Statistical Analysis Plan (SAP) for Vertebral artery Ischaemia Stenting Trial (VIST)

1. SHORT DESCRIPTION OF PROJECT

Does vertebral artery stenting prevent recurrent stroke in symptomatic vertebral artery stenosis?

See VIST clinical study protocol Version 8.0 (10th June 2014) for details.

VIST is an international multicentre randomised controlled trial with the main aim to investigate the risks and benefits of vertebral angioplasty and stenting plus best medical treatment for symptomatic vertebral stenosis compared with best medical treatment alone. The efficacy is determined for the cohort as a whole and for extracranial and intracranial vertebral stenosis separately.

From an analytic point of view, we are treating VIST as a non-inferiority or equivalence trial, that is, a trial aimed to determine whether stenting is as good as best medical therapy alone in preventing recurrent stroke in patients with vertebral artery stenosis.

2. DATA

A summary of the participant assessments and data collection is described in the table below.

	Baseline Visit (Hospital Visit 1)	Time of Procedure* (Hospital Visit 2)	1 month (Hospital Visit 3)	6 months (Telephone Follow-up Call)	1 year (Hospital Visit 4)	Annual Telephone Follow-up from Year 2 until Trial End
Informed Consent	√					
Patient Diary	√					
Entry Form†	√					
Imaging Form	√				√	
Stenting Form		√				
Follow-up Forms‡			√	√	√	√
Cross-Over Form		√	√	√	√	√
Endpoint Form			√	√	√	√
Adverse Event Form		√	√	√	√	√
Death Report Form		√	√	√	√	√

*If allocated angioplasty/stenting.

†Baseline data, including patient details, cerebral events (presenting and past events), risk factors, medication prior to trial entry, modified Rankin at time of randomisation, quality of life form completed, imaging prior to randomisation, and final screening prior to randomisation.

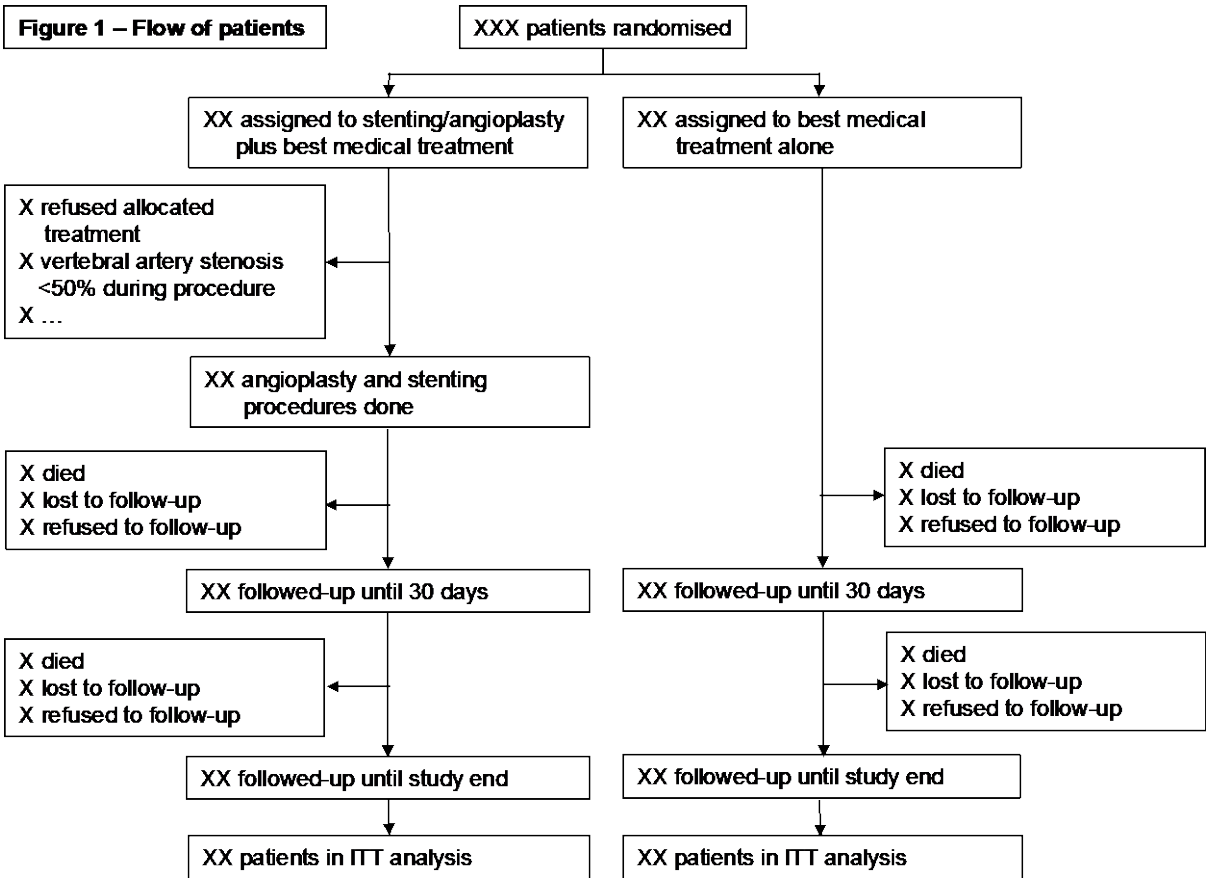
‡Follow-up forms include details on events since last follow-up, modified Rankin at time of follow-up, quality of life form completed, risk factors, medications at follow-up, and procedures performed since randomisation.

3. PLANNED STATISTICAL ANALYSES

3.1. Flow diagram

See Figure 1 for a proposed detailed presentation of participant flow.

The number of participants randomised to each treatment arm, followed-up, and analysed will be presented with a CONSORT flow diagram.



3.2. Descriptive statistics

See Table 1 below for a proposed presentation of the baseline characteristics.

Participants of each randomised treatment group will be described with regards to baseline demographic and clinical characteristics as recorded at the Baseline Visit. Categorical variables will be presented as numbers and proportions, and groups will be compared using χ^2 or Fisher's exact test. Continuous variables will be presented as means with standard deviations, and groups will be compared using *t* tests.

3.3. Comparison of treatment strategies

See Table 2 below for a proposed presentation of primary and secondary endpoints.

Main analyses will be performed on an intention-to-treat (ITT) basis, with inclusion of all randomised patients in the analysis according to the treatment group they were initially allocated. Analyses will also be done per-protocol (PP), including participants who met the inclusion criteria and received the assigned treatment. During trial monitoring is has become apparent that, for some cases, vertebral stenosis of at least 50% has not been confirmed on central imaging review.

The per-protocol analysis will include:

1. Patients with symptomatic vertebral stenosis from presumed atheromatous disease
2. Patients in whom central imaging review confirmed vertebral stenosis of ≥50%
3. Patients who received the allocated treatment

ITT and PP analyses will be performed for the primary and secondary endpoints, which are listed below. Not all secondary endpoints may be reported in the published article but the following analyses will be presented in the study plan;

Primary endpoint:

- Fatal and non-fatal stroke in any arterial territory during trial follow-up

Secondary endpoints:

- Fatal or non-fatal stroke in any arterial territory at 3 months post-randomisation
- Posterior circulation stroke (including periprocedural stroke) during follow-up
- Periprocedural stroke or death (within 30 days of procedure)
- Posterior circulation stroke and TIA during follow-up
- Any disabling stroke (defined by a Modified Rankin score ≥3) during follow-up
- Death of any cause during follow-up
- Restenosis (stenosis >50% in the treated artery) in treated artery during follow-up
- NHS and personal social services costs (UK patients only)*
- Quality-adjusted life years*
- Within-trial and long-run incremental cost-effectiveness*

*As specified in the protocol (pages 12-13).

The main analyses will be repeated for intracranial and extracranial strokes separately.

The intensity of medical treatment will be compared between the two groups over the first 30 days and over the full trial duration by assessing presence/absence and number of the following treatments: anti-platelets; statins; antihypertensives. Blood pressure measurements during follow-up in the two groups will be compared. Treatment of diabetes mellitus and current smoking will be recorded.

In analyses of primary and secondary endpoint events at 3 months post-randomisation and during complete follow-up, follow-up will start immediately after randomisation. Follow-up will range from 1 year for the last recruited patients to about 7.5 years for first recruited patients. If the event numbers are sufficient, hazard ratios with 95% confidence intervals will be estimated by using Cox proportional hazards regression models, with patients censored at the time of first event of each type, death, last contact date, or the end of follow-up. The proportional hazards assumption for the treatment will be tested using Schoenfeld residuals. Kaplan-Meier survival analysis will be used to construct time-to-event curves, and the log-rank test will be used to evaluate whether there is a statistical significance difference in the cumulative risk of stroke between the two treatment groups.

We will also analyse short term outcomes to assess the operative risk. For this we have chosen a 30 day follow-up period but this may be adjusted before unblinding to results and analysis if we find stenting has not been carried out by 30 days in a significant number of individuals. For 30-days events, follow-up for each patient will start immediately after recruitment for patients allocated medical treatment alone and immediately after the stenting procedure for patients allocated stenting. If stenting was not performed in a patient allocated stenting, follow-up will begin directly after randomisation. The proportions of outcome events within 30-days of treatment will be compared with exact logistic regression to estimate odds ratios and 95% confidence intervals.

In additional analyses, provided that the event numbers are sufficient, we will adjust for centre and predefined risk factors (i.e., age, sex, body mass index and the vascular factors presented in Table 1). Hypothesis tests will be 2-sided using a significance level of 0.05. Statistical analysis will be performed using Stata (StataCorp, College Station, TX).

3.4. Adverse Events

Adverse events (AEs), including serious adverse events (SAEs), have been recorded as specified in the protocol (pages 10-12). AEs and SAEs will be defined as in the protocol and presented stratified by treatment group.

3.5. Sample size calculations

At trial initiation, we did power calculations using a power of 80% and two-sided significance level of 5%, and assuming that the risk of stroke in the medically treated arm would be 12% in year 1, 7% in years 2, and 5% in years 3 (i.e. 24% over a 3-year period). It was further assumed that the risk reduction in the stented arm would be 45% (including periprocedural rate). Based on these assumptions, the number of patients needed was estimated to be 490 (245 per arm). This number was increased by 10% to allow for stent failure, crossover, and loss to follow-up, thus giving a sample size of 540 patients. Because of early termination of the trial owing to low recruitment rate, the actual number of patients enrolled was 182.

4. PROPOSED TABLES AND FIGURE LEGENDS

Table 1. Baseline characteristics of patients enrolled into the VIST, according to treatment group (intention-to-treat population) (per protocol data will be presented in columns to the right or in a separate similar table)

Characteristic[a]	Best medical treatment group (n = xx)	Angioplasty/stenting group (n = xx)	*P* value[b]
Age (years)			
Male, n (%)			
Body mass index[c]			
Vascular risk factors			
Treated hypertension			
Treated hyperlipidaemia			
Previous myocardial infarction			
Angina in last 6 months			
Peripheral artery disease			
Atrial fibrillation			
Qualifying event			
TIA			
Non-disabling stroke[d]			
Location of vertebral artery target stenosis			
Extracranial (V1 to V3)			
Intracranial (V4)			
Modified Rankin Score			

TIA, transient ischemic attack; VIST, Vertebral artery Ischaemia Stenting Trial.

[a] Values are number (%) of patients or mean (± SD).

[b] Treatment groups are compared using Fisher's exact test or *t* tests.

[c] BMI is calculated as weight (kg) divided by height (m) squared.

[d] Modified Rankin scale score ≤3 at inclusion.

Table 2. Medical treatment and blood pressure and risk factor control over the first 30 days over the whole study follow-up

	Best medical treatment group (n = xx)		Angioplasty/stenting group (n = xx)	
	First 30 days	**Whole follow-up[a]**	**First 30 days**	**Whole follow-up[a]**
Antiplatelet medication				
Aspirin alone				
Clopidogrel alone				
Aspirin and clopidogrel				
Other				
Oral anticoagulants				
Statin therapy				
Antihypertensive medication				
Blood pressure[b]				
Systolic (mmHg)				
Diastolic (mmHg)				
Treated diabetes mellitus				
Non-insulin dependent				
Insulin dependent				
Current smoking				

[a] Where treatments changed during follow-up the treatment given for the majority of follow-up is recorded.

[b] Blood pressure measurements were only recorded at clinic follow-ups at 3 months and 1 year.

Table 3. Primary and secondary endpoint events during follow-up[a] (intention-to-treat population) (per-protocol data will be presented in columns to the right or in a separate similar table)

	No. (%) of patients/person-months			
	Best medical treatment group (n = xx)	Angioplasty/stenting group (n = xx)	HR (95% CI)	*P* value
Primary endpoint				
Fatal or non-fatal stroke in any arterial territory[b]				
Extracranial vertebral artery target stenosis				
Intracranial vertebral artery target stenosis				
Secondary endpoints				
Fatal or non-fatal stroke in any arterial territory[b] at 3 months				
Posterior circulation stroke[b]				
Periprocedural stroke or death				
Posterior circulation stroke or TIA				
Death from any cause				

CI, confidence interval; HR, hazard ratio; mRS, modified Rankin Scale; TIA, transient ischemic attack.

[a] Complete follow-up (≥1 year) if not otherwise indicated.

[b] Including periprocedural (30 days post-procedure) stroke.

Table 4. Serious adverse events within the first 30 days (intention-to-treat population)

	No. (%) of patients			
	Best medical treatment group (n = xx)	**Angioplasty/stenting group (n = xx)**	**OR (95% CI)**	***P* value**
Cerebrovascular event				
Fatal or non-fatal stroke				
Posterior circulation stroke				
Extracranial				
Intracranial				
Posterior circulation stroke or TIA				
Any disabling stroke (mRS score ≥3)				
Major operation related SAEs				
…				
…				
Death from any cause				

CI, confidence interval; mRS, modified Rankin Scale; OR, odds ratio; TIA, transient ischemic attack.

Table 5. Imaging of symptomatic vertebral artery stenosis (per-protocol analysis)

ANALYSIS OF ANGIOGRAPHIC IMAGING DURING STENTING		
	Pre-Stenting	**Immediate post-stenting**
Angiographic stenosis	? mean (SD)	? mean (SD)
REPEAT NON-INVASIVE IMAGING AT 1 YEAR		
	At randomisation	**At 1 year**
No. (%) with stenosis ≥50%		
Angioplasty/stenting		
Best medical therapy		

FIGURE LEGENDS

Figure 1. Flow of patients (see page 2)

Figure 2: Kaplan-Meier curves of cumulative probability of any stroke during follow-up, according to treatment group (intention-to-treat population)

Log-rank test is used to test the hypothesis that the cumulative incidence of stroke is the same in the two groups.