A Randomized Trial Comparing Platinum and Hydrogel-coated Coils in Patients Prone to Recurrence after Endovascular Treatment (The PRET Trial)

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Summary

New coils have been designed to preserve the safety of coil embolization while improving on long-term efficacy. There is currently no scientific evidence that one type of coil material is better than another.

The recurrence problem may be more pressing in certain types of patients, such as patients with large aneurysms or those already presenting with angiographic recurrences.

The Proposed Trial

The PRET trial is a multicentric prospective randomized trial of endovascular management of aneurysms prone to recurrence after endovascular treatment, comparing hydrogel-coated and standard platinum coisl. It aims to recruit 500 patients in 23-40 centres in two years, 250 patients with large (≥10mm) aneurysms and 250 patients with recurrences after coil embolization, to detect a statistically significant difference for each type of patients, with a power of 80% and an alpha error of 2.5%.

The primary hypothesis is that hydrogel coil embolization will decrease recurrences from 50 to 30% at 18 months (range 40-50% to 21-30%). Recurrences will be adjudicated by an independent core laboratory masked to types of coils used. Secondary endpoints include procedural complications, clinical outcome, safety of hydrogel coiling and overall morbidity and mortality. The PRET trial is part of the ICONE project, the International Consortium of Neuro-Endovascular centres. The study is supported by a grant from the industry, but study design, coordination, data management, study monitoring, and reporting of results will be fully independent.

Introduction

Endovascular treatment with platinum coils is safe and effective in preventing rebleeding of intracranial aneurysms in the acute phase after subarachnoid hemorrhage. It is now the preferred method of treatment in many centers, because it can improve the outcome of patients compared to surgical clipping[1-5]. While treatment of ruptured aneurysms is imperative to prevent rebleeding, the management of unruptured aneurysms remains controversial because of a low annual risk of hemorrhage and a high surgical risk[6,7].

An effective endovascular treatment could offer a less morbid alternative to surgical treatment of unruptured aneurysms and thus pre-

vent the morbidity associated with SAH [6, 8-10]. A randomized trial testing the value of preventive endovascular treatment of unruptured aneurysms is ongoing [11-13].

Unfortunately, endovascular treatment is frequently incomplete and may lead to angiographic recurrences in 10 to 20% of patients, sometimes necessitating further treatment, or causing a genuine concern for future hemorrhages. This has been rare so far (in less than 1% of patients) [14-20]. A multicenter registry has reported up to 15% retreatment rates two years after coiling of ruptured aneurysms, but a yearly re-rupture rate of only 0.20% after the first year [21-22].

The use of endovascular approaches in the management of patients with intracranial aneurysms will continue to increase to the extent that long-term efficacy will be improved, without significant compromise regarding safety [14-20,23-24]. For this purpose coils with surface modifications have been introduced [25-27]. Unfortunately there is still no scientific evidence that these new coils improve the angiographic or clinical outcome of patients treated endovascularly. Randomized trials are underway to address this question. The HELPS trial, comparing hydrogel and platinum coiling in all-comers, has recently completed the recruitment of 500 patients, but results will not be available for another one to two years. Few patients will have been treated for large aneurysms and recurrences from previously coiled lesions were exclusion criteria [28].

Initial results of series and registries have not been promising with coils covered with resorbable suture material [29-31]. A similar types of registry has been more positive with hydrogel-coated coils, at least for small aneurysms with satisfactory packing densities [32-36], but in the absence of reliable evidence [37], most centres are comfortable limiting their treatment to standard platinum coils except perhaps in two special circumstances that we could call 'aneurysms with a high propensity for recurrences after endovascular treatment' (PRET): in cases of large aneurysms, or patients in whom platinum coil embolization has already been followed by an angiographic recurrence. In both cases recurrences with platinum are frequent (50% or more) [19]. These patients do not represent a profitable market for the industry, but they are most pertinent to our practices since these are the patients in whom our interventions need significant improvement. In an effort to promote a practice based on evidence, an international consortium of neurovascular centers, dedicated to the realization of independent clinical trials designed to provide reliable knowledge to our patients, has recently been proposed [38]. It was only natural that one of the first goals of this clinical research effort would address the problems of patients in whom our treatments have failed or are likely to fail. The present article is a presentation of the background and methodology of the PRET trial.

Background

Recurrences in large aneurysms and in patients with previous recurrences

We prospectively collected all cases treated by endovascular coiling since our first patients in 1992 [19]. Major recurrences, defined as sizable angiographic recurrences that ideally would need further treatment, appeared in 20.7% at a mean of 16 months. If we look more precisely at risks of recurrence after endovascular treatment of large aneurysms, numbers are much higher: we have observed a 34 to 50% recurrence rate among aneurysms 10mm or more in size [19]. In patients electively retreated for a first recurrence after coiling, the re-recurrence rate reached 50-59%. Others have found similar results [39].

Hydrogel-coated coils

The outer polymer layer of the hydrogel-coated coil is designed to expand after exposure to blood (approximately 90% expansion after 20 minutes). This expansion in volume is anticipated to facilitate exclusion of the aneurysm from the blood stream. While it is not expected that the hydrogel will fill 100% of the space, the amount of space filling is expected to be significantly greater than that of platinum coils alone.

This results in a mechanical stabilization of the coil mass. The increased aneurysm filling is intended to reduce the risk of 'coil compaction' and aneurysm recanalization, and improve long-term patient outcomes. A registry and case series have shown that recurrences are decreased from 50 to 20% in cases treated after a previous recurrence with platinum, and from 34-50% to 22-44% in cases of large aneurysms (>10 mm), as compared to historical 'controls' [32-35,40-41]. Other case series have proposed

that hydrogel-coated coils may improve long-term results [40-44].

A randomized trial comparing the safety and efficacy of hydrogel-coated and platinum coils in the treatment of intracranial aneurysms is ongoing (HELPS). This trial is crucial to determine the relative safety and efficacy of hydrogel-coated coils as compared with platinum coils, the current reference standard (the coil used in most cases included in the landmark trial ISAT) [2]. In this trial, however, patients with recurrences from previous treatment with platinum coils were excluded. As HELPs trial addresses treatment of "all comers", most patients recruited were patients with medium (5-10 mm) aneurysms (58%); it does not include a small proportion of patients with aneurysms ≥10 mm. Only 128 patients with aneurysms ≥10 mm have been equally randomized between platinum and hydrogel (P. White; Personal communication). Thus the safety and efficacy of hydrogel-coated coils compared to platinum coils in the treatment of large aneurysms will likely remain unknown, and for recurrences will definitely remain so, even after HELPs.

Some patients with large and giant unruptured aneurysms treated with hydrogel-coated coils have presented hydrocephalus after treatment; others suffered fever, elevated white blood cell counts, or enhancement on contrast MR imaging around the mass of coils, or "abscess"-like enhancing ring lesions. The relationship between the hydrogel material and these manifestations remains uncertain [44-45].

Most events were self-limited, or patients recovered after administration of steroids or antibiotics; rarely was ventricular drainage necessary in cases with hydrocephalus Early hydrocephalus (<3 months post coiling) occurred in 1.8-2.7% of unruptured lesions in HELPS, as reported at the WIN meeting in 2007. There has been one report of a small multicentre prospective study where 8% of patients treated for unruptured aneurysms needed shunting [46].

The overall incidence of these 'inflammatory reactions' is estimated to be around 1.5%-3% [40,45,47]. The incidence of this phenomenon after platinum coil embolization is currently unknown, but has been previously reported, and only a trial could offer a valid comparison between coils [42,48]. Nevertheless, even if hydrogel coil embolization would entail such an added risk of 2-3%, many clinicians could estimate that this risk would be worth it, if the decrease in the recurrence and retreatment rates, which also entail complications, is substantial.

The Proposed Trial

Design

This trial is a multi-centre randomized controlled trial with concealed allocation comparing hydrogel-coated coils to standard platinum coils in two types of patients. All patients with an intracranial aneurysm ≥10mm, (PRET-1) or with a major recurrence after previous coiling (PRET-2), eligible for endovascular treatment, will be invited to participate. Adjudication of angiographic results will be done by a committee blinded to treatment allocation in an independent core laboratory. The study will be conducted in 23-40 centers. The entire study aims to enroll approximately 500 patients equally divided between the two groups (platinum versus hydrogel) to obtain statistical significance for both PRET-1 and PRET-2. The duration forecast of the study will be five years, the first two to three and a half years being for patient recruitment plus a minimum of 18 months of follow-up.

Hypotheses

Primary hypothesis

The use of hydrogel-coated coils in patients with large aneurysms or presenting major recurrences after a previous endovascular treatment decreases the recurrence rate from 50% to 30% (range: 40-50% to 23-32%) at 18 months as compared to bare platinum coils.

Secondary hypotheses

The number of adverse events is similar for both groups. Morbidity and mortality related to treatment remains unchanged. Assuming a 6-8% complication rate for standard platinum coil treatment, the sample size of 250 for each group should allow a precision of 3-3.5% in the estimate (95% C.I.) of complication rates associated with both treatments.

Interventions

The goal of the study is to assess if substitution of platinum by hydrogel-coated coils could improve angiographic results of treatment with little if any additional risk. The premise is that the current standard coil is the bare platinum coil. Thus the interventions will consist of either:

A/ Standard platinum coil embolization of aneurysms, using standard techniques or adjunct techniques, without the use of hydrogel-coated coils (any type of platinum coil can be used, provided it is approved by relevant agencies);

B/ The substitution, as far as possible, of platinum by hydrogel-coated coils, the operator always being allowed to use the coil s/he believes is appropriate at any time during the procedure, all other aspects or principles of endovascular treatment remaining unchanged (such as systemic heparinization, preoperative use of antiplatelet agents, the use of adjunct techniques etc…) .

The aim of treatment is the complete angiographic exclusion of the aneurysm, or, as complete an exclusion from circulation as is possible while minimizing risks of the procedure. This goal is considered the standard of practice.

Table 1 **Selection Criteria.**

Inclusion Criteria

All patients presenting at least one aneurysm 'prone to recurrence after endovascular treatment' (PRET); defined for the sake of this study as:

- **PRET-1**: One ruptured or unruptured aneurysms, never treated, with a dimension ≥10mm (longest axis, including thrombosed portions of large or giant aneurysms); For ruptured lesions, patients should be in WFNS grade I, II or III.
- **PRET-2**: Aneurysms presenting a major recurrence after previous coiling; and judged by the neurovascular team to require elective treatment.

and

- The anatomy of the lesion is such that endovascular treatment is possible with both types of coils (not necessarily certain or probable);
- The endovascular physician is content to use either type of coils (platinum or hydrogel-coated coils) but no other type of coils;
- Patient is 18 or older;
- Life expectancy is more than two years;
- Patient or authorized representative has given fully informed consent and has signed consent form.

Exclusion Criteria

- If other aneurysms require treatment at the same session patients will be excluded.
- Patients with associated cerebral arteriovenous malformations.
- When parent vessel occlusion, without simultaneous endosaccular coiling of the aneurysm, is the primary intent of the procedure.
- Any absolute contraindication to endovascular treatment, angiography, or anaesthesia such as severe allergies to contrast or medications.

The interventionist and therefore the clinical and interventional research team cannot be blinded to the nature of the coils used, but the imaging center (core lab) that will determine the success of the procedure will be blinded during its evaluation. A potential bias, suspected from a previous registry (HEAL) is the tendency of certain interventionists to presume that hydrogel-coated coils may be more efficacious than platinum, thus leading to unjustified early interruption of the procedure. Alternatively, the concern for potential added costs of hydrogel-coated coils may explain a tendency to interrupt the procedure earlier than necessary. Hence for the current trial we insist that the endovascular procedure should be identical for both groups, except for the use of a number of coils of a different nature.

Although one mechanism evoked to support the potential benefit of hydrogel-coated coils is an increase in so-called 'packing density', the trial does not require the use of a minimal number or length of coils of either nature, nor to reach a certain packing density. To attempt to introduce more coils, even after angiographic exclusion of the lesion, to increase packing density, could be seen as taking unjustified additional risks.

The use of balloon assistance for coil deployment, stents or TriSpan is authorized but will be recorded. Parent vessel occlusion concomitant to endosaccular coiling is also permitted. The use of stent or aneurysmal neck-bridge devices will be recorded.

Selection criteria

Selection criteria are detailed in Table 1.

Randomization

PRET is designed as two parallel trials. Thus PRET-1 and PRET-2 cases will be randomized separately. A minimization algorithm will be used in PRET-1 to ensure balance between groups on a parameter that directly relates to long-term recurrences. The criteria are: the aneurysm is ruptured or unruptured. We will also minimize for the anticipated use of stents.

Type, frequency and duration of follow-up

For the analysis of the safety data, clinical examinations will be recorded at 24 hours, at dis-

charge, at one month and at the time of follow-up imaging (six and 18 months). Follow-up CT scan or MRI will be performed at 24 h or before discharge to detect silent periprocedural events. In order to detect inflammatory reactions, patients will be asked to report any fever, chills or progressive headaches during follow-up visits and additional tests performed as clinically indicated.

Adverse events will be recorded immediately after the procedure and during the 18-month follow-up period. First, the number and nature of adverse events for each patient is recorded. Then the relation to the aneurysm itself, to the endovascular coil embolization or to the hydrogel (not possibly or probably related) will be recorded. Clinical assessments will include the modified Rankin scale (mRS) at one, six (four to eight) and 18 (16 to 20) months. Follow-up imaging studies will be performed at six (four to eight) months by either catheter angiography or MRA according to the preference of the participating center.

The 18 (16-22) months imaging study will be performed by MRA unless absolute contraindication to this examination or the attending physician thinks that catheter angiography is more appropriate. The commonly recommended six month follow-up angiogram is not sufficient to detect most recurrences [19] but remains important to preserve a standard way of minimizing risks of bleeding by retreatment of early recurrences. To limit the follow-up to six months would weaken the pretension to improve "long-term" results, decrease the incidence of the primary endpoint and necessitate recruitment of a larger number of patients for statistical power.

Outcomes

Primary outcome

The primary outcome determines the size of the population to be studied to reach statistical significance. Although the clinical significance of angiographic recurrences remains to be determined, the primary outcome cannot be limited to hemorrhagic events, estimated to be quite rare, in the range of 0.1-1% per year.

New coils or embolic agents are meant to improve long-term results. Thus the primary outcome should be the recurrence rate. For the sake of this clinical trial, a recurrence is defined as 1) a radiographic recurrence of the lesion or the presence of a 'residual aneurysm' at last follow-up [19] 2) an intracranial bleeding episode or 3) retreatment of the same lesion by endovascular or surgical means during the follow-up period or 4) occurrence or progression of a mass effect in relation to the treated aneurysm.

Concerning radiographic evidence of recurrence, the angiographers at each participating center will ensure that best projections showing residual necks at the time of treatment are repeated during follow-up evaluations. Two independent neuroradiologists blinded to the treatment groups will determine the presence of an angiographic recurrence. For the purpose of this study, only major recurrences or residual aneurysms that are of a size that would ideally necessitate retreatment, will be counted. Angiographic results will also be scored according to a previously published classification system 19 as complete obliteration, residual neck or residual aneurysm and groups will be compared initially and at follow-up at six and 18 months.

The primary outcome, the recurrence rate, will be defined as the number of recurrences divided by the number of aneurysms in each group for both intent-to-treat and per-protocol populations. Recurrences will be recorded (present or absent) as they are discovered, at the routine follow-up assessments (six and 18 months), as clinical symptoms appear at any time during the 18 months that follow the intervention or at time of death. The independent core lab will determine the presence of angiographic recurrences.

Secondary outcomes

The secondary endpoints will consist of safety data (mortality rate, number of adverse events, and severity of adverse events). Morbidity and mortality will be considered secondary endpoints.

A morbid event will be defined as an adverse event of any severity being possibly or probably related to the disease or the treatments and happening during the 18-month follow-up period. A clinical Adjudication Committee will be responsible for the attribution of secondary outcome events.

Initial technical success

For the patients allocated to hydrogel-coated treatment, the interventionists will have a choice to use hydrogel-coated or platinum coils

during the embolization procedure, in order to guaranty the same safety and immediate efficacy as the standard procedure. The initial technical success or failure of the procedure will be determined after treatment by the Adjudication Committee by reviewing angiographic images, volumetric measurements and coils as recorded in the data collection sheets.

Mortality

The death rate will be recorded for the intent-to-treat analyses. It will be obtained by dividing the number of deaths by the number of patients in each group. Mortality will be categorized as being a/ related to the illness, b/ related to coil embolization or c/ unrelated.

Adverse events

Adverse events will be recorded immediately after the procedure and during the 18-month follow-up period. Severe adverse events (SAE), those that are life-threatening, leading to hospitalizations or prolonged hospitalizations, as well as unexpected events will all be reported within 48 hours to the data coordination centre that will transmit the information to the DSMC. The number and severity of all reported adverse events will be recorded for each patient and for each treatment group.

Morbidity

The number and the severity of morbid events per patient will be recorded for each patient. The modified Rankin scale will be measured at follow-up appointments. This scale classifies the patients according to their neurological outcome [49].

Safety of hydrogel-coated coil strategy

Patients will be asked to report any fever, chills, progressive headache or new neurological deficit occurring during follow-up. Clinical evaluation could then include, according to the attending physician's judgement, further brain imaging, blood samples or CSF analysis.

Sample size

From a retrospective study of patients treated in our institution by embolization, the angiographic recurrence rate for PRET-1 lesions was found to be 50% and 35% for recurrences and major recurrences respectively. Depending on publications, the rate of rerecurrence (PRET-2) varies from 50 to 59%. A sample size of 250 patients for PRET-1 and 250 patients for PRET-2, equivalent to 125 patients in each treatment arm (platinum vs hydrogel), is sufficient to detect a decrease in the recurrence rate from 50 to 30% (range from 50-40% to 30-21%) with an alpha error of 2.5% and a beta error of 20% for each of the PRET subgroups (odd ratio 0.58). Summary statement: A two-sided log rank test with an overall sample size of 250 subjects (of which 125 are in treatment group 1 and 125 are in treatment group 2) achieves 80% power at a 0.0250 significance level to detect a difference of 0.1972 between 0.3028 and 0.5000 - the proportions surviving in groups 1 and 2, respectively. This corresponds to a hazard ratio of 0.5802. The proportion of patients lost during follow-up was 0.1000. We have to expect that in 5% of randomized patients receiving either treatment the initial endovascular procedure will fail (they will be cross-overs, treated by open surgery or remain untreated) and 5% lost at follow-up. To compensate for patients that will not contribute to statistical comparison of the per-protocol populations (and to a lesser degree the intent-to-treat population), we believe that a total number of 250 patients for each of PRET-1 and PRET-2 is necessary to reach the desired statistical power.

Recruitment rate and centres

The targeted aneurysms are not frequent lesions; thus we expect from six to ten patients per year per center. We need to recruit 23-40 centers that will recruit six to ten patients/year for two to three years to reach the necessary sample size. Because recruitment rates are usually less than expected, recruitment of 40-50 centers would be ideal. Centers will be experienced in endovascular treatment of aneurysms using both platinum coils (at least 100 patients will have been treated previously) and hydrogel-coated coils (at least ten patients previously treated).

Planned analyses

Descriptive statistics will be done on demographic variables and pre-operative and perioperative 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 center and by treatment arm. Comparability of the groups

will be assessed through independent ANOVAs (quantitative data) or Mantel-Haentzel and chi-square tests (categorical data). The primary outcome, recurrence rates (for both intent-to-treat end per-protocol populations) will be compared between groups through a z-test for independent proportions at three months and 18 months. 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. Secondary outcomes and safety data will be compared between groups through independent t-tests (quantitative variables) or chi-square statistics (categorical data).

The analyses of neurological data at follow-up will control for baseline data when possible (for tests done before discharge and at follow-up) using logistic regression, ANCOVA or Cox regression multivariate models. All tests will be interpreted with adjustment for the interim analysis to have the 0.05 level of confidence at 18 months only. 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.

Pilot phase

The trial will start with a one year pilot phase that is meant to verify recruitment rates, compliance with treatment group allocation, safety of the hydrogel-coated coil strategy, morbidity of treatment, and overall feasibility of the trial. The data will be reviewed and analyzed by the DSMC and recommendations will be forwarded to the Steering Committee.

Protection against bias

Classic biases such as selection bias or information bias will be dealt with by randomizing patients and blinding in the assessment of the primary outcome. Random allocation of treatment is best for insuring internal validity and is the best approach to control for confounding and selection bias. To verify potential selection in each center, all eligible patients treated by the endovascular route and not recruited for the study, and reasons for exclusion, will be logged in all participating centers.

Finally, control variables will be measured and compared between treatment groups in order to ensure group comparability (initial angiographic success, periprocedural events, and disease characteristics). Protocol compliance will be carefully monitored in every centre.

Regulatory considerations

The study will only start after approval by the Institutional Review Board/Institutional Ethics Committee (IRB/IEC) of each center. The study will be performed in accordance with the national regulatory requirements of each participating centre. Each participant will be fully aware of the study purposes, the procedure and the risks of each intervention. When signing the study consent form, they will be informed that participation is voluntary and they can request to be withdrawn from the study at any time. Patient enrolment in this trial will comply with the principles enunciated in the Declaration of Helsinki. All the information collected with the questionnaires will be kept confidential and will be used on an anonymous basis.

Trial management and coordination

PRET is meant to be the first clinical research project of the ICONE project [38]. The financial support for the trial will be supplied by the industry (Microvention Inc., Aliso Viejo, CA). It is agreed that the support will be fully dedicated to the realization of the trial, but the industry has no control over the design or conduct of the trial and no access to the data until publication.

The results will be published whether they are favorable or not, and publications will be fully independent and autonomous, but as authorized by the Steering Committee. The Steering Committee will have full responsibilities regarding the conduct and progress of the trial, as well as reporting of results, with no interference from the industry. The Steering Committee will not have access to the unmasked data before completion or interruption of the trial. The Clinical Events Committee, the Endpoint Review Committee, and the Adverse Event Committee, once nominated, will work independently from the Steering Committee. These committees will regularly send progress reports, notices and warnings when appropriate, to the independent DSMC. The Committees that will have access to unmasked data are lim-

ited to the Adverse Event Committee, responsible for reviewing each adverse event, and the DSMC, any time members judge that unmasking of groups is mandatory to protect the safety of participants, or once they are convinced that significantly different results have occurred. The DSMC will follow the progress of the trial, results and events being masked (tagged as group A and B) at all times, but with the possibility of unmasking results in case of necessity. The DSMC will inform the Steering Committee if the trial should be interrupted if any concern arises during the trial. The Steering Committee will act according to the DSMC recommendations.

Discussion

One important principle in designing a trial is that no patient is denied a known effective treatment by entering the clinical trial. An equally important principle is that the degree of scientific rigour adopted in the evaluation of a new treatment is sufficient to prevent any ineffective, unsafe or inferior treatments gaining widespread use [50].

Trials are often described as belonging to two categories, 'explanatory' or 'management' types of trials. Explanatory trials are designed to discern any potential benefit of treatment in ideal circumstances. Explanatory trials call for tight eligibility criteria that select patients who are most likely to benefit, restriction of outcome events, and analysing just those outcome events that answer the precise research question. Explanatory trials assess if a novel therapy shows any promise, and allow to rapidly abandon the new treatment in the face of negative results. The clinical problem we are facing here calls for a slightly different approach however. What we really want to know is not if hydrogel coils could have some value in optimal circumstances, but how to manage patients with recurrences or lesions likely to recur, using coils that are already approved. Hence our design is in many aspects closer to a 'management' type of trial.

The trial is not designed to defend the product, or to detect any potential use for the product. The design is dedicated to the search for the best treatment for these difficult patients. This calls for a large, simple trial, looking for a pragmatic answer 1) with loose eligibility criteria based on uncertainty, 2) taking all comers; 3) retaining every admitted patient in the analysis; 4) proceeding with non-obstructive monitoring; 5) ascertaining a range of outcome events [51]. Hence, although the trial targets two categories of patients, the selection criteria remain loose, the prescriptions for the two types of treatment general and pragmatic, with minimal modification of standard treatment; the case report forms are simple, and the analyses are meant to determine if there is in general a benefit in treating these patients with hydrogel coils rather than platinum coils, without restricting analyses to patients in whom optimal packing could be obtained.

The philosophy of the trial is assess if a policy of using hydrogel coils instead of platinum coils, whenever possible, leads to better long term outcomes, with little compromise regarding immediate efficacy and safety.

The trial is not design to submit patients to the rigor of science. It is rather meant to use scientific methods to determine what is best for patients. In this spirit, the goal of the endovascular procedure is to realize the most complete exclusion of the lesion that is judged possible, while keeping risks as small as possible, using one or the other type of coils. Hence at any time during the procedure the interventionist is permitted to use any device, technique or drug, judged important to preserve the safety or success of the endovascular procedure. In fact it is the physician's responsibility to assure that the procedure is conducted in the safest possible manner.

The primary endpoint, angiographic recurrences (plus rare intracranial bleeding episodes during follow-up and occasional re-treatments that are considered recurrences) is a surrogate endpoint and as such it is theoretically a suboptimal choice as compared to clinical endpoints. The problem is that given the rarity of hemorrhages after coiling, trials limited to the detection of significant differences in clinical endpoints would necessitate impossibly large sample sizes, in the range of thousands of patients, precluding any hope of showing progress in aneurysm therapy. The adjudication of angiographic outcomes has previously been shown to be repeatable, with an acceptable inter and intra-observer variability [52-53]. Two other trials on coils in aneurysm therapy are currently using similar primary endpoints [54].

PRET is a designed as two parallel trials, with separate randomization for PRET-1 and

PRET-2; this could have been interpreted as allowing an alpha error of 5% for the two hypotheses, but we preferred to adjust the alpha error to 2.5%, as if two subgroups were analysed within the same trial. The power of the study is moderate, 80%. Keeping in mind that the incidence of outcome events in the control group is often over-estimated, and expectations from using a new device over-optimistic, all factors combine to increase the chances of not demonstrating a small but real benefit. However, the hydrogel coils are more expensive; they are unlikely to be safer than platinum coils; they may entail additional procedural or post-procedural complications. Thus we prefer to risk a type II error, and miss a small but real advantage on a surrogate endpoint, than risk a type I error, and falsely claim superiority of a potentially more dangerous device with no real clinical benefit. A non-inferiority trial, a design sometimes appropriate when comparing a proven effective but more invasive treatment with a novel less invasive approach with a questionable efficacy (such as radical mastectomy versus tumorectomy) may require smaller sample sizes, but there is no point in showing non-inferiority of a new, more expensive product, used during the basically same endovascular procedure, but possibly associated with increased procedural complications or unknown delayed adverse events [50].

The problem regarding sample size and statistical power resurfaces when one considers the secondary endpoints of the study. The use of a more 'powerful' tool could be associated with added risks, either during the procedure or after.

The key question will remain how much added morbidity, if there is any, are we willing to accept to improve follow-up images. Presumably very little. It is important here to remember that a failure to demonstrate a statistical difference between two treatments does not allow one to assert that the two treatments are equivalent or even similar. Since the trial is powered to detect a difference in more frequent angiographic recurrences, the sample size does not allow a small but potentially important difference to be detected in other less frequent events, such as procedural complications. We calculated that the precision we will be able to obtain in the evaluation of procedural complications will be acceptable, in the range of ± 3%, but this may mean that we could not exclude up to a 50% increase in immediate morbidity, assuming a basal rate of 6%. It is true that recurrences may be associated with future bleeding episodes, but these have been quite rare [19,21-22].

In addition, recurrences could also lead to morbidity related to additional treatments, although re-treatments with coils have so far been qualified as very safe [19,37].

There is no reason to anticipate interruption of the trial once results of HELPS become available, because they do not apply to the same target populations. Hence results may differ between these groups. Since endpoints are identical, results could be combined into a meta-analysis.

The type of trial management that we propose is meant to be transparent, fully independent from the industry, in accordance with standard procedures and international norms, and aims at preserving the scientific integrity of the research enterprise and the welfare of participants. Because it may allow the realization of trials faster and at lower costs, we hope it will promote a more frequent scientific assessment of the value of new devices than is currently the case. Trials at lower costs also mean less revenue for research institutions and perhaps individuals. It may force us to do more with fewer resources.

While the industry may be concerned by the loss of control over the design, conduct and results of the trial, we believe that the added objectivity and credibility of the research enterprise will in the end be beneficial to all parties involved. There must be convergence between revenues for the industry, progress in our field, and demonstrable benefits for our patients.

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