24 hours. Patient **randpat_id**= '01139' was randomised after a delay of 10.83 hours (for reasons unknown.

For patients who received rtPA the delay from stroke to treatment (variable **treatdelay**) was defined as the difference between the stroke time and the time that the bolus was given (recorded on the treatment form, see below). For patients who did not receive rtPA a putative value of 18 minutes was added to the value of **randdelay** to create the variable **treatdelay**. The rationale for this approach was explained in the published Statistical Analysis Plan.

1.8 Death dates and Survival times

In order to preserve anonymity dates of death are not included in the dataset.

Variable **dead7** records whether a patient died within 7 days of stroke (death date <= randomisation date+7). Variable **dead6mo** records whether a patient died within 6 months of randomisation (death date <= randomisation date + 183). Each of these is a 0-1 variable.

There were 11 patients who were known (eg from GP letters) to have died but for whom date of death was unknown. This is indicated by the variable **deathdate_unknown** (1=Yes, i.e. unknown, 2=No, i.e. known, .=Missing, i.e. not dead). Ten of these 11 patients returned a six month follow-up form, so can be assumed to have survived at least 183 days. The remaining case, patient **randpat_id**= '00690', returned a 7 day form but did not return a six month form. In the analysis for the primary paper (Reference 1, Table 2) it was assumed on the basis of his health state at 7 days that this patient died before six months and therefore he was given an OHS=6; however the survival time for this patient is missing so he was omitted from Kaplan-Meier analysis of survival.

For analysis of survival we have given two pairs of variables, for survival to six and eighteen months respectively.

For analysis of survival to six months patients who did not die in the first 183 days after randomisation were censored at 183 days. Variable **censor6** =0 if death in the first 183 days was known, and =1 if not. Thus **censor6** is identical to 1- **dead6mo** except for the one case with **randpat_id**='00690', for whom **censor6** is set to missing but **dead6mo** is set to 1.

Variable **surv6** gives the survival in days of those who died in the first 6 months (183 days). For those who did not die in the first 183 days the variable **surv6** was given by the last known date of contact if this was before 183 days and the six month form was not received, but otherwise **surv6** was set equal to 183. Thus exact death dates beyond the first six months were only used to confirm that the patient was alive at 183 days, but were not used in this dataset to define values of **surv6** >183. Acquisition of data relating to the last known date of contact was haphazard, depending on communication from GPs, so there would be questions of bias in using it for statistical analysis. Assumptions regarding 'missing at random' might well not be tenable.

For analysis of survival to eighteen months, variable **censor18** =0 if death in the first 548 days was known, and =1 if not. Variable **surv18** gives the survival in days of those who died in the first 18 months (548 days). Patients who did not die in the first 548 days after randomisation and returned an 18 month form were censored at 548 days. Some who did not return an 18 month form had a date of death beyond 548 days. Thus **censor18**=1 and **surv18**=548 if either the 18 month form was returned or there was a death date after 548 days. For those who did not return an 18 month form and had no death date the variable **surv18** was set to 183 if a six month form was returned and no other information was available, (this included 8 cases where it was known that the patient had died after returning the 6 month form but there was no death date), or **surv18** was set to the time till the last known date of contact if that was between 6 and 18 months.

There were 2348 patients with planned 18 month follow-up since Portugal and Switzerland did not plan to follow up beyond six months, and in all other countries except Australia, Norway and Sweden there was no 18 month follow up of patients recruited after June 2010. These 2348 patients were analysed in the Lancet Neurology paper (2); they are identified by variable **plan18**=1.

Although there was no planned follow-up of 18 month health state for the remaining 687 out of 3035 (**plan18**=2), mortality information for all UK patients continues to be flagged by the NHS Central Register. (Updated mortality for patients from Norway and Sweden will also be added to the database in due course.) Therefore since the publication of the Lancet Neurology paper the status of the 109 members of that cohort who were missing OHS data at 18 months has changed slightly. Whereas at the time of publication in 2013 vital status (but not disability) was known for 51 out of these 109, in the public dataset, based on death data available in June 2015, the values of censor18 and surv18

indicate that 60 out of 109 were alive with disability unknown at 548 days, and 49 had both vital status and disability unknown.

Although we have some mortality information on patients who were not part of the planned 18 month follow-up (**plan18**=2), for simplicity censor18 and surv18 are set to missing for all of this group.

Update to vital status of patients recruited from UK, Norway and Sweden

Data on deaths up to 3 years after randomisation in these 3 countries will be collated and it is reasonable to assume that vital status at 18 months will be clarified, for some of the patients for whom this was unknown,. The updated survival analyses to 3 years will be published in due course, and subject to relevant approvals, subsequently the data made available for data sharing.

1.9 Cause of death

IST3 classified cause of death in two distinct ways. A classification into 10 distinct causes, as shown on page 4 of the 7 day form was initially applied to all deaths, including those after 7 days. However after consideration of further information a broader classification into 7 levels was considered more appropriate. This is contained in variable **deathcode**, with formats as shown in Appendix 1. Since all deaths in the first 7 days were considered by the adjudication committee a more detailed classification of deaths due to cerebral causes in the first 7 days was available from the variable **final_status** recorded by the adjudication committee (see Appendix 2).

For 232 patients who died of a cerebral cause in the first 7 days **deathcode** ='E1' (Cerebrovascular) and **final_status** takes values between '01' and '05'. For 38 patients who died of a non-cerebral cause in the first 7 days **final_status**='06', and **deathcode** may have a range of values from 'E2' to 'E9'. For deaths recorded after 7 days cause of death is defined by **deathcode**. Note that some of these have a **final_status** code corresponding to a nonfatal cerebral event in the first 7 days.

All deaths have an associated **deathcode**, including those which occurred after the scheduled follow-up time. Thus patients with censor18 =1 or missing may still have a **deathcode**.

Variables related to death are listed below.

Variable name	Variable label	Variable Format
dead7	Died <=7 days after randomisation	Y01N
dead6mo	Dead at 6 months?	Y01N
Censor6	Censored at 6 months?	Y01N
Surv6	Survival up to 183 days	
Censor18	Censored at 18 months?	Y01N
Surv18	Survival up to 548 days	
deathcode	IST3 cause of death	$DEATHCODE
deathdate_unknown	Binary variable for identifying pts who were known to have died but for whom date of death was unknown (1=Yes, i.e. unknown, 2=No, i.e. known)	YNM

2. Randomisation form

The main variables taken from (or derived from) the randomisation form are shown below.

Variable name	Variable label	Variable Format
livealone_rand	Lived alone before stroke?	YNDQ
indepinadl_rand	Independent in ADL before stroke?	YNDQ
infarct	Recent ischaemic change likely cause of this stroke?	INFARCT
antiplat_rand	Received antiplatelet drugs in last 48 hours?	YNDQ
atrialfib_rand	Patient in atrial fibrillation at randomisation?	YNDQ
sbprand	Systolic BP at randomisation (mm Hg)	
dbprand	Diastolic BP at randomisation (mm Hg)	
weight	Estimated weight (kg)	
glucose	Blood glucose (mmol/L)	
gcs_eye_rand	Best eye response (Glasgow Coma Scale) at randomisation	GCSEYE
gcs_motor_rand	Best motor response (Glasgow Coma Scale) at randomisation	GCSMOTOR
gcs_verbal_rand	Best verbal response (Glasgow Coma Scale) at randomisation	GCSVERBAL
gcs_score_rand	Total Glasgow Coma Scale score at randomisation	
nihss	Total NIH Stroke Score at randomisation	
liftarms_rand	Able to lift both arms off bed at randomisation	YNDQ
ablewalk_rand	Able to walk without help at randomisation	YNDQ
weakface_rand	Unilateral weakness affecting face at randomisation	YNDQ
weakarm_rand	Unilateral weakness affecting arm or hand at randomisation	YNDQ
weakleg_rand	Unilateral weakness affecting leg or foot at randomisation	YNDQ
dysphasia_rand	Dysphasia at randomisation	YNDQ
hemianopia_rand	Homonymous hemianopia at randomisation	YNDQ
visuospat_rand	Visuospatial disorder at randomisation	YNDQ
brainstemsigns_rand	Brainstem or cerebellar signs at randomisation	YNDQ
otherdeficit_rand	Other neurological deficit at randomisation	YNDQ
stroketype	Stroke subtype	STROKETYPE
pred_nihss	NIHSS predicted?	Y01N
konprob	Probability of good outcome based on Konig model	
randvioltype	Protocol deviation at randomisation	$

Yes/No questions have generally been coded as Yes=1, No=2; so the coding shown on the randomisation form for such questions should be ignored. The variable format YNDQ assigns values for a variety of other possibilities such as “Don’t know”, “Cannot assess”, “Question not answered”, “Question not asked”. See Appendix 1 for a list of all formats.

Most of the above variables should be self-explanatory after looking at the randomisation form, but we note here some details of interpretation of specific variables.

The NIH Stroke scale is the most important measure of severity of the initial stroke. The variable **`nihss`** is numeric, ranging in value from 0 to 37. The assessment form is included in Appendix 8. For 244 patients at the start of the trial, NIHSS was not recorded. The value of **`nihss`** for these patients was subsequently predicted from a regression estimated for a set of patients who were not part of IST3, with Glasgow Coma Scale values and seven indicators of neurological deficit as explanatory variables. (See Appendix 3 for details of the regression.) Variable **`pred_nihss`** indicates whether the value of **`nihss`** was predicted by this method.

Variable **`konprob`** is the estimated probability of a good outcome at 6 months based on the model of Konig et al (2008) which used a regression on age and NIHSS. (See Appendix 3.)

Variable **stroketype** uses the OCSP (Oxford Community Stroke Project) classification of stroke subtypes. This is based on the pattern of neurological deficit and the Glasgow Coma Scale (see Appendix 4).

The Glasgow Coma Scale variables are coded as shown on the form and the total GCS score is the sum of the scores on the eye, motor and verbal scales.

Variable **nobleed_rand** had value 1 (Yes) for all cases, as required for patients to be randomised. It has therefore been omitted from the dataset. However subsequent re-examination of pre-randomisation scans revealed one protocol violation in this regard.

Variable **infarct** has 3 possible values and is coded as shown on the randomisation form.

Variable **dbprand** has 19 missing values (values of diastolic BP less than 10 were set to missing). Also there are two values of 35 and 36 which are protocol deviations. These were not recorded in Lancet webtable 2.

There are no missing values for the two variables relating to functional ability on page 2 of the randomisation form. However in relation to the 8 variables denoting types of neurological deficit varying numbers of patients could not be assessed – visuospatial disorder had the highest percentage (20%) of patients that could not be assessed.

During the early part of the trial, glucose levels had to be within the protocol-specified range, but were not recorded at randomisation. The **glucose** level was therefore not measured on the first 282 patients recruited.

The randomisation form asked whether the patient had received antiplatelet therapy in the 48 hours before stroke onset. However there were 85 patients for whom the response to this question was 'Unknown'. Variable **antiplat_rand** therefore incorporates some information from the seven day form to fill the missing values; 32 of the 85 had had pre-admission treatment with aspirin, dipyridamole or clopidogrel, according to the first part of the 7 day form; their values of **antiplat_rand** were set to 1 (Yes). Among the remaining 53, 42 had definite 'No' in response to the pre-admission aspirin, dipyridamole and clopidogrel questions and 11 had missing responses to these questions; all these cases had their values of **antiplat_rand** set to 2 (No). Where there were inconsistencies between the pre-admission treatment information from the seven day form and definite responses regarding antiplatelet treatment on the randomisation form the latter were taken as correct.

A variable **other_antiplatelet_pre** was created to represent pre-admission treatment with anti-platelets other than aspirin. This was indicated if the value of **antiplat_rand** was 1 (Yes) but the seven day form indicated no aspirin treatment pre-admission.

There were 42 cases of protocol violation reported in Webtable 1 of the Lancet paper. These are given in character variable **randvioltype**. This variable enables particular identification of patients such as those mentioned in 1.7 above.

3. Pre-randomisation scan (R Scan) form

There were 18 patients with no R scan form (**recR**=0 if not received, 1 if received).

Variable **R_scantype** records whether the scan was CT or MR.

269 patients had a completely normal scan (Question 1, variable **R_scannorm**)) and so most of the following questions were skipped. Another 1524 had a non-normal scan but had no sign of acute ischaemic change in Q2 (variable **R_acuteic**), and this meant that they skipped to Q17. Variable **R_isch_change** combines Questions 1 and 2 into a single three-level variable. For the primary analysis (Lancet 2012) a variable **vis_infarct** was created combining information on visible signs of infarct from the scan form with information from clinical completion of the randomisation form. If there was a sign of acute ischaemic change from the scan form, or if the R scan form was missing but the variable **infarct** on the randomisation form indicated recent ischaemic change (possible or definite) then **vis_infarct** was set to 1 (Yes). Otherwise **vis_infarct** was set to 2 (No).

Information on the side of the brain in which the acute stroke lesion was located (left, right or midline) was taken from the R scan form (variable **sideaic**) and considered together with similar information from the P scan and the seven day form. Where there were disagreements an adjudication was made after looking again at the scans and clinical record. The variable **asl** (adjudicated side of lesion) is included in the dataset, and the variables **sideaic** from the scan form and **side_brain** from the seven day form have been omitted . See Appendix.

3.1 Derived variables from scan form

A small number of derived variables have been added to the scan datasets.

R_infarct_size has been constructed from questions 6, 7 and 10-15 (see Appendix 5).

The same questions were used to define **R_infarct_territory** (see formats for details).

R_swelling is a condensed version of responses to question 16.

R_hypodensity is simply a numeric version of the character variable `hypodeg`.

R_hyperdense_arteries has been constructed from question 17 by grouping MCA, ICA and ACA as ‘anterior’ and PCA, VA and BA as ‘posterior’.

The ASPECTS score, **R_mca_aspects**, has a maximum value of 10 and has one point subtracted for each of the aspects in question 8. The total aspects score, **R_tot_aspects**, has a maximum of 12, calculated by subtracting one point for each of the aspects in question 8 and subtracting a further one or two points if PCA or ACA were affected.

We have also added 0/1 variables denoting presence or absence of infarcts in the regions covered by questions 10-15 : **aca1, pca1, subinf1, cbzinf1, cinf1, stem1.**

R_atrophy and **R_whitematter** are binary variables reflecting whether there was any evidence at all of atrophy or white matter in questions 26 and 27.

Note, the variables from the expert read of R scans are coded as .= Missing when the form was not returned.

3.2 Questions on haemorrhage, microhaemorrhage and minor lesions

According to protocol there should be no patients with haemorrhage on the R scan. Although there were 8 'Yes' responses to Q20, after further examination of the scans only one of these cases was considered a true protocol violation (see below). Variables **anyhaem, haemtype, haemsize anymicrohaem and microhaemcount** were only pertinent for the post-treatment scan and were omitted in this dataset.

There were just 15 patients considered to have a second minor new ischaemic lesion (Q18). Variables **silreg1, silside1** and **silsize1** record the region, side and size of these lesions. There were just two cases where a second minor lesion was also noted, but these data have not been included.

4. Patient treatment form (infusion form)

Treatment forms were not returned for 6 patients (one rt-PA and 5 Control), as recorded in variable **recinfus**.

Infusion compliance is summarised in Webtable 1 of the Lancet 2012 paper, based largely on the variables **gotbolus, infus_start, infus_halt** and **totdose**. The interpretation of **gotbolus** depends on the phase and treatment group. In the Blinded phase all patients should have received a bolus, but there was 1 protocol deviation, with **gotbolus** ='N'. In the Open phase only patients in the rtPA group were supposed to get a bolus; so patients in the rtPA group who did not receive the bolus have **gotbolus** ='N' and patients in the Control group who did not receive a bolus have **gotbolus** =' '. If a treatment form was not received **gotbolus** =' '.

Among 1635 patients with **gotbolus** ='Y', 5 did not start the infusion that was supposed to follow the bolus and 97 had the infusion started but halted before completion. There are codes, **nostartcode** and **haltcode**, which give some additional information with regard to the reasons why a full treatment may not have been given (see Appendix for brief description of codes). In some cases where the full treatment was given the codes just give further information.

Variable **totdose** was missing for 7 patients who received some treatment (**gotbolus**='Y'). The same missing value (.) was assigned to these 7 as to those who did not get any bolus or did not return an infusion form.

5. Seven day form

Forms were received for 3034 out of 3035 patients. The one Control patient for whom no form was received returned a six month follow up, so was known to be alive at seven days. He also returned an 18 month form. But there was no R scan for this patient, and because the seven day form is missing there are no details on consent. (Variables relating to consent are taken from this form.)

Questions on pre-admission treatments, intravenous fluids insulin, feeding via nasogastric tube and antibiotics (all on page 1 of the form) were not asked until 2004. The coding preserves a distinction between cases where a question was not asked and cases where a question was asked but no response was provided (format YNDQ).

The table below shows variables defined by the first page of the seven day form.

Variable name	Variable label	Variable Format
rec7	Seven day form received	Y01N

consent_type	Type of patient consent	CONSENT
aspirin_pre	Aspirin before admission?	YNDQ
dipyridamole_pre	Dipyridamole before admission?	YNDQ
clopidogrel_pre	Clopidogrel before admission?	YNDQ
lowdose_heparin_pre	Low dose heparin before admission?	YNDQ
fulldose_heparin_pre	Full dose heparin before admission?	YNDQ
warfarin_pre	Warfarin before admission?	YNDQ
antithromb_pre	Other thrombotic agents before admission?	YNDQ
hypertension_pre	Treatment for hypertension before admission?	YNDQ
Anticoag_pre	Pre-trial treatment with anti-coagulants	Anticoag_pre
diabetes_pre	Treatment for diabetes before admission?	YNDQ
stroke_pre	History of previous stroke or TIA?	YNDQ
aspirin_day1	Aspirin in first 24 hours?	YNDQ
antiplatelet_day1	Other antiplatelets in first 24 hours?	YNDQ
lowdose_heparin_day1	Low dose heparin or low molecular weight heparin in first 24 hours?	YNDQ
full_anticoag_day1	Full anti-coagulation in first 24 hours?	YNDQ
lowerBP_day1	Treatment to lower blood pressure in first 24 hours?	YNDQ
nontrial_thromb_day1	Non-trial thrombolysis in first 24 hours?	YNDQ
iv_fluids_day1	Intravenous fluids in first 24 hours?	YNDQ
insulin_day1	Insulin in first 24 hours?	YNDQ
aspirin_days2to7	Aspirin between 24 hours & 7 days?	YNDQ
antiplatelet_days2to7	Other antiplatelets between 24 hours & 7 days?	YNDQ
lowdose_heparin_days2to7	Low dose heparin or low molecular weight heparin between 24 hours & 7 days?	YNDQ
full_anticoag_days2to7	Full anti-coagulation between 24 hours & 7 days?	YNDQ
lowerBP_days2to7	Treatment to lower blood pressure between 24 hours & 7 days?	YNDQ
nontrial_thromb_days2to7	Non-trial thrombolysis between 24 hours & 7 days?	YNDQ
nasogastric_days2to7	Nasogastric tube or percutaneous gastrostomy between 24 hours & 7 days?	YNDQ
antibiotics_days2to7	Antibiotics between 24 hours & 7 days?	YNDQ

The questions on the left in the top half of page 2 of the seven day form have been combined into a single variable **`findiag7`**, with three levels corresponding to the clinician's final diagnosis of the initial randomising event. Although 2 cases of haemorrhagic stroke are recorded here, after expert assessment of the R scan only one of these (randpat_id 01018) was considered a true protocol violation. (Thus variable **`haem_type7`** has only two nonmissing values and one of these is incorrect.) There were 47 patients recorded as having non-stroke causes and the types of non-stroke cause are recorded in variable **`nonstroke_type7`**. Most of these cases were recorded as 'other', and little further information was available. (12 out of 34 'other' had a TIA.)

The information relating to the side of the brain affected by the acute stroke lesion recorded at the top of page 2 was considered together with similar variables from the pre- and post-randomisation scans. Where there was disagreement between these three records an independent specific investigation of the scans was carried out. As a result a variable **`asl`** (adjudicated side of lesion) was constructed. (See Appendix 6 for hierarchy rules used to define **`asl`**.)

The information on whether the R scan type was CT or MR was less reliable on the hospital form than on the actual scan records. Therefore this information was taken from the scan records (see section 3 above.)

The bottom of page 2 of the seven day form asks for the number of nights, in the first 7 days, that the patient spent in each of 7 types of ward. A hierarchy was assumed whereby patients might move from medical admissions through a high dependency/intensive care unit, then into a stroke unit and then into a general ward. (Neurology, geriatric medicine and general internal medicine were grouped together as general wards.) This assumption was needed when the total number of nights recorded exceeded 7. So the number of nights was cumulated across these four categories and truncated to 7. For example if a patient was recorded as having spent 3 nights in the medical admissions area, 5

nights in a stroke unit and 1 night in a general ward; these numbers were truncated to 3, 4 and 0 respectively, with a total of 7. The table below shows the variables transferred from page 2 of the seven day form.

Variable name	Variable label	Variable Format
findiag7	Final diagnosis of initial randomising event (7 day form)	FINDIAG
brainsite7	Location of initial ischaemic stroke (7 day form)	BRAINSITE
haem_type7	Type of initial haemorrhagic stroke (7 day form)	HAEMTYPE
nonstroke_type7	Type of non-stroke cause (7 day form)	NONSTROKETYPE
med_adno	Number of nights in Medical Admissions Unit in first 7 days	
critcareno	Number of nights in Critical Care Unit in first 7 days	
strk_unitno	Number of nights in Stroke Unit in first 7 days	
genwardno	Number of nights in General Ward in first 7 days	

The detailed data collected in the upper half of page 3 of the seven day form were considered by the adjudication committee in conjunction with scan data. A unique secondary outcome, defined by the text variable **`final_status`**, was assigned to all patients who had a cerebral event recorded on the seven day form or died of a non-cerebral cause within seven days (see IST3 Protocol and Statistical Analysis Plan). The definitions of final status are in Appendix 2; where **`final_status`**='NE' this means that on adjudication no cerebral event was deemed to have occurred. A numeric variable, **`sevendaycase`**, was created corresponding to the text variable **`final_status`**, with **`sevendaycase`**=0 for all patients who had no event in the first seven days. The number of days from day of randomisation to day of **non-fatal** adjudicated event is variable **`event_days`**. Note that for fatal events in the first 7 days variable **`surv6`** gives the corresponding information, and **`event_days`** is missing. The most important secondary outcome is variable **`sich7`** which defines symptomatic intracranial haemorrhage in the first 7 days. The table below shows the variables which replace the detailed information collected in the top half of page 3 of the seven day form.

Variable name	Variable label	Variable Format
adjudicated	Patient had adjudicated event in first 7 days	Y01N
sevendaycase	Type of adjudicated event in first 7 days	SEVENDAYCASE
final_status	Adjudicated final status	$
sich7	Symptomatic intracranial haemorrhage in first 7 days	Y01N
event_days	Days from randomisation to adjudicated nonfatal event	

The bottom of page 3 of the seven day form records non-cerebral events occurring in hospital in the first 7 days. Most of the variables below should be self-explanatory.

Variable name	Variable label	Variable Format
myocard_infarct	Myocardial infarction in first 7 days	YNM
extracranial_bleed	Major extracranial bleed in first 7 days	YNM
allergic_reaction	Major allergic reaction in first 7 days	YNM
other_effect	Other possible side effect in first 7 days	YNM
adverse_reaction	Other adverse reaction in first 7 days	YNM
Other_effect_code	D code for other side effects on 7 day form	$

As mentioned above the likely cause of death from the top of page 4 of the 7 day form has been simplified into the variable deathcode. The variables relating to current neurological status and functional ability at 7 days are self-explanatory, and coded in the same way as the corresponding

variables recorded at randomisation. The question on activities of daily living was not asked until 2004.

Discharge **destination** is defined on page 5 of the seven day form. Among the 270 cases who died in the first 7 days, four had destination codes in that list. It is presumed that the other 266 died in hospital. The **destination** variable has been enhanced to distinguish these 266 from the 1898 who were still alive and in hospital at day 7.

Variable name	Variable label	Variable Format
gcs_eye_7	Best eye response at 7 days (Glasgow Coma Scale)	GCSEYE
gcs_motor_7	Best motor response at 7 days (Glasgow Coma Scale)	GCSMOTOR
gcs_verbal_7	Best verbal response at 7 days (Glasgow Coma Scale)	GCSVERBAL
liftarms_7	Able to lift both arms off bed at 7 days	YNDQ
ablewalk_7	Able to walk without help at 7 days	YNDQ
indepinadl_7	Independent in activities of daily living at 7 days	YNDQ
destination	Destination to which patient discharged from hospital	DESTINATION

6. Six month form

2124 six month follow-up forms were returned. There were two slightly different follow-up forms, depending whether the patient was expected to be at home or in hospital. 15 out of 2124 were forms for patients still in hospital at six months (variable **sixmonthform**).

The principal outcome was the Oxford Handicap Score. This has six levels coded 0 to 5 corresponding to the six health states described at the top of page 2 of the six month form. In addition level 6 was used for patients who died before 6 months, ie <=183 days post-randomisation (815 patients). This variable is **OHS6**. [Note **OHS6**=6 is equivalent to **dead6mo**=1 and **OHS6**<6 is equivalent to **dead6mo**=0.]

There were 96 patients who did not return a six month form but were either known to be alive (because we had a death date more than 183 days after randomisation) or assumed to be alive at 6 months (where we had no death date). For these patients an imputed value for **OHS6** was calculated using the reported health state in the seven day form (supplemented in a few cases by information from the 18 month follow-up) – see Appendix 7 for more details. Variable **imputed6** records whether OHS6 was imputed.

One patient (**randpat_id**=00110) died after 179 days but submitted a six month form; for consistency with the other cases who died before six months the information on this form was replaced by missing values.

Variables **aliveind6** and **alivefav6** are 1-2 variables corresponding to **OHS6**<=2 and **OHS6**<=1 respectively. Variable **ordinal6** has levels 1,2,3,4 corresponding to **OHS6** =0,1,2,3, and level 5 corresponding to **OHS6** =4,5,6 combined.

The coding for questions on page 1 of the six month form is a little complicated – see format YNDQ. There are separate codes for (i) cases where the question was not relevant as the patient died before 6 months (815 cases); (ii) cases where the question was on the form but no response was given; (iii) cases where the form was not returned (96 cases who survived to six months); (iv) cases where the question wasn't asked (early forms before 2004); and for the first four questions there is a "Don't know" response as well. Note that no imputations have been made for the 96 alive non-responders, except for the OHS score. These non-responders were divided (in Table 2 of Lancet, 2012) into those who were known to be alive at the six month date, eg because we had a later death date or other

contact date, and those for whom nothing further was known. Two variables **disab_unknown6** and **vital_and_disabunknown6** define these categories. However since more information has become available since 2012 there are now more who are known to have been alive at six months and fewer in the second category. There is also a variable missing6 which in fact takes the value 1 for all cases, because it refers to whether OHS6 is missing, and since we imputed missing values for OHS6 there were none missing.

The coding for the 'Health Today' questions on page 2 of the six month form is similar.

It is worth noting that six month forms could be completed well after the due date. It appeared that only about 75% of returned six month forms had been completed within seven months of randomisation. Just under 5% of forms had apparently been completed more than a year post-randomisation.

Variables from the six month form that have been included in the dataset are listed below.

Variable name	Variable label	Variable Format
recsix	Six month follow-up returned?	Y01N
sixmonthform	Type of six month form	SIXMONTHFORM
sixcompleted_by	Person completing 6 month follow-up form	COMPLETER
ohs6	Oxford Health Scale 6 months	
ordinal6	Ordinal health state (5 levels) at 6 months	
aliveind6	Alive and independent at 6 months (OHS 0-2)	YN
alivefav6	Favourable outcome at 6 months (OHS 0-1)	YN
deadordep6	Dead or dependent at 6 months (OHS >=3)	YN
imputed6	OHS at 6 months imputed?	YN
aspirin6	Aspirin given on admission day (6 month form)	YNDQ
bloodthin6	Blood thinning injections given on admission day (6 month form)	YNDQ
clotbust6	Clot busting drugs given on admission day (6 month form)	YNDQ
stocking6	Special stockings given on admission day (6 month form)	YNDQ
gotprobs6	Stroke left patient with problems (6 month form)	YNDQ
needhelp6	Needs help with everyday activities (6 month form)	YNDQ
walkhelp6	Needs help to walk (6 month form)	YNDQ
speakprob6	Major problems speaking (6 month form)	YNDQ
mobility6	Mobility problems (6 month form)	MOBILITY
selfcare6	Washing or dressing problems (6 month form)	SELFCARE
activities6	Usual activities problems (6 month form)	ACTIVITIES
pain6	Pain or discomfort (6 month form)	PAIN
anxiety6	Anxiety or depression (6 month form)	ANXIETY
wherelive6	Where patient lives now (6 month form, patient not in hospital)	WHERELIVE
howlive6	How patient lives now (6 month form, patient not in hospital)	HOWLIVE
euroqol6	Health state (Euroqol) at 6 months	

7. Eighteen month form

The form for follow-up at 18 months was identical to the 6 month follow-up form. The variable names are therefore the same except that '6' is replaced by '18'.

Variable **receighteen** takes values 1 or 0 according as the 18 month form was or was not returned. Among the 2348 with planned follow-up to 18 months there were 822 who died before the due date and 109 who did not return the form but were either known to be alive at 18 months (because we had a later death date) or were not known to have died before the due date. The OHS values are recorded in variable OHS18. Thus there were 1417 patients with OHS18 values in the range 0 to 5.

There were two cases (among the planned 2348) who returned the 18 month form before the due date but did in fact die just before their due date. These cases have OHS18=6, and most other data from their form were coded as 10 ('died so question not relevant' – see format yndq in Appendix) or as missing. However these two cases have **receighteen**=1 (Yes) and **missing18**=2 (No) because they did return their form.

There are two variables **disab_unknown18** and **vital_and_disabunknown18,** defined as for the 6 month follow-up, except that they are only defined for patients in the scheduled 18 month follow-up (**plan18**=1); they take missing values for the rest of the patients.

There were 10 cases where the 18 month form was returned even though the patients were not among the 2348 with planned follow-up. Nine of these cases were from Portugal and one was from UK. Their 18 month data have been left in the database, but were not used in the analyses published in Lancet Neurology 2013.

The follow-up form at 18 months was identical to the six month follow-up form. The variables have been treated in the same and variable names distinguished merely by changing '6' for'18'. The variable **yrfu_code** has L codes for reasons why an 18 month follow-up was missing (reasons only available for a few cases; see Appendix 8 for codes).

Variable name	Variable label	Variable Format
receighteen	Eighteen month follow-up returned?	Y01N
eighteenmonthform	Type of eighteen month form	SIXMONTHFORM
eighteencompleted_by	Person completing 18 month follow-up form	COMPLETER
Ohs18	Oxford Health Scale 18 months	
ordinal18	Ordinal health state (5 levels) at 18 months	
aliveind18	Alive and independent at 18 months (OHS 0-2)	YN
alivefav18	Favourable outcome at 18 months (OHS 0-1)	YN
deadordep18	Dead or dependent at 18 months (OHS >=3)	YN
aspirin18	Aspirin given on admission day (18 month form)	YNDQ
bloodthin18	Blood thinning injections given on admission day (18 month form)	YNDQ
clotbust18	Clot busting drugs given on admission day (18 month form)	YNDQ
stocking18	Special stockings given on admission day (18 month form)	YNDQ
gotprobs18	Stroke left patient with problems (18 month form)	YNDQ
needhelp18	Needs help with everyday activities (18 month form)	YNDQ
walkhelp18	Needs help to walk (18 month form)	YNDQ
speakprob18	Major problems speaking (18 month form)	YNDQ
mobility18	Mobility problems (18 month form)	MOBILITY
selfcare18	Washing or dressing problems (18 month form)	SELFCARE
activities18	Usual activities problems (18 month form)	ACTIVITIES
pain18	Pain or discomfort (18 month form)	PAIN
anxiety18	Anxiety or depression (18 month form)	ANXIETY
wherelive18	Where patient lives now (18 month form, patient not in hospital)	WHERELIVE
howlive18	How patient lives now (18 month form, patient not in hospital)	HOWLIVE
euroqol18	Health state (Euroqol) at 18 months	

8. Definitions of intra-cranial haemorrhage

The primary definition of intracranial haemorrhage in IST-3 was symptomatic haemorrhage within 7 days of randomisation. If a patient died in the first seven days, or had a symptomatic cerebral event recorded on the seven day form, the adjudication committee considered which

(if any) of the events listed in Appendix 2 had occurred. There were 120 adjudicated cases of symptomatic intracranial haemorrhage. Among the 62 fatal cases there were four who died within one day of randomisation before a P scan could be taken; in the remainder the expert read of the P scan showed a haemorrhage as defined in section 2 of Appendix 2. All 62 had **final_status**='02'. Among the 58 non-fatal cases there were 54 where the data recorded by the expert reader of the post-randomisation scan satisfied the criteria described in section 8 of Appendix 2; in four other nonfatal cases an adjudication of symptomatic ICH was made on the basis of clinical events although the reading of the post-randomisation scan, which was blind to clinical events, did not satisfy the criteria described in section 8 of Appendix 2. All 58 had **final_status**='08'. Patients with **final_status** ='02' or '08' had variable **sich7**=1, otherwise **sich7**=0.

Previous trials have used slightly different definitions of intracranial haemorrhage, which were not measured directly in IST3. However, good approximations can be constructed as follows:

1. *SITS MOST definition* : local or remote parenchymal haemorrhage type 2 on the 22–36 h post-treatment imaging scan, combined with a neurological deterioration of 4 points or more on the NIHSS from baseline, or from the lowest NIHSS value between baseline and 24 h, or leading to death.
We have approximated this by choosing all cases with an IST-3 defined SICH on days 0 or 1, ie on the day of randomisation or the following day. Note that IST-3 did not assess NIHSS post-randomisation so there was no way to assess the magnitude of deterioration on the NIHSS scale.

2. *PH2 definition* : dense blood clot(s) exceeding 30% of the infarct volume with significant space-occupying effect.
We have approximated this by 'evidence of significant intracranial haemorrhage (with or without evidence of clinical deterioration) before 7 days'. Operationally, we included all cases adjudicated as SICH plus any case not so adjudicated which nevertheless had a (P or X) scan within the first seven days on which the criteria described in Appendix 2 section 8 were fulfilled. It should be noted that the expert readers of the scans were blind to clinical details. There were 39 non-fatal cases not adjudicated as SICH where the expert scan reader considered haemorrhage was a significant component of the lesion (Q25) and at least one of the haemorrhages was not petechial (Q24). Together with 120 cases adjudicated as SICH this gives a total of 159 PH2 cases. There were three cases who died within seven days and had P scans satisfying the criteria on Q25 and Q24, but since they were adjudicated as having died from a cause other than SICH they were excluded from the PH2 count.

9. Effects of anonymisation and database updates

Most of the published analyses of IST3 data have used statistical models adjusting for exact age. Since the public database does not give exact ages for the very young and very old (1.3 above) analyses using the public dataset give very slightly different results for adjusted analyses.

There are also some changes due to database updates, which are explained more fully in the programs that reproduce (as closely as possible) the published results. As more patients died following our publications we were able to determine in some cases whether nonrespondents had been alive at the time of the six and eighteen month follow-ups. This makes no difference

to the substantive conclusions of the primary results but it produces a different distribution between the categories ‘vital status and disability both unknown’ and ‘vital status known but disability unknown’. There were also some late changes to the data on expert reads of the pre-randomisation scans. Some late updates were not incorporated in the statistical analyses and these cause a large number of small differences in the analyses of the CT scans, but no change to substantive conclusions.

Appendix 1 : SAS formats

```
value $asl
'B'='Both sides'
'L'='Left'
'M'='Midline'
'R'='Right'
'U'='Unknown';

value $deathcode
'E1'= 'Cerebrovascular'
'E2'= 'Cancer'
'E3'= 'Cardiovascular'
'E4'= 'Infection'
'E7'= 'Multiple Causes'
'E8'= 'Other'
'E9'= 'Unknown';

value $scannorm
' '='Missing'
'Y'='Yes'
'N'='No';

value activities
1='No problems with usual activities'
2='Some problems with usual activities'
3='Unable to perform usual activities'
10='Died so question not relevant'
20='Question not answered'
30="Form not returned"
40="Question not asked";

value acutechange
.='Missing'
0='Scan normal, question skipped'
1='Yes'
2='No';

value anticoag_pre
-1,.='Unknown'
0='None'
1='Warfarin or other antthrombotic agent'
2='Low dose heparin'
3='Full dose heparin';

value anxiety
1='Not anxious or depressed'
2='Moderately anxious or depressed'
3='Extremely anxious or depressed'
10='Died so question not relevant'
20='Question not answered'
30="Form not returned"
40="Question not asked";

value brainsite
0='Unknown'
1='Cerebral hemisphere'
2='Posterior circulation';

value completer
```

```
1='Patient'
2='Friend'
3='Doctor';

value consent
1='Patient signed consent'
2='Patient verbal consent'
3='Assent by relatives'
4='Waiver of consent';

value depthcode
.='Missing'
0='None'
1='Mild hypodensity'
2='Severe hypodensity';

value destination
.='Missing'
0='Still in hospital'
1='Own home'
2='Home of relative or friend'
3='Nursing home'
4='Residential home'
5='Another hospital'
6='Elsewhere'
7='Died in hospital < 7 days';

value findiag
1='Definite ischaemic stroke'
2='Definite or probable haemorrhagic stroke'
3='Non-stroke cause';

value gcseye
0='Missing'
1='Never'
2='To Pain'
3='To command'
4='Spontaneously'
10='Died so question not relevant'
20='Question not answered'
30="Form not returned"
40="Question not asked";

value gcsmotor
0='Missing'
1='None'
2='Extend to pain'
3='Abnormal flex to pain'
4='Normal flex to pain'
5='Localises movements to pain'
6='Normal'
10='Died so question not relevant'
20='Question not answered'
30="Form not returned"
40="Question not asked";

value gcsverbal
0='Missing'
1='None'
2='Noises only'
3='Inappropriate words'
```

```
4='Confused in time, place or person'
5='Orientated in time, place and person'
10='Died so question not relevant'
20='Question not answered'
30="Form not returned"
40="Question not asked";

value gender
1='F'
2='M';

value haemtype
1='Primary intracranial haemorrhage'
2='Subdural haemorrhage'
3='Subarachnoid haemorrhage';

value hdart
.='Missing'
0='None'
1='Anterior'
2='Posterior';

value howlive
1='On my own'
2='With my partner or relative'
10='Died so question not relevant'
20='Question not answered'
30="Form not returned"
40="Question not asked"
50='Still in hospital so not relevant';

value infarct
0='No'
1='Possibly Yes'
2='Definitely Yes';

value isch_change
1='Scan completely normal'
2='Scan not normal but no sign of acute ischaemic change'
3='Signs of acute ischaemic change'
.='Missing';

value mobility
1='No problems walking'
2='Some problems walking'
3='Confined to bed'
10='Died so question not relevant'
20='Question not answered'
30="Form not returned"
40="Question not asked";

value nonstroketype
1='Cerebral tumour'
2='Migraine'
3='Epilepsy'
4='Other';

value pain
1='No pain or discomfort'
2='Moderate pain or discomfort'
3='Extreme pain or discomfort'
```

```
10='Died so question not relevant'
20='Question not answered'
30="Form not returned"
40="Question not asked";

value scantype
.='Missing'
0='Unknown'
1='CT'
2='MR';

value selfcare
1='No problems with self care'
2='Some problems washing or dressing'
3='Unable to wash or dress self'
10='Died so question not relevant'
20='Question not answered'
30="Form not returned"
40="Question not asked";

value sevendaycase
 1='Fatal massive swelling of original infarct'
 2='Fatal intracranial haemorrhage'
 3='Death from initial stroke - other'
 4='Fatal recurrent ischaemic stroke'
 5='Fatal recurrent stroke of unknown type'
 6='Fatal non-cerebral event'
 7='Nonfatal neurological deterioration, infarct swelling'
 8='Nonfatal symptomatic intracranial haemorrhage'
9='Nonfatal neurological deterioration not due to swelling or haemorrhage'
10='Nonfatal recurrent ischaemic stroke'
11='Nonfatal recurrent stroke of unknown type'
0='No event';

value sixmonthform
1='Six month follow up form for patient at home'
2='Six month follow up form for patient in hospital';

value size
.='Missing'
0='None visible'
1='Small'
2='Medium'
3='Large'
4='Very large';

value stroketype
1='TACI'
2='PACI'
3='LACI'
4='POCI'
5='OTHER';

value swellcode
.='Missing'
0='None'
1='Sulcal'
2='Minor Ventricular'
3='Moderate (C or D)'
4='Severe (E or F)';
```

```
value territory
.='Missing'
0='None'
1='MCA or ACA or Borderzone'
2='PCA or Cerebellar or Brainstem'
3='Acute subcortical';

value visinf
1='Visible infarct according to expert read or clinical record'
2='No visible infarct'
.='Missing';

value wherelive
1='In my own home'
2='In the home of a relative'
3='In a residential home'
4='In a nursing home'
10='Died so question not relevant'
20='Question not answered'
30="Form not returned"
40="Question not asked"
50='Still in hospital so not relevant';

value y01n
1='Yes'
0='No';

value yn
1='Yes'
2='No';

value yndq
1='Yes'
2='No'
3="Don't Know"
4= 'Cannot assess'
10='Died so question not relevant'
20='Question not answered'
30="Form not returned"
40="Question not asked";

value ynm
1='Yes'
2='No'
.='Missing';
```

Appendix 2

ADJUDICATION AND ANALYSIS OF EVENTS WITHIN SEVEN DAYS NOTES FOR ADJUDICATORS

Please review the data for the following patients who are reported to have had a symptomatic cerebral event listed below within 7 days of randomisation. The data are extracted directly from the trial database (from the treatment form, the 7 day form and the form for the expert's blinded reading of any further brain imaging between randomisation and day 7). If you are completely unable to categorise the event, but feel that sight of the relevant scan image would provide information to permit categorisation, you can view the scans using Sirs. Please note that the categories are all mutually exclusive, so each patient may only be assigned to a single category. If all 3 adjudicators agree, that verdict will be used in the final analysis. If they disagree, a teleconference will be arranged to resolve any disagreement by discussion to reach an agreed final verdict.

If the patient is dead by day 7 please assign the 'status at 7 day code' using one of the following death categories:

1. Death from initial stroke within 7 days of randomisation, attributed to infarct swelling.

There should be evidence of significant brain swelling on a post-randomisation scan (or autopsy if not re-scanned before death). This corresponds to either a response on Question 16 of the Expert CT Readers Form (ECTRF) 'Shift of the midline away from the side of the ventricle' or 'Effacement of the basal cisterns' OR a response to Question 5 of 'Midline shift' or 'Uncal herniation'. The presence of some degree of haemorrhagic transformation is permitted, provided it is not considered by the expert CT reader to be a major contributor to the mass effect.

2. Death from initial stroke within 7 days of randomisation, attributed to intracranial haemorrhage.

There should be clear evidence of significant intracranial haemorrhage on the post-randomisation scan (or autopsy if not re-scanned before death). Significant haemorrhage is present on any post-randomisation scan if the expert reader gives any response to Question 24 other than a blank value or 'Petechial haemorrhage' (i.e. significant HTI, parenchymal haematoma, etc) AND a response to Question 25 of 'yes', indicating that haemorrhage is a major component of the lesion (or is remote from the lesion and likely to have contributed significantly to the burden of brain damage). This event includes deaths attributed to a clinical event of recurrent stroke within 7 days, in which the recurrent stroke was confirmed to be due to an intracranial haemorrhage.

3. Death from initial stroke within 7 days of randomisation, not definitely attributable either to infarct swelling or haemorrhage.

A post randomisation scan may show a large infarct with some degree of swelling, but swelling was coded in response to Question 5 as 'sulcal effacement', 'ventricular effacement' or 'sulcal effacement + ventricular effacement' AND response to Question 16 as 'None', 'Effacement of the sulci overlying the infarct', 'Minor effacement of the adjacent lateral ventricle', 'Complete effacement of the lateral ventricle', or 'Effacement of the lateral and third ventricle' AND no significant haemorrhage was present. If the initial stroke was severe, include deaths within 7 days from pneumonia, and deaths within 7 days with no additional information available.

4. Death due to recurrent ischaemic stroke within 7 days.

There should be clear clinical evidence of recurrent stroke and no evidence of significant haemorrhage on the post-randomisation scan (or autopsy if not rescanned before death).

5. Death due to recurrent stroke of unknown type within 7 days.

Death should only be assigned to this category if there was clear clinical evidence of recurrent stroke, and no scan was performed after the recurrence and no autopsy was performed.

6. Death due to non-cerebral causes.

If the clinician completing the 7 day form attributes the death to a non neurological cause (extracranial haemorrhage, ischaemic heart disease, pulmonary embolism, other vascular cause, or a non-vascular cause) the assigned cause will be employed in the main analyses.

7. Neurological deterioration within 7 days of randomisation, attributed to swelling of initial ischaemic stroke.

There should be evidence of significant brain swelling on the post-randomisation scan (or autopsy if not re-scanned within 7 days and death occurs after 7 days). There should be evidence of significant brain swelling on a post-randomisation scan (or autopsy if not re-scanned before death). This corresponds to either a response on Question 16 of the Expert CT Readers Form (ECTRF) 'Shift of the midline away from the side of the ventricle' or 'Effacement of the basal cisterns' OR a response to Question 5 of 'Midline shift' or 'Uncal herniation'. The presence of some degree of haemorrhagic transformation is permitted, provided it is not considered by the expert CT reader to be a major contributor to the mass effect.

8. Symptomatic intracranial haemorrhage within 7 days of randomisation.

There should be clear evidence of significant intracranial haemorrhage on the post-randomisation scan (or autopsy if not re-scanned and death occurs after 7 days). Significant haemorrhage is present on any post-randomisation scan if the expert reader gives any response to Question 24 other than a blank value or 'Petechial haemorrhage' (i.e. significant HTI, parenchymal haematoma, etc) AND a response to Question 25 of 'yes', indicating that haemorrhage is a major component of the lesion (or is remote from the lesion and likely to have contributed significantly to the burden of brain damage). This event includes clinical events described as a recurrent stroke within 7 days, in which the recurrent stroke was confirmed to be due to an intracranial haemorrhage.

9. Neurological deterioration within 7 days of randomisation, not attributable to brain swelling.

A post randomisation scan may show a large infarct with some degree of swelling, but swelling was coded in response to Question 5 as 'sulcal effacement', 'ventricular effacement' or 'sulcal effacement + ventricular effacement' AND response to Question 16 as 'None', 'Effacement of the sulci overlying the infarct', 'Minor effacement of the adjacent lateral ventricle', 'Complete effacement of the lateral ventricle', or 'Effacement of the lateral and third ventricle' AND no significant haemorrhage was present.

10. Recurrent ischaemic stroke within 7 days.

There should be clear clinical evidence of recurrent stroke, and no evidence of significant haemorrhage on the post-randomisation scan (or autopsy if not re-scanned and death occurs after 7 days).

11. Recurrent stroke of unknown type within 7 days.

Clear clinical evidence of recurrent stroke, but no post-randomisation scan or autopsy was performed.

Appendix 3 : Prediction of NIHSS and probability of good outcome based on age and NIHSS

Prediction of NIHSS

```
nihss_pred=44.61684-(3.40485*gcs_eye_rand)-(3.76352*gcs_motor_rand)-
(1.80578*gcs_verbal_rand);
if weakface_rand=1 then nihss_pred=nihss_pred+2.45786;
if weakarm_rand=1 then nihss_pred=nihss_pred+1.68676;
if weakleg_rand=1 then nihss_pred=nihss_pred+1.66184;
if dysphasia_rand=1 then nihss_pred=nihss_pred+0.69439;
if hemianopia_rand=1 then nihss_pred=nihss_pred+3.04825;
if visuospat_rand=1 then nihss_pred=nihss_pred+3.12773;
if brainstemsigns_rand=1 then nihss_pred=nihss_pred+1.35313;
```

***Estimated probability of being alive at 3 months & independent in activities of daily living (**Barthel Index >=95) **on Konig novel model** ;

```
konlinpred= -5.112+ 0.046*age +0.196*nihss ;
konprob=1/(1+exp(konlinpred));
```

Reference:
Konig I, Ziegler A, Bluhmki E, Hacke W, Bath P, Sacco R et al . Predicting Long-Term Outcome After Acute Ischemic Stroke : A Simple Index Works in Patients From Controlled Clinical Trials. Stroke 2008;39;1821-1826.

Appendix 4 : Determination of OCSP (Stroketype)

SAS code to determine the stroke type (OCSP type) from questions asked on randomisation form

```
ocsp='xxxxx';
if weakface='Y' and weakarm='Y' and dysphasia='Y' and hemianopia='Y' and
bs_signs ne 'Y' then ocsp='TACI ';
else if weakarm='Y' and weakleg='Y' and dysphasia='Y' and hemianopia='Y'
and bs_signs ne 'Y' then ocsp='TACI ';
else if weakarm='Y' and weakleg='Y' and hemianopia='Y' and visuospat='Y'
and bs_signs ne 'Y' then ocsp='TACI ';
else if weakface='Y' and weakarm='Y' and hemianopia='Y' and visuospat='Y'
and bs_signs ne 'Y' then ocsp='TACI ';
else if weakface='Y' and weakarm='Y' and dysphasia='Y' and hemianopia in
('C','C/A') and bs_signs ne 'Y' then ocsp='TACI ';
else if weakarm='Y' and weakleg='Y' and dysphasia='Y' and hemianopia in
('C','C/A') and bs_signs ne 'Y' then ocsp='TACI ';
else if weakface='Y' and weakarm='Y' and hemianopia in ('C','C/A') and
visuospat='Y' and bs_signs ne 'Y' then ocsp='TACI ';
else if weakarm='Y' and weakleg='Y' and hemianopia in ('C','C/A') and
visuospat='Y' and bs_signs ne 'Y' then ocsp='TACI ';
else if weakface='Y' and weakarm='Y' and hemianopia='Y' and visuospat in
('C','C/A') and bs_signs ne 'Y' then ocsp='TACI ';
else if weakarm='Y' and weakleg='Y' and hemianopia='Y' and visuospat in
('C','C/A') and bs_signs ne 'Y' then ocsp='TACI ';
else if weakface='Y' and weakarm='Y' and dysphasia in ('C','C/A') and
hemianopia='Y' and bs_signs ne 'Y' then ocsp='TACI ';
else if weakarm='Y' and weakleg='Y' and dysphasia in ('C','C/A') and
hemianopia='Y' and bs_signs ne 'Y' then ocsp='TACI ';
else if gcs_score=15 and weakface='Y' and weakarm='Y' and dysphasia='N' and
hemianopia='N' and visuospat='N' and bs_signs='N' and other_nd='N' then
ocsp='LACI ';
else if gcs_score=15 and weakarm='Y' and weakleg='Y' and dysphasia='N' and
hemianopia='N' and visuospat='N' and bs_signs='N' and other_nd='N' then
ocsp='LACI ';
else if bs_signs='Y' then ocsp='POCI';
else if weakface='N' and weakarm='N' and weakleg='N' and dysphasia='N' and
hemianopia='Y' and visuospat='N' and bs_signs='N' and other_nd='N' then
ocsp='POCI ';
else if weakface='N' and weakarm='N' and weakleg='N' and dysphasia='N' and
hemianopia='N' and visuospat='N' and bs_signs='N' and other_nd='Y' then
ocsp='Other';
*else if weakface ne 'Y' and weakarm ne 'Y' and weakleg ne 'Y' and
dysphasia ne 'Y' and hemianopia ne 'Y' and visuospat ne 'Y' and bs_signs ne
'Y' and other_nd ne 'Y' then ocsp='????';
else ocsp='PACI';
```

Note. Above code uses old variable names, but correspondence with new names should be obvious. All predictor variables are from randomisation form. Eg bs_signs has been renamed brainstemsigns_rand.

Appendix 5 : Algorithm for coding lesion size

For primary IST3 analysis of lesion visibility/extent on imaging.
From IST-3 lesion coding (Q5 or 7 depending on version of form used).

a) site		**Condensed code**
M*	=MCA = any lesion in the MCA territory	see b below
AS	=Infarct of up to half of ACA territory	1
AL	=Infarct of more than half of ACA territory	2
PS	=Infarct of up to half of PCA territory	1
PL	=Infarct of more than half of PCA territory	3
MAS=M+AS*		3 if MCA 1 or 2; 4 if MCA 3 or 4
MAL=M+AL*		3 if MCA 1 or 2; 4 if MCA 3 or 4
MPS=M+PS*		3 if MCA 1 or 2; 4 if MCA 3 or 4
MPL=M+PL*		3 if MCA 1 or 2; 4 if MCA 3 or 4
MAP=Infarct of whole MCA, ACA and PCA territories		4
L*	=Lacunar	1
B*	=Borderzone	1
C*	=Cerebellum	see b below
S*	=Brainstem	see b below
CS*	=Cerebellum and brainstem	3

* code sub-territory sites in b

b) sub-territory sites

MCA sub-territory codes	
1=small cortical infarct	1
2=basal ganglia infarct (>2x2x2cm)	2
3= infarct of white matter lateral to the lateral ventricle (>2x2x2cm)	2
4=infarct of anterior half of peripheral MCA territory	2
5=infarct of the posterior half of peripheral MCA territory	3
6=infarct of the whole of peripheral MCA territory	3
7=6+infarct of lateral part of basal ganglia	4
8=infarct of whole of MCA territory	4

Lacunar/Borderzone sub-territory codes	all 1
9=lacune in internal capsule/lentiform	
10=lacune in internal border zone	
11=lacune in centrum semiovale	
12=lacune in thalamus	
13=lacune in brainstem, inc. pons (not shown)	
14=anterior (mainly) border zone	
15=posterior (mainly) border zone	

Cerebellum sub-territory codes	
16=small cortical (not shown)	1
17=<1/2 hemisphere (medium) (not shown)	2
18=>1/2 hemisphere (not shown)	3

Brainstem sub-territory codes	
11=small, i.e.<1/2 medulla (not shown)	1
12=extensive, i.e. pons + medulla (not shown)	2

Variable R_infarct_size takes value 0 if no visible infarct, or values 1 .... 4 as determined by 'condensed code' above. These are called 'small, 'medium', 'large' or 'very large'. See format 'size'.

Appendix 6 : Resolution of disagreements regarding side of acute ischaemic changes

1. If the both R & P scans show no acute lesion and the 7 day form specifies R or L, ASL*= 7 day report.
2. If there are no scans at all and the 7 day form specifies R or L, ASL= 7 day report.
3. If R & P scans agree and there is no 7 day report: ASL= Scan report
4. If there is just R or P scan and there is no 7 day report: ASL = Check.
5. If R & P scans agree but there is discrepancy with the 7 day report: ASL= Scan report.
6. If there is discrepancy between P scan and the 7 day report: Check
7. If there is discrepancy between R & P scans: Check. **Done (61 pt)**
8. If there is discrepancy between R scan and 7 day form and the P scan data is missing or no P scan: Check: **Done (29 pt)**
9. If P scan = "B" (both), is compatible with 7 day report = "midline", "R", or "L".**
10. If 7 day report = "midline", is compatible with Scan = "R" or "L".**

*ASL= Adjudicated side of lesion.

Note the P scan was taken 24 to 48 hours post randomisation. It recorded the same variables as the R scan (except that brain history questions such as atrophy were not repeated).

Appendix 7 : Algorithm for imputing missing six month health status

1. Death defined by death date <= randomisation date + 183 days
2. If not dead before 6 months and six month form returned then disability taken from form (irrespective of completion date)
3. If (death date later than randomisation date + 183 days or no death date reported) and six month form not returned and seven day form returned with independent in ADL=Yes, then imputed 6 month status is OHS=2 (Alive and Independent, at lowest level for independence).
4. If (death date later than randomisation date + 183 days or no death date reported) and six month form not returned and seven day form returned with independent in ADL=No, then imputed 6 month status is OHS=5 (Alive and Dependent, at lowest level for dependence).
5. If (death date later than randomisation date + 183 days or no death date reported) and six month form not returned and seven day form returned with (independent in ADL=Missing and (Able walk=No or Lift arms=No)) then imputed 6 month status is OHS=5 (Alive and Dependent, at lowest level for dependence).
6. If (death date later than randomisation date + 183 days or no death date reported) and six month form not returned and seven day form returned with (independent in ADL=Missing and (Able walk=Yes and Lift arms=Yes)) then imputed 6 month status is OHS=2 (Alive and Independent, at lowest level for independence).
7. If (death date later than randomisation date + 183 days or no death date reported) and six month form not returned and no seven day form returned or seven day form returned with unknown levels for the three measures of functional ability then imputed 6 month status is OHS=5 (Alive and Dependent, at lowest level for dependence).

Appendix 8 : CODING FOR FREE TEXT AREAS (IST-3)

IST-3 Hospital follow up form

Reason for waiver of consent

A1 Aphasia
A2 Decreased level of consciousness
A3 Pre morbid cognitive impairment
A4 Neurological deterioration
A5 Executive consent
A6 Other

Not a stroke (not in shared dataset)

B1 Cerebral abscess
B2 Hypoglycaemia
B3 Multiple sclerosis
B4 TIA
B5 Other

Site of major extracranial bleed requiring transfusion

C1 Gastrointestinal tract
C2 Intraabdominal
C3 Intramuscular
C4 Epistaxis
C5 Haematuria
C6 Other

Other possible side effects not recorded elsewhere

D1 Localised bruising e.g. around venepuncture sites/ sites where BP cuff applied
D2 Minor bleed
- D21 epistaxis
- D22 gastrointestinal
- D23 gingival haemorrhage
- D24 haematuria

D5 Localised reaction to infusion
D6 Orolingual angioedma
D7 Anaphylaxis
D8 Seizures
D9 Other

Cause of Death (after 7 days)

E1 Cerebrovascular
E2 Cancer
E3 Cardiovascular
E4 Infection

E7 Multiple Causes
E8 Other
E9 Unknown

Discharged elsewhere

F1 Sheltered/warden controlled accommodation
F2 Rehabilitation Centre
F3 Prison
F4 Other

Additional Information

G1 Additional contact details
G2 Additional medical information
G3 Information about probable treatment received
G4 Participation in other trials
G5 Reason for interruption of infusion/delay in starting treatment
G6 Additional technical details re trial
G7 Post-admission, pre-randomisation thrombolysis
G8 Discharge information
G9 Other

Location Patient Treated (page 2)

H1 Stroke Rehab Unit
H2 Critical Care Area (or ICU)
H3 Neurosurgical Ward
H4 Geriatric Ward
H5 CCU (Coronary Care Unit)
H6 Rehab Ward
H7 A&E (or Emergency Department)
H9 Other

Reason for Non-Trial Thrombolysis

K1 Acute MI
K2 Communication Error
K3 Other

Reason for Missing Scans

S1 Died
S2 Recovered and discharged early
S3 Patient too unwell
S4 Event scan is 2nd scan
S5 Scan received but not readable
S9 Other

Patient treatment record

Treatment not started

J1 Clinical decision not to give thrombolysis
- J11 High BP
- J12 Rapid improvement
- J19 Other reason

J2 Patient or relative refused treatment
J3 Error in randomisation system
J4 Exclusion criteria identified post randomisation
J5 Delay between stroke onset and treatment was over 6 hours
J6 Clinical decision to give thrombolysis
J9 Additional treatment information
- J91 Dose information
- J92 Delay to treatment information
- J99 Other information

Reason for interruption of infusion

I1 Neurological Deterioration
I2 Bleeding
I3 Resite IV
I4 Allergic Reaction
I5 Deterioration in Patients Condition
- I51 Haemorrhage
- I52 Low BP
- I53 High BP
- I54 Vomiting
- I55 Cardiac Arrest
- I56 Loss of Consciousness
- I57 Haematoma
- I59 Other Deterioration in Condition

I6 Technical IV Problem
- I61 Change of Syringe
- I62 Blocked Syringe
- I63 Machine Malfunction

I69 Other Technical Problem

I7 Infusion Problem

I71 Delay during Infusion

I72 Incorrect Infusion Rate

I73 Incorrect Infusion Dose

I79 Other Infusion Problem

I9 Other

Death codes at any time point after seven day form

E1 Cerebrovascular

E2 Cancer

E3 Cardiovascular

E4 Infection

E7 Multiple Causes

E8 Other

E9 Unknown

Follow up form codes

Reason for 18 Month follow up form given up

L1 Country not eligible

L2 Randomised after cut off date (30th June 2010)

L3 Patient or Relatives did not want to be contacted again/ withdrew consent

L4 Died before form could be obtained

L5 Emigrated

L6 GP asked us not to follow up patient due to poor health

L7 No trace/ No available contact details

L8 6 Month form obtained at close to 18 months, can be used instead

L9 Other

Appendix 9 : NIH Stroke Scale

This form is to help you calculate the total NIHSS score.

1a Level of *Consciousness* **(LOC)**	0 1 2 3	Alert – *keenly responsive* Drowsy – *arousable by minor stimulation to obey, answer, or respond* Stuporous – *requires repeated stimulation to attend, or is obtunded and requires strong or painful stimulation to make movements (not stereotyped*) Comatose – *responds only with reflex motor or autonomic effects or totally unresponsive, flaccid*
1b LOC Questions	0 1 2	Answers both correctly Answers one correctly Both incorrect Patient is asked to state the month & his/her age
1c LOC Commands	0 1 2	Obeys both correctly Obeys one correctly Both incorrect Patient is asked to open & close eyes, grip & release normal hand
2. Best Gaze	0 1 2	Normal Partial gaze palsy – *gaze is abnormal in one or both eyes, no forced deviation/total gaze paresis* Forced deviation – *or total gaze paresis not overcome by oculocephalic maneouvre*
3. Visual Fields	0 1 2 3	No visual loss (or in coma) Partial hemianopia Complete hemianopia Bilateral Hemianopia – *including cortical blindness*
4. Facial Palsy	0 1 2 3	Normal Minor - *flattened nasolabial fold, asymmetry on smiling* Partial – *total or near total paralysis of lower face* Complete - *absent facial movement in upper and lower face on one or both sides*
5. Best Motor RIGHT ARM	0 1 2 3 4	No drift – *holds limb at 90 degrees for full 10 seconds* Drift - *drifts down but does not hit bed* Some effort against gravity No effort against gravity No movement
6. Best Motor LEFT ARM	0 1 2 3 4	No drift – *holds limb at 90 degrees for full 10 seconds* Drift - *drifts down but does not hit bed* Some effort against gravity No effort against gravity No movement
7. Best Motor RIGHT LEG	0 1 2 3 4	No drift – *holds limb at 45 degrees for full 5 seconds* Drift - *drifts down but does not hit bed* Some effort against gravity No effort against gravity No movement
8. Best Motor LEFT LEG	0 1 2 3 4	No drift – *holds limb at 45 degrees for full 5 seconds* Drift - *drifts down but does not hit bed* Some effort against gravity No effort against gravity No movement
9. Limb Ataxia	0 1 2	Absent (or in coma) Present in 1 limb Present in 2 or more limbs
10. Sensory	0 1 2	Normal Partial loss – *patient feels pinprick is less sharp or is dull on affected side* Dense loss (or in coma) - *patient is unaware of being touched on face, arm, leg*
11. Best Language	0 1	No dysphasia

	2 3	Mild – moderate dysphasia *obvious loss of fluency or comprehension, without significant limitation on ideas expressed or form of expression. Makes conversation about provided material difficult or impossible, e.g. examiner can identify picture or naming card from patient's response.* Severe dysphasia - *all communication is through fragmentary expression; great need for inference, questioning, and guessing by the listener who carries burden of communication. Examiner cannot identify materials provided from patient response* Mute *no usable speech or auditory comprehension, or in coma.*
12. Dysarthria	0 1 2	Normal articulation Mild – moderate dysarthria - *patient slurs some words, can be understood with some difficulty.* Unintelligible or worse - *speech is so slurred as to be unintelligible (absence of or out of proportion to dysphasia) or is mute/anarthric, or in coma*
13. Neglect	0 1 2	No neglect (or in coma) Partial neglect - *Visual, tactile, auditory, spatial, or personal inattention or extinction to bilateral simultaneous stimulation in one of the sensory modalities* Complete neglect - *Profound hemi-inattention or hemi-inattention to more than one modality. Does not recognise own hand or orients to only one side of space*

Total : _____ **Remember to write this total score on the IST-3 randomisation form**

Notes for completion of NIHSS for IST-3:

Administer stroke scale items in the order listed. Record performance in each category after each sub-scale exam. Do not go back and change scores. Follow directions provided for each exam technique. Scores should reflect what the patient does, not what the clinician thinks the patient can do. The clinician should record answers while administering the exam and work quickly. Except where indicated, the patient should not be coached (i.e., repeated requests to patient to make a special effort). For the rare event of an IST-3 patient being in coma special scoring rules apply for some sections (see below). The NIHSS is merely a summary of the sort of neurological examination you should be performing.

1a. Level of Consciousness: The investigator must choose a response, even if a full evaluation is prevented by such obstacles as an endotracheal tube, language barrier, orotracheal trauma/bandages. A 3 is scored only if the patient makes no movement (other than reflexive posturing) in response to noxious stimulation.

1b. LOC Questions: The patient is asked the month and his/her age. The answer must be correct - there is no partial credit for being close. Aphasic and stuporous patients who do not comprehend the questions will score 2. Patients unable to speak because of endotracheal intubation, orotracheal trauma, severe dysarthria from any cause, language barrier or any other problem not secondary to aphasia are given a 1. It is important that only the initial answer be graded and that the examiner not "help" the patient with verbal or non-verbal cues.

1c. LOC Commands: The patient is asked to open and close the eyes and then to grip and release the non-paretic hand. Substitute another one step command if the hands cannot be used. Credit is given if an unequivocal attempt is made but not completed due to weakness. If the patient does not respond to command, the task should be demonstrated to them (pantomime) and score the result (i.e., follows none, one or two commands). Patients with trauma, amputation, or other physical impediments should be given suitable one-step commands. Only the first attempt is scored.

2. Best Gaze: Only horizontal eye movements will be tested. Voluntary or reflexive (oculocephalic) eye movements will be scored but caloric testing is not done. If the patient has a conjugate deviation of the eyes that can be overcome by voluntary or reflexive activity, the score will be 1. If a patient has an isolated peripheral nerve paresis (CN III, IV or VI) score a 1. Gaze is testable in all aphasic patients. Patients with ocular trauma, bandages, pre-existing blindness or other disorder of visual acuity or fields should be tested with reflexive movements and a choice made by the investigator. Establishing eye contact and then moving about the patient from side to side will occasionally clarify the presence of a partial gaze palsy.

3. Visual: Visual fields (upper and lower quadrants) are tested by confrontation, using finger counting or visual threat as appropriate. Patient must be encouraged, but if they look at the side of the moving fingers appropriately, this can be scored as normal. If there is unilateral blindness or enucleation, visual fields in the remaining eye are scored. Score 1 only if a clear-cut asymmetry, including quadrantanopia is found. If patient is blind from any cause score 3. Double simultaneous stimulation is performed at this point. If there is extinction patient receives a 1 and the results are used to answer question 11. Score 0 if comatose.

4. Facial Palsy: Ask, or use pantomime to encourage the patient to show teeth or raise eyebrows and close eyes. Score symmetry of grimace in response to noxious stimuli in the poorly responsive or non-comprehending patient. If facial trauma/bandages, orotracheal tube, tape or other physical barrier obscures the face, these should be removed to the extent possible.

5–8. Motor Arm and Leg: The limb is placed in the appropriate position: extend the arms (palms down) 90 degrees (if sitting) or 45 degrees (if supine) and the leg 30 degrees (always tested supine). Drift is scored if the arm falls before 10 seconds or the leg before 5 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic arm

9. Limb Ataxia: This item is aimed at finding evidence of a unilateral cerebellar lesion. Test with eyes open. In case of visual defect, insure testing is done in intact visual field. The finger-nose-finger and heel-shin tests are performed on both sides, and ataxia is scored only if present out of proportion to weakness. Ataxia is absent in the patient who cannot understand or is paralyzed. In case of blindness test by touching nose from extended arm position.

10. Sensory: Sensation or grimace to pin prick when tested, or withdrawal from noxious stimulus in the obtunded or aphasic patient. Only sensory loss attributed to stroke is scored as abnormal and the examiner should test as many body areas [arms (not hands), legs, trunk, face] as needed to accurately check for hemisensory loss. A score of 2, "severe or total," should only be given when a severe or total loss of sensation can be clearly demonstrated. Stuporous and aphasic patients will therefore probably score 1 or 0. The patient with brain stem stroke who has bilateral loss of sensation is scored 2. If the patient does not respond and is quadriplegic score 2. Patients in coma (item 1a=3) are arbitrarily given a 2 on this item.

11. Best Language: A great deal of information about comprehension will be obtained during the preceding sections of the examination. The patient is asked to describe what is happening in the attached picture, to name the items on the attached naming sheet, and to read from the attached list of sentences. Comprehension is judged from responses here as well as to all of the commands in the preceding general neurological exam. If visual loss interferes with the tests, ask the patient to identify objects placed in the hand, repeat, and produce speech. The intubated patient should be asked to write. The patient in coma (question 1a=3) will arbitrarily score 3 on this item. The examiner must choose a score in the patient with stupor or limited cooperation but a score of 3 should be used only if the patient is mute and follows no one step commands.

12. Dysarthria: If patient is thought to be normal an adequate sample of speech must be obtained by asking patient to read or repeat words from the attached list. If the patient has severe aphasia, the clarity of articulation of spontaneous speech can be rated. Do not tell the patient why he/she is being tested.

13. Extinction and Inattention (formerly Neglect): Sufficient information to identify neglect may be obtained during the prior testing. If the patient has a severe visual loss preventing visual double simultaneous stimulation, and the cutaneous stimuli are normal, the score is normal. If the patient has aphasia but does appear to attend to both sides, the score is normal. The presence of visual spatial neglect or anosagnosia may also be taken as evidence of abnormality. Since the abnormality is scored only if present, the item is never untestable. Score 0 if in coma.

Appendix 10 : References

1. The IST-3 Collaborative Group. The benefits and harms of intravenous thrombolysis with recombinant tissue plasminogen activator within 6 h of acute ischaemic stroke (the third international stroke trial [IST-3]): a randomised controlled trial. ***Lancet*** 2012; 379(9834):2352-2363. http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(12)60768-5/fulltext

2. IST-3 Collaborative Group. Effect of thrombolysis with alteplase within 6h of acute ischaemic stroke on long-term outcomes (the third international stroke trial [IST-3]): 18-month follow-up of a randomised controlled trial. ***Lancet Neurology*** 2013;12:768-76. doi:10.1016/S1474-4422(13)70130-3. http://www.thelancet.com/journals/laneur/article/PIIS1474-4422(13)70130-3/fulltext

3. Lindley RI, Wardlaw JM, Whiteley WN, Cohen G, Blackwell L, Murray GD et al. Alteplase for Acute Ischemic Stroke: Outcomes by Clinically Important Subgroups in the Third International Stroke Trial. Stroke 2015 published online before print January 22 2015, http://dx.doi.org/10.1161/STROKEAHA.114.006573

4. The IST-3 collaborative Group. Association between brain imaging signs, early and late outcomes, and response to intravenous alteplase after acute ischaemic stroke in the third International Stroke Trial (IST-3): secondary analysis of a randomised controlled trial. *The Lancet Neurology* 2015 May;14(5):485-96.http://dx.doi.org/10.1016/S1474-4422(15)00012-5

Appendix 11 : Revised tables for imaging signs paper (Lancet Neurology 2015)

The published results in Reference 4 used scan data from the dataset frozen in June 2012 when the primary IST3 paper was published. Subsequently there were some changes to the expert reads of the scans, which had been made while readers were blinded to results, but had not been uploaded to the database in June 2012.

There were 17 changes to acute change status, 30 changes to lesion size, 29 to hypodensity, 14 to swelling, 13 to hyperdensity, 9 to old lesion and none to atrophy or leukoaraiosis.

The shared database incorporates the changed data, hence the results below differ slightly from those published in Lancet Neurology 2015. There were no differences in substantive conclusions.

Table 1 Baseline clinical and imaging variables

	rt-PA (N=1507)	Control (N=1510)
Age		
18-50	58 (4%)	68 (5%)
51-60	98 (7%)	102 (7%)
61-70	187 (12%)	175 (12%)
71-80	350 (23%)	370 (25%)
81-90	703 (47%)	697 (46%)
> 90	111 (7%)	98 (6%)
NIHSS		
0 to 5	303 (20%)	304 (20%)
6 to 10	419 (28%)	428 (28%)
11 to 15	304 (20%)	295 (20%)
16 to 20	268 (18%)	271 (18%)
> 20	213 (14%)	212 (14%)
Delay		
<= 3 hours	431 (29%)	415 (27%)
>3, <= 4.5 hours	575 (38%)	596 (39%)
> 4.5, <= 6 hours	501 (33%)	497 (33%)
>6 hours	. (.%)	2 (0%)
Randomising clinician		
No change	890 (59%)	892 (59%)
Possibly change	359 (24%)	339 (22%)
Definitely change	258 (17%)	279 (18%)
Expert reader's assessment of acute ischaemic change on initial scan		
Scan completely normal	141 (9%)	129 (9%)
Scan not normal but no sign of acute ischaemic change	749 (50%)	781 (52%)
Signs of acute ischaemic change	617 (41%)	600 (40%)
Lesion territory		
Indeterminate	891 (59%)	914 (61%)
MCA or ACA or Borderzone	586 (39%)	555 (37%)

	rt-PA (N=1507)	Control (N=1510)
Posterior	20 (1%)	36 (2%)
Lacunar	10 (1%)	5 (0%)
Changes in MCA territory		
None	928 (62%)	960 (64%)
<=1/3	351 (23%)	351 (23%)
>1/3	228 (15%)	199 (13%)
Lesion size		
None visible	891 (59%)	914 (61%)
Small	105 (7%)	94 (6%)
Medium	246 (16%)	251 (17%)
Large	125 (8%)	136 (9%)
Very large	140 (9%)	115 (8%)
ASPECTS		
0-4	164 (11%)	141 (9%)
5-7	201 (13%)	230 (15%)
8-10	1142 (76%)	1139 (75%)
Depth of tissue damage		
None	899 (60%)	922 (61%)
Mild	502 (33%)	502 (33%)
Severe	106 (7%)	86 (6%)
Degree of swelling		
None	1151 (76%)	1168 (77%)
Mild Sulcal	285 (19%)	268 (18%)
Mild Ventricular	71 (5%)	73 (5%)
Severe	. (.%)	1 (0%)
Location of hyperdense arteries		
None	1128 (75%)	1145 (76%)
Anterior	363 (24%)	348 (23%)
Posterior	16 (1%)	17 (1%)
ICA or BA or (MCA + ACA)	42 (3%)	33 (2%)
MCA or ACA or PCA main	337 (22%)	332 (22%)
Evidence of atrophy	1161 (77%)	1166 (77%)
Evidence of leukoaraiosis	765 (51%)	782 (52%)
Evidence of old lesions	688 (46%)	655 (43%)
Evidence of non-stroke lesions	73 (5%)	77 (5%)

Table 2 Adjusted associations between imaging and clinical variables

	Age adjusted for NIHSS		NIHSS adjusted for Age		Delay adjusted for Age & NIHSS	
Imaging variable	**Adjusted OR (95% CI)**	**P**	**Adjusted OR (95% CI)**	**P**	**Adjusted OR (95% CI)**	**P**
Visible infarct	0.98 (0.97, 0.98)	<.001	1.11 (1.09, 1.12)	<.001	1.09 (1.01, 1.16)	0.02
Hypodensity	0.98 (0.97, 0.98)	<.001	1.11 (1.09, 1.12)	<.001	1.10 (1.03, 1.18)	0.006
Large lesion	0.98 (0.97, 0.99)	<.001	1.11 (1.10, 1.13)	<.001	1.03 (0.94, 1.12)	0.56
Swelling	0.98 (0.97, 0.99)	<.001	1.09 (1.08, 1.11)	<.001	1.05 (0.97, 1.13)	0.26
Hyperdense arteries	0.98 (0.97, 0.98)	<.001	1.11 (1.09, 1.12)	<.001	1.02 (0.94, 1.10)	0.67
Atrophy	1.11 (1.10, 1.12)	<.001	0.99 (0.98, 1.00)	0.18	0.98 (0.89, 1.07)	0.62
Leukoaraiosis	1.09 (1.08, 1.09)	<.001	0.99 (0.98, 1.00)	0.22	0.99 (0.93, 1.06)	0.84
Old lesion	1.03 (1.03, 1.04)	<.001	0.99 (0.98, 1.00)	0.01	0.99 (0.93, 1.05)	0.71

Table 3 Adjusted associations between imaging variables and outcomes

	Symptomatic ICH		Death <= 7 days		Death <= 6 months		Alive & Independent OHS 0-2		Favourable Outcome OHS 0-1	
Imaging variable	**OR (95% CI)**	**P**	**OR (95% CI)**	**P**	**OR (95% CI)**	**P**	**OR (95% CI)**	**P**	**OR (95% CI)**	**P**
Visible infarct	1.38 (0.93, 2.03)	0.11	1.64 (1.25, 2.16)	<.001	1.40 (1.15, 1.69)	<.001	0.68 (0.56, 0.83)	<.001	0.65 (0.52, 0.81)	<.001
Hypodensity	1.43 (0.97, 2.11)	0.07	1.65 (1.25, 2.17)	<.001	1.39 (1.15, 1.69)	<.001	0.68 (0.56, 0.82)	<.001	0.64 (0.51, 0.80)	<.001
Severe Hypodensity	1.31 (0.67, 2.56)	0.43	1.04 (0.63, 1.74)	0.87	0.92 (0.63, 1.33)	0.65	0.88 (0.60, 1.27)	0.48	0.78 (0.51, 1.19)	0.25
Large/very large lesion	1.30 (0.83, 2.01)	0.25	2.26 (1.70, 3.01)	<.001	2.12 (1.68, 2.66)	<.001	0.51 (0.38, 0.67)	<.001	0.39 (0.27, 0.57)	<.001
Very large lesion	1.46 (0.86, 2.49)	0.16	3.24 (2.33, 4.51)	<.001	2.33 (1.71, 3.16)	<.001	0.29 (0.17, 0.47)	<.001	0.22 (0.10, 0.45)	<.001
Swelling	1.29 (0.86, 1.95)	0.22	1.60 (1.21, 2.11)	0.001	1.46 (1.19, 1.80)	<.001	0.59 (0.47, 0.75)	<.001	0.56 (0.43, 0.75)	<.001
Hyperdense arteries	1.56 (1.05, 2.32)	0.03	1.42 (1.07, 1.87)	0.01	1.40 (1.14, 1.72)	0.001	0.60 (0.47, 0.76)	<.001	0.64 (0.49, 0.84)	0.001
Any Leukoaraiosis	1.01 (0.68, 1.50)	0.97	1.09 (0.82, 1.45)	0.54	1.38 (1.14, 1.67)	0.001	0.72 (0.59, 0.87)	<.001	0.61 (0.50, 0.76)	<.001
Severe Leukoaraiosis	1.15 (0.77, 1.70)	0.50	1.17 (0.89, 1.54)	0.27	1.43 (1.18, 1.73)	<.001	0.66 (0.54, 0.80)	<.001	0.62 (0.50, 0.77)	<.001
Atrophy	0.97 (0.58, 1.64)	0.91	0.83 (0.57, 1.20)	0.31	1.23 (0.93, 1.61)	0.14	0.74 (0.59, 0.94)	0.01	0.64 (0.50, 0.82)	<.001
Severe Atrophy	1.02 (0.64, 1.63)	0.93	0.87 (0.63, 1.22)	0.42	1.28 (1.03, 1.59)	0.02	0.79 (0.63, 1.01)	0.06	0.75 (0.57, 0.98)	0.04
Old lesion	1.71 (1.17, 2.50)	0.006	0.93 (0.71, 1.21)	0.59	1.04 (0.86, 1.24)	0.70	0.89 (0.74, 1.07)	0.21	0.79 (0.65, 0.96)	0.02

Table 4 Logistic models of functional outcome at 6 months and Symptomatic ICH outcome at 7 days : estimates from models with all imaging variables

	OHS0-2 vs 3-6		SICH	
	OR (95% CI)	P	OR (95% CI)	P
Age (yr)	0.97 (0.96, 0.97)	<.001	1.00 (0.98, 1.02)	0.886
NIHSS	0.83 (0.82, 0.85)	<.001	1.06 (1.03, 1.10)	<.001
Time to randomisation (hr)	1.04 (0.96, 1.13)	0.291	0.98 (0.83, 1.15)	0.766
rtPA vs Control	1.13 (0.94, 1.35)	0.197	6.69 (3.92, 11.41)	<.001
Antiplatelets		.	1.59 (1.07, 2.36)	0.023
Lesion size : Large/Very large vs Small/Medium/None	0.68 (0.48, 0.96)	0.030	0.96 (0.54, 1.72)	0.904
Swelling	0.78 (0.56, 1.09)	0.147	0.98 (0.55, 1.74)	0.945
Hyperattenuated artery	0.70 (0.54, 0.91)	0.008	1.51 (0.95, 2.38)	0.079
Hypoattenuation : Mild vs None	0.92 (0.70, 1.20)	0.525	1.25 (0.72, 2.18)	0.425
Hypoattenuation : Severe vs None	1.14 (0.74, 1.76)	0.559	1.33 (0.60, 2.92)	0.485
Old lesions	0.92 (0.76, 1.12)	0.400	1.74 (1.15, 2.61)	0.008
Leukoaraiosis : Mild vs None	0.80 (0.64, 1.00)	0.045	1.00 (0.64, 1.58)	0.995
Leukoaraiosis : Severe vs None	0.64 (0.48, 0.85)	0.002	0.91 (0.50, 1.64)	0.743
Atrophy : Mild vs None	0.86 (0.67, 1.11)	0.254	0.84 (0.47, 1.49)	0.555
Atrophy : Severe vs None	0.71 (0.51, 0.99)	0.044	0.84 (0.41, 1.71)	0.630

Table 5 Selected logistic models of functional outcome at 6 months and Symptomatic ICH outcon

	OHS 0-2 vs 3-6		SICH	
	OR (95% CI)	P	OR (95% CI)	P
Age (yr)	0.96 (0.95, 0.97)	<.0001	0.99 (0.98, 1.01)	0.5591
NIHSS	0.83 (0.82, 0.85)	<.0001	1.07 (1.04, 1.10)	<.0001
Time to randomisation (hr)	1.04 (0.96, 1.13)	0.2912	0.98 (0.83, 1.15)	0.7883
rtPA vs Control	1.12 (0.94, 1.34)	0.1976	6.73 (3.94, 11.49)	<.0001
Antiplatelets		.	1.59 (1.07, 2.36)	0.0222
Lesion size : Small/medium vs None	0.89 (0.70, 1.13)	0.3390		.
Lesion size : Large/Very large vs None	0.54 (0.39, 0.74)	0.0001		.
Hyperattenuated artery	0.71 (0.54, 0.91)	0.0083	1.64 (1.09, 2.46)	0.0179
Old lesions		.	1.66 (1.13, 2.45)	0.0106
Leukoaraiosis : Mild vs None	0.76 (0.61, 0.93)	0.0087		.
Leukoaraiosis : Severe vs None	0.59 (0.45, 0.78)	0.0002		.