

Second-Generation Hydrogel Coils for the Endovascular Treatment of Intracranial Aneurysms

A Randomized Controlled Trial

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Background and Purpose—Endovascular embolization of intracranial aneurysms with hydrogel-coated coils lowers the risk of major recurrence, but technical limitations (coil stiffness and time restriction for placement) have prevented their wider clinical use. We aimed to assess the efficacy of softer, second-generation hydrogel coils.

Methods—A randomized controlled trial was conducted at 22 centers in France and Germany. Patients aged 18 to 75 years with untreated ruptured or unruptured intracranial aneurysms measuring 4 to 12 mm in diameter were eligible and randomized (1:1 using a web-based system, stratified by rupture status) to coiling with either second-generation hydrogel coils or bare platinum coils. Assist devices were allowed as clinically required. Independent imaging core laboratory was masked to allocation. Primary end point was a composite outcome measure including major aneurysm recurrence, aneurysm retreatment, morbidity that prevented angiographic controls, and any death during treatment and follow-up. Data were analyzed as randomized.

Results—Randomization began on October 15, 2009, and stopped on January 31, 2014, after 513 patients (hydrogel, n=256; bare platinum, n=257); 20 patients were excluded for missing informed consent and 9 for treatment-related criteria. Four hundred eighty-four patients (hydrogel, n=243; bare platinum, n=241) were included in the analysis; 208 (43%) were treated for ruptured aneurysms. Final end point data were available for 456 patients. Forty-five out of 226 (19.9%) patients in the hydrogel group and 66/230 (28.7%) in the control group had an unfavorable composite primary outcome, giving a statistically significant reduction in the proportion of an unfavorable composite primary outcome with hydrogel coils—adjusted for rupture status—of 8.4% (95% confidence interval, 0.5–16.2; $P=0.036$). Adverse and serious adverse events were evenly distributed between groups.

Conclusions—Our results suggest that endovascular coil embolization with second-generation hydrogel coils may reduce the rate of unfavorable outcome events in patients with small- and medium-sized intracranial aneurysms.

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Endovascular coil embolization is the preferred treatment modality for many patients with intracranial aneurysms because the results of the ISAT (International Subarachnoid Aneurysm Trial) showed better clinical outcomes with endovascular coiling than neurosurgical clipping in patients with ruptured aneurysms.¹ Nevertheless, incomplete aneurysm occlusion or recanalization of completely occluded aneurysms may occur after endovascular coiling. In aneurysms treated with bare platinum coils, the recanalization rates reported in the literature ranged from 4.7% to 28%,² and the rehemorrhage rates ranged from 0.12% to 0.4% per year.^{3,4}

Earlier studies on aneurysm recanalization suggested a correlation between packing density—the percentage of the aneurysmal volume occluded with coils—and the recanalization rate.⁵ To enhance the durability of endovascular coiling, coated coils were brought to clinical practice. Platinum coils coated with polymers including polyglycolic acid/polylactic acid were meant to enhance the inflammatory response at the neck of the aneurysm, to promote organization of clot in the aneurysm and the formation of neointima at the neck, but the concept did not prove effective in 2 randomized controlled trials.^{6,7}

A different approach consists of platinum coils coupled with hydrogel, which expands once in contact with liquids, resulting in increased packing density. The results of the HELPS (Hydrocoil Endovascular Aneurysm Occlusion and Packing Study) that assessed the efficacy and safety of a corresponding hybrid hydrogel-coated platinum detachable coil (HydroCoil; MicroVention, Inc, Tustin, CA) indicate that their use lowers major recurrence,⁸ but technical limitations of the HydroCoil (coil stiffness and time restriction for placement) have prevented its wider clinical use. To circumvent these limitations, softer hydrogel coils (HydroSoft, HydroFrame [3D]; MicroVention, Inc) containing less hydrogel and expanding more slowly than the HydroCoil have been developed.

In GREAT (German-French Randomized Endovascular Aneurysm Trial), we aimed to establish whether the use of softer, second-generation hydrogel coils for the treatment of intracranial aneurysms improves clinical and angiographic outcomes compared with the use of bare platinum coils.

Methods

The data that support the findings of this study are available from the corresponding author on reasonable request.

Study Design

GREAT was an investigator-initiated, pragmatic, postmarket, multicenter clinical trial with randomized parallel treatment group assignments, open-label treatment, and blinded end point evaluation for angiographic data. The study was conducted in 15 centers in France and 7 in Germany. The study protocol was approved by the leading ethics committee (Faculty of Medicine, University of Freiburg, 077/09) and the local ethics committees and was authorized by the competent French and German authorities. Members of the trial steering committee and the local investigators designed the study, collected and analyzed the data, wrote the article, and made the decision to submit the article for publication.

Patients

Patients were eligible for enrolment if they were 18 to 75 years of age and had untreated ruptured (World Federation of Neurosurgical

Societies [WFNS] grade 0–3) or unruptured aneurysms measuring 4 to 12 mm in diameter with an anatomy such that endovascular occlusion with either bare platinum or hydrogel coils was considered possible. We chose to restrict the aneurysm size because the largest second-generation hydrogel coil available when the trial started measured 12 mm. Detailed inclusion and exclusion criteria are listed in the study protocol.⁹ We did not keep a log of patients screened for eligibility. All patients or their legal representatives provided written informed consent. In Germany, the ethics committee approved randomization without prior informed consent, with the option to obtain consent at a later stage, but patients with missing informed consent were excluded from further analysis.

Randomization and Masking

Endovascular embolization of intracranial aneurysms with second-generation hydrogel coils was compared with endovascular embolization with bare platinum coils. Randomization occurred immediately before the study intervention. The randomization procedure was web based (Randoulette; Institute for Medical Informatics, Biometry, and Epidemiology, Ludwig-Maximilians-University, Munich, Germany). Allocation to a coil group was by block randomization in a 1:1 ratio, stratified by rupture status (ruptured versus unruptured aneurysm); block sizes were 2, 4, and 6. Centers were not informed about the block sizes. Masking of the interventional team to the randomly allocated treatment was not possible. Masking of patients was not mandatory; however, investigators were encouraged to refrain from unnecessary disclosure of treatment allocation.

Procedures

Participants in the intervention group underwent endovascular embolization with second-generation hydrogel coils (HydroSoft, HydroFrame; MicroVention, Inc). Standard local procedures for the coiling of aneurysms were followed. All procedures were performed under general anesthesia. Within the hydrogel arm of the study, second-generation hydrogel coils had to constitute >50% of the total coil length deployed. Any bare platinum coils were permitted, as were assist devices such as remodeling balloons or endovascular stents. Only devices that had received Conformité Européenne marking were used in the trial. The antiplatelet and anticoagulation regimens were left to the discretion of the individual operator as part of the standard operation procedure at each center. Detailed information about the coiling procedure was reported elsewhere.¹⁰

Clinical and Radiological Assessments

All patients underwent clinical examination and angiographic assessment of the underlying aneurysm. At the time of randomization, the following parameters were collected: sex, age, and rupture status (unruptured versus recently ruptured [<30 days]). Baseline data collected included number of aneurysms, aneurysm size (in mm), aneurysm neck size (in mm), dome-to-neck ratio, and aneurysm location. In patients with ruptured aneurysms, the WFNS grade was determined. After the coiling procedure, data were obtained on coils used, use of assist devices, disease- and procedure-related complications, and the initial angiographic outcome.¹⁰ Study data were entered locally by the treating physician or a dedicated study nurse into the trial database via web-based electronic case report forms. Digital copies of angiographic images of the aneurysm before treatment, immediately after treatment, at 6-month follow-up, and at 18-month follow-up were sent to the trials office. Digital subtraction angiography was preferred to magnetic resonance angiography, but magnetic resonance angiography was considered acceptable for centers where angiographic controls routinely are performed with magnetic resonance angiography. Imaging data were entered into the picture archiving and communication system in a pseudonymised way and reviewed by the core laboratory (H.D. and J.F.), who were masked to both treatment allocation and treatment received. The core laboratory reviewed imaging data together and were asked to assess the degree of aneurysm occlusion according to the 3-class Raymond scale (complete occlusion, neck

remnant, and residual aneurysm).¹¹ A major recurrence was defined as any change from complete aneurysm occlusion or neck remnant at the end of the index procedure to residual aneurysm at angiographic follow-up. In patients with residual aneurysms at the end of the index procedure, major recurrence was defined as any increase in size of the residual aneurysm as judged by the independent core laboratory. The modified Rankin Scale (mRS) score was assessed by the team treating the patient during follow-up. The formulas used to calculate the total aneurysm volume, the volume of 1 coil, the total coil volume, and packing density have previously been published.¹⁰

Study End Points

Primary end point was a composite outcome of predefined unfavorable angiographic and clinical events. The composite primary end point included major aneurysm recurrence on follow-up angiography within 18 months after treatment (judged by a blinded core laboratory), any aneurysm retreatment, morbidity that prevented patients from having angiographic controls (mRS score, 3–5), and any death during treatment and follow-up. When angiographic results at 18 months were not available, angiographic results at 6 months were used. In patients subject to >1 of the predefined unfavorable outcome events, only 1 was considered for the primary end point. In patients with retreatment or death during follow-up, the result of angiographic follow-up was disregarded for the composite primary end point. A composite angiographic and clinical end point was used rather than an angiographic end point alone because some patients die or are left so disabled after coiling or subarachnoid hemorrhage that they do not have follow-up angiographies. Secondary outcomes included clinical outcomes at 18 months using the mRS score, total coil length deployed, and coil packing density obtained. We did not compare the ease of use of second-generation hydrogel coils with that of bare platinum coils.

Statistical Analysis

The initially planned study size was 306 patients, but the target sample size was amended after the publication of the results of the HELPS, based on the assumption that unfavorable outcomes occur in 10% (hydrogel) versus 20% (bare platinum).⁸ Two hundred eighteen patients per group were needed to detect this difference between hydrogel and bare platinum coils with a power of 80% using Fisher exact test at a 2-sided significance level of 5%. With expected non-compliance or drop-out of patients after randomization in the order of 10%, 486 patients had to be randomized to observe the desired amount of compliant patients. The Trial Steering Committee decided to increase the target sample size to 500 patients in July 2012. This decision was driven exclusively by the external HELPS data.

Randomized patients without informed consent, patients who received flow-diverting stents or intrasaccular flow diverters, and patients in whom the intervention was stopped after the initial digital subtraction angiography were excluded. The lead investigator (C.A.T.) determined these treatment-based patient exclusions after final data cleaning of the database with respect to procedural data blinded for treatment allocation. Corresponding exclusions are indicated in Figure 1 (aneurysm not accessible, no aneurysm found, received flow diverters, and received web devices). The remaining patients formed the analysis population in which nonmissing data were analyzed as randomized.

For binary outcomes, the absolute difference of the proportion of outcome events between the 2 arms, expressed as percentages, was calculated along with a 2-sided Newcombe 95% confidence interval (CI) and *P* value with Cochran–Mantel–Haenszel weights, stratified by rupture status.¹² A preplanned sensitivity analysis of the primary end point explored the worst-case scenario in the analysis population where all missing outcomes for patients randomized to the hydrogel arm were evaluated as unfavorable and all those in the bare platinum arm as favorable. For post hoc analyses, we calculated Newcombe CI for the absolute difference in the proportion of unfavorable outcomes between treatments within subgroups, and we examined odds ratios ($\pm$ the interaction with treatment) by Wald tests from logistic

regression. Ordinal and continuous data were compared using van Elteren Wilcoxon rank-sum test stratified for rupture status.¹³ Adverse events (AE) were evaluated by received treatment in the analysis population. Periprocedural AE and specific items requested in the electronic case report form describing treatment were evaluated jointly. AE with onset >14 days from initial aneurysm treatment were coded using the medical dictionary for regulatory activities. *P* values were 2 sided and considered statistically significant if <0.05 and exploratory except for the primary analysis. All analyses were performed using version 9.2 of the Statistical Analysis System (SAS; SAS Institute, Cary, NC). The statistical analysis plan has been described in detail⁹ (online-only Data Supplement).

Two interim analyses were undertaken, after randomization of 100 and 300 patients, which included assessment of trial data on procedure-related complications, postoperative degree of aneurysm occlusion, AE, and mortality. Results of these analyses were reviewed by an independent data safety monitoring board in strict confidentiality, and relevant information from other sources was considered. The data safety monitoring board advised the lead investigator (C.A.T.) both times to continue with the trial. The primary end point had not been evaluated in the interim analyses.

Results

Baseline Results

From October 15, 2009, to January 31, 2014, 513 patients underwent randomization in 15 centers in France and 7 centers in Germany. Recruitment was stopped after the predetermined sample size was reached. Twenty-nine patients were excluded from the analysis population (Figure 1). The mean age of the 484 patients in the analysis population was 52.4 years (range, 21–82); 151 (31%) patients were men. Two hundred eight patients (43%) were treated for ruptured aneurysms. Two hundred forty-three patients (50.2%) in the analysis population were assigned to the hydrogel group, and 241 (49.8%) were assigned to the bare platinum group. Among patients allocated to hydrogel, 5 were treated with bare platinum coils alone; among patients allocated to the control group, 6 received additional hydrogel coils. The use of assist devices (balloon remodeling and stent-assisted coiling) was balanced between the 2 arms of the study (Table 1). Potential risk factors for unfavorable angiographic and clinical outcomes (age, rupture status, WFNS grade ≥ 3 , aneurysm dome-to-neck ratio <1.5, target aneurysm size, and target aneurysm neck size) were evenly distributed between the 2 treatment groups (Table 1).

AE and serious AE (SAE) collected during treatment and through to discharge included perforation, dissection or occlusion of the parent vessel, procedure-related aneurysm rupture, thromboembolic events, stroke, coil migration, or procedure-related AE with outcome death. AE and SAE with onset >14 days from coiling were also collected.

Primary end point data were available in 456 patients (Figure 1).

Hydrogel Arm

Among patients allocated to the hydrogel group (*n*=243), 103 (42%) were treated for ruptured aneurysms. Ninety-six patients (40%) were treated without the use of assist devices. Balloon remodeling alone was used in 88 patients (36%), stent-assisted coiling alone in 18 patients (7%), and both balloon remodeling and stent-assisted coiling in 41 patients (17%). On core laboratory–assessed final angiographic

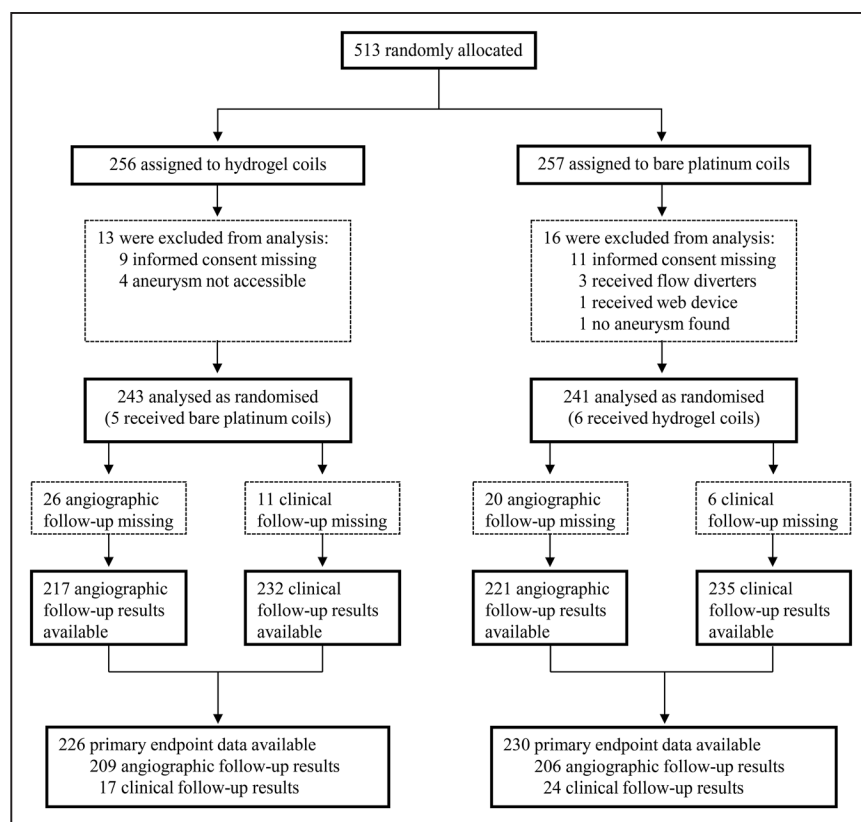


Figure 1. Trial profile. Centers did not keep comprehensive eligibility logs.

controls (n=239), 130 (54%) aneurysms were completely occluded, 47 (20%) showed a neck remnant, and 62 (26%) were residual aneurysms.

Primary end point data for the analysis population were available in 226 of 243 patients. Of 226 patients, 28 (12%) had major aneurysm recurrences, 7 (3%) had aneurysm retreatment, 3 (1%) had morbidity that prevented them from having angiographic follow-up, and 7 (3%) died. AE and SAE occurring during treatment through to discharge were reported in 31 patients. AE and SAE with onset >14 days from coiling were reported in 20 patients. Hydrocephalus was reported in 2 patients (Tables I and II in the [online-only Data Supplement](#)).

Bare Platinum Arm

Among patients allocated to the bare platinum arm (n=241), 105 (44%) were treated for recently ruptured aneurysms. One hundred and ten patients (46%) were treated without the use of assist devices. Balloon remodeling alone was used in 81 patients (34%), stent-assisted coiling alone was performed in 21 patients (9%), and both balloon remodeling and stent-assisted coiling in 29 patients (12%). On core laboratory-assessed final angiographic controls (n=237), 124 (52%) aneurysms were completely occluded, 55 (23%) showed a neck remnant, and 58 (24%) were residual aneurysms. These results did not differ significantly from those in the hydrogel arm ($P=0.80$).

Primary end point data for the analysis population were available in 230 of 241 patients allocated to the bare platinum arm of the study. Of 230 patients, 42 (18%) had major aneurysm recurrences, 14 (6%) had aneurysm retreatment, and 10 (4%) died. AE and SAE occurring during treatment through

to discharge were reported in 27 patients. AE and SAE with onset >14 days from coiling were reported in 17 patients. Hydrocephalus was reported in 1 patient (Tables I and II in the [online-only Data Supplement](#)).

Six-month instead of 18-month angiographic controls were used for 31 (14.3%) of 217 patients in the hydrogel arm with available angiographic results and 50 (22.6%) of 221 patients in the control group.

Primary and Secondary End Point Results

There was a shift in the distribution of the unfavorable composite primary outcome toward the control group (Table 2). This difference was statistically significant: among patients with recently ruptured aneurysms, 27 (28.7%) of 94 in the hydrogel group versus 38 (37.6%) of 101 in the control group experienced unfavorable composite primary outcome, yielding an absolute increase in the risk of unfavorable composite primary outcome in the control group of 8.9% (95% CI, -4.3 to 21.6; $P=0.19$). Among patients with unruptured aneurysms, 18 (13.6%) of 132 in the hydrogel group versus 28 (21.7%) of 129 in the control group experienced unfavorable composite primary outcome, yielding an absolute increase in the risk of unfavorable composite primary outcome in the control group of 8.1% (95% CI, -1.2 to 17.3; $P=0.089$).

Adjusted for rupture status by stratified analysis, the absolute increase in the risk of unfavorable composite primary outcome for the control arm was 8.4% (95% CI, 0.5–16.2; $P=0.036$; number needed to treat, 12; relative increase, odds ratio, 1.61; 95% CI, 1.04–2.50; $P=0.034$).

Subgroup analysis stratifying for rupture status (ruptured versus unruptured) and aneurysm size (aneurysm size <10

Table 1. Demographic and Baseline Characteristics by Randomized Treatment

	Randomized Treatment	
	Hydrogel Coils, n (%)	Bare Platinum Coils, n (%)
Total no. of patients	243	241
Sex		
Female	172 (71)	161 (67)
Male	71 (29)	80 (33)
Age, y		
Mean±SD, range	52.9±12.6 (24–79)	54.1±11.8 (21–82)
Baseline rupture status		
Yes, in previous 30 d	103 (42)	105 (44)
No	140 (58)	136 (56)
WFNS scores in patients with previously ruptured aneurysms		
WFNS 1	65 (64)	74 (71)
WFNS 2	21 (21)	15 (14)
WFNS 3	11 (11)	11 (11)
WFNS 4	4 (4)	3 (3)
WFNS 5	1 (1)	1 (1)
Missing	n=1	n=1
Aneurysm location		
Anterior	177 (74)	182 (76)
Posterior/other	62 (26)	56 (24)
Missing	n=4	n=3
Target aneurysm size, mm		
Median, range	7 (2–15)	7 (2–18)
Mean±SD, range	6.8±2.1 (2–15)	7.1±2.5 (2–18)
Missing	n=1	n=0
Size aneurysm neck, mm		
Mean±SD, range	3.5±1.3 (1–8)	3.6±1.3 (2–9)
Missing	n=5	n=4
Dome-to-neck ratio		
<1.5	90 (38)	90 (38)
≥1.5	147 (62)	150 (63)
Missing	n=6	n=1
Aneurysm shape		
Regular	136 (56)	133 (55)
Irregular/lobulated	107 (44)	107 (45)
Missing	n=0	n=1
Assist device used		
None	96 (40)	110 (46)
Balloon, no stent	88 (36)	81 (34)
Stent, no balloon	18 (7)	21 (9)
Balloon+stent	41 (17)	29 (12)

WFNS indicates World Federation of Neurosurgical Societies.

Table 2. Composite Angiographic and Clinical Outcomes

	Hydrogel, n=226	Control, n=230
Good, n (%)		
No major aneurysm recurrence on angiographic follow-up	181 (80)	164 (71)
Unfavorable, n (%)		
Major aneurysm recurrence on angiographic follow-up without retreatment	28 (12)	42 (18)
Retreatment	7 (3)	14 (6)
No angiographic follow-up because of morbidity, mRS, 3–5	3 (1)	0
Any death, mRS score 6	7 (3)	10 (4)
Refused or lost to angiographic follow-up	17	11

Data are represented as n (%). In 81 (18%) patients, 31 (14.3%) from the hydrogel arm and 50 (22.6%) from the control arm, 6-month angiographic results were used because 18-month angiography was not done or available. In patients with retreatment or death during follow-up, the result of any angiographic follow-up was disregarded for the composite primary end point. mRS indicates modified Rankin Scale.

versus ≥10 mm) showed that the effect of second-generation hydrogel coils seemed more pronounced in unruptured aneurysms and in aneurysms <10 mm (Figure 2).

A sensitivity analysis was performed under a worst-case scenario: for additional 28 patients of the analysis population with missing primary outcome data, we assumed an unfavorable composite primary outcome for patients in the hydrogel group and a favorable outcome for patients in the control group. The sensitivity analysis failed to show a statistically significant increase in the risk of unfavorable composite primary outcome in the control group (1.7%; 95% CI, –9.5 to 6.2; $P=0.67$).

Angiographic outcomes at follow-up are displayed in Table III in the [online-only Data Supplement](#). The test for between-group differences in the 7-level mRS score for the clinical status at 18 months was not statistically significant ($P=0.76$; Table IV in the [online-only Data Supplement](#)). Greater aneurysm packing density was achieved in the hydrogel group (median, 39%; range, 8–152) than in controls (median, 31%; range, 6–95). This difference was statistically significant ($P<0.001$). The analysis of administered coil lengths showed a nonsignificant trend that less total coil length was administered in the hydrogel arm (median, 38 cm; range, 2–259) than in the control arm (median, 41 cm; range, 3–352; $P=0.065$).

Procedural complications occurred in 31 (12.7%) patients treated with hydrogel coils and 30 (12.4%) who received platinum coils (rate difference, 1.6%; 95% CI, –4.2 to 7.5; $P=0.59$). Procedure-related stroke or death occurred in 9 patients (3.7%) treated with hydrogel coils and 7 patients (2.9%) who had received bare platinum coils (Table I in the [online-only Data Supplement](#)). The 14-day mortality rates were comparable in both arms of the study: 5 patients per arm (2.0% versus 2.1%; rate difference, 0.1%; 95% CI, –3.2 to 3.1; $P=0.96$). There was no significant between-group difference in the occurrence

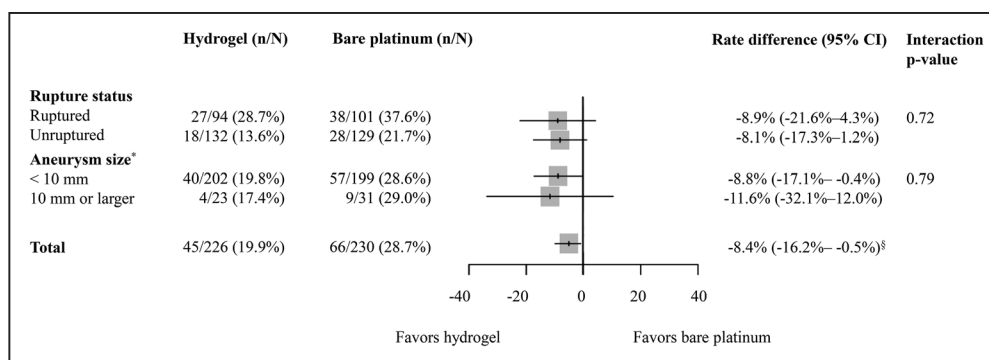


Figure 2. Subgroup analysis of composite primary end point (differences in unfavorable outcome rates in percentage). *Aneurysm size missing in 1 patient assigned to hydrogel. §Adjusted for rupture status. CI indicates confidence interval.

of AE and SAE during the 18-month follow-up period (Table II in the [online-only Data Supplement](#)).

Twelve deaths (5 in the hydrogel group and 7 in the control group) occurred in the subgroup of patients with recently ruptured aneurysms and available clinical follow-up (n=195). Seven additional patients with recently ruptured aneurysms had poor clinical outcomes (mRS score, 3–5; 5 in the hydrogel group and 2 in the control group). In the subgroup of patients with incidental aneurysms and available clinical follow-up (n=270), 5 deaths (2 in the hydrogel group and 3 in the control group) occurred. Three additional patients with incidental aneurysms (2 in the hydrogel arm and 1 in the control group) had poor clinical outcomes (mRS score, 3–5). This results in a morbidity and mortality rate (mRS score ≥ 3) of 9.6% for patients with recently ruptured aneurysms and 3.0% for patients with incidental aneurysms.

Discussion

In this study, the risk of meeting the unfavorable composite primary end point of major angiographic recurrence and poor clinical outcome at 18 months after treatment was significantly lower in patients treated with second-generation hydrogel coils than in the control group of patients treated with bare platinum coils.

Our findings stand in clear distinction to those of recent randomized controlled trials on embolization with polyglycolic acid/polylactic acid-coated coils for the treatment of intracranial aneurysms that failed to show a benefit when compared with bare platinum coils.^{6,7} The results of 2 other randomized controlled trials on embolization with hydrogel coils showed variable results.^{8,14} HELPS, which investigated the effectiveness of first-generation hydrogel coils (HydroCoils; MicroVention, Inc), failed to show significant differences for the composite primary end point of the trial. Analysis of a secondary end point showed an 8.6% reduction in major recurrences for aneurysms treated with hydrogel coils when compared with aneurysms treated with bare platinum coils.⁸ The PRET trial (Patients Prone to Recurrence After Endovascular Treatment) analyzed the potential effect of first- and second-generation hydrogel coils on 2 different cohorts: patients with large aneurysms (PRET 1) and patients with aneurysms that had previously recurred after coiling (PRET 2). The PRET trial did not show any benefit of hydrogel coils over bare platinum coils with respect to an

unfavorable composite primary end point of residual/recurrent aneurysm, retreatment, intracranial bleeding, or mass effect during an 18-month follow-up period in both cohorts.¹⁴

Differences in inclusion criteria and primary end points among these randomized controlled trials make a head-to-head comparison difficult (Table V in the [online-only Data Supplement](#)). The inclusion criteria in HELPS and PRET did not restrict aneurysm size, a factor known to have a major influence on the recurrence rate of coiled aneurysms. In GREAT, enrolment was restricted to patients with aneurysms 4 to 12 mm in diameter. This might explain the better results obtained in GREAT and corroborates findings from a recent post hoc subgroup analysis of data from patients with medium-sized (5–9.9 mm) ruptured aneurysms in the HELPS that showed a significantly lower major recurrence rate in the hydrogel group than in the control group (18.6% versus 30.8%; $P=0.03$) at 15 to 18 months after treatment.¹⁵

The primary end points for HELPS, PRET, and GREAT seem comparable. All 3 were measured at 18 months after the index aneurysm procedure and combined angiographic and clinical measures. The MAPS trial (Matrix and Platinum Science) used target aneurysm recurrence as a measure of clinical effectiveness after aneurysm treatment. Target aneurysm recurrence composed of target aneurysm rupture, sudden unexplained death, and target aneurysm retreatment and is meant to capture the clinical events that are most important to patients after aneurysm treatment.⁷ In GREAT, we used a comparable composite end point but added angiographic measures (recurrent aneurysm).

Comparison of clinical outcomes between studies seems difficult because we excluded per-protocol patients with WFNS grade >3 from randomization into the trial. The rate of death or disability (mRS score ≤ 3) at 18 months in the overall group of patients treated for ruptured aneurysms was 9.6% (19/197), which is comparable with the reported rate of 10.5% (30/287) death or disability at 3 to 6 months follow-up in a subgroup of patients presenting with WFNS grades 1 to 3 (n=287) and treated with bare platinum coils in the CLARITY study (Clinical and Anatomical Results in the Treatment of Ruptured Intracranial Aneurysms), a prospective registry conducted in France that included 405 patients with ruptured aneurysms.¹⁶ In HELPS (WFNS grades 1–3 in patients with ruptured aneurysms) and MAPS (WFNS grades in patients with ruptured aneurysms not indicated), the death or disability

rate for patients treated for ruptured aneurysms were 17.7% and 9.6%, respectively.^{7,8} The authors of the Cerecyte Coil Trial unfortunately did not provide corresponding data.⁶

In our study, the death or disability rate (mRS score ≥ 3) at 18 months was 3.0% (8/270) for patients treated for unruptured aneurysms, which compares favorably with the 3.1% rate reported at 1-month follow-up in the ATENA study (Analysis of Treatment by Endovascular approach of Non-ruptured Aneurysms), a prospective registry conducted in France that included 649 patients treated for unruptured aneurysms.¹⁷ In HELPS and MAPS, the death or disability rate for patients treated for unruptured aneurysms was 11.1% and 4.2%, respectively.^{7,8} These favorable comparisons might be explained by improved materials and increased experience among neurointerventionalists. Another factor playing a certain role is the restriction of GREAT to aneurysms measuring 4 to 12 mm, thereby excluding small and large aneurysms—both known to have higher procedural complication rates. In addition, the inclusion of patients with ruptured aneurysms in GREAT was limited to WFNS grades 1 to 3, potentially influencing the overall clinical outcome of the study cohort.

The inclusion of a broad international panel of treatment teams increased representativeness of the cohort because 12 of 22 participating centers randomized ≥ 10 patients per center (range, 1–85).

The median packing density was significantly higher in the hydrogel group and seems to have translated into better long-term angiographic results and lower retreatment rates in our study. This observation corroborates findings from PRET that showed a correlation between packing density and angiographic recurrences for both the hydrogel and the control arms of that study.¹⁴

GREAT had several limitations. The generalizability of our findings is limited because of the restrictions in aneurysm size. There were more patients missing primary end point data in the hydrogel group ($n=17$) than in the control group ($n=11$). In irregularly shaped aneurysms and in aneurysms carrying multiple blebs, the ellipsoid model used for the calculation of the total aneurysm volume may result in inaccurately small aneurysm volumes potentially exaggerating the packing density.¹⁰

The worst-case scenario analysis showed no statistically significant reduction in the composite end point for the second-generation hydrogel arm compared with the bare platinum arm. Although some of these outcomes were missing for reasons unrelated to treatment, the reasons are not known for all patients. The clinical end point (mRS score) was self-assessed. Because the composite outcome included morbidity that prevented angiographic controls, the primary end point is not complexity blinded to the allocated arm. The study was designed in December 2008; at that time, flow-diverting stents and intrasaccular flow disruptors had not been introduced to standard interventional neuroradiology practice. We decided during the course of the trial to exclude patients treated with these novel devices from further analyses. The option practiced in Germany, to obtain informed consent in patients with WFNS grades 2 and 3 at a later stage, may have led to under-reporting of treatment or disease-related mortality, because patients with missing informed consent were excluded from analysis. The follow-up period of 18 months

was not completed by all patients; we used 6-month follow-up for 18% of patients.

Conclusions

Our results suggest that endovascular coil embolization with second-generation hydrogel coils may reduce the rate of unfavorable outcome events, composed of major aneurysm recurrence, aneurysm retreatment, morbidity that prevented angiographic controls, and any death during treatment and follow-up in patients with small- and medium-sized intracranial aneurysms.

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Disclosures

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Second-Generation Hydrogel Coils for the Endovascular Treatment of Intracranial Aneurysms: A Randomized Controlled Trial

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1. Table I. Adverse events during treatment and procedure-related adverse events
2. Table II. Incidence of adverse events with onset >14 days from initial aneurysm treatment (coded by MedDRA)
3. Table III. Angiographic outcomes at follow-up (Core-lab assessed)
4. Table IV. Modified Rankin Scale at follow-up 18 months after treatment
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7. GREAT study protocol version 12, (01.07.2012)
8. Statistical analysis plan, version 01, (20.09.2011)
9. Amendment to the Statistical Analysis Plan, (07.06.2013)
10. Additional changes to statistical analysis

**1. Table I. Adverse events during treatment and procedure-related adverse events
(treatment through discharge)**

	Received Treatment			
	Hydrogel Coils		Bare Platinum Coils	
	No.	%	No.	%
Total no. patients	244		240	
Parent vessel perforation	1	0.4%	1	0.4%
Parent vessel dissection	1	0.4%	1	0.4%
Parent vessel occlusion	2	0.8%	4	1.7%
Procedure-related aneurysm rupture	6	2.5%	6	2.5%
Thromboembolic event	12	4.9%	12	5.0%
Stroke	7	2.9%	5	2.1%
Coil migration	9	3.7%	6	2.5%
Procedure-related AEs with outcome death	2	0.8%	3	1.3%
Any of the previous complications and AEs	31	13%	27	11%
Other procedure related AE	21	8.6%	19	7.9%
14-day mortality	5	2.0%	5	2.1%
Distal embolization	7	5.0%	6	4.6%
<i>Missing / incomplete DSA images</i>	<i>n=4</i>		<i>n=3</i>	

AEs = adverse events, DSA = digital subtraction angiography

2. Table II. Incidence of adverse and serious adverse events with onset >14 days from initial aneurysm treatment by received treatment (coded by MedDRA)

	Received Treatment			
	Hydrogel		Bare Platinum	
	Coils		Coils	
	No.	%	No.	%
Total no. patients	244		240	
Serious adverse event with onset >14 days	14	5.7	14	5.8
Any adverse event with onset >14 days	20	8.2	17	7.1
Nervous system disorders	10	4.1	7	2.9
Cerebrovascular accident	2	0.8	1	0.4
Hydrocephalus	2	0.8	1	0.4
Dysarthria	1	0.4	1	0.4
Transient ischemic attack	1	0.4	1	0.4
Basilar artery thrombosis	0	0	1	0.4
Brain compression	1	0.4	0	0.0
Brain edema	0	0.0	1	0.4
Dizziness	1	0.4	0	0.0
Facial paralysis	1	0.4	0	0.0
Neurological decompensation	1	0.4	0	0.0
Paraesthesia	1	0.4	0	0.0
Subarachnoid hemorrhage	0	0	1	0.4

Surgical and medical procedures	3	1.2	6	2.5
Hospitalization	1	0.4	3	1.3
Intra-cerebral aneurysm operation	0	0	2	0.8
Aneurysm repair	0	0	1	0.4
Arterial therapeutic procedure	1	0.4	0	0.0
Radioactive iodine therapy	1	0.4	0	0.0
Vascular disorders	4	1.6	3	1.3
Aneurysm	3	1.2	2	0.8
Vasospasm	1	0.4	1	0.4
Investigations	3	1.2	1	0.4
Angiogram	3	1.2	0	0.0
Investigation	0	0	1	0.4
Cardiac disorders	0	0	2	0.8
Arrhythmia	0	0	1	0.4
Myocardial infarction	0	0	1	0.4
Congenital, familial and genetic disorders	1	0.4	0	0.0
Arteriovenous malformation	1	0.4	0	0.0
Cerebrovascular arteriovenous malformation	1	0.4	0	0.0

Endocrine disorders	1	0.4	0	0.0
Diabetes insipidus	1	0.4	0	0.0
General disorders and administration site conditions	1	0.4	0	0.0
Vascular stent restenosis	1	0.4	0	0.0
Infections and infestations	0	0	1	0.4
Meningitis	0	0	1	0.4
Injury, poisoning and procedural complications	1	0.4	0	0.0
Vascular pseudoaneurysm	1	0.4	0	0.0
Psychiatric disorders	1	0.4	0	0.0
Completed suicide	1	0.4	0	0.0

MedDRA = Medical Dictionary for Regulatory Activities. MedDRA System Organ Classes are printed in bold face above the corresponding MedDRA Preferred Terms. Numbers are numbers of patients in whom the event was reported at least once.

3. Table III. Angiographic outcomes at 18 month follow-up

	Randomized treatment			
	Hydrogel		Control (Bare platinum)	
	No.	%	No.	%
Total number of patients with available angiographic follow-up data*	217		221	
Complete obliteration	150	69%	118	53%
Residual neck	24	11%	44	20%
Residual aneurysm	43	20%	59	27%
Missing angiographic follow-up data	26		20	

*Note: Six-month instead of 18-month angiographic controls for 31 (14.3%) patients in the hydrogel arm and 50 (22.6%) patients in the control group

4. Table IV. Modified Rankin Scale at follow-up 18 months after treatment

	All patients		Target aneurysm ruptured within 30 days		Target aneurysm not ruptured within 30 days	
mRS	Hydrogel (n=243)	Control (n=241)	Hydrogel (n=103)	Control (n=105)	Hydrogel (n=140)	Control (n=136)
0	198 (85%)	202 (86%)	75 (78%)	76 (75%)	123 (90%)	126 (94%)
1 + 2	20 (9%)	20 (9%)	11 (11%)	16 (16%)	9 (7%)	4 (3%)
3 – 5	7 (3%)	3 (1%)	5 (5%)	2 (2%)	2 (1%)	1 (1%)
6	7 (3%)	10 (4%)	5 (5%)	7 (7%)	2 (1%)	3 (2%)
<i>Missing</i>	<i>11</i>	<i>6</i>	<i>7</i>	<i>4</i>	<i>4</i>	<i>2</i>

Data are n (%). mRS = modified Rankin Scale. mRS 6 = death

5. Table V. GREAT results compared to other randomised controlled coil trials

Study	Year	Number of patients	Coil type assessed	SAH	Aneurysm size mean (range) in mm	Primary endpoint (Duration of follow-up)	Result primary endpoint		
							Coil type assessed	Control (bare platinum coil)	<i>p</i> value
HELPS ⁸	2007	499	First generation hydrogel (HydroCoil)	53%	6.5 (2–25)	Residual / recurrent aneurysm, missing angiographic follow-up due to mRS 3–6 (18 months)	28%	36%	0.13
CCT ⁶	2012	500	Cerecyte	47%	n.a. (2–18)	Complete aneurysm occlusion, stable neck remnant, improved angiographic appearance compared with post-procedural angiogram (6 months)	59%	54%	0.17
MAPS ⁷	2014	626	Matrix	36%	7.6 (4–20)	Target aneurysm haemorrhage, re-treatment, mRS 6 (15 months)	13%	15%	0.76
PRET ¹⁴	2017	447	First- (HydroCoil) and second-generation hydrogel (HydroSoft and/or HydroFrame)	36%	11.3 (2–25)	Residual / recurrent aneurysm, re-treatment, intracranial bleeding, or mass effect (18 months)	48%	46%	n.a.
GREAT	2017	484	Second-generation hydrogel (HydroSoft and/or HydroFrame)	43%	7.0 (4–12)	Recurrent aneurysm, re-treatment, missing angiographic follow-up and mRS 3–5, any death (18 months)	20%	29%	<u>0.036</u>

SAH = subarachnoid hemorrhage (ruptured aneurysm at baseline), n.a. = not available, HELPS = Hydrocoil Endovascular aneurysm occlusion and Packing Study, MAPS = Matrix and Platinum Science, CCT = Cerecyte Coil Trial, PRET = Patients Prone to Recurrence After Endovascular Treatment, GREAT = German-French Randomized Aneurysm Trial. *p*-values indicating statistical significance are underlined.

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The number of patients randomized in each center is given in parentheses.

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GREAT - A Randomised Endovascular Aneurysm Trial

Protocol, version 12

July 2012

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

DRKS-ID: DRKS00003132

Study Protocol

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GREAT – a randomised aneurysm trial

I. Aims & Objectives

We aim to compare the following in patients allocated to HydroSoft (including Hydroframe) versus patients allocated to bare platinum:

Primary outcome:

- Composite outcome of major aneurysm recurrence on follow-up angiography and clinical outcome within 18 months.

Secondary outcomes:

- Packing density
- Coil length deployed
- Clinical outcome at 6 and 18 months post-coiling, as measured by the modified Rankin scale

II. Trial Design & Methods

Inclusion criteria

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

AND

- Patient WFNS Grade 0-3 and aged 18-75 years
 - In patients WFNS Grade 0+1 fully informed consent will be obtained for participation in the study.
 - For patients WFNS Grade 2+3 the attending senior neuroradiologist and senior neurosurgeon will have to sign for inclusion in the study. This procedure seems justified as at this level since inclusion in the study means randomization between two treatment arms with CE-labelled medical devices (bare platinum coils versus HydroSoft/HydroFrame coils). At a second stage consent will be obtained by the patient or the legal guardian to decide whether the patient data may be processed.
- Aneurysm from 4 – 12 mm in diameter
- Anatomy such that endovascular occlusion is deemed possible (not necessarily probable)
- The neurointerventionist is content to use either bare platinum or HydroSoft/HydroFrame depending on randomisation result

Non-inclusion criteria

Subjects will not be considered for the trial unless they meet all the inclusion criteria and unless none of the following non-inclusion criteria is present:

- The patient has already been randomized in this trial
- The aneurysm has already been treated (by coiling or clipping)

- 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.

Exclusions criteria

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

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.

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 Neurointerventionalist 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 (WFNS Grade 0+1) agrees to participate in the trial, he/she will be randomised once written informed consent has been obtained. For patients with WFNS Grade 2+3, see inclusion criteria. A copy of the consent will be retained in the case notes, one given to the patient, one retained by local investigators and a copy sent with to the coordinating centre.

Randomisation

The Neurointerventionalist or the person recruiting the patient into the trial will then perform randomisation via a web based randomisation application <https://wwwapp.ibe.med.uni-muenchen.de/randoulette/> (web site developed by the Institut für medizinische Informationsverarbeitung, Biometrie und Epidemiologie Marchioninstr. 15, 81377 München, Germany).

A blocked randomisation with blocks of variable size, stratified by rupture status will be employed on randomisation into the trial to ensure balance concerning the aneurysm status (Recently ruptured (within 30 days) versus not recently ruptured) between the groups.

Treatment

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

Patient safety is paramount

If a patient is randomised to HydroSoft/HydroFrame but the operator prefers for strong clinical reasons not to deploy predominantly HydroSoft 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 HydroSoft 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 HydroSoft or bare platinum depending on randomisation result (see trial inclusion criteria)

Follow-up

Angiographic outcome:

An angiographic control will be performed at 18 months post-coiling using Digital subtraction angiography [DSA] or MRA. In addition, it is common practice in the participating centres to perform angiographic controls at 6 months post coiling. The 6 months angiographic exams will be collected when available, as they will be used for assessing the primary outcome in case the 18 months images are missing. Incidental follow-up exams showing early recanalisation will also be collected if they lead to a retreatment.

These controls should include an antero-posterior (AP) and a lateral view as well as the working projection. If possible a 3D DSA should be performed in order to better visualize any recanalisation.

A core lab composed of two independent investigators blinded to treatment, will confirm:

- Degree of occlusion at end of treatment and on check angiograms using standard criteria (Stroke 2001;32:1998-2004). DSA preferred to MRA but MRA acceptable for centres where the 18 months control is routinely performed with MRA. If this finds any major recanalisation it needs to be confirmed by DSA.
- Recurrences will be divided into minor and major (Stroke 2003;34:1398-1403).

Packing density will be analysed using the volume data determined by the core lab and details of coils used provided by participating centres. This will be more consistent & reproducible than individual centres undertaking the analysis.

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 (Cerebrovasc Dis 1994;4:314-324) assessment done in the centre by the team treating the patient.

Recurrence and composite primary outcome:

- Classification of recurrences is based on the core lab assessments.
- If the degree of occlusion at the end of treatment was assessed as Montreal class 1 or 2 (complete or residual neck), major recurrence within 18 months will be classified as present if the degree of occlusion is judged as Montreal class 3 (residual aneurysm) at any follow-up assessment within 18 months (6 months-, 18 months- or incidental follow-up leading to a retreatment within 18 months).
- If the degree of occlusion at the end of treatment was assessed as Montreal class 3 (residual aneurysm), major recurrence within 18 months will be classified as present if the core lab judges the state of aneurysm as worsened in comparison to the end of treatment assessment at any follow-up assessment within 18 months (6 months-, 18 months- or incidental follow-up leading to a retreatment within 18 months).
- The composite primary outcome will be classified as poor outcome (1) in case of major recurrence within 18 months (2) in case of patient death within 18 months of treatment (3) in case that procedural/disease related morbidity prevented the check angiography/MRI to take place. (3) is defined as the patient having a Modified Rankin Score of 3 or higher.

Adverse events (AE)

Accurate recording and reporting of adverse events are a fundamental requirement of participation in the trial.

Events requiring expedited reporting to the Principal Investigator:

- Suspected Unexpected Serious Adverse Reaction (SUSAR)
 - 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
- An increase in the rate of expected SAEs occurring in a centre

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

III. Value of HydroSoft Study to health policy and clinical practice

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.

The present study 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 HydroSoft 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 will seek Freiburg University Hospital Ethics Committee approval and is funded by MicroVention Inc.

If neurointerventionalists can show conclusively that HydroSoft 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 HydroSoft for the benefit of patients. Conversely if no substantial advantage for HydroSoft is demonstrated the trial would provide good evidence not to switch to widespread routine use of a more expensive product.

IV. Statistical Methods

Original sample size estimate and power of the study

Angiographic outcome- major recurrence at 18 months

The major recurrence rate using bare platinum is 15% based on review of the literature [2-5,17-19]. Assuming the rate is 5% for HydroSoft (based on unpublished data obtained with hydrocoils – HYPER registry in France)

- Sample size:

278 subjects for a trial with 80% power to detect a significant difference at the 5% level.

Significance level (alpha): 5%

Power (1-beta): 80%

Percentage of major recanalisation in control group: 15%

Percentage of major recanalisation in experimental group: 5%

- Sample size required per group: 139
- Total sample size required: 278

[Size Sample Calculator on www.thesealedenvelope.com]

References:

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However a proportion of subjects can be anticipated not to complete the 18 month angiographic endpoint due to lost to follow-up, refusal of further imaging etc. A reasonable estimate of this drop-out rate in the context of a prospective trial would be ~10%, **so a total of 306 subjects is required.**

Original assessment of feasibility of recruitment rate

306 subjects will be recruited in order to allow for a 10% drop-out rate after randomisation. This would be possible in 10 to 12 centres with coiling rates of at least 80 cases per year within a 12 month period.

Amended sample size estimate, power and recruitment rate (protocol version 12)

Recent research has shown that major recurrence rates at 18 months can be considerably higher than anticipated. In the HELPS trial (Lancet 2011; 377:1655-62), major recurrence rates of 10% (coated coils) vs 20% (bare platinum) were expected at the planning stage, 27% vs 36% were observed, and the composite angiographic and clinical endpoint at 18 months follow-up had 31% vs 38% adverse outcomes. To detect these differences with adequate power requires a higher sample size than the scenario which was originally planned for in the GREAT trial. Assuming that poor outcomes at 18 months occur at a rate of 10% (HydroSoft coils) vs 20% (bare platinum), 218 patients per group are needed to detect this difference between HydroSoft and bare platinum with a power of 80% using Fisher's exact test at two-sided significance level of 5% (STPLAN 4.3). When non-compliance and/or drop-out of patients after randomisation is assumed to be in the order of 10%, 486 patients have to be randomised to observe the desired amount of compliant patients. If the rates of recurrence, poor outcomes or drop-out are higher, even higher sample sizes are needed to obtain 80% power. Although other scenarios requiring higher sample sizes would also be scientifically relevant, the trial steering committee decided to increase the target sample size to 500 patients, the maximum number assessed to be feasible in a reasonable time window.

Statistical Analysis

The trial statistician at the Clinical Trials Unit, University Hospital Freiburg, will perform data analysis in collaboration with the Chief Investigator and Trial Steering Committee. All analyses will be by modified intention-to-treat, i.e. they will compare all patients with non-missing outcomes allocated to HydroSoft with all those with non-missing outcomes allocated to bare platinum. Reasons for missingness will be reported. Funding bodies of the study have no role in study design, data analysis, data interpretation or writing of the report. The TSC will nominate a writing committee.

Primary outcome

We will present the absolute differences along with a two-sided 95% confidence interval in the proportion of patients who have a poor outcome on the composite primary endpoint of major aneurysm recurrence on follow-up angiography and clinical outcome within 18 months, as described above. The analysis will be stratified by rupture status as documented at registration. Sensitivity analyses will explore the worst-case scenario where all missing outcomes in the HydroSoft arm are evaluated as poor and all those in the bare platinum arm are evaluated as favourable. Explorative secondary analyses of the primary outcome will be performed separately by rupture status.

Secondary outcomes

A variety of other secondary analyses (with due allowance for their exploratory nature) will be performed to compare: relative differences in the primary outcome, packing density, coil length deployed, degree of occlusion at end of treatment, follow-up angiography results at 6 months, clinical outcome at 6 and 18 months post-coiling as measured by the modified Rankin scale, re-bleed and re-treatment rates. The details are described in the statistical analysis plan.

Interim analysis

Two interim analyses with respect to safety (post-operative outcome after surgery) will be performed (see Data Monitoring Committee below). The details were fixed in the statistical analysis plan.

V. Data Management/Administration

Data collection

A nominated local coordinator will record the data on a day-to-day basis, onto a dedicated password-protected web-based database (<http://www.thegreatstudy.org/>). This database utilises 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).

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 or MRA images (DICOM images).
- Clinical course data
- Discharge/Death data
- Adverse events including complications

Data verification

Trial structures will be put in place in each center 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).

Pseudonymised data will be reviewed during the course of the trial by Freiburg Neuroradiology department and Clinical Trials Unit personnel (plausibility check).

Serious Adverse events (SAE)

Any serious adverse event must be reported immediately by point-to-point fax transmission to the trials office (PD Dr. C. Taschner, Fax: + 49 (0)761 2705195) along with an indication as to whether it was related to participation in the trial or not.

Accurate recording and reporting of adverse events are a fundamental requirement of participation in the trial.

Definition of serious adverse event (SAE):

- 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

Events requiring expedited reporting to the Principal Investigator:

- Any SAE, including
 - Suspected Unexpected Serious Adverse Reaction (SUSAR)
 - Serious & Unexpected event or outcome
 - Periprocedural death (within 30 days of procedure)
 - When requested, PIs should provide additional information on serious AE's resulting in death
- An increase in the rate of SAE's occurring in a centre

Trial Steering Committee

The Trial Steering Committee will meet every 4 to 6 months. 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.

Members

Prof. Martin Schumacher (Neurointerventionalist, University Hospital Freiburg)

Prof. Vera van Velthoven (Vascular Neurosurgeon, University Hospital Freiburg)

Prof. Matthias Reinhard (Vascular Neurologist, University Hospital Freiburg)

Chief Investigator

PD Dr. Christian Taschner (Neurointerventionalist, Freiburg)

Data Monitoring Committee

The independent Data Monitoring committee will be supplied, in strict confidentiality, with an interim analysis of trial data on post-operative 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 upon continuation, possible modifications or early stopping of the trial (details are fixed in a separate charter of the Data Monitoring Committee). Upon recommendation of the DMC after the first interim analysis, a second interim analysis with respect to post-operative outcomes will be performed as soon as feasible in all patients then randomised. The primary endpoint will not be evaluated in the interim analyses.

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.

Members

Prof. Daniel Rüfenacht, Neurointerventionalist, Zürich (centre not involved in the trial)

Prof. W. Hacke, Vascular Neurologist, Heidelberg (centre not involved in the trial)

Independent Statistician: Prof. M. Kieser, Statistician, Heidelberg (centre not involved in the trial)

Trial Executive Group

The trial Executive group are responsible for the day to day running of the trial at the coordinating centre in Freiburg. 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).

Members

Mrs. Bergmann (Study nurse, University Hospital Freiburg)

PD Dr. Christian Taschner (Neurointerventionalist, University Hospital Freiburg)

Trial Statistician

Dr. Erika Graf (Clinical Trials Unit, University Medical Center Freiburg)

Core lab

The Core lab is responsible for analyzing the angiographies/MRA, confirming or correcting the size of treated aneurysms (unblinded for assessment by local centre) and for determining degrees of occlusions of treated aneurysms (blinded to treatment allocation and to assessment of degree of occlusion at local center), after treatment and at 6 months, 18 months and incidental follow-ups. Packing density will be calculated based on the core lab assessment if differences from the sizes assessed by local centres arise.

Members

Two Neurointerventionalists from centers not involved in the trial:

- Prof Jens Fiehler (Hamburg, Germany)

- Prof Hubert Desal (Nantes, France).

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 advice on appropriate journals for submission.

Financial Support

Trial funding comes from MicroVention GmbH.

VI. Centre Requirements

- Participating centres must be neuroscience units treating significant numbers of patients with acute SAH.
- 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 5 coiling procedures using HydroSoft 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 should be DSA at 6 months and DSA or MRA at 18 months. Timing of follow-up control angiography should be such that it can correspond with the trial schedule for follow-up (6 and 18 months).
- A HydroSoft/HydroFrame procedure must involve the aneurysm substantially treated using HydroSoft/HydroFrame (see HydroSoft/HydroFrame guidance notes in section IX).
- Each centre must identify a local coordinator who will be responsible for the data collection at that centre. They will upload the data and angiogram images into the web-based database on a daily basis. 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 patient files 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.
- The trial principal investigator is responsible for obtaining German Multicentre Research Ethics Committee approval for the trial. Other centres must obtain ethical approval for the trial from their local research ethics committee [or IRB] and submit 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 lead local investigator will also be responsible for obtaining local institutional management approval for participating in the trial and for submitting a copy of the approval with the trial office.
- All treatments must be performed on modern DSA equipment with a 1024 matrix, roadmapping facility and 3D DSA. A biplane facility should be used.

VII. Local Principal Investigator Responsibilities

- Local PI should be qualified by education/training/experience (evidenced through CV & any other relevant documentation) e.g. documented training in consent or training in Good Clinical Practice for trials. PI will obtain local R&D/Management approval.
- 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.

VIII. Guidance notes on using HydroSoft and HydroFrame

- As per bare platinum, aim to coil to angiographic occlusion whenever possible.
- Aim to use longest length of HydroSoft/HydroFrame appropriate- just as one would do when using bare platinum.
- The HydroSoft/HydroFrame coil must be properly positioned in the aneurysm within 30 minutes. The reposition time is the time between introduction of the device into the microcatheter and the time of detachment. If the coil cannot be positioned and detached within this time, simultaneously remove the device and the microcatheter. Positioning the device outside of an aneurysm may diminish the reposition time.
- Within the HydroSoft/HydroFrame group, the HydroSoft and HydroFrame coils should constitute >50 % of the total length deployed. This threshold is for guidance only & not a rigid requirement. A planned subgroup analysis will be performed comparing HydroSoft/HydroFrame cases that meet this target with those that do not.
- In practice, many operators may want to deploy 1-2 bare platinum framing coils before deploying any HydroSoft/HydroFrame coils. However “filling” should be obtained with HydroSoft or HydroFrame. “Finishing” should preferentially be obtained with HydroSoft coils. Again this is not a rigid requirement. If the operator prefers for strong clinical reasons not to deploy HydroSoft or HydroFrame in this particular situation, they may proceed using bare platinum coils.
- Consider use of assist device for HydroSoft/HydroFrame 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 HydroSoft/HydroFrame and bare platinum. If you believe it does please report this onto the web-based database under comments section.

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X. 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 HydroSoft/HydroFrame coils (Hydrocoil Embolic System, MicroVention Inc.) offer the prospect of improved aneurysm packing and angiographic outcomes.

The present trial aims to compare a composite outcome of major aneurysm recurrence on follow-up angiography and clinical outcome within 18 months between patients allocated HydroSoft/HydroFrame versus patients allocated bare platinum coiling. Secondary outcomes to be compared between the two groups include: packing density; coil length deployed; clinical outcome at 6 and 18 months post-coiling (measured by the modified Rankin scale); re-bleed and re-treatment rates. 500 patients will be required to demonstrate a reduction in poor outcomes from 20% with bare platinum to 10% with HydroSoft/HydroFrame treatment. Angiographic analysis will be done by a core lab blinded to patient allocation.

XI. Appendices

List of centres enrolled in the trial

**Internal Project-No.
(Clinical Trials Unit, University Medical Center Freiburg):
ZKS000620**

German Randomised Endovascular Aneurysm Trial (GREAT)

Interim Analyses and Final Analysis

Statistical Analysis Plan (SAP)

Date: 20.09.2011

Version: 01

Function	Name	Date	Signature
Author Statistician	Dr. Rotraut Schoop	-----	Vor Finalisierung ausgeschieden
accepted and approved Trial Statistician	Dr. Erika Graf		
accepted and approved Chief Investigator	PD Dr. Christian Taschner		
accepted and approved Data Monitoring Committee Statistician	Prof. Dr. Meinhard Kieser		

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1. Scope of this document

This document describes the objectives of the first and second interim analysis as well as the final analysis. It defines the analysis populations and the statistical methods to be used. The contents of this document are based on the study protocol version 10, dated March 2010 of the German Randomized Endovascular Aneurysm Trial (GREAT), with modifications as indicated below.

The statistical analysis will be performed according to the SOPs of the Clinical Trials Unit, University Medical Center Freiburg (Studienzentrum).

2. Study design

This is a randomised controlled observer-blind bi-national multi-centre trial. Patients fulfilling the eligibility criteria are randomised to receiving either a novel endovascular treatment (deploy a mixture of bare platinum and HydroSoft coils) or the standard endovascular treatment (only use bare platinum coils). Randomisation is performed via an internet tool, results are communicated to the neurointerventionalist who coils the aneurysm. A core lab blinded to patient allocation will assess the degree of occlusion of the aneurysm using the 'Montreal' classification scheme (Stroke 2001; 32:1998-2004) at the end of treatment (directly post surgery) and at follow-up angiographies (6 months and 18 months). These assessment results will be used to derive the primary outcome (major aneurysm recurrence on follow-up angiographies within 18 months of treatment; clarification of study protocol) as described in section 6 of this document.

3. Study objectives and endpoints

The aim of this trial is to assess the efficacy and safety of the novel endovascular treatment (deploy a mixture of bare platinum and HydroSoft coils) as compared to the standard endovascular treatment (only use bare platinum coils).

3.1 Study objectives

3.1.1 Primary objective (Study protocol sections I and IV)

To compare the major aneurysm recurrence rate on follow-up angiographies within 18 months of treatment (clarification of study protocol) in patients allocated to the novel endovascular treatment (deploy a mixture of bare platinum and HydroSoft coils) versus patients allocated to the standard endovascular treatment (only use bare platinum coils).

3.1.2 Secondary objectives (Study protocol sections I and IV)

Secondary objectives are the comparison between the two groups (patients allocated to the novel endovascular treatment [deploy a mixture of bare platinum and HydroSoft coils] versus patients allocated to the standard endovascular treatment [only use bare platinum coils]) with respect to

- major aneurysm recurrence rate on follow-up angiographies within 6 months of treatment (modification to study protocol)
- recurrence on follow-up angiographies within 18 months of treatment (major/minor/none)
- packing density
- coil length deployed
- clinical outcome at 6 and 18 months post coiling
- re-bleed rate
- re-treatment rate
- degree of occlusion at end of treatment (addition to study protocol)

3.2 Study endpoints (efficacy)

The endpoints described in the study protocol in section I, II and IV (pp . 2, 4 and 7) are as follows.

3.2.1 Primary endpoint

Major aneurysm recurrence on follow-up angiographies within 18 months of treatment (yes/no) as assessed by a core lab blinded to patient allocation (see also section 6.4 for derivation and 6.5 for the handling of missing values) (clarification of study protocol). Digital subtraction angiography (DSA) is preferred to magnetic resonance angiography (MRA) but MRA is acceptable for centres where the 18 months control is routinely performed with MRA. If this finds any major recanalisation it needs to be confirmed by DSA.

3.2.2 Secondary endpoints

- Major aneurysm recurrence on follow-up angiographies within 6 months of treatment (yes/no) as assessed by a core lab blinded to patient allocation (see also section 6.4 for derivation) (modification of study protocol).
- Recurrences (major / minor / none) determined by the core lab according to Stroke (2003; 34:1398-1403) (modification of study protocol).
- packing density in per cent

- coil length deployed (see also section 6.4. for definition)
- clinical outcome at 6 months post coiling as measured by the modified Rankin scale (Cerebrovasc Dis 1994; 4:314-324).
- clinical outcome at 18 months post coiling as measured by the modified Rankin scale
- re-bleeding post coiling (yes/no) (see also section 6.4. for definition)
- re-treatment post coiling (yes/no)
- degree of occlusion at end of treatment using the 'Montreal' classification scheme (Stroke 2001; 32:1998-2004) as assessed by a core lab blinded to patient allocation (addition to study protocol)

4. Interim analyses

4.1 Objectives of interim analyses

As outlined in the study protocol (sections IV and V, pp. 7 and 9), two interim analyses regarding safety will be performed during the study.

4.2 Performance of interim analyses

4.2.1 Interim analyses to be performed

The evaluations described in section 9 (Safety evaluation) will be done. Additionally, the secondary endpoint "degree of occlusion at end of treatment" will be evaluated as described in section 8 (Efficacy evaluation), however, based on the safety analysis set (addition to study protocol). No other efficacy endpoints will be evaluated in the interim analyses (modification of study protocol, p. 9).

4.2.2 Time points of interim analyses and data included

The first interim analysis will be based on the data of the first 100 randomised patients. All data collected until and including 14 days after the date of coiling of the 100th patient will be included. If additional data is available at the time of the first interim analysis, it will be reported in listings. However, summary tables will be based on data restricted to the 14 days time window.

The second interim analysis will be based on the data of the first 200 randomised patients. All data collected until and including 14 days after the date of coiling of the 200th patient will be included. If additional data is available at the time of the second interim analysis, it will be reported in listings. However, summary tables will be based on data restricted to the 14 days time window.

4.2.3 Unblinding procedure

This SAP was written in complete blindness with respect to any aggregated outcome data grouped by treatment arm.

To enhance the integrity and credibility of the trial, procedures were implemented to ensure that before final end of the study, only members of the Data Monitoring Committee (DMC) and the trial statistician have access to evolving information from the clinical trial regarding comparative results of safety data separated by treatment arm.

The trial statistician will prepare the interim analysis reports, which will be confidentially communicated only to the DMC (study protocol section V), who then gives recommendations regarding continuation and/or modification of the trial to the trial executive group. Only if the DMC recommends that the trial executive group be unblinded and if the trial executive group consents to being unblinded will they receive information contained in the interim reports.

5. **Analysis sets**

5.1 Definition of Full Analysis Set

The full analysis set (FAS) consists of all randomised patients, to enable an intention to treat analysis. Subjects with missing primary and secondary endpoints are treated according to section 6.5 (data handling when missing values are present).

Subjects randomised without informed consent and in whom consent to have their data processed was not obtained after randomisation (if any) are excluded from the FAS. The number of these patients will be reported.

Descriptive analyses and listings according to the FAS are separated by randomised treatment.

5.2 Definition of Safety Analysis Set

The safety analysis set (SAF) includes all randomised patients who received any of the two competing treatments. Patients randomised but not operated are excluded. Subjects randomised without informed consent and in whom consent to have their data processed was not obtained after randomisation (if any) are excluded from the SAF. The number of these patients will be reported.

Descriptive analyses and listings according to the SAF are separated according to received treatment. If a patient received any HydroSoft coils, no matter what percentage, the received treatment will be HydroSoft.

6. Statistical methods

The statistical methods described in this SAP are in accordance with the analysis planned in the study protocol, except for modifications pointed out in this document.

6.1 Software

Statistical programming will be performed with the Statistical Analysis System (SAS) Version 9.

6.2 Descriptive statistics

Continuous data will be summarised by arithmetic mean, standard deviation (SD), minimum, 25% quantile, median, 75% quantile, maximum, and the number of complete and missing observations. If appropriate, continuous variables can also be presented in categories.

Categorical data will be summarised by the total number of patients in each category and the number of missing values. Relative frequencies are displayed by the total % (100 times the number of patients divided by the total number of patients).

6.3 Multiplicity

The primary analysis of the primary endpoint is done only once, therefore no adjustment for multiplicity is necessary.

6.4 Calculation of derived variables

Primary endpoint ‘Major aneurysm recurrence at follow up angiographies within 18 months of treatment’:

A core lab blinded to patient allocation will assess the degree of occlusion of the aneurysm using the ‘Montreal’ classification scheme with three classes (1: ‘Complete’, 2: ‘Residual Neck’, 3: ‘Residual Aneurysm’) at the end of treatment (directly post surgery) and at follow-up angiographies within 18 months of treatment. A ‘major recurrence within 18 months’ is defined if any of the following combinations take place in any follow-up assessment within 18 months of treatment:

End of treatment assessment	Follow-up assessment at 6 months OR follow-up assessment at 18 months OR incidental follow-up within 18 months of treatment
Class 1 (‘Complete’)	Class 3

Class 2 ('Residual Neck')	Class 3
Class 3 ('Residual Aneurysm')	Class 3 and core lab judges state of aneurysm as worsened in comparison to end of treatment assessment

All other combinations will be evaluated as 'no major recurrence within 18 months'.

Secondary endpoint 'Major aneurysm recurrence on follow up angiography at 6 months':

This endpoint will be derived in analogy to the primary endpoint. A 'major recurrence within 6 months' is defined if any of the following combinations take place at the 6 months follow-up assessment or an incidental follow-up within 6 months of treatment:

End of treatment assessment	Follow-up assessment at 6 months OR incidental follow-up within 6 months of treatment
Class 1 ('Complete')	Class 3
Class 2 ('Residual Neck')	Class 3
Class 3 ('Residual Aneurysm')	Class 3 and core lab judges state of aneurysm as worsened in comparison to end of treatment assessment

All other combinations will be evaluated as 'no major recurrence within 6 months'.

Secondary endpoint 'packing density':

The packing density is automatically calculated by the eCRF. This variable will be used for the analyses. There will be no separate derivation of packing density that uses volume assessments by the core lab (modification to study protocol).

Secondary endpoint 'coil length deployed':

The total coil length deployed will be derived by summing up all individual coil lengths used.

Secondary endpoint 're-bleed rate':

Re-bleeding is defined as the occurrence of the adverse events 'Re-bleeding' or 'Aneurysm Rupture' **after** treatment (i.e. time of onset of the adverse event is neither 'initial' nor 'intra-operative' in the electronic Case Report Form).

Eligibility criterion 'diameter of aneurysm':

The diameter of the aneurysm is defined as the maximum of the measurements size, height and width of the aneurysm.

6.5 Data handling

6.5.1 Missing values (study protocol section II)

Missing values in the **primary endpoint** 'major recurrence at follow-up angiographies within 18 months of treatment' are replaced by 'yes' (major recurrence, poor outcome) if one of the following situations is present

- a. patient died during treatment or the 18 months follow-up period
- b. procedural/disease related morbidity prevented the check angiography/MRA to take place. This is defined as the patient having a modified Rankin score at 18 months ≥ 3 (addition to study protocol).

If any further missing values are present in the amended data set in the primary endpoint, a conservative strategy favouring standard endovascular treatment will be applied: Patients allocated to standard endovascular treatment will be evaluated as 'no major recurrence', while patients randomised to the novel endovascular treatment (deploy a mixture of bare platinum and HydroSoft coils) will be evaluated as 'major recurrence' (addition to study protocol).

Partially missing dates are treated as follows: If the day is unknown, the value 15 will be inserted as day, and in the listings a footnote will indicate that the day was unknown. If the day and the month are unknown, the date 1st July will be inserted as day and month, and in the listings a footnote will indicate that the day and month were unknown. If the date is completely unknown, it will not be replaced.

Missing values in **other covariates** are not replaced and only observed cases are analysed.

6.5.2 Coding

All AE will be coded using MedDRA Version 14.0. If more than one symptom or diagnosis was reported in the description of the same AE, the AE was split by the medical reviewer.

6.5.3 Further details and conventions

Incorporation of time variables: The time-intervals used in the analysis are calculated on the basis of visit days. Concerning AE start and end date, the start date is included (date resolved – onset date +1).

7. Study patients

The patient data listings specified in this paragraph will be generated with respect to the population FAS in the final analysis.

Summarising tables will be given for both populations FAS and SAF in the final analysis. Exceptions to this rule are indicated in the respective sections below

An overview of generated patient data listings and summarising tables is given in the appendix (section 11).

7.1 Patient recruitment, disposition of patients

The disposition of patients is reported including

- date of first and last randomisation
- number of patients randomised by clinical centre and by treatment group
- number of patients in the analysis sets FAS/SAF, by treatment group and in total
- number of patients per treatment group who did not complete 6 months follow-up, grouped by reason
- number of patients per treatment group who did not complete 18 months follow-up, grouped by reason

A CONSORT flow chart (see appendix) is given for the time after randomisation. Since data is not available in the electronic Case Report Form (eCRF) for patients screened but not randomised, this information will be provided externally by the Trial Executive Group.

7.2 Protocol deviations (study protocol section II)

Violations of eligibility criteria, i.e. the inclusion and exclusion criteria, will be listed by patient.

Inclusion criteria as stated in the study protocol (section II, p.3) are:

- patient WFNS Grade 0-3 and aged 18-75 years
- in patients WFNS Grade 0+1 fully informed consent to endovascular coiling procedure will be obtained for participation in the study
- for patients WFNS Grade 2+3 the attending senior neuroradiologist and senior neurosurgeon will have to sign for inclusion in the study. This procedure seems justified as at this level inclusion in the study means randomization between two treatment arms with CE-labeled medical devices (bare platinum coils versus Hydrosoft coils). At a second stage consent will be obtained by the patient or the legal guardian to decide whether the patient data may be processed.
- aneurysm from 4 to 12 mm in diameter

Exclusion criteria as stated in the study protocol (section II, p.3.) are:

- patient requires treatment of multiple aneurysms at the same treatment episode

- aneurysm has previously been treated (by coiling or clipping)
- patient has previously been randomised into this trial.

Other eligibility criteria listed in the study protocol (concerning the neurointerventionist's judgement of the patient's suitability for the trial) are not included in the eCRF. Therefore they will not be evaluated. Informed consent will be evaluated on the basis of the summary question in the eCRF: 'Has appropriate consent been obtained'.

To summarise the frequency of different eligibility violations, the number and percentage of patients for whom the eligibility violation occurred will be given.

7.3 Data sets analysed

The affiliations of patients to the analysis sets FAS and SAF are listed. A patient data listing is provided for those patients excluded from the SAF, separated by treatment and grouped by reason of exclusion.

7.4 Description of patients' baseline characteristics

Demographic and other baseline characteristics will be listed by patient and summarised.

Patient data listings will be given for demographic variables (age, gender), and disease severity variables:

- WFNS grade at registration, Hunt & Hess scale, Fisher scale, rupture status as indicated at randomisation, rupture status as indicated in the eCRF
- size of target aneurysm (height, width, depth, diameter), neck size, dome to neck ratio
- aneurysm shape, location of aneurysm, treatment side, vessel identification code of target aneurysm

Summarising tables will be generated for FAS and SAF, by treatment group and total, for

- demographic variables (age, gender)
- past medical history (previous smoker, current smoker, illicit drugs/ETOH abuse, allergies, diabetes, hypertension, hypercholesterolemia, history of head trauma, history of ischemic stroke, COPD/emphysema, peripheral vascular disease, coronary artery disease, family history of SAH, other)
- routine medications before treatment (aspirin, clopidogrel (plavix), ticlopidine, statin, other)
- presence of symptoms for intracranial aneurysm diagnosis (headaches, N/V, seizure, subarachnoid, incidental, epilepsy, mass effect, other)

- pre-treatment imaging used (CT, MRI, angiography); results (evidence of dilated/ventricular enlargement, hemorrhage, tumor, infarcts, vasospasm, other)
- disease severity variables (see above)

7.5 Treatment and compliance with treatment (study protocol section VIII)

A patient data listing of medication during surgery will be produced for the safety analysis set (SAF).

The following summary information will be given (respective analysis sets in parentheses):

- descriptive analysis of procedure- and coil-related items of the eCRF, except medication during surgery (SAF, FAS)
- number of patients in standard treatment arm who are compliant, i.e. who were treated only with bare platinum coils (FAS)
- number of patients in standard treatment arm that are non-compliant, i.e. who were also treated with HydroSoft coils (FAS)
- number of patients in novel treatment arm who are compliant, i.e. who were treated with HydroSoft coils to an extent greater 40% in total length deployed (modification to study protocol) (FAS)
- number of patients in novel treatment arm who were non-compliant (FAS)

7.6 Compliance with planned examinations at 6 and 18 months follow-up

For each required examination the following information will be given:

- number of patients for whom the examination was due (PEdue)
- number of patients and percentage of PEdue for whom the examination was not performed
- descriptive statistics (arithmetic mean, standard deviation and quantiles as described in section 6.2) regarding the timing of follow-up (number of months post treatment) of the performed examination

8. Efficacy evaluation

The efficacy evaluation will be done according to the intention-to-treat (ITT) principle, i.e. based on the 'full analysis set' FAS. Patients are analysed as belonging to their randomised arm, regardless of whether they refused treatment or whether other protocol deviations are known. The analyses described in this section will exclusively be performed in the final analysis.

8.1 Analysis of primary endpoint (study protocol section IV)

Missing data will be treated as described in section 6.5: The FAS is checked for missing values in the primary endpoint and amended as described in section 6.5.

The **primary analysis** to compare the novel endovascular treatment (deploy a mixture of bare platinum and HydroSoft coils) versus the standard endovascular treatment (only use bare platinum coils) with regard to the primary endpoint 'major aneurysm recurrence at follow-up angiographies within 18 months of treatment' will be done in the FAS. The absolute risk difference in recurrence rates between treatment groups will be reported with a two-sided 95% confidence interval. The analysis will be stratified by the binary variable 'rupture status' as documented at registration (stratified analysis is a modification to study protocol).

Within strata, estimation of the absolute risk difference and its variance will be done in a standard manner, using a normal approximation for the confidence interval. The DerSimonian-Laird estimator for the average absolute risk difference and its confidence interval is then employed (Der Simonian and Laird, Controlled Clinical Trials 1986, 7:177-188), thus accounting for possible heterogeneity of the risk difference in the two strata.

The null hypothesis: "There is no difference with regard to the major aneurysm recurrence rate within 18 months of treatment between both treatments" is tested at the two-sided 5%-level against the alternative hypothesis: "There is a difference with regard to the major aneurysm recurrence rate within 18 months of treatment between both treatments". The null hypothesis is rejected if the two-sided 95% confidence interval of the absolute risk difference does not contain 0.

Secondary analyses of the primary endpoint are either descriptive or of exploratory nature and will handle missing values in the same way as above. Recurrence rates will be reported by randomised treatment group, and by both patient group (with/without recent rupture) and randomised treatment group. The absolute risk difference in recurrence rates between treatment groups will be reported with a 95% two-sided confidence interval per patient group (with/without recent rupture). In addition, the numbers of patients in whom missing outcomes were imputed will be reported for each category described in section 6.5.

8.2 Analyses of secondary endpoints (study protocol section IV)

Secondary analyses are of an exploratory nature, which needs to be taken into consideration when p-values and confidence intervals are involved.

Major aneurysm recurrence on follow-up angiography at 6 months (yes/no)

This will be analysed in the same way as the primary endpoint. This is not a confirmatory analysis, however.

Recurrences (major / minor / none)

This will be analysed in a descriptive manner, displaying relative frequencies per treatment group and by rupture status.

Packing density in per cent

The Wilcoxon-Mann-Whitney test (stratified for rupture status) will be used to test at the two-sided 5% level whether there is a difference in packing density regarding the treatment groups. Point estimates of mean and quantiles of packing density by treatment group and stratification variable will be supplied together with the p-value of the two-sided Wilcoxon-Mann-Whitney test indicating whether the difference in the point estimates is statistically significant. This is not a confirmatory analysis, however.

Coil length deployed

This will be analysed like packing density.

Clinical outcome at 6 months post coiling as measured by the modified Rankin scale (Cerebrovasc Dis 1994; 4:314-324).

This will be analysed like packing density.

Clinical outcome at 18 months post coiling as measured by the modified Rankin scale

This will be analysed like packing density.

Re-bleeding post coiling (yes/no)

This will be analysed in the same way as the primary analysis of the primary endpoint.

Re-treatment post coiling (yes/no)

This will be analysed in the same way as the primary analysis of the primary endpoint.

Degree of occlusion at the end of treatment as measured by the 'Montreal' classification scheme (addition to study protocol)

This will be analysed like packing density.

8.3 Further analyses

Further analyses that are deemed interesting will be decided upon at a later time point and will be of a purely exploratory nature.

9. Safety evaluation

The patient data listings and summarising tables specified in this paragraph will be generated for the population SAF and will be reported both in the interim reports and in the final report.

An overview of generated patient data listings and summarising tables is given in the appendix (section 11).

9.1 Adverse events

The first and second interim report will include adverse events only of the first 100/200 randomised patients. For these patients, summary tables will only include adverse events with onset date earlier than 14 days after the date of coiling. If additional data for these 100/200 patients is available at the time of the interim analyses, it will be included into the listings, but not into the summary tables. In the final report all adverse events will be reported. All analyses will additionally include information about the study treatment group and the received treatment.

Listings

AEs are listed by patient providing the following information:

Patient identifier, % length HydroSoft coils, age at randomisation, gender, description of adverse event as reported by investigator, MedDRA preferred term, MedDRA System Organ Class (SOC), date of coiling, start date of adverse event, timing of onset of the adverse event (initial treatment / intra-operative / Post-OP through discharge / Followup), end date of adverse event, severity (mild, moderate, severe), seriousness (serious/non-serious), causality assessment (related to: existing disease / procedure / device / non-procedure / other), treatment, outcome/patient status.

This listing will be produced for the following four AE sets:

- all adverse events with onset date from the date of coiling
- AEs with onset date before date of coiling.
- AEs with onset date from the date of coiling indicated as 'procedure related' or 'device related' in the eCRF
- AEs with onset date from the date of coiling indicated as 'device related' in the eCRF.

An additional listing will show the adverse event items entered into the procedure (surgery) part of the eCRF. This is duplicate information, since all of these items had also to be documented in the AE part of the eCRF. No details on seriousness etc. are available in the procedure part of the eCRF.

Summary tables

The adverse events are displayed in summary tables as described below. In the tables, the AEs with onset date before date of coiling will be excluded. They are only included in a separate listing as outlined above. If the day of AE start date is unknown, AEs will be included from the month of study start. If the day and the month of AE start date is unknown, AEs will be included from the year of study start.

A table of the Preferred Terms of all AEs will be presented including the number and percentage of patients in whom at least one event with the respective PT occurred, with 95% confidence interval for the percent difference between treatment groups. The PTs will be grouped by MedDRA System Organ Class (SOC) and sorted by frequency. Additionally, the number and percentage of patients in whom at least one event in the respective SOC occurred will be given.

For each treatment group, additional tables will show these numbers and percentages of patients in whom at least one event with the respective PT occurred divided into the defined severity categories (mild, moderate, severe) and grouped by relatedness of the event to treatment (related to procedure / related to device / related to neither procedure nor device).

Every table will be produced for the following three AE sets:

- all adverse events whether or not they are considered to be related to the procedure or device.
- AEs indicated as 'procedure related' or 'device related' in the eCRF
- AEs indicated as 'device related' in the eCRF.

9.2 Serious adverse events and deaths

Such AEs which were documented as SAEs will be reported in the same way as the AEs.

Additionally, all deaths during the study, including post treatment follow-up period, and deaths that resulted from a process that began during the study, are listed by patient.

10. List of abbreviations

AE	Adverse Event
DMC	Data Monitoring Committee
DSA	Digital subtraction angiography
eCRF	electronic Case Report Form
FAS	Full Analysis Set
GCP	Good Clinical Practice
ICH	International Conference on Harmonization
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging
PEdue	Number of patients for whom the examination is due
PT	MedDRA Preferred Term

SAE Serious Adverse Event
SAF Safety Analysis Set
SAP Statistical Analysis Plan
SOC MedDRA System Organ Class

.

11. Appendix

This appendix contains an overview of patient data listings and summarising tables that will be created as described in previous sections. To facilitate cross-referencing, the reference to the section where the respective listing/table is mentioned is given in parentheses, as well as the analysis set to be used in the process.

11.1 List of listings: Interim and final reports

Listing of all Adverse Events (AEs) with onset date from date of coiling (section 9.1 / SAF)

Listing of Adverse Events (AEs) with onset date before date of coiling (section 9.1 / SAF)

Listing of Adverse Events (AEs) with onset date from date of coiling indicated as 'procedure related' or 'device related' in the eCRF (section 9.1 / SAF)

Listing of Adverse Events (AEs) with onset date from date of coiling indicated as 'device related' in the eCRF (section 9.1 / SAF)

Listing showing the adverse event items entered into the procedure (surgery) part of the eCRF (section 9.1 / SAF).

Listing of all Serious Adverse Events (SAEs) with onset date from date of coiling (section 9.2 / SAF)

Listing of Serious Adverse Events (SAEs) with onset date from date of coiling indicated as 'procedure related' or 'device related' in the eCRF (section 9.2 / SAF)

Listing of Serious Adverse Events (SAEs) with onset date from date of coiling indicated as 'device related' in the eCRF (section 9.2 / SAF)

Listing of Serious Adverse Events (SAEs) with onset date from date of coiling with outcome death (section 9.2 / SAF)

11.2 List of listings: Only final report

Violations of eligibility criteria (section 7.2 / FAS)

Affiliation of patients to analysis sets FAS and SAF (section 7.3 / FAS, SAF)

Patients excluded from SAF and reasons (section 7.3 / FAS, SAF)

Baseline characteristics (section 7.4 / FAS)

Medication during surgery (section 7.5 / SAF)

Description of primary endpoint (section 8.1 / FAS)

Description of secondary endpoints (section 8.2 / FAS)

11.3 List of tables: Only interim report

Analysis of secondary endpoint 'degree of occlusion at end of treatment' on the safety analysis set (sections 4.2.1 and 8.2 / SAF)

11.4 List of tables: Interim and final reports

In the interim reports, tables will only include adverse events with onset date from date of coiling and earlier than 14 days after the date of coiling.

Incidence of AEs by System Organ Class (SOC) and Preferred Term (PT): All AEs (section 9.1 / SAF)

Incidence of AEs by System Organ Class (SOC), Preferred Term (PT) and intensity (mild, moderate, severe): All AEs (section 9.1 / SAF)

Incidence of AEs by System Organ Class (SOC) and Preferred Term (PT): Only AEs indicated as 'procedure-related' or 'device-related' (section 9.1 / SAF)

Incidence of AEs by System Organ Class (SOC) and Preferred Term (PT): Only AEs indicated as 'device-related' (section 9.1 / SAF)

Incidence of AEs by System Organ Class (SOC), Preferred Term (PT) and intensity (mild, moderate, severe): Only AEs indicated as 'procedure-related' or 'device-related' (section 9.1 / SAF)

Incidence of AEs by System Organ Class (SOC), Preferred Term (PT) and intensity (mild, moderate, severe): Only AEs indicated as 'device-related' (section 9.1 / SAF)

Incidence of SAEs by System Organ Class (SOC) and Preferred Term (PT): All SAEs (section 9.2 / SAF)

Incidence of SAEs by System Organ Class (SOC) and Preferred Term (PT): Only SAEs indicated as 'procedure-related' or 'device-related' (section 9.1 / SAF)

Incidence of SAEs by System Organ Class (SOC) and Preferred Term (PT): Only SAEs indicated as 'device-related' (section 9.1 / SAF)

11.5 List of tables: only final report

Disposition of patients: Date of first and last randomisation, frequency counts (section 7.1 / FAS, SAF)

Frequency of violations of eligibility criteria (section 7.2 / FAS, SAF)

Summary of baseline characteristics (section 7.4 / FAS, SAF)

Descriptive analysis of procedure- and coil-related items of the eCRF except medication during surgery (section 7.5/ FAS, SAF)

Compliance with treatment (section 7.5/ FAS)

Compliance with planned examinations at 6 and 18 months follow up (section 7.6/ FAS, SAF)

Analysis of primary endpoint (section 8.1 / FAS)

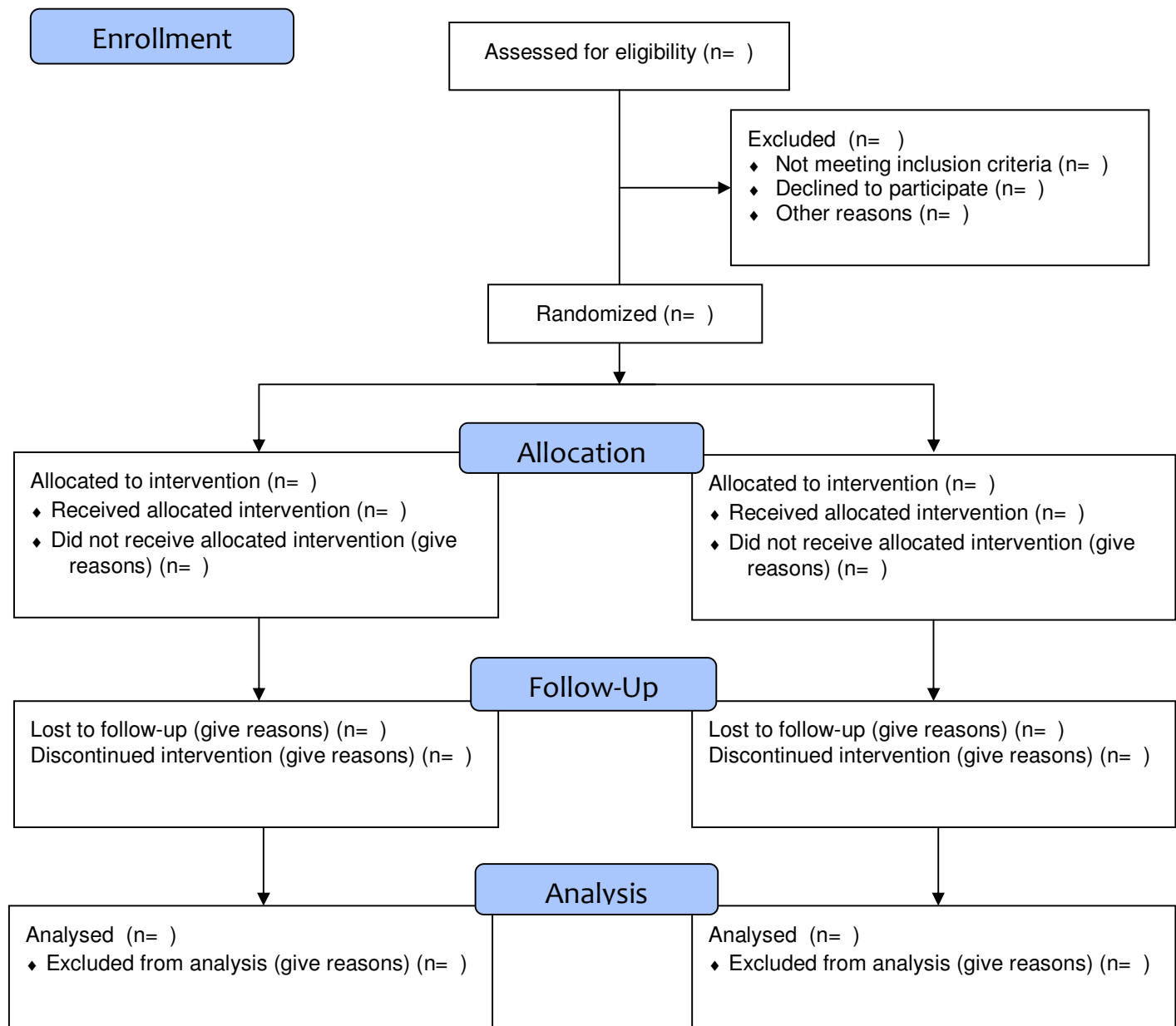
Analyses of secondary endpoints (section 8.2 / FAS)

Incidence of SAEs by System Organ Class (SOC) and Preferred Term (PT): Only SAEs with outcome death. (section 9.2 / SAF)

11.6 List of figures: Only final report

CONSORT 2010 Flow chart (section 7.1 / FAS)

11.7 CONSORT 2010 flow chart



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German Randomized Endovascular Aneurysm Trial (GREAT)

Interim Analyses and Final Analysis

**Amendment to the
Statistical Analysis Plan (SAP) dated 20.09.2011 (Version 01)**

Date: 07.06.2013

Final Version 01

Function	Name	Date	Signature
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1. Scope of this document

This document is an amendment to the Statistical Analysis Plan (date: 20.09.2011, Version 01) of the German Randomized Endovascular Aneurysm Trial (GREAT). It describes modifications of the planned statistical analysis which result from the amended protocol version 12, dated July 2012.

The Statistical Analysis Plan (date: 20.09.2011, Version 01) describes objectives of the first and second interim analysis as well as the final analysis. It defines the analysis populations and the statistical methods to be used according to the study protocol version 10, dated March 2010, and includes clarifications and planned modifications to that version of the study protocol. Most of these modifications have been implemented in the amended protocol version 12, dated July 2012.

2. Modifications to the Statistical Analysis Plan

2.1 Modification of the term used for the primary outcome

Term used for primary outcome (Statistical Analysis Plan (date: 20.09.2011, Version 01):

Major aneurysm recurrence on follow-up angiographies within 18 months of treatment

Amendment:

Composite outcome of major aneurysm recurrence on follow-up angiography and clinical outcome within 18 months

Reason for amendment:

Clarification – use of clinical outcome (modified Rankin Score) in the absence of angiographies was planned from the beginning.

2.2 Modification of the number of patients for second interim report

Number of patients for second interim report according to Statistical Analysis Plan (date: 20.09.2011, Version 01):

The first 200 randomised patients

Amendment:

The first 300 patients

Reason for amendment:

In response to the first interim report, the Data Monitoring Committee asked for the second report to be performed on the patients randomised at the time of the their review of the first report (then 273). In the amended protocol version 12, dated July 2012, the target sample size was changed from 306 to 500 randomised patients. Therefore, the study team decided to perform the second interim analysis with the first 300 randomised patients. In order to present a report based on improved data quality, it was decided to perform the analysis after resolution of data queries resulting from a newly implemented data cleaning process based programmed data plausibility checks and reinforced clinical monitoring.

2.3 Modification of the efficacy evaluation

Efficacy evaluation according to Statistical Analysis Plan (date: 20.09.2011, Version 01) – A):

The efficacy evaluation will be done according to the intention-to-treat (ITT) principle, i.e. based on the 'full analysis set' FAS. Patients are analysed as belonging to their randomised arm, regardless of whether they refused treatment or whether other protocol deviations are known.

Amendment:

All efficacy analyses will be by modified intention-to-treat, i.e. they will compare all patients with non-missing outcomes allocated to HydroSoft with all those with non-missing outcomes allocated to bare platinum.

Efficacy evaluation according to Statistical Analysis Plan (date: 20.09.2011, Version 01) – B):

Missing values in the primary endpoint 'major recurrence at follow-up angiographies within 18 months of treatment' are replaced by 'yes' (major recurrence, poor outcome) if one of the following situations is present

- a. patient died during treatment or the 18 months follow-up period
- b. procedural/disease related morbidity prevented the check angiography/MRA to take place. This is defined as the patient having a modified Rankin score at 18 months ≥ 3 (addition to study protocol).

Amendment:

This section remains unchanged except for the fact that the term used for the primary outcome has been modified to clearly reflect the mixture of imaging and clinical data used in the definition of the primary outcome.

Efficacy evaluation according to Statistical Analysis Plan (date: 20.09.2011, Version 01) – C):

If any further missing values are present in the amended data set in the primary endpoint, a conservative strategy favouring standard endovascular treatment will be applied: Patients allocated to standard endovascular treatment will be evaluated as 'no major recurrence', while patients randomised to the novel endovascular treatment (deploy a mixture of bare platinum and HydroSoft coils) will be evaluated as 'major recurrence' (addition to study protocol).

Amendment:

Sensitivity analyses of the primary outcome will explore the worst-case scenario where all missing outcomes in the HydroSoft arm are evaluated as poor and all those in the bare platinum arm are evaluated as favourable.

Reason for amendment:

The worst-case analysis originally planned was deemed too conservative. Therefore it was amended to the modified intention-to-treat strategy in protocol version 12, dated July 2012.

2.4 Safety evaluation: Clarification

Safety evaluation according to Statistical Analysis Plan (date: 20.09.2011, Version 01)

The safety evaluation will be performed in the Safety Analysis Set, as described in the Statistical Analysis Plan. This is a clarification of the following phrase in the amended protocol version 12, dated July 2012: "All analyses will be by modified intention-to-treat, i.e. they will compare all patients with non-missing outcomes allocated to HydroSoft with all those with non-missing outcomes allocated to bare platinum." - which was meant to refer to the efficacy evaluation.

10. Additional changes to statistical analysis

1. Originally, the procedure planned to reflect randomization stratified by rupture status in the estimation of the overall absolute difference of a proportion of outcome events between the two arms was the DerSimonian-Laird estimator (Statistical Analysis Plan, section 8.1). This was erroneous since the DerSimonian-Laird estimator does not generate overall absolute differences weighted by the proportion of ruptured and unruptured aneurysms from the within-stratum, between-arm differences of proportions. Therefore, the DerSimonian-Laird estimator was replaced by the Newcombe estimator.

2. Use of 6 months instead of 18 months results when angiographic results at 18 months were not available was prespecified in the protocol but not mentioned in the SAP or Amendment to the SAP. The decision to do so was motivated by the study procedures and methods of the HELPS trial (White PM et al. Hydrogel-coated coils versus bare platinum coils for the endovascular treatment of intracranial aneurysms (HELPS): a randomised controlled trial. *Lancet*. 2011;377:1655–1662).

3. Adverse events and serious adverse events were split into those with onset within and those with onset after 14 days from coiling in order to separate post-procedural from long-term safety data. Restriction to events with onset within 14 days had been planned and performed during the two interim analyses (Statistical Analysis Plan, section 4).

None of these changes were motivated by inspection of outcome data.