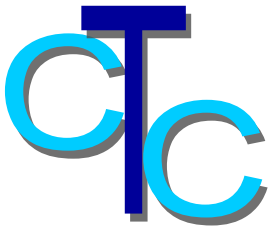
Cerecyte Coil Trial

CLINICAL PROTOCOL



Neurovascular Research Unit, The Radcliffe Infirmary
Woodstock Rd, Oxford, OX2 6HA
Tel: +44 (0) 1865 224114 Fax: +44 (0) 1865 224490

Cerecyte Coil Trial

Trial Sponsor: Micrus Endovascular Corporation
(UK entity: Micrus Endovascular UK Ltd)
ISRCTN82461286

Contents: **Page**

Introduction and Back ground	**3 – 4**
Design and Methods	**4 – 6**
Aims and Objectives	**5**
Entry Criteria	**6**
Statistical Methods	**7**
Sample Size and Power Calculations	**7**
Recruitment Projections	**7**
Treatment Plan	**8**
Steering and Data Monitoring Committee	**9**
Trial Executive Group	**9**
Publication Plans	**10**
Value to Health Policy and Clinical Practice	**10 - 11**
Planned Participating Centres	**11**
Statistical Methods (Appendix)	**13 – 16**
References	**17**

Introduction and Background

Endovascular platinum coil treatment is now established as the treatment of choice for a majority of patients with ruptured intracranial aneurysms following publication of the results of the International Subarachnoid Aneurysm Trial (ISAT), a randomised trial comparing coil treatment with surgery (1). Endovascular coil treatment is also widely used in the treatment of unruptured intracranial aneurysms (UIA). Although no randomised data for this indication currently exists, data from large U.S. observational studies suggest significantly lower rates of morbidity associated with coil treatment in UIA (2). Endovascular treatment is also a popular option with patients desiring to avoid the trauma of a craniotomy. The main ongoing concern about coiling amongst the clinical community is the long-term durability of the treatment and whether the risk of re-bleeding (or first bleeding when un-ruptured aneurysms are treated) is eliminated or reduced to a level similar that following surgical clipping.
This risk is very low based on data from the ISAT study (0.16% per patient year) and other published studies of the risk of re-bleeding after coil treatment. (1, 3) thus it would not be possible to determine whether this very low risk is reduced with different coil devices or designs, unless very long-term follow up and very large observational studies were performed. Because the frequency of such events is so small, such studies are not practicable.

To date, almost all endovascular treatment of intracranial aneurysms has been performed with bare platinum coils. Recently coils have been introduced which incorporate a widely used surgical suture material. In animal studies this leads to a greater tissue reaction at the aneurysm neck. Such coils contain approved surgical suture materials which induce a biological response. A coil coated with a hydrogel material (which expands when in contact with blood) is also in use and is designed to produce superior aneurysm filling and thus better occlusion rates. All these devices have received regulatory approval from the U.S. Food and Drug Administration (FDA) and the relevant regulatory bodies in Canada and the European Union. Thus, they are available and are currently in daily use in patients both in Europe and North America.

It is widely believed that aneurysms which show complete angiographic occlusion at follow up angiography are extremely unlikely to re-bleed. This has been used therefore as a surrogate marker following both surgery and coiling for evidence of the adequacy of treatment and reassurance that re-bleeding is very unlikely.

The frequency of angiographic re-opening, neck remnants or incomplete occlusion of an aneurysm following coiling is quoted at between 17 and 33% (3, 4). In some cases re-treatment with either surgery or endovascular re-treatment is undertaken in patients when significant aneurysm recurrence has occurred. Recent data, available from the large ISAT database, show that rates of angiographic occlusion on follow up angiography are 65% complete occlusion, 25% neck remnant or subtotal, and 9% incomplete occlusion. This is based on angiographic outcomes in 701 patients. (ISAT unpublished data). Whilst platinum coil technology has evolved and the rates of complete angiographic occlusion have probably improved, recent papers (5) in the literature concerning long-term follow up still show relatively high rates of incomplete angiographic occlusion (3).

To try to improve this occlusion rate and to encourage "healing" of the aneurysm neck, platinum coils (with a variety of surface coatings or with various materials incorporated into the coil) have been developed and have shown in experimental aneurysms to produce an increased tissue response with a greater reaction and more dense fibrous tissue and intimal layer covering the aneurysm neck. (Unpublished company data)

A "bioactive" coil, Matrix™ (manufactured by Boston Scientific) received European device clearance (CE marking) and U.S. Food and Drug Administration (FDA) approval in 2002. It has been widely marketed and gained some acceptance. However, only a single prospective observational study of this device in 100 patients was conducted and publication of the full results of this study is still pending.

There was no control group in this study and no randomisation was conducted, thus there is no contemporary objective comparative data on the overall benefit in terms of angiographic occlusion rates at follow-up, re-bleeding, or procedural risk, and the follow up of patients remains incomplete. The lack of a contemporary control group and missing data for this study will make comparison with existing results difficult or impossible. No robust scientific conclusions will be possible. There have been some anecdotal cases showing evidence of vascular re-modelling and healing reaction to the device where a line of thickened tissue is seen on angiographic follow up between the vessel lumen and the coils. This appears to differ from that which would be expected with bare platinum.

Micrus Corporation developed and recently received regulatory clearance in the United States, Europe, and Canada for a modified coil called "Cerecyte." This device contains a Polyglycolic Acid suture material (widely used in surgery) and this has been shown in experimental aneurysms to produce an increased fibrous reaction over the neck of experimental aneurysms.

It is essential that before such new technology is introduced into wide general use that the benefits that it offers for the increased costs of the coils are properly evaluated against the existing platinum coil technology in a scientifically robust manner. This is in line with the recommendations of NICE Interventional Procedures Committee that whilst such Phase 3 studies are not mandatory in the medical device field (as they are with the introduction of new drugs), it is increasing recognised they should be conducted during the introduction of new medical devices.

Objective evidence of such benefit can best be achieved by conducting a prospective randomised trial of sufficient size comparing standard platinum coils with the new active coils with careful follow-up evaluation of the short and medium term angiographic occlusion rates.

Trial Design and Methods

This will be a prospective randomised trial comparing Micrus Cerecyte (polymer loaded) coils with Micrus platinum coils. Patients will be enrolled who fulfil the inclusion criteria and consent to participate. Patients will be randomly assigned to Micrus platinum coil treatment or Micrus Cerecyte treatment. Independent blinded outcome assessment of the angiographic outcome will be performed at six months.

Randomisation will be by central web-based clinical trials system and baseline data collected prior to issuing of the allocation.

Purpose

To systematically evaluate the clinical and angiographic outcome of intracranial aneurysm embolisation using the Micrus Cerecyte (polymer loaded) coil system.

Primary Hypothesis

Micrus Cerecyte coils produce superior angiographic occlusion rates at 6 months after treatment compared with bare platinum coils in patients undergoing endovascular platinum coil treatment for cerebral aneurysms.

Secondary Hypothesis

That the rate of procedural and clinical complications does not differ between bare platinum coils or with Cerecyte coils.

Primary Objective

To determine if Cerecyte (polymer loaded) coils improve the proportion of patients with angiographic occlusion of the aneurysm at 6 months by 50%, from a rate of 75% to 87.5% as set out in the definition of success.

Definition of success:

Complete angiographic occlusion, improvement or no change in the angiographic appearances from the post procedural angiography, as determined by the core lab. The core lab will be blinded to the coil used. Follow-up intra-arterial angiography will be performed between 5 and 7 months after treatment. Any deterioration in angiographic appearances will be defined as failure and the need for re-treatment will be defined as failure.

Secondary Objectives

To observe if the rate of procedural complications and adverse events are not statistically different from bare platinum coils.

To observe if the re-treatment rates are different between the two groups.

.

To observe if a healing reaction is seen in a proportion of patients treated with Cerecyte (polymer loaded) coils and in no patients treated with standard platinum coils.

To determine the 1 year angiographic outcome based on Magnetic resonance angiography.

Definition of Procedural Complications:

a) Procedural aneurysm rupture
b) Clinically manifest transient or permanent thromboembolic events
c) Neurological deterioration within 24 hours of procedure

The events will be categorised by the operator and reviewed by the clinical events committee as:

i) Disease related: unrelated to procedure or device e.g. delayed ischaemic deficit due to vasospasm or development of hydrocephalus
ii) Procedure related: for example groin complications or aneurysm perforation with microcatheter or wire
iii) Device related: for example a thromboembolic event leading to neurological deterioration

Definition of healing reaction:

A healing reaction is defined as the presence on follow-up angiography of a lucent line of equal to or > 0.5mm between the platinum coil ball and the lumen of the parent artery seen on follow-up intra-arterial angiography at six months after treatment. Presence of a healing reaction will be determined by the core lab. For accurate comparison, follow up angiograms must be taken in the same projections used in the initial treatment procedure.

Entry Criteria

Inclusion Criteria

1. Patients aged between 18 and 70 with a ruptured or un-ruptured intracranial aneurysm judged suitable for endovascular treatment by platinum coil occlusion.
2. Aneurysm sizes of less than an 18 mm maximum lumen diameter and a neck width 2mm wide or greater. 3D visualisation of neck on CTA or 3D angiography desirable.
3. Patient planned for treatment of their aneurysm(s).
4. Patients capable of providing their own written informed consent i.e. WFNS Grade 1 & 2 following SAH or Rankin score 1 & 2 for those undergoing treatment for an unruptured intracranial aneurysm (UIA).
5. Patient willing and likely to return for follow-up angiography at 6 months (range 5 -7 months normal practice) after treatment.
6. Patient is willing to undergo a further imaging study between 12 and 24 months after treatment (MRI angiogram or cerebral angiogram) if deemed necessary and possible in line with normal practice at the recruiting centre. This is desirable but not mandatory.
7. Informed consent as set out by the Multi-centre or Local Ethics Committee or Institutional Review Board (IRB).

Exclusion criteria

1. Patients in poor grade after SAH (grade 3, 4, or 5).
2. Large aneurysms greater than 18 mm and giant aneurysms.
3. Aneurysm neck narrower than 2mm.
4. Patient in whom stent placement is planned or performed (balloon assistance techniques allowed).
5. Patients unwilling or unlikely to return for follow up angiogram.
6. Patients in whom that centre regard follow up intra-arterial angiography not to be indicated.
7. Lack of informed consent.
8. The patient has undergone prior coil treatment or attempted treatment of the target aneurysm including prior surgical treatment.

Randomisation: it is desirable if randomisation, in acute patients, is performed shortly before procedure.

Exclusions from Analysis and Protocol violations

1. If stent placement is performed before or after aneurysm coiling; this is a protocol violation and the patient will be excluded from the analysis.
2. If Cerecyte coils are mixed with any another modified coil (Matrix or Hydrogel) these patients will be excluded from the analysis of efficacy. Safety data will still be collected.
3. If there is a crossover to bare platinum because of technical performance reasons of the Cerecyte coil then that patient will be analysed per protocol on an intention to treat basis.

Use of Other Coils

As far as possible, the intention is to maintain the use of all Cerecyte or all Micrus standard, platinum coils in the study. Another manufacturer's platinum coils may be used in patients allocated to bare platinum coils.

Sample size, Power Calculations and Statistical Methods (for detail see appendix):
Sample size is for a randomized parallel group study of platinum coils compared with Cerecyte coils. It is appropriate to power the study at a significance level of P = 0.05 at an 80% power (Table 1). Allowing for some attrition of available follow-up angiographic data in each group, (assumed at 5 - 10% because of procedural events, leading to morbidity or mortality or patient withdrawal prior to follow-up) a sample size of 250 patients in each arm is suggested. This should yield between 420 and 450 follow-up angiograms to determine the primary endpoint at 6 months.

Recruitment projections:
A total of between 14 and 20 centres would be planned to participate in the randomised study, including 4 - 6 U.K. centres. These are all large neurosurgical centres with case volumes between 80 and 150 endovascular aneurysm treatment cases each year, At least half of these patients are likely to be eligible and assuming

half of those eligible are recruited and a mean of 25 per centre per year, recruitment could be completed in 12 to 18 months.

Table 1. Sample Sizes for a Randomized Trial of Coils

Sample Size (per group)	Rate of Failure* Platinum coil group (Controls)	Rate of Failure * Cerecyte Group	Alpha	Power (%)
217	0.25	0.15	0.05	80
92	0.25	0.10	0.05	80
65	0.25	0.075	0.05	80
48	0.25	0.05	0.05	80
753	0.20	0.15	0.05	80
177	0.20	0.10	0.05	80
109	0.20	0.075	0.05	80

Treatment Plan

1. Patient with an intracranial aneurysm suitable for and presenting for endovascular treatment with detachable platinum coils and fulfilling the entry criteria.
2. Patients capable of providing informed consent to entry will be invited to participate by the centre investigator or designated and trained deputy, e.g. Research nurse or Specialist registrar.
3. Central randomisation by a secure web-based system, immediately prior to procedure.
4. Procedure performed as per standard endovascular technique of the centres concerned.
5. Use of either all standard Micrus platinum coils or all Cerecyte coils as determined by randomisation.
6. Completion of electronic case record form (eCRF) collecting procedure details, including detailed findings of angiographic anatomy, size, location, neck size, and dome to fundus ratio. Details of angles of working projection angles recorded on films and eCRFs.
7. A DICOM readable CD with anonymised image data will be sent to coordinating centre for logging and forwarding to core lab for independent assessment. This may be direct to the core-lab form North American Centres.
8. Discharge and adverse event form completed at time of hospital discharge.
9. Patient invited for follow-up angiogram at between 5 and 7 months after treatment.
10. Images in the form of a DICOM readable CD from follow up angiogram forwarded to core lab. Previously used angles for treatment procedure reproduced for optimum comparison.
11. Clinical outcome on Modified Rankin scale collected using standard ISAT collection questionnaire, (attached).
12. Magnetic Resonance scan MR angiogram may also be performed at 12 - 24 months after enrolment.

13. Patient deemed to have completed study after collection of delayed follow up (12-24 months) data on MRI and angiogram, or at 6 months in centres who deem longer follow up is not required. The delayed follow up would be in line with standard practice of the recruiting institution.
14. Any data on further aneurysm treatments or re-treatment of Target aneurysm collected during study period.

Interim Analysis and the Data Monitoring and Ethics Committee

The TSC and DMEC Chairman do not consider an interim analysis necessary.

An independent clinical events and monitoring panel will be appointed to oversee the study and advise on patient safety within the study and receive notification of deaths or serious adverse events.

Trial Steering Committee:

Chair: Mr. Richard Kerr, Consultant Neurosurgeon,
Principal Investigator ISAT, Oxford.
Chief Investigator: Dr. Andrew Molyneux,
Members: Dr. Dennis Briley, Consultant Neurologist, Oxford.
Dr. Nicholas Higgins, Consultant Neuroradiologist, Cambridge.
Statistician: Ziyah Mehta, Stroke Prevention Research Unit, Oxford

Data Monitoring & Ethics Committee (Independent of Trial):

Chair: Professor Peter Rothwell, Stroke Prevention Research Unit, Radcliffe Infirmary, Consultant Neurologist & Senior Lecturer in Clinical Neurology, University of Oxford, The Radcliffe Infirmary.

Members: Professor David Mendelow, Consultant Neurosurgeon, Newcastle.
Dr Martin Jeffree, Consultant Neuroradiologist, Hurstwood Park.

Remit: To oversee the safety and ethical aspects of the study and protect the interests of patients enrolled. To examine un-blinded interim analyses during the study and advise the Steering Committee on any safety issues.

Trial Executive Group
An executive group to oversee day to day running of the trial will be set up at the Neurovascular Research Unit (NVRU) with the Trial Coordinator and Trial Manager, and the Chief Investigator coordinating the meetings of the Trial Steering committee and the Data Safety Monitoring Board.

Ethical Aspects
The trial has been submitted to a U.K. Multi-centre Research Ethics Committee for approval and in other countries to the Ethics Committee or Institutional Review Board in the centre concerned. No patient can be enrolled by a centre unless copies of all the relevant ethics or IRB approvals are held by the coordinating centre in Oxford.

Track record of the Investigators and Trial coordinators and organisation of the Trial

The Chief Investigator is co-principal Investigator of the MRC sponsored International Subarachnoid Aneurysm Trial (ISAT), the largest randomised trial of SAH management ever conducted which first reported in 2002 after an 8 year study. The NVRU is the Coordinating centre for ISAT and the European Coordinating centre for the International Study of Unruptured Aneurysms (ISUIA), funded by the NINDS (part of the US National Institutes of Health). These are two of the largest studies ever conducted of intracranial aneurysm management.

The coordinating centre in Oxford for this study is the NVRU. The study will employ a full time coordinator who will be part of the NVRU team overseen by Julia Yarnold & Mary Sneade, Trial Manager and Assistant Trial Manager. Local centre coordinators will be nominated at the participating centres responsible for collection of the data at the various time points, together with collection and dispatch of the angiographic data to the Core Lab. The data will remain under the control of the NVRU and will not be controlled by the sponsor.

Role of Study Sponsor and Publication Policy

The study design is the responsibility of the Chief Investigator and has been designed in consultation with the sponsor. The data will be blind to investigators and study sponsor during the period of the study recruitment. The data will be reported independent of the study sponsor though the sponsor will have access to study results only after recruitment is completed. The sponsor will have access to any manuscript prior to submission but will not have control over any paper, publication, or presentations or its content by the investigators.

A publication and writing group, independent of the sponsor and the Chief Investigator (CI), will be responsible for the reporting and publication of the trial results.

Conflict of Interest

The CI acts in a Medical advisory role to Micrus Corporation and has a financial interest in the company. Whilst from a logistic view point he is the best person to organise the trial logistics and supervise the trial staff, it is appropriate that he is not involved in any analysis or assessment of the primary outcomes in the study, nor the writing up of the study. All outcome assessments of angiographic results will be based on the independent blinded review by the Core Lab. coordinated by Prof. Alan Fox in Toronto. Writing up and publication of the results will be by a separate writing group of trial investigators.

Contribution to Health Policy and Clinical Practice

The introduction of Medical devices, unlike drugs, is not subject to phase 3 evaluation. They require confirmation of safety for regulatory approval, both in North America and Europe. Thus when a device is introduced which may have an impact on Health care costs an evaluation of the clinical benefit that may be observed with such

a cost increase is essential to determine whether such a device provides significant and measurable clinical benefit. This is best provided through the medium of a prospective randomised trial.

Centre and Investigator Requirements

1. Neurosurgical centres with case volume of aneurysm treatment greater than 60 cases per year.
2. Experienced endovascular treatment centres and operators.
3. High quality digital subtraction angiography equipment, preferably with 3D and biplane capability.
4. Willing to adhere to protocol and only use Micrus platinum coils or Cerecyte coils in enrolled patients and not polymer loaded/enhanced and bare platinum coils in same patient.
5. Local ethics approval Multi-centre ethics approval in process by coordinating centre.
6. The overall study both randomised and observational will be subject of a U.K. multi-centre research ethics application (COREC).

Planned Global Centres

Coordinating Office: Neurovascular Research Unit, Radcliffe Infirmary, Oxford. [Coordinating Centre for International Subarachnoid Aneurysm Trial (ISAT), European Coordinating centre International Study of Unruptured Intracranial Aneurysms (ISUIA)].

The number of enrolling centres may not exceed 25.

Centres confirming interest in participation in the study as of February 2006:
Royal Hallamshire Hospital, Sheffield, U.K. - Dr. Stuart Coley & Dr. Tim Hodgson
Kings College Hospital, U.K. - Dr. Neil Deasy & Dr Tim Hampton
Wessex Neuro Centre, Southampton General Hospital, U.K. - Dr. John Millar
Newcastle General Hospital, U.K. - Dr. Anil Gholkar
Southern General Hospital, Glasgow, UK- Dr. Jo Bhattacharya & Dr. Sarah Jenkins
Radcliffe Infirmary, Oxford, UK, Dr. James Byrne

Würzburg, Germany- Dr. Laszlo Solymosi & Dr. Martin Bendszus
Homburg, Germany- Prof. Wolfgang Reith
Hamburg, Germany- Prof. Hermann Zeumer & Dr. Thomas Kucinski
Frankfurt, Germany- Dr. Richard Du Mesnil de Rochemont
Nancy, France- Prof. Serge Bracard
Toulouse, France- Dr. Christophe Cognard
Paris, France- Dr. Jean-Noel Vallée
Murcia, Spain- Dr. Antonio Moreno
Ankara, Turkey- Dr. Saruhan Cekirge

Stanford, USA– Dr. Michael Marks
Mayo Clinic, Rochester, USA- Dr. David Kallmes
Massachusetts General Hospital, Boston, USA-Dr. John Pryor
St Luke's Episcopal Hospital, Houston, USA- Dr. Michel Mawad
Florida Hospital, Orlando, USA- Dr. Frank Hellinger
Cleveland Clinic, Cleveland, USA- Dr. Peter Rasmussen

Notre Dame Hospital, Montreal, Canada- Dr. Jean Raymond & Dr. Daniel Roy

Sydney, Australia- Dr. Jason Wenderoth

Peer Review
This protocol has been subject to Peer review as required by U.K. MREC conditions.

Appendix:
Statistical Methods:

Primary Objective

The primary effectiveness variable is the rate of angiographic occlusion at six months. The primary study objective is to demonstrate that the rate of occlusion is superior for patients treated with Cerecyte coils than for patients treated with bare platinum coils. The primary effectiveness hypothesis is provided below.

H_0: $P_t \geq P_c$

Versus

H_a: $P_t < P_c$

Where P_t is the rate of occlusion at 6 months in Cerecyte treated patients and P_c is the rate of occlusion at six months in bare platinum coil treated patients.

The primary safety variable is the rate of clinical and procedural adverse events at six months. The primary safety hypothesis is that the rate of clinical and procedural adverse events is not higher in Cerecyte treated patients than for the bare platinum coil treated patients. The null and alternative hypotheses for this objective appear below.

H_0: $P_t \geq P_c + \delta$

Versus

H_a: $P_t < P_c + \delta$

Where P_t is the rate of clinical and procedural adverse events at six months in Cerecyte treated patients, P_c is the rate of clinical and procedural adverse events at six months in bare platinum coil treated patients, and δ is the region of indifference.

Secondary variables include the rate of re-treatment, the presence or absence of a healing reaction (observed as a > 0.5 mm lucent line on angiography), and the one-year angiographic characteristics of the treated lesions.

Sample Size

The sample size for the effectiveness hypothesis above is based on the following formula taken from Fleiss (1981).

$$n' = \frac{\left(z_{\alpha}\sqrt{2\bar{P}(1-\bar{P})} - z_{1-\beta}\sqrt{P_c(1-P_c) + P_t(1-P_t)} \right)^2}{(P_c - P_t)^2}$$

Where z_{α} and $z_{1-\beta}$ are standard normal variates corresponding to significance level, α, and power, 1-β; P_c is the proportion of the patients experiencing incomplete occlusion in the control group; P_t is the proportion of population experiencing incomplete

occlusion in the Cerecyte treated group; and P with the bar over the top is the mean proportion of the control and treated group experiencing incomplete occlusion. The sample size, n′ needs to be adjusted for correction for continuity with the following formula.

$$n = \frac{n'}{4}\left(1+\sqrt{1+\frac{4}{n'|P_c - P_t|}}\right)^2 .$$

The rate of incomplete occlusion for bare platinum coils is about 25% (3, 4). It is expected that the Cerecyte coils can reduce the rate of incomplete occlusion condition by about 50%. To be conservative however, we have assumed the difference to be smaller. Thus, if we use an estimate of $P_c = 0.25$, and our estimate of $P_t = 0.154$. The number of patients needed to complete the study, obtained by inserting these values into the formula, is 236 in each group with the continuity adjustment.

To study the safety hypothesis of non-inferiority, the sample size formula is taken from Blackwelder (1982) (7) and is given below.

$$n = \frac{(z_{1-\alpha} + z_{1-\beta})^2 [P_c(1-P_c) + P_t(1-P_t)]}{(P_t - P_c - \delta)^2}$$

Where n is the sample size needed for each group, $z_{1-\alpha}$ is the standard normal variable corresponding to a Type I error rate of sizeα, $z_{1-\beta}$ is the standard normal variable corresponding to a statistical power of 1-β, and the other variables are defined above.

If one assumes that the rate of adverse events is 0.25 and $\delta = 0.10$, 233 patients in each arm will provide 80% power to declare non-inferiority between the two groups.

It is assumed that about 5% of the patients may be discontinued by one year. To account for this loss, the sample size that needs to be recruited and enrolled is 236/0.95 = 249 patients in each arm. The sponsor has decided to enrol 250 in each arm for a total enrolled sample size of 500.

Analysis Populations

There are two primary study populations, the intention to treat (ITT) population and the evaluable (EV) population. The ITT population is all patients randomized in the trial. The EV population consists of all patients who have completed the study and have measured outcomes at one year.

Data Pooling

Data will be pooled from multiple study sites for this analysis. The justification for pooling is made on a clinical basis (8). The basis for pooling comes from three critical factors. The study sites must implement one common protocol. The sponsor must provide very close monitoring of study site compliance, and the study sites must use common data collection procedures.

In addition, an analysis will be made of outcomes to determine if there is a site by treatment interaction. Site by treatment interactions of a quantitative nature, i.e., all

sites show the treatment to be beneficial, but perhaps to a different degree by study site, will not be considered to be an impediment to pooling. Site by treatment interactions that are qualitative in nature, i.e., the vast majority of sites show the treatment to be beneficial, but one or more sites show the treatment to be detrimental, will require extensive evaluation of the sites with contrary results to attempt to determine what factors at those sites led to the result (See expert statistical testimony from Dispute Resolution Panel transcript September 6, 2001) (10).

Statistical Analysis

The character of the observed primary, secondary, and influencing variables will be determined and their consistency to the underlying assumptions of the anticipated test procedures will be verified. In all cases, the most suitable statistical method consistent with the data will be used.

Preliminary analysis of the study subjects by baseline demographic and prognostic characteristics will be done to determine comparability, to identify possible influencing variables. The characteristics that will be considered in this analysis include age, gender, weight, disease severity and others. These variables will also be compared across study sites. These analyses will be done using the most appropriate test procedure consistent with the data such as parametric or nonparametric analysis of variance procedures for continuous variables and homogeneity Chi-square (or Fisher's Exact test) for categorical variables. Variables found to be out of balance between treatment groups or study sites will be eligible as covariates for subsequent safety and effectiveness analyses.

The primary effectiveness hypothesis will initially be tested by Fisher's exact test. In addition, multivariate analyses will be done to identify other factors that may influence the rate of incomplete occlusion. This analysis will be done by logistic regression by methods for variable screening and inclusion into the final model by the methods described by Hosmer and Lemeshow (9). Univariate logistic regressions will be run with the variable of interest, treatment arm, and interaction. Variables with a P-value in univariate analysis that is 0.2 or less will be allowed to compete in the final model. To be retained in the final model, the variable or its interaction with treatment must have a P-value of 0.05 of less. The final model will be analyzed by backward elimination or forward stepwise regression.

The primary safety hypothesis will be analyzed by Blackwelder's test. The test statistic is given by the following.

$$z' = \frac{p_t - p_c - \delta}{SE}$$

Where p_t and p_c are sample estimates of P_t and P_c, respectively, and SE is given.

$$SE = \left[\frac{p_t (1 - p_t)}{n_t} + \frac{p_c (1 - p_c)}{n_c} \right]^{1/2}.$$

In addition, logistic regression will also be done to determine if there are other variables that are associated with clinical or procedural adverse events. Covariate screening and model inclusion will be done as described above.

If the occurrence of incomplete occlusion or adverse events is dispersed in time over the six months, a more appropriate analysis is the use of Kaplan-Meier product moment survival and Cox proportional hazards regression. The screening process is the same as that described above for logistic regression. The initial test of the primary effectiveness hypothesis however is by log rank test.

Secondary variables will be analyzed. Point estimates of binary variables will be presented with 95% exact confidence limits and statistical tests will be done with Fisher's exact test. Continuous variables will be displayed with mean, standard deviation, median, minimum, and maximum. Continuous variables will be analyzed by Wilcoxon sum rank test.

The evaluation of withdrawn patients presents a special concern. All clinical studies analyze the results based on the evaluable patients, i.e., those who complete the study. Because withdrawn patients do not have final data, they present a problem. The statistical community (6, 10, 13, 11) recommends that multiple analyses should be conducted to determine the robustness of the result in patients who complete the study. The intention of these analyses is to demonstrate that the results obtained from the evaluable patients is not biased.

As a result, sensitivity analyses using multiple imputation analyses will be conducted to evaluate the robustness of the study result accounting for missing observations. One imputation which is biased against an effective test device will randomly assign patients outcome using the rate of the control group as the missing rate for any study patient. A second imputation will be a non-parametric multiple imputation in which patients withdrawn from the study will be randomly assigned outcomes by grouping on demographic and prognostic characteristics including treatment assignment maintaining masking, matching the characteristics to the withdrawn patients, and randomly selecting the result for the missed observation from the results for patients with similar characteristics by method such as "hot deck" imputation or imputation by regression (14). All imputations will be stochastic imputations to preserve the variability of the imputed value.

The primary effectiveness and safety hypotheses of superiority and non-inferiority will be tested with a one-sided P-value of 0.05. All other hypothesis tests will be two-sided with a P-value of 0.05. The primary analysis software is SAS Version 8.2 or higher.

References:

1. Molyneux A. J., Kerr R.S.C., Stratton I., Sandercock P., Clarke M., Shrimpton J., Holman R. International Subarachnoid Aneurysm Trial (ISAT) Collaborative Group. International Subarachnoid Aneurysm Trial (ISAT) of neurosurgical clipping vs. endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised trial. *Lancet* 2002; 360 1267 – 7
2. Johnston SC, Zhao S, Dudley RA, Berman MF, Gress DR. Treatment of Unruptured Cerebral Aneurysms in California. *Stroke* 2001 Mar; 32(3): 597-605
3. Raymond J, Guilbert F, Weill A, et al. Long-term angiographic recurrence after selective endovascular treatment of aneurysms with detachable platinum coils. *Stroke* 2003;34: 1398-1403
4. International Subarachnoid Trial Study Group. Molyneux A.J., Kerr RSC et al. Final one year results of a randomised trial of 2143 patients comparing neurosurgical clipping with endovascular coiling of ruptured intracranial aneurysms. Submitted for publication *Lancet* September 2004. Presented at Scientific meetings.
5. Niemann D, Aviv R, Cowsill C, Sneade M, Molyneux AJ. Anatomically conformable, three-dimensional, detachable platinum microcoil system for the treatment of intracranial aneurysms. AJNR *Am J Neuroradiol*. 2004 May; 25(5):813-8
6. Fleiss, J. (1981). *Statistical Methods for Rates and Proportions*. John Wiley and Sons, Inc., New York.
7. Blackwelder, W. Proving the null hypothesis in clinical trials. *Controlled Clinical Trials* 3: 345-353, 1982.
8. Meinert, C. (1986). Clinical Trials: Design, Conduct, and Analysis. Oxford University Press, New York.
9. Hosmer, D. and Lemeshow, S. (2000). *Applied Logistic Regression (Second Edition)*. John Wiley and Sons, New York.
10. Medical Devices Dispute Resolution Panel Meeting of September 6, 2001 (Panel Transcript).
11. International Conference on Harmonisation. Guidance on Statistical Principles for Clinical Trials. Availability. Federal Register 63 (179): 49583-49598, September 16, 1998.
12. Pocock, S. (1983). *Clinical Trials (A Practical Approach)*. John Wiley and Sons, Chichester.
13. Friedman, L., C. Furberg, and D. DeMets. (1985). *Fundamentals of Clinical Trials.* Mosby Year Book, St. Louis.
14. Little, R. and D. Rubin. (2001). *Statistical Analysis with Missing Data.* John Wiley and Sons, New York.