ICSS Safety (30 day) Results – Statistical Analysis Plan

Background:

ICSS is a randomised controlled trial of carotid artery stenting (CAS) versus carotid endarterectomy (CEA) for the long term prevention of disabling and fatal stroke in patients with symptomatic carotid artery stenosis. A total of approximately 1700 patients will be randomised; 1500 from centres which are 'non-probationary' and 200 from centres which are 'probationary' (i.e. do not yet satisfactorily meet the CAS and/or CEA 'previous experience' criteria as a centre overall). This statistical analysis plan is limited to the main secondary endpoint of the trial - morbidity and mortality during the 30-day post procedural period – which will be published prior to the primary analysis results.

Section 1: PLANNED TIMING OF DATASET CLOSURE FOR 30 DAY RESULTS

- Only CEA and CAS procedures that have taken place up to 90 days after the last patient has been randomised into ICSS will be included in the main paper results.

- The dataset for analysis will be locked approximately 5.5 months after the last patient was randomised (17th April 2009).

Section 2: KEY DEFINITIONS

- **Probationary patients**
  These are defined as ALL patients within a centre (whether allocated to CEA or to CAS) randomised into ICSS whilst the whole centre has a 'probationary' status. In the case of probationary centres which lack the necessary experience in CAS only, a centre is promoted to being a non-probationary centre after a total of 10 CAS procedures have been performed with a complication rate of less than 7 % (i.e. all 10 CAS procedures must be successful). Probationary and non-probationary patients will be identified prior to analysis of the safety results.

- **Procedure initiation**
  A patient is considered to have had an ipsilateral procedure if the procedure has been 'initiated' (i.e. the patient has been given either local or general anaesthetic), even if the procedure is subsequently aborted. Any events occurring within 30 days of initiated but aborted procedures will therefore be included in the main analyses as post-procedural events.

- **Procedure timing**
  All first ipsilateral procedures (see definition of procedure completion above) will be analysed irrespective of time from randomisation.

- **Procedural event**

A procedural event is one that occurs 0 to 30 days after the procedure (day 0 = day of the procedure).

- **Fatal, disabling and non-disabling stroke events**
  A fatal event is one that leads directly to the death of the patient (within 30 days of the event). For this analysis, a stroke will be classified as disabling if the Rankin score is ≥ 3 for 30 or more days after onset.

- **Cranial nerve palsy severity**
  Disability after cranial nerve palsies will be assessed in the same way as for stroke events (see above).

- **Per protocol analysis**
  Secondary per protocol analysis of the ITT Kaplan Meier analysis will be performed. A patient will be excluded in the per-protocol analyses if they:
    - Did not receive the allocated procedure as their first ipsilateral procedure after randomisation.
    - Are known to have been entered into ICSS contrary to inclusion and exclusion criteria at the time of randomisation e.g. Rankin score >=4 at randomisation

- **Primary endpoint**

  The primary endpoint for the 30 day results analyses will be "any stroke, death or peri-operative MI" (non-fatal MI only collected during 30 days post procedure)

- **Secondary endpoints**

  Secondary endpoints will include the following:
    - Any stroke or death
    - Any stroke or death (excluding non-disabling strokes lasting < 7 days)
    - Any stroke / Fatal or disabling stroke / Fatal stroke / Disabling stroke / Non-disabling stroke
    - Any perioperative MI / Fatal perioperative MI
    - Non-stroke, non-MI death
    - All cause death
    - Cranial nerve palsies (disabling and non-disabling)
    - Haematoma requiring surgery, transfusion or prolonging hospital stay
    - All neurological events
    - Rankin score at 30 days post-procedure

Section 3: ANALYSES – KEY POINTS

- **Primary Analyses**

  1) Procedural risk analysis:
    - Excluding those who never had (or are not yet known to have had) a procedure AND those that did not receive the allocated procedure as their first ipsilateral procedure after randomisation
    - The main outcome is risk of an event within 30 days post-procedure (so only follow-up after the procedure is considered and hence pre-procedural events are excluded).
    - The main statistical results will be absolute risk differences, risk ratios and 95% confidence intervals.
    - Any patients with a non-fatal pre-procedural (but post-randomisation) event that go on to have the ipsilateral procedure will still be considered at risk and included in the analysis.
    - All patients (probationary and non-probationary) will be included (see Definitions section above).
    - All first allocated ipsilateral procedures will be included (at any point after randomisation) except where first crossed-over to best medical treatment.

  2) Kaplan- Meier plot

    - Time to event from randomisation by allocated treatment group (ITT) with censoring at 120 days after randomisation if the patient has been followed up for 120 days and is event free (so any pre-procedure and > 30 days post-procedure but < 120 days post-randomisation events will be included). Patients without an event and with <120 days of follow-up will be censored on date of last known event status.
    - The main statistical results will be a KM plot, log rank test and Cox model hazard ratio plus 95% confidence interval. Absolute risk differences at 120 days with 95% CI (from KM plots) may also be estimated.
    - All patients (probationary and non-probationary) will be included (see Definitions section above).

- **Secondary Analyses**

  3) Kaplan-Meier - per protocol:
    - Repeat of Kaplan-Meier plot analyses set out in 2) above, but for the 'per-protocol' population of patients only (see Definitions section above).

  4) Pre-defined treatment by risk factor interaction analyses:
    - Repeat primary ITT analysis with sub-group analysis (based on HR and interaction test) using the following pre-defined baseline risk factor

subgroups (categories may be collapsed or changed prior to analysis if numbers of events are small):

- ✓ Age (<70 and >=70 years: approx. median age)
- ✓ Gender (Male, Female)
- ✓ Time from most recent pre-randomisation event to procedure (<=14 days, >14 days)
- ✓ Type of most recent event prior to randomisation (TIA, stroke, AF)
- ✓ More than one event of any type prior to randomisation (Yes, No)
- ✓ Stroke prior to most recent event pre-randomisation (Yes, No) – only if sufficient numbers
- ✓ Ipsilateral stenosis (50-69%, 70-99%)
- ✓ Status of contralateral artery at randomisation (0-49%, 50-69%, 70-99%, Occluded)
- ✓ Size of centres (<50 , >=50 patients)
- ✓ Diabetes
- ✓ Hypertension

5) **Adjustment for pre-determined risk factors:**
   - For all these 30 day analyses, there will be no adjustment for pre-determined risk factors. A sensitivity analysis controlling for predetermined risk factors e.g. age (<60, 60-69, 70+), sex, contralateral occlusion, side of artery will also be performed. An additional analysis adjusting for centre will also be performed. As there are 50 centres, a modified 'centre' variable will be used instead of the centre variable itself e.g. countries stratified by probationary status of centres.

6) **Probationary patients:**
   - Using dataset with probationary + non-probationary patients, perform treatment x probationary status interaction tests to identify whether any evidence of a difference in treatment effect by probationary status (but probably small numbers).
   - A sensitivity analysis of the primary analyses (with non-probationary patients and probationary patients combined) will be performed where the 2 centres that were stopped to poor results will be excluded.

7) **Meta-analysis**
   - A provisional literature based meta-analysis of the stroke or death 30 day outcome may be performed.

8) **Learning curve:**
   - Analysis of learning curve of surgeons and interventionalists. This will be a separate analysis and paper and as such will have a separate statistical analysis plan. (NB/ could extract information from files on prior experience of interventionalists taking part in the trial)

Section 4: ADDITIONAL ANALYSES

- CONSORT trial flow diagram.

The following analyses will all be performed by allocated treatment:

- Tabulation of summary statistics for baseline characteristics (demography, medical risk factors, severity of stenosis, disability).
- Tabulation of summary statistics for baseline cerebrovascular symptoms, by allocated treatment.
- Tabulation of summary statistics for time from randomisation to first ipsilateral treatment and from index event to first ipsilateral treatment.
- Tabulation of summary statistics for technical information on the first ipsilateral procedure (types of stents, protection device used [y/n], type of protection device, time from procedure to discharge for those without an event).

ICSS Safety Long-term Results – Statistical Analysis Plan

Background:

ICSS is a randomised controlled trial of carotid artery stenting (CAS) versus carotid endarterectomy (CEA) for the long term prevention of disabling and fatal stroke in patients with symptomatic carotid artery stenosis. A total of approximately 1700 patients have been randomised; 1500 from centres which are 'non-probationary' and 200 from centres which are 'probationary' (i.e. do not yet satisfactorily meet the CAS and/or CEA 'previous experience' criteria as a centre overall). This statistical analysis plan describes the long-term analyses of the trial.

Section 1: TRIAL POPULATION

Individuals randomised in the study excluding those randomised to the MRI sub-study after randomisation in the main study was completed.

Section 2: PLANNED TIMING OF DATASET CLOSURE FOR LONG-TERM RESULTS

- **July 2011-28th February 2012**
  - Data cleaning and final collecting

- **Oct 2011 -28th February 2012**

  - Steering committee teleconference Nov 21st
    - Primary and secondary outcomes finalised and agreed upon
  - Internal adjudication
    - Strokes
    - Other deaths
  - Send to external adjudication
    - Strokes
  - **End of follow-up: 31st December 2011**

- **Database locked: 28th February 2012** (to allow two months for final adjudication and cleaning)
- i.e. Centres will be asked to return all data by 31st December 2011 in order that cleaning and final checks be performed by 28th February 2012
- Statistical analysis code pre-planning and testing of analyses in SAP using a cut of the data from January 2012

- **March 2012 – May 2012**
  - Data analysis
  - Note: A minimum of 3 months (i.e. of a part-time statistician) is required for analysis when a CLEAN final data set has been received i.e. For a CLEAN data set (i.e. with all events adjudicated) received on 1st March 2012, results would be anticipated for June 1st 2012.

Section 3: KEY DEFINITIONS

- **Probationary patients**
  These are defined as ALL patients within a centre (whether allocated to CEA or to CAS) randomised into ICSS whilst the whole centre has a 'probationary' status. In the case of probationary centres which lack the necessary experience in CAS only, a centre is promoted to being a non-probationary centre after a total of 10 CAS procedures have been performed with a complication rate of less than 7 % (i.e. all 10 CAS procedures must be successful). Probationary and non-probationary patients were identified prior to interim analyses and will be described in the final analysis. All probationary patients will be included in the final analyses.

- **Procedure initiation**
  A patient is considered to have had an ipsilateral procedure if the procedure has been 'initiated' (i.e. the patient has been given either local or general anaesthetic), even if the procedure is subsequently aborted.

- **Procedure timing**
  All first ipsilateral procedures will be analysed irrespective of time from randomisation according to the definition used for the short-term paper (i.e. no additional procedures will be included over and above those already considered in that paper).

- **Procedural event**
  A procedural event is one that occurs 0 to 30 days after the procedure (day 0 = day of the procedure).

- **Fatal, disabling and non-disabling stroke events**
  A fatal event is one that leads directly to the death of the patient (within 30 days of the event). For this analysis, a stroke will be classified as disabling if the Rankin score is ≥ 3 at 30 days after onset and is one which has increased by at least 1 point compared to

the Rankin score before onset where the increase is attributable to stroke. Note that the ICSS protocol mentions disability at 6 months but the TSC felt that disability at 1 month was preferable. Note further that, although worded here slightly differently for clarity, this definition is that used for all analyses in the short-term results paper.

- **Cranial nerve palsy (CNP) severity**
  Disability after cranial nerve palsies will be assessed in the same way as for stroke events (see above). [Note: any other disability will be defined accordingly.]

- **Per protocol, post-treatment analysis (modified per-protocol)**
  Secondary per protocol, post treatment analysis will be performed to compare non-procedural outcomes in patients whose allocated procedure was completed (i.e. not aborted). This analysis 'starts' at 31 days after the allocated ipsilateral procedure i.e. it includes all follow-up from this point onwards, and excludes the following patients:
  - those that did not have their allocated procedure initiated (i.e. either x BMT or x CEA/CAS without an attempt at their allocated procedure)
  - those whose allocated procedure was initiated but the stent was not deployed or the surgery was aborted
  - those that died between randomisation and 30 days after the allocated ipsilateral procedure
  - those that left follow-up between randomisation and 30 days after the allocated ipsilateral procedure
  - those that had a fatal event during 30d but died > 30 days after procedure

Patients with earlier non-fatal strokes are therefore included (and any second events they have) although a sensitivity analysis will be performed in which patients with an earlier non-fatal stroke are excluded.
Note, this is a NON-RANDOMISED comparison between treatment groups (i.e. it is a selected group of patients and thus there may differences in patient characteristics between the treatment groups that are not due to chance).

- **Outcome events of interest**

  - Ipsilateral Stroke
  - Stroke (any territory)
  - Death
  - Vascular death
  - Myocardial Infarction death
  - TIA

- **Primary endpoint for analysis**

  Fatal or disabling stroke (in any territory).

  Note that this as stated in the ICSS short-term results paper and the protocol. It will not include other peri-procedural non-stroke deaths.

- **Timepoint for Kaplan-Meier vs time-point for estimates for primary analyses**

    - KM plots will be provided up to a point in time for which there are a reasonable number of events which the TSC agreed will likely be at 8 years of follow-up
        - It was noted at the TSC that it preferable to include as much of the data as possible despite caveats about not plotting KM plots when few events/patients remain. (See Pocock, Clayton and Altman, Lancet 2002; 359:1686-89.) Numbers at risk in each treatment arm will be provided for each year of follow-up.
        - Cumulative outcomes (i.e. risk differences) will be reported at 8 years subject to sufficient data (See Pocock, Clayton and Altman), whereas hazard ratios from Cox PH model will use all data up to locking of database (see below). Such comparisons will also be presented at 1- and 5-years.
    - Cox PH estimates
        - All clean follow-up events (for events prior to 31st Dec 2011) up to database locking on February 2012 will be included (i.e. including follow-up data beyond that shown in KM plots) except, of course, for events for individuals who have formally withdrawn from ICSS. Specifically, such patients will be considered censored from the day after withdrawal so that even if data on death is available from ONS such events will not be included.
            - A further note on the use of ONS data: blinded assessment of the patterns of visit follow-up will be considered to ascertain how many deaths would be identified only from ONS (i.e. not reported by recruiting centres). It is anticipated that all such data on deaths would be included, at least up to 12 months after last known follow-up.
        - A concern could be non-proportionality because of few individuals and few events later on. Such assumptions will be checked but it is not anticipated that events later on will affect this assumption.

- **Secondary endpoints for analysis**

    - Any stroke or death
    - Death of any cause
    - Any stroke
    - Ipsilateral stroke / Non-ipsilateral stroke
    - Ipsilateral stroke and peri-procedural stroke or death
    - Vascular death
        - Note: these are neither internally nor externally adjudicated
    - Myocardial Infarction death
        - Note: these are not externally adjudicated with internal adjudication only up to 30 days

- TIA
    - Note: these are not adjudicated
- Further treatment of the randomised artery by interventional radiology techniques or surgery after the initial attempt
- Modified Rankin score at set time periods e.g. 1, 5 and 8 years
- Note: restenosis and quality of life will each form the basis of separate papers hence will not be reported in the ICSS long-term results.

Section 4: ANALYSES – KEY POINTS

- **Primary Analyses**

1) ITT analysis:

- Time to event from randomisation by allocated treatment group (ITT). All follow-up time will be used (see specifics for KM plot below). Patients without an event will be censored on date of last known event status.
- The main statistical results will be
    1. KM plot
    2. Log rank test
    3. Cox model hazard ratio plus 95% confidence interval. Model proportionality assumption will checked with appropriate techniques e.g. Schoenfeld residuals
    4. Absolute risk differences at 1, 5 and 8 years with 95% CI (from KM plots) in line with timings reported above.
- All patients (probationary and non-probationary) will be included (see Definitions section above).

- **Secondary Analyses**

2) Per-protocol, post treatment analysis (modified per-protocol):

- Same analysis as 1) but restricting to 'modified per protocol' population as defined in section 3.

3) Characterisation of timing of events

- Only first events will be considered except for the modified Rankin score for which we would like to know whether changes in Rankin scores between time points is caused by new events.
    - Note: Rankin score will form the basis of another paper with simple summary measures only reported in the main paper
    - It is anticipated that the full frequency distribution will be included.
- A table like Table 2 included in the EVA-3S long-term paper (*Lancet Neurol* 2008;7:885–892) will be included which splits events in to peri-procedural and non-procedural. Note that for ICSS, there will be less information in the table since the primary endpoint does not include peri-procedural deaths due to causes other than stroke.

4) Pre-defined treatment by risk factor interaction analyses:

Interaction analyses will be undertaken as for interim analyses: i.e. for ITT only from time of randomisation, except for time from event to treatment, which is analysed per protocol (here defined as from time of treatment for all patients whose allocated treatment was initiated).

Subgroups to analyse in ITT analyses (except for time to treatment which will be per-protocol) are those included in the interim analyses, specifically:

- ✓ Age (<70 and >=70 years: approx. median age)
- ✓ Gender (Male, Female)
- ✓ Time from most recent pre-randomisation event to procedure (<=14 days, >14 days)
- ✓ Type of most recent event prior to randomisation (TIA, stroke, AF)
- ✓ More than one event of any type prior to randomisation (Yes, No) (Multiple ipsilateral symptoms)
- ✓ Stroke prior to most recent event pre-randomisation (Yes, No) – only if sufficient numbers
- ✓ Ipsilateral stenosis (50-69%, 70-99%)
- ✓ Status of contralateral artery at randomisation (0-49%, 50-69%, 70-99%, Occluded)
- ✓ Size of centres i.e. centre recruitment (<50 , >=50 patients)
- ✓ Diabetes
- ✓ Treated Hypertension
- ✓ Centre experience (probationary, non-probationary)

5) Adjustment for pre-determined risk factors:

- For all these long-term analyses, there will be no adjustment for pre-determined risk factors. A sensitivity analysis controlling for predetermined risk factors e.g. age (<60, 60-69, 70+), sex, contralateral occlusion, side of artery will also be performed. An additional analysis adjusting for centre will also be performed. As there are 50 centres, a modified 'centre' variable will be used instead of the centre variable itself e.g. countries stratified by probationary status of centres.

6) Exclusion of stopped centres:

- No sensitivity analyses excluding the stopped centres will be performed as all the problems were periprocedural.

7) Meta-analysis

- Meta-analysis is required by the Lancet as part of their recommendations for reporting of clinical trials.
- However, since it is anticipated that a revised Cochrane review of CAS vs. CEA will be completed before publication of the ICSS long-term results, we could simply add the ICSS data to the long-term meta-analysis in the Cochrane review

Section 5: ADDITIONAL ANALYSES

- CONSORT trial flow diagram.
- Summary statistics for length of follow-up during trial e.g. median duration of follow-up.

Since the goal of the long-term results paper is as a stand-alone paper, the following analyses will all be performed by allocated treatment (even though some of them were reported in short-term results paper).

- Tabulation of summary statistics for baseline characteristics (demography, medical risk factors, severity of stenosis, disability).
- Tabulation of summary statistics for baseline cerebrovascular symptoms, by allocated treatment.

Additionally, the following table by treatment will be created:

- A table of treatment during follow-up – e.g. proportion of patients comparing the 2 arms receiving BP treatment, antiplatelet agents, statins and data on their blood pressure readings during follow-up.

- Since information concerning medications will be collected at different times during follow-up and may change over the course of follow-up, comparisons between the two treatment arms will be performed at fixed time points like those defined above (anticipated to be 1 year, 5 years and 8 years). A table like Table 3 in the SPACE long-term paper (*Lancet Neurol* 2008;7:893–902) will be produced.

ICSS Effect of white-matter lesions on the risk of periprocedural stroke – Statistical Analysis Plan

We will test two hypotheses using the methods and analyses described before any results are analysed.

1 Compared with less extensive white-matter lesions, more extensive white-matter lesions are associated with an increased risk of procedural stroke after treatment of carotid artery disease by either carotid artery stenting or carotid endarterectomy.
2 The increase in procedural risk would differ in patients treated by carotid artery stenting compared with carotid endarterectomy.

The analyses to be done for the following outcome measures: any stroke, non-disabling stroke, and disabling or fatal stroke.

Data will be analysed per protocol—i.e., the analysis will include only patients who received the allocated treatment as their first ipsilateral revascularisation procedure. Patients who received the alternative revascularisation procedure as their first treatment (cross-overs), or who received no revascularisation treatment, will be excluded from this analysis.

All outcome events occurring within 30 days after initiation of the first allocated treatment will be included.

Patients to be dichotomised into two groups at the median value for the age-related white-matter changes score. The median has been chosen as the cut-point for the analysis to ensure equal-sized groups of patients for the comparisons and to avoid the risk of the bias introduced by selecting an optimum cut point after initial analysis of the data.

The baseline characteristics in the two treatment groups will be compared according to whether their ARWMC score is lower than 7 versus 7 or greater using Pearson's $\chi 2$ test or analysis of variance.

We will compare the 30-day risk of the various outcome events between the two treatment groups using a Cox proportional hazards model. We will estimate the cumulative incidences of the different outcome measures using Kaplan-Meier analysis and compare them using log-rank tests stratified by treatment with ARWMC score dichotomised at the median.

All analyses will be adjusted for age, sex, and vascular risk factors