Hydrocoil: Endovascular Aneurysm Occlusion & Packing Study [HELPS]

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A randomised controlled trial of hydrocoil versus bare platinum in the endovascular treatment of intracranial aneurysms

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## Hydrocoil: Endovascular Aneurysm Occlusion Packing Study [HELPS]

### Trial Protocol

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Hydrocoil: Endovascular Aneurysm Occlusion Packing Study [HELPS]

Aims & Objectives

We aim to compare the following in patients allocated hydrocoil versus patients allocated bare platinum:

Primary outcome:

- Major aneurysm recurrence on follow-up angiography at 15-18 months. Deaths and procedural related morbidity that result in patients not having angiography will also be counted as poor outcomes.

Secondary outcomes:

- Clinical outcome at 3 and 18 months post-coiling, as measured by the modified Rankin scale [Clinical outcome is critical to patients & doctors alike. There is a priori no expectation that one coil system will be associated with greater mortality or morbidity than another but it is crucial to establish this – albeit within the limits of a trial powered to a different primary outcome]

- Re-bleed and re-treatment rates [These are important because they obviously matter to patients and clinicians and retreatment is associated with a mortality/morbidity risk as well as economic costs healthcare system ± to the individual patient/family]

- Coil length deployed [This will enable an assessment of coil required per mm of aneurysm dome size. That in turn can enable clinicians to assess the respective costs of competing coil systems within their own healthcare environment]

- Packing density [There is some evidence, discussed below, that the higher the packing density achieved by coiling the lower the chance of aneurysm recurrence]
Background to the study

Following the publication of the ISAT trial results [1], endovascular treatment is now the preferred treatment option for many intracranial aneurysms. However, aneurism recurrences and rebleeds are more frequent after endovascular treatment than neurosurgical clipping [2]. Therefore follow-up imaging is mandatory and important to the ongoing patient management [3]. Major recurrences following endovascular treatment are associated with both a high retreatment rate (58.8% overall in one prospective series) [2] and with a substantially increased risk of aneurysmal rebleed-increased from 0.4% prevalence in stable aneurysms to 7.9% in recurrent aneurysms in a study by Byrne et al [4]. Major recurrences occur in 15% [2,4] to 19% [5] of cases by 3-6 months, rising to 21% at a mean of 16 months of follow-up [2].

An endovascular treatment that substantially reduced the major recurrence rate would be expected to reduce both the rebleed rate and the retreatment rate, which would be to the benefit of patients and health care systems alike.

The Hydrocoil Embolic System (HES) offers the prospect of improved aneurysm packing and angiographic outcomes. Hydrocoils consist of porous hydrogel wound round a platinum wire core and in turn a thin platinum “overcoil” is wound over the hydrogel with gaps allowing expansion to occur. Hydrogel is a copolymer of acrylamide and sodium acrylate crosslinked. It has been widely used in other medical applications for a number of years (e.g. wound dressings, contact lenses, glucose biosensors to name but a few). Hydrocoils are CE marked for endovascular aneurysm treatment (CE 0123). Hydrocoils swell with water once exposed to the pH of blood/tissue to between 5 (Hydrocoil 10), 7 (Hydrocoil 14) and 11 times (Hydrocoil 18) the volume of a Platinum 10 coil and 3-6 times the volume of a Platinum 18 coil respectively. Thus the Hydrocoil Embolic System (HES) can fill small interstices that bare platinum coils cannot. As a result considerably greater packing densities can be achieved but with the added advantage that overall a lesser length of coil is deployed.

There is evidence that using the HES, major recurrence in aneurysms is substantially reduced, particularly in aneurysms <25mm in maximum dimension. In the early data from a prospective non-randomised study of Hydrocoil for Endovascular Aneurysm occlusion Study (HEAL), the recurrence rate at 12-18 months was only 3% for aneurysms <25mm (1/35) [6]. The HEAL study is a prospective registry of 200 aneurysms treated using hydrocoil. However, the population recruited is not typical of the generality of aneurysms treated in Europe. Only 42% of cases in HEAL were ruptured aneurysms. This is a significant variance from treatment practice in UK and Europe where >75% of aneurysms treated by coiling are ruptured (86% in the recent UK Neurointerventional Group Workload Study). The HEAL study figures indicated a desirable hydrocoil:bare platinum ratio of approximately 8:2; i.e. 80% of coil length deployed (or of the volume packed) should be hydrocoil [R Greene, Vice President Research & Development, Microvention Corp., Personal Communication, January 2004]. Note: from late 2006 through 2007, so after HELPS recruitment was virtually completed, reasonable size hydrocoil case series and the HEAL registry follow-up data have been published [7-9]. In HEAL registry, recurrence rate overall was not reduced compared with historical controls except where a) hydrocoil comprised 75% of coil length used (p=0.035) or b) final coil deployed was a hydrocoil (p=0.047). By comparison in prospective single centre case series recurrence rate was more than halved in hydrocoil group in one report (p=0.046) [7] and reduced in another sizeable series [8].

The HEAL recruitment, like most non-randomised uncontrolled studies, suggests selection bias was operating as the study group was not representative of the generality of aneurysms treated by coiling. Selected case series of mostly unruptured aneurysms do not provide robust scientific
evidence on which to advocate widespread use of HES in preference to bare platinum. This trial would help answer this valid and important criticism.

Coil packing density has been related to long-term outcome following endovascular coil treatment of intracranial aneurysms [10-12]. A packing density of 20% was initially claimed to lead to a very low recanalisation rate or retreatment rate [10], this threshold subsequently increased to 24% in a later Dutch series [11] and in the latest published report the mean packing density with bare platinum coils to ensure stable occlusion has risen yet again to 30% [12]. Mean packing densities greater than 30% can be difficult to achieve with bare platinum coils other than in very small aneurysms. In the paper by Kanawabe et al, all aneurysms (33) were 5mm or larger and the mean packing density achieved was 24.7% [10]. In a prospective series of 72 aneurysms treated in Edinburgh (using the latest bare platinum coil systems), in the 31 aneurysms where the largest diameter coil deployed was at least 5mm, mean packing density was 28.7%; whereas in 41 aneurysms <5mm, mean packing density was 35.5%. Only one study of aneurysm treatment with hydrocoils was published prior to HELPS starting recruitment but this only examined packing density [13]. Eleven patients treated by hydrocoil were compared to 11 historical controls and most were small aneurysms (all 3.5-8.5mm). PD for HES was 73% versus 32% for bare platinum.

Early clinical experience with the hydrocoil system suggests that approximately 20-30% fewer coils are deployed per aneurysm treated. Thus usage of HES could be essentially cost neutral though precise pricing of bare platinum coils is difficult as it varies considerably between units depending upon the local pricing arrangements that pertain. The nominal list price can bear little relation to the actual price charged to a unit depending on volumes of product usage and prevailing market conditions.

The following examples are helpful for illustrative purposes:

8mm aneurysm:
10 bare platinum 10 coils - 2 3D/complex shape, 6 helical coils and 2 finishing coils (ultrasoft etc.).
Coil cost ~£4500. Typical packing density = 26%

Same sized aneurysm packed using hydrocoil system - 1 3D/complex shape, 2 short finishing coils and 3 hydrocoils, Coil cost ~ £4400. Packing density = 61% (90% by hydrocoil + 10% by bare Platinum).

18mm aneurysm:
20 bare platinum coils - 2 complex/3D shape 18s, 16 helical (6x18 system & 10 x 10 system) and 2 finishing coils. Coil cost ~ £8400. Packing density = 12%

Same sized aneurysm packed using hydrocoil system - 1 3D/complex shape, 7 hydrocoils (5 HES 18, 2 HES 14) and 2 short finishing coils. Coil cost ~ £8200.
Packing density = 34% (97% by hydrocoil + 3% by bare Platinum)

(these examples are based on clinical cases undertaken in Edinburgh in early 2004 compared to similar cases treated before hydrocoil became available).

Can we rely on the packing density figures with hydrocoil?

I.E. will the coils expand to the volume assumed in the packing density model programme?

- NB. Packing density is not the primary aim of the study
- Where hydrocoil is not restrained against the aneurysm wall, animal cases indicate it will generally expand fully within the anticipated time window of 20 minutes. In most cases 1-2
framing coils will be deployed first so that hydrocoils will not be tightly constrained against the aneurysm wall and will be able to expand to nearly their maximum potential.

- Cf animal lab data- [14,15]
- The packing model assuming full hydrocoil expansion is therefore a small but not a substantial overestimate based on the animal experience.
- Work is ongoing within MicroVention to assess the size of the effect
- Use of appropriate coiling techniques with HES allows room and time for hydrogel expansion to occur
- We know that in aneurysms coiled with bare platinum most of the aneurysm volume is filled with blood/clot. Therefore there is a lot of space for hydrocoil to expand into. Supporting the concept of good hydrocoil expansion is human in vivo data on pressure effects in an aneurysm during coiling with hydrocoils. There was no increase in pressure with hydrocoil compared to GDC but flow was substantially reduced [16]. The absence of pressure rises but reduced flow in vivo (compared with bare platinum coils) suggests hydrocoil is indeed able to expand well in vivo in human aneurysms.
Trial Design & Methods

Inclusion criteria

Patient presenting with a cerebral aneurysm deemed to require endovascular treatment by the neurosurgeon/neurointerventionist (generically referred to subsequently as “the neurovascular team”).

AND

- Patient has given fully informed consent to endovascular coiling procedure or where they are good grade but yet can’t consent for themselves, appropriate written “assent” has been sought from their next of kin for coiling on clinical grounds in the best interest of the patient
- Aneurysm 2-25mm in maximum diameter
- Anatomy such that endovascular occlusion is deemed possible (not necessarily probable)
- The neurointerventionist is content to use either bare platinum or HES depending on randomisation result (i.e clinical equipoise principle applies)
- The neurointerventionist is content not to use any other type of coated coil
- Patient WFNS Grade 0-3 and aged 18-75 years
- The patient has not been previously randomised into this trial
- Aneurysm has not previously been treated (by coiling or clipping).

Exclusions

Subjects will not be considered for the trial unless they meet all the inclusion criteria.

If the patient has more than one aneurysm requiring treatment at the same treatment episode they will not be eligible for the trial. If treatment will be staged in a patient with multiple aneurysms and only one aneurysm will be treated at one sitting then the patient is eligible. However, a patient may not be randomised into the study more than once.

From the moment of randomisation, the patient is in the trial whether they receive trial treatment or not, and will be followed up and accounted for in the final analysis (intention-to-treat).

Death or procedural/disease related morbidity may result in some subjects not having check angiography (or MRA if unit uses this as standard mode of follow-up). These patients will be counted as poor outcomes in the primary analysis.

Retreatment of previously coiled or clipped aneurysm is an exclusion criteria

Use of coil assist devices (stent, balloon, trispan etc) should be recorded but is not an exclusion criteria. It must be recorded in order to ascertain if any difference in use between control & hydrocoil groups acts as a potential confounding variable.

Recruitment

Eligibility will be assessed once the neurovascular team makes a decision on endovascular treatment of an aneurysm. A local log of all eligible patients will be kept and a copy returned to the trials office at end of the trial.

If a patient fulfils the inclusion criteria, a suitable senior neuroradiologist will discuss the trial and provide the patient with written information. Usually the local principal investigator will do this.
This person will allow the patient adequate time to reflect following their approach about the trial before returning (preferably overnight where exigencies of clinical care allow).

If the patient agrees to participate in the trial, he/she will be randomised once written informed consent has been obtained. A copy of the consent will be retained in the casenotes, one given to the patient, one retained by local investigators and a copy sent with entry case record form to the coordinating centre.

**In a fluctuating, confused grade 2/3 patient (i.e an incapable adult), where assent for the clinical coiling procedure has been obtained from relatives, a local senior investigator, after discussion with the responsible neuroclinician, may decide to discuss the trial with the same relatives (legally this cannot & will not be applied in Scotland). They will be provided with a specific version of the participant information sheet for relatives or carers for this purpose. They will have the opportunity to consider the information and ask questions, and their views should be taken into account. They will be asked to sign a specific “assent form” for the study to record the outcome of discussion. A copy of the assent will be retained in the casenotes, one given to the relative who signed it, one retained by local investigators and a copy sent with entry case record form to the coordinating centre. If and when the adult regains capacity, informed consent must be sought from them. If they decide not to take part, they will be withdrawn from the study. Where possible, their data will be withheld from analysis and destroyed.**

**Randomisation**

The person recruiting the patient into the trial will then perform randomisation via a web based randomisation process run through the Neurosciences Trials Unit in Edinburgh. They will communicate the result of randomisation to the neurointerventionist who will coil the aneurysm (it may be one and the same person on occasion)

A minimisation algorithm will be employed on randomisation into the trial to ensure balance between the groups on **those parameters that directly relate to endovascular coiling & ability to pack densely to occlusion**. The criteria are as follows:

<table>
<thead>
<tr>
<th>Aneurysm size:</th>
<th>2-4.9mm</th>
<th>5-9.9mm</th>
<th>10-25mm</th>
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<td>Dome:neck ratio:</td>
<td>&lt;1.5</td>
<td>≥1.5</td>
<td></td>
</tr>
<tr>
<td>Aneurysm status:</td>
<td>Recently ruptured (within 30/7) versus Not recently ruptured</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aneurysm shape:</td>
<td>Irregular (multilobulated) versus regular</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Intention to use assist device:</strong></td>
<td>Yes or No</td>
<td>[replaces question on aneurysm site]</td>
<td></td>
</tr>
<tr>
<td>Randomisation in Americas:</td>
<td>Yes or No</td>
<td></td>
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Age is not included in the above criteria, as it has not been demonstrated to relate to the risk of recurrence or packing density achieved [2].

One group will not be anatomically substantially more difficult than another by chance if aneurysms are matched by size and dome:neck ratio (<1.5 likely to be more difficult, ≥1.5 likely to be more straightforward to pack). Both HES and control groups will have equal proportions of acutely ruptured aneurysms (when operators may be more reluctant to pack densely or use assist devices). Beyond 30/7 post rupture there is in practice little difference between how ruptured and unruptured aneurysms are managed. Matching by aneurysm site is not critical, as this also has not been demonstrated to significantly relate either to risk of recurrence [2] or packing density achieved [10]. However aneurysm site will be recorded on randomisation using a coding system similar to that used in the ISAT trial.
In multilobulated (or otherwise very irregularly shaped) aneurysms, it can be difficult to achieve complete occlusion and aneurysm volume calculations are less accurate than for regularly shaped aneurysms so it is important to balance the proportion of these between the treatment arms. Use of assist devices may alter coiling outcome, so where it is planned to use such a device (balloon, stent, trispan) it is sensible to minimise on their use.

**Treatment**

Standard local procedures for the coiling of aneurysms will be followed.

**Patient safety is paramount**

If a patient is randomised to HES but the operator prefers for strong clinical reasons not to deploy predominantly HES in this particular case, they should proceed using bare platinum in the best interests of the patient. Conversely if patient is randomised to bare platinum but operator decides to use HES for pressing clinical reasons they should proceed to use it. In any such case, please detail reasons on the endovascular treatment case record form, which must be completed and returned to the trials office. Analysis will be on an intention to treat basis.

*NB. To minimise such treatment “crossover”, please do not aim to recruit a patient unless you are content to use either HES or bare platinum depending on randomisation result (see trial inclusion criteria)*

Copies of angiogram films (these will preferably be digital such as DICOM images burnt onto CD ROM) will be sent to the trials office for collation. They will be sent in batches to the independent core lab (CHUM Research Center, Notre-Dame Hospital, Montreal, Canada) for analysis.

A treatment record form will be completed at the end of the procedure and returned to the trials office. Any subsequent adverse events should also be notified.

**Follow-up**

**Angiographic outcome:**

Check angiograms should be performed at 3 to 6 months and 15-18 months post coiling and copies of these will also be forwarded to the trials office for collation and subsequent core lab analysis.

**Independent core lab** (Montreal) using standard criteria to confirm:

- aneurysm size/volume and dome:neck ratio
- degree of occlusion at end of treatment and on check angiograms using standard criteria (Stroke 2001;32:1998-2004 [17]). DSA preferred to MRA but MRA acceptable for 15-18 month angio for centres where only one check angiogram is routinely performed. If this is done consider obtaining 3-6/12 MRA as well as DSA as baseline.
- recurrences will be divided into minor and major [2].
- Intraobserver reliability will be assessed by sending a sample of subjects for review twice
- As a minimum MRA study must include 3D Time-of-flight sequence and T2 axial of brain

Packing density will be analysed centrally using the volume data determined by the core lab and details of coils used provided by participating centres on procedure case record form. This will be more consistent & reproducible than individual centres undertaking the analysis.
MRA has become the standard imaging tool for the follow-up of coiled aneurysms in many centres around the world. A large number of reports on these have been published including a systematic review [18]. The Montreal grading system will be applied to MRA studies as per DSA [17]. However, for MRA all base images from time-of–flight sequence will be reviewed and dataset reviewed as MIP/Volume rendered images on workstation in core lab to adjudicate Montreal grade. If additional contrast enhanced MRA sequences are available, they will also be reviewed.

Clinical outcome:

Clinical status at 6 months and 18 months follow-up will be recorded as a secondary endpoint. This will be done by Modified Rankin Score [19]) using a questionnaire sent out from the central trials office with prepaid envelope for UK recruited patients. **For patients recruited outwith the UK, the trials office will endeavour to arrange wherever possible for local researchers to send out/receive questionnaires before forwarding to coordinating trials office.** By sending these direct to the patient rather than getting an assessment done in clinic by the team treating the patient we aim to reduce bias and get a direct and independent assessment of outcome [1]. This is the more valid approach. Centres must notify trials office immediately by fax or email of any deaths of trial patients to prevent questionnaires being sent out inappropriately. GP letter of notification about the trial will also ask the GP to notify trials office if they have any concerns about the ability of a patient to complete such a questionnaire.

Where no reply is received within 4 weeks, an initial postal reminder will be sent out. If no reply is received within further 4 weeks, telephone contact will be made with the patient but this will be by the local investigators who are known to the patient. They will encourage return of patient questionnaire. If patient desires help to complete questionnaire, trials office & local investigator will liaise together to arrange for this to be done by a practitioner independent of the team treating the patient- either over the phone or face to face depending on patient preference. **For centres outwith the UK, questionnaires (in appropriate language) will be sent out & returned to the local centre and subsequently forwarded &/or faxed to trials office. Reminders of overdue questionnaires will also be sent out from local centre for these patients.**

Safety assessment

Form 4 of the case record form delineates the main categories of disease/treatment related adverse events expected/anticipated in aneurysmal SAH and endovascular aneurysm treatment. It also allows for reporting of any adverse event not specifically listed. Local Principal Investigators are responsible for ensuring form 4 is accurately completed and returned expeditiously to the trials office for every patient randomised into HELPS.

ADVERSE EVENTS (AE)

Accurate recording and reporting of adverse events are a fundamental requirement of participation in the trial and of the ethical approval granted to HELPS.

Events requiring expedited reporting:

- Suspected Unexpected Serious Adverse Reaction (SUSAR)
- Only example so far in HELPS is of hydrocephalus in unruptured aneurysm cases
- Must be both serious & unexpected to report in this way
- Periprocedural death (within 30 days of procedure)
  - When requested, PIs should provide additional information on serious AEs resulting in death
- An SAE
- Other Adverse events not covered by form 4, should be reported to the Chief Investigator where these are unexpected but not serious
- An increase in the rate of expected SAEs occurring in a centre

Chief investigator will report SUSARs to the Main REC - where fatal or life threatening within 15 working days of notification and all others expeditiously. CI will take advice from Main REC/sponsor on need for reporting to MHRA. CI includes a report on subject safety in the annual progress report submitted to the Main REC.

Definition of serious adverse event:
- Results in death or is life threatening
- Requires hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity or is otherwise considered medically significant by the investigator

A range of adverse events are specifically listed in the case record form and require completion for each patient whether they have occurred or not. These are listed below:
An adverse event/additional procedured form must be completed for each admission episode

**Disease related adverse events**
- Rebleed
- Delayed Ischaemic Neurological deficit
- Hydrocephalus
- Cerebral haematoma
- Cardiorespiratory complications
- Death
- Other complication/AE

**Procedure related adverse events**
- Aneurysm rupture
- Coil migration
- Parent artery occlusion
- Thromboembolic complication
- Other

**Additional Procedures**
- Neurosurgical procedure on aneurysm
- Recoiling
- Intra-arterial “thrombolytic” usage
- Antiplatelet regimen
- Triple H &/or angioplasty for vasospasm
We require robust, substantive evidence of the efficacy of a new product in order to justify its use and its cost. We have an ethical and moral duty to properly evaluate new products. In part, it is up to the neurointerventional community to do this-in practical terms this is better done in partnership with industry.

Evidence based medicine requires robust properly constructed trials to answer specific focussed questions. Where feasible, these should be randomised controlled trials (RCTs) - see Cochrane Collaboration -www.cochrane.org. Non-randomised observational studies (e.g ACTIVE, HEAL, CAMEO studies), especially when relatively small, are rightly criticised for considerable methodological weaknesses. The evidence they provide is not of an adequate level to convince many interventionists or purchasers that practice should be radically changed. The faster such high quality scientific evidence can be obtained the better for all, especially patients.

*HELPS has inclusive entry criteria allowing a high recruitment rate and is a modestly sized controlled trial = a “do-able” trial with an answer within a reasonable time frame. Information on packing density will be available soon after recruitment into the trial is completed. It is ethical as we are comparing a relatively new (but CE marked) coated coil with an established proven treatment and we allow use of any assist devices felt necessary by the operator. The trial has the added advantage of providing robust RCT evidence of the number/length of coils/platinum used with hydrocoil compared with bare platinum alone. This is a pragmatic trial but will give level 1 evidence of efficacy in aneurysm Rx and give some indicative data on cost implications. The trial has UK Multicentre Research Ethics Committee approval (granted June 2004- main REC = Newcastle & North Tyneside REC 1) and is sponsored (on behalf of the UK NHS) by Lothian Health- University Hospitals Division.*

If neurointerventionists can show conclusively that hydrocoil usage results in a substantially reduced major recurrence rate plus a significantly increased packing density and that such an approach is largely cost neutral, it becomes a strong case as to why they should use HES for the benefit of patients. Conversely if no substantial advantage for hydrocoil is demonstrated the trial would provide good evidence not to switch to widespread routine use of a more expensive product.
Statistical Methods

Sample size estimate and power of the study

Angiographic outcome- major recurrence at 15-18 months

The major recurrence rate using bare platinum is 20% based on review of the literature [2-5]. Assuming the rate is 10% for hydrocoil (this is a conservative figure as on the limited available data from the HEAL study the major recurrence rate was 2.9%)

Sample size:
406 subjects for a trial with 80% power to detect a significant difference at the 5% level.

However a proportion of subjects can be anticipated not to complete the 15-18 month angiographic endpoint due to death, lost to follow-up, refusal of further imaging etc. Death/morbidity precluding angiography will be included in poor outcome for primary endpoint so these don’t lead to a drop out as such from HELPS.

In ISAT trial of coiling [1], the drop out rate to angiographic follow-up not due to poor clinical state was <8%. Allowing for crossovers of up to 2% (which was the approximate level in the ISAT trial) as well, a reasonable estimate of the drop out rate in the context of HELPS would be ~10%, so a total of at least 452 subjects is required. In fact, as a greater proportion of patients will be recruited outwith UK than in ISAT, which may result in higher than predicted drop out rate, a rather larger sample will be recruited.

[www.thesealedenvelope.com programme used + Power & Size Sample Calculator by Dupont and Plummer, 1997]

Feasibility of recruitment rate

500 subjects will be recruited in order to allow for a conservative drop out rate after randomisation. This would be possible in 11 large centres with coiling rate >60% within a 24 month period. If more centres join, time to complete recruitment would be sooner.

In fact 499 subjects were recruited in 29 months

Units that randomised: Barrow Neurosurgical Institute, Birmingham, Cardiff, Cleveland Clinic, Edinburgh, ENERI Buenos Aires, Essen, Henri Mondor Paris, Henry Ford Hospital [Detroit], Liverpool, Manchester, Methodist [Houston], Newcastle, Nottingham, Oregon [OHSU], RPAH Sydney, Sao Paulo, Toulouse, University of Virginia, U Texas Southwester,n Wessex Neurological Institute Montpellier, Belfast

Units with all approvals in place but didn’t randomise:, Charing Cross, Royal Free

Many of these units have a recent history of successful RCT participation. Many are large volume units with coiling rates in excess of 80%. For instance, Liverpool, Manchester, Nottingham, Edinburgh, Newcastle in the UK cover ~15 million population for neurointervention and all have a >80% coiling rate.
Statistical Analysis

The Chief Investigator and Trial Steering Committee will perform data analysis in collaboration with the trial statistician at the Neurosciences Trials Unit, Edinburgh University. Trial data will be presented according to the CONSORT guidelines. All analyses will be by intention-to-treat and will compare all patients allocated to hydrocoil with all those allocated to bare platinum. By intention-to-treat we mean that patients will be analysed in the group they were randomised to, no matter what treatment they received, and regardless of whether they violated the protocol in any way. We will make every effort to get every item of data on every patient.

Where possible, missing data will be listed as a separate category. However, when necessary, patients with missing data will be excluded from analyses. Patients will from only the analyses affected by the particular item of missing data.

Sponsors of the study have no role in study design, data collection, data analysis, data interpretation or writing of the report. The TSC will nominate a writing committee. All analyses will be performed using SAS version 9.1.

Descriptive statistics will be done on demographic variables and pre-operative and peri-operative data to compare groups at baseline. Means, standard deviations and range will be presented for quantitative variables and frequency tables for categorical variables. Those statistics will be broken down by treatment arm.

Primary outcome

We will present the relative and absolute differences in the proportion of patients who have a poor outcome. The relative difference will be adjusted for the variables in the minimisation algorithm, using logistic regression, with statistical significance taken from the change in log likelihood when allocated treatment is added to the model (this analysis will be the primary analysis).

The absolute difference in the proportion of outcome events between the two treatment arms will be calculated and expressed as a percentage, with 95% confidence limits. Subgroup analyses will be performed on the primary outcome measure, again using logistic regression, by examining the change in log likelihood when the interaction term is added. The subgroup analyses that will be performed will be:

- Assist device used vs not used (categorised by ruptured/not recently ruptured)
- Hydrocoil usage target met vs not (categorised by ruptured/not recently ruptured)
- Americas versus Rest of the World (categorised by ruptured/not recently ruptured)
- Aneurysm size groups
- Neck width

A sensitivity analysis will be considered to try and establish if there is evidence for a threshold level of hydrocoil usage associated with reduced recurrence rate.

Patients who: have a major aneurysm recurrence on follow-up angiography at 15-18 months; or die before the angiogram can be performed; or have procedural/disease related morbidity that result in angiography not being performed will be counted as poor outcomes.

In order to describe how and when recurrences occur, Kaplan-Meier analysis of the recurrences will be done and the “survival” functions will be compared graphically and using a log-rank statistic. Finally, a logistic regression will be used to find variables capable of predicting recurrences. The method planned is a stepwise forward with alpha < 0.05 to enter a predictor. Possible predictors include the type of the aneurysm, location, ruptured or unruptured, size of the aneurysm, size of the neck of the aneurysm as well as other baseline characteristics.

Secondary outcomes

A variety of other secondary analyses (with due allowance for their exploratory nature) will be performed to compare: coil length deployed, clinical outcome at 3 and 12 months post-coiling as
measured by the modified Rankin scale, re-bleed and re-treatment rates. For binary outcomes, the statistical methods to be used will be the same as for the primary outcome. For continuous outcomes that are normally distributed, means and standard deviations will be presented and t-tests will be used. For non-Normally distributed continuous variables, medians and interquartile ranges will be presented and two sample Wilcoxon tests will be performed. Ordered categorical data will be analysed using robust rank order statistics.
Data Management/Administration

Data collection

A nominated local coordinator will complete the case record forms and be responsible for their regular return to the coordinating centre. A database has been designed for the study, which will utilise field level data validation to ensure all required data are entered before the information is incorporated into the database (QA). Use of drop down selection lists etc. will be incorporated to aid the speed, accuracy and consistency of data entry (QA). Database is backed up regularly & backups stored in fireproof safe

Data to be collected include:
- Screening registry- completed for all possible entrants to ensure meet eligibility criteria
- Demographic data (including any relevant past medical history)
- Admission data (including WFNS at presentation to hospital, Fisher grade, focal deficits etc.)
- Procedural data
- Angiograms (preferably local investigator sends appropriate DICOM images to central trials unit by secure mail on CD). Hard copy angio films to be sent where this is not possible.
- Clinical course data
- Discharge/Death data

Complications (of procedures or of disease process) will also be documented and reported to the trial unit regularly. Collection/collation will be the responsibility of the local study coordinator in conjunction with the local principal investigator. A copy will be kept locally. Data transfer from local centres will be via secure mail (recorded delivery etc.) or point-to-point fax transmission if urgent. Any severe unexpected adverse event must be reported immediately to the trials office along with an indication as to whether it was related to participation in the trial or not.

All data will be stored on computers in secure (lockable) rooms and computers and databases will be password protected to protect patient confidentiality. Paper records or angiogram films will be stored in a locked filing cabinet in a locked office within a secure research facility.

Schedule of data return:

1. On randomisation: screening, demographic & admission data (by end of month following entry)
2. On discharge: procedural data, imaging data, clinical course data, discharge data (by end of month following discharge)
3. Serious complications (procedural or otherwise) or deaths- notification to be faxed or mailed within 48 hours. These data will be blinded to operator but used for early detection of unexpected complications.

Trial structures will be put in place to ensure and maintain data quality (Quality Control). Data software design will aid accurate and complete entry (QA) but will be checked by regular data audits supplemented by review of patient records in a random sample of cases against the data held on the central trial database (i.e. source data verification checking as QC process). Electronic queries of the database will check for missing data and crosscheck data between tables for consistency (QA).

An external independent review of trial procedures and data collection/quality will also be undertaken during the course of the trial. Trial Steering Committee of the Cerecyte trial have agreed to undertake this independent audit/review as part of a reciprocal arrangement with HELPS.
Trial Steering Committee
The Trial Steering Committee will meet 4-6 monthly. Its main function is to monitor and supervise the progress of the randomised trial. It will consider recommendations of the DMC and relevant ethics committees. It will review at regular intervals relevant information arising from other sources and make decisions regarding trial presentation/publication of interim and final results.

Membership:
Chairman
Chairman- Dr Anil Gholkar OBE (Neurointerventionist, Newcastle)

Members
Professor Joanna Wardlaw (Neuroradiologist & experienced clinical trialist, University of Ed.)
Dr Hans Nahser (Consultant Neurointerventionist, Liverpool)
Professor Christophe Cognard (Neurointerventionist, Toulouse)
Dr Robin Sellar (Consultant Neurointerventionist and Chair of UK Joint Neurosciences Council)
Dr Steff Lewis (Trial Statistician, Neurosciences Trials Unit, University of Edinburgh)
Mr J Malcolm Flinn- Patient representative

Dr Phil White- Chief Investigator

Data Monitoring Committee
Oversight of the trial will accord to MRC guidelines.
At an initial meeting before patients were randomised, the DMC finalised the terms of reference in conjunction with the chief investigator.
The independent Data Monitoring committee will be supplied, in strict confidence, with an interim analysis of trial data on mortality/complication rates after the first 100 patients are randomised, along with any other analyses that the committee may request. They will also consider relevant information from other sources (e.g. any other relevant trials). In the light of these analyses, the DMC will advise the chairman of the steering committee if, in their view, the randomised comparisons have provided proof “beyond reasonable doubt” that i) one coil type achieves a significantly reduced recurrence rate with no greater risk of adverse events or ii) one coil type is associated with a substantially poorer clinical outcome. The DMC will make recommendations regarding trial continuation or protocol modification relative to patient safety and outcomes to the steering committee. A second interim analysis will be performed after 250 patients are randomised (unless the results of first interim analysis indicate this should occur earlier or later).
The DMC will remain independent of the trial staff and steering committee.
Collaborators, and all others associated with the study, may write through the trials office to the chairman of the DMC, drawing attention to any worries they may have about patient outcomes, or about any other matters that may be relevant.

Membership:
Chairman- Dr Rick Bartlett (Neurointerventionist, Hull, centre not involved in the trial)

Members
Professor Peter Sandercock (Professor of Neurology & experienced clinical trialist, Edinburgh)
Independent Statistician- Dr Niall Anderson, School of Public Health, University of Edinburgh
**Trial Executive Group**

The trial executive group are responsible for the day to day running of the trial at the co-ordinating centre in Edinburgh. They will meet monthly to review progress and address management issues as they arise. The executive group will liaise with the trial steering committee, data management centre and the trial statistician(s).

Membership: Dr Phil White, Prof Joanna Wardlaw, Ms L Horribine (trial coordinator), Dr Robin Sellar, Dr Steff Lewis **Mrs Helen Cullion (Administrator, Neurosciences Trials Unit)**

**Publication policy**

The trial steering committee will be responsible for organising a writing committee once trial recruitment is completed. That committee will formulate timelines for presentation / publication of results on behalf of the TSC and advise on appropriate journals for submission.

**Financial & Insurance Support**

Web based randomisation system- commissioned through DCN Trials Unit Edinburgh

**Trial Manager**  **Lynn Horribine**

**Data Puncher**  **Sheila Grant**

**Image Handling**  **Eleni Lees**

**Trial Statistician**  **Dr Steff Lewis**

Trial Committees: Steering + Data Monitoring
- costs of meetings (travel + small honorarium)
- 4-5 meetings (start up, 2-3 interim and end of trial)
- At least one or both of interim-point meetings, teleconference only
- **Writing committee subgroup 1-2 meetings**

Stationery/postage/telephone/CD & DVDs etc. for Trials Office to supply

Core Lab [CHUM Research Center, Notre-Dame Hospital, Montreal, Canada]- to analyse 3 sets of angios/MRA on 500 cases. Start up costs of $12500 US paid in advance

**Insurance**

Insurance was purchased for French centre participation in trial of up to 100 patients at cost of 12000 Euros. US IRB submission costs and centre reimbursement costs are agreed locally. Reimbursement for recruiting each patient in EU agreed at 125 pounds to cover coordinator costs & consumables.

**Majority of funding comes from Microvention Inc. but they have no direct or indirect access to the data or source documents. As SPA element of consultant contracts, NHS supports UK based CI and PI work connected with the trial**
Centre Requirements

- Participating centres must be neuroscience units treating significant numbers of patients with acute SAH. It should have a referral base of \( \geq 1.5 \) million for neurointervention.

- The years of neurointerventional experience & number of aneurysm treatments (total or per annum) should be declared to the trial steering committee (by the local lead investigator) for each centre. The supervising operator should have at least 3 years neurointerventional coiling experience and the centre should have performed at least 10 coiling procedures using hydrocoils before randomising patients into the trial.

- Units must have defined care pathways and protocols for the management of patients with aneurysmal SAH. Each centre must have defined protocols for the imaging follow-up of patients treated by coiling. This can be DSA or MRA or both. Timing of follow-up control angiography should be such that it can correspond with the trial schedule for follow-up (3-6 and 15-18 months).

- A hydrocoil procedure must involve the aneurysm substantially treated using hydrocoil (see hydrocoil guidance notes on p17)

- Each centre must identify a local coordinator who will be responsible for the data collection at that centre. They will make returns of copies of case record forms (CRF) and angiogram copies (film or on CDs) to the trial office. They will also be responsible for maintaining a log of all aneurysmal SAH patients admitted to their unit during the trial period. This will enable subsequent determination of recruitment rate and analysis of how representative the recruited population was. Original CRF forms must be kept securely in an appropriate storage facility within the centre for at least 5 years following recruitment of a patient. These comprise the source documents for the trial.

- Every centre must obtain ethical approval for the trial from their local research ethics committee [or IRB] and lodge a copy with the trial office. The lead local investigator will be responsible for this but most of the necessary information/documentation to complete this will be sent to them electronically from the trial office. The trial principal investigators have obtained UK Multicentre Research Ethics Committee approval for the trial. The lead local investigator will be responsible for obtaining local institutional management approval for participating in the trial and for lodging a copy of the approval with the trial office.

- All treatments must be performed on modern DSA equipment with a 1024 matrix and roadmapping facility. Where possible 3D DSA and biplane facility should be used.

Local Principal Investigator Responsibilities

Local PI should be qualified by education/training/experience (evidenced through CV & any other relevant documentation- in UK this forms part of SSA procedure by LREC) e.g. documented training in consent or training in Good Clinical Practice for trials. PI will obtain a) local R&D/Management approval b) LREC Site Specific Assessment via COREC or country equivalent

Any delegation of trial related duties by PI must be recorded and appropriate. Delegation of PI responsibilities during leave periods should be clear within the centre & recorded

Adherence to the trial protocol in particular with regard to safety assessment & adverse event reporting is the responsibility of the PI on behalf of that centre
Guidance notes on using hydrocoil

- As per bare platinum, aim to coil to angiographic occlusion whenever possible
- Patient safety is the paramount consideration at all times
- Detachment should be performed within 5 minutes of the hydrocoil entering the microcatheter
  - If not, withdraw coil along with microcatheter
  - Get someone to use a stopwatch or use angio machine timer
  - *Time may be extended if using HES14 via 18 microcath or HES10 via 14 microcath*
- Use hydrocoil 18 where feasible: e.g. in aneurysms >10mm, start with HES 18 then move down to HES 14 and then 10 towards end. Likewise in aneurysm of intermediate size, say 8mm, use HES 14 first then move down to HES 10.
- Aim to use longest length of hydrocoil appropriate- just as one would do when using bare platinum.
- Consider allowing time between hydrocoils for good expansion to occur (by the time coil deployment complete, a control angio performed, the coil detached and next coil prepared for deployment some 5-6 minutes will have elapsed so there should not be too much extra procedural time engendered)

- **Hydrocoil group:**
  - **Aneurysm 2-9.9mm:** “50% rule”
    - Hydrocoil should constitute
      - i) at least 50% of the total coil length deployed
      - &/or ii) >50% of the aneurysm packing achieved
      - + total aneurysm packing should exceed 50%
  - **Aneurysm 10mm+:**
    - *HES should constitute at least 2/3 of the total coil length deployed &/or ≥70% of the aneurysm packing achieved*
    - + total aneurysm packing should exceed 40%
  - These figures are for guidance only & not a rigid requirement. A planned subgroup analysis will be preformed comparing hydrocoil cases that meet this target with those that do not.
- In practice many operators will want to deploy 1-2 bare platinum framing coils before deploying any hydrocoils. Some may also wish to use 1-2 supersoft “finishing” coils at the end of a “hydrocoil case” as well.

Consider use of assist device for hydrocoil cases using the same criteria you would use for coiling using bare platinum. Your practice regarding assist devices may differ from another operator/centre, but should not differ between HES and bare platinum. If you believe it does please report this on CRFs to the trial office under comments section.
References


Abstract

Endovascular coiling treatment is now the preferred treatment option for many intracranial aneurysms. However, aneurysm recurrences and rebleeds are more frequent after endovascular treatment than neurosurgical clipping. Therefore follow-up is mandatory and important to the ongoing patient management. Major recurrences following endovascular treatment are associated with both a high retreatment rate and with a substantially increased risk of aneurysmal rebleed. Major recurrences occur in 15% to 19% of cases by 3-6 months, rising to 21% at a mean of 16 months of follow-up. An endovascular treatment that substantially reduced the major recurrence rate would be expected to reduce both the rebleed rate and the retreatment rate, which would be to the benefit of patients and health care systems alike. The Hydrocoil Embolic System (HES) offers the prospect of improved aneurysm packing and angiographic outcomes.

The HELPS [Hydrocoil: endovascular aneurysm occlusion & packing study] trial aims to compare major aneurysm recurrence rate on follow-up angiography at 15-18 months between patients allocated hydrocoil versus patients allocated bare platinum coiling. Secondary outcomes to be compared between the two groups include: packing density; coil length deployed; clinical outcome at 3 and 18 months post-coiling (measured by the modified Rankin scale); re-bleed and re-treatment rates. Five hundred patients will be required to demonstrate a reduction in major recurrence rate from 20% with bare platinum to 10% with hydrocoil treatment. Angiographic analysis will be by an independent core lab blinded to patient allocation.