Does Embolization with Larger coils lead to better Treatment of Aneurysms trial

An Investigator-initiated Randomized Trial Comparing Treatment with 15-caliber Platinum Coils to Standard 10-caliber Platinum Coils

Version 1.8 | June 23, 2015
ClinicalTrials.gov Identifier:
NCT01943591

Principal Investigators
Jean Raymond, MD

Sponsor:
Centre hospitalier de l'Université de Montréal
Hôpital Notre-Dame

Financial support:
DePuy Synthes – Codman Neuro and Johnson & Johnson Medical Companies

EXECUTIVE SUMMARY

Endovascular treatment with platinum coils is safe and effective in preventing rebleeding of intracranial aneurysms. Unfortunately, endovascular treatment has been associated with incomplete occlusion at initial treatment (remnant) or at follow-up (recurrence). This in some studies has been as high as 33%. While many such aneurysm remnants or recurrences exhibit benign behavior, many require retreatment to prevent future hemorrhage.

A recent randomized controlled trial of aneurysm coiling revealed that aneurysms between 2 and 9.9 mm diameter were more likely to have an improved angiographic and composite clinical outcome when treated with hydrogel-coated coils, an improvement inferred to result from higher packing density afforded by hydrogel expansion.[1] The use of hydrogel coils is associated with technical difficulties related to expansion and limited time for deployment. We theorize that similar results could be achieved by using more voluminous bare platinum coils, leading to improved packing density compared to smaller caliber coils, and thus result in lower incidence of remnants or residuals. Aneurysms varying in size from 4 to 12 mm are most prevalent, and it is in these smaller aneurysms that both smaller caliber or larger caliber coils can be used. The relationship between packing densities and clinical endpoints having never been shown in a robust fashion in these small aneurysms, we therefore propose a randomized clinical trial opposing coiling with soft 15-caliber coils to 10-caliber bare platinum coils in aneurysms varying in size from 4 to 12 mm.

To test the hypothesis that 15-caliber coiling systems are superior to standard 10-caliber coils in achieving better composite outcomes, we propose the DELTA trial: Does Embolization with Larger coils lead to better Treatment of Aneurysms trial, a randomized controlled blinded trial with 2 subgroups of 282 patients each, 564 total:

- Subgroup 1: Coiled with a maximum proportion of 15-caliber platinum coils (including Deltamaxx) as conditions allow
- Subgroup 2: Coiled with 10-caliber platinum coils.

The pivotal trial will be preceded by a pilot phase of approximately 165 patients designed to verify the feasibility of the coiling strategy, compliance to treatment group allocation, the safety of an 15-caliber platinum coil embolization strategy, recruitment rates, and the capacity to improve packing density (to 28%) with a standardized effect size (E/S) of 0.6, with a power of 95% and a two-sided alpha error of 0.05 (assuming the packing density of the control group will be approximately 25%).

PROTOCOL SUMMARY

Title:	**DELTA**: Does Embolization with Larger coils lead to better Treatment of Aneurysms trial
Patients:	**Inclusion Criteria:** ▪ At least one ruptured or unruptured aneurysms with a dimension ≥4mm (longest axis) and ≤12 mm ▪ For ruptured lesions, patients should be in WFNS grade ≤ III. ▪ The anatomy of the lesion is such that endovascular treatment is possible with caliber 0.015 (including Deltamaxx) or caliber 0.010 platinum types of coils (not necessarily certain or probable) ▪ Patient is 18 or older ▪ Life expectancy is more than 2 years **Exclusion Criteria:** ▪ Patients with planned treatment of an associated cerebral arteriovenous malformations ▪ When parent vessel occlusion, without simultaneous endosaccular coiling of the aneurysm, is the primary intent of the procedure ▪ Any absolute contraindication to endovascular treatment, angiography, or anaesthesia such as severe allergies to contrast or medications
Number of Sites (Pilot phase):	12-14 centres
Study Duration (Pilot Phase):	24 months accrual + 12 months follow-up
Subject Participation Duration:	12 months
Description of Intervention:	Comparison of endovascular aneurysm coiling with 15-caliber coils (including Deltamaxx coils) vs. coiling with other commercially available 10-caliber platinum coils.

Hypotheses:

Primary Hypothesis of the pivotal phase:

The use of Deltamaxx, within a strategy of using larger caliber coils for small aneurysms (4-12mm) will lead to a lesser number of incomplete occlusions at 12 months, as compared with smaller caliber 0.010 coils. The primary endpoint will be mainly composed of major angiographic recurrences or the presence of a 'residual aneurysm' as judged by the core lab at 12 month.

Secondary Endpoints:

Secondary endpoints will include:

- Major recurrence on 12-month follow-up angiography
- Morbidity and mortality that precludes angiographic follow-up
- Initial technical success of the coiling strategy
- Packing density
- Number of coils implanted.
- Time of fluoroscopic exposure
- Immediate angiographic results
- Peri-procedural serious adverse events
- mRS at 1 year follow-up

Description of Study Design:

Allocation:	Randomized
Endpoint Classification:	Safety/Efficacy Study
Intervention Model:	Parallel Assignment
Masking:	Single-blind
Primary Purpose:	Treatment

Estimated Time to Complete (Pilot phase) 36 months

Key Roles

Individuals:

	Principal Investigators:	Jean Raymond, MD
	Core Lab:	TBD
Sponsor:	CHUM (Centre Hospitalier de l'Université de Montréal)	
Financial support:	DELTA is an investigator-initiated study that is supported through research funding from DePuy Synthes – Codman Neuro and Johnson & Johnson Medical Companies	

SCHEMATIC OF STUDY DESIGN:

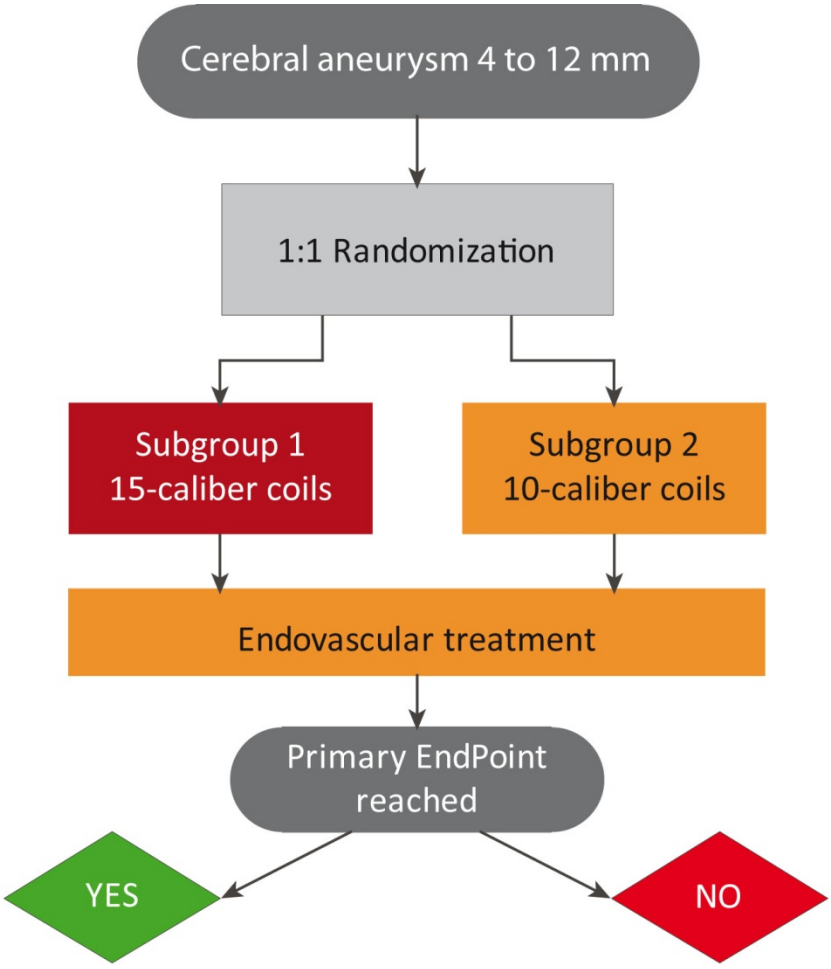

TABLE OF CONTENTS

EXECUTIVE SUMMARY II

PROTOCOL SUMMARY III

OBJECTIVES: IV
KEY ROLES V

SCHEMATIC OF STUDY DESIGN: VI

SECTION 1: BACKGROUND 9

ENDOVASCULAR TREATMENT 9
PACKING DENSITY 9
MISSION STATEMENT 10

SECTION 2: THE PROPOSED TRIAL 11

DESIGN 11
HYPOTHESES 11
INTERVENTIONS 11
SELECTION CRITERIA: INCLUSION AND EXCLUSION CRITERIA 12
INCLUSION CRITERIA: 12
EXCLUSION CRITERIA: 12
TECHNICAL FREEDOM 12
RANDOMIZATION 13
TYPE, FREQUENCY AND DURATION OF FOLLOW-UP 13
TABLE 1: SCHEDULE OF EVALUATION 14
OUTCOMES 14
PRIMARY OUTCOME 14
PRIMARY ENDPOINT: 14
SECONDARY OUTCOME: 15
INITIAL TECHNICAL SUCCESS 15
MORTALITY 16
ADVERSE EVENTS 16
MORBIDITY 16
SAMPLE SIZE 16
RECRUITMENT RATE AND CENTRES 17
DURATION OF THE TRIAL 17
PLANNED ANALYSES 17
PILOT PHASE 18
PROTECTION AGAINST BIAS 18
PUBLICATION OF RESEARCH FINDINGS 18
REGULATORY CONSIDERATIONS 18
TRIAL MANAGEMENT AND COORDINATION 19

SECTION 3: TRIAL MANAGEMENT 20

INVESTIGATORS 20
STEERING COMMITTEE (SC) 20
DELTA STEERING COMMITTEE TERMS OF REFERENCE 20
DATA SAFETY AND MONITORING COMMITTEE (DSMC) 20
DATA SAFETY AND MONITORING COMMITTEE TERMS OF REFERENCE 21
IMAGING CENTER (CORE LAB) 21
OTHER COMMITTEES TO BE DETERMINED BY DECISION OF STEERING COMMITTEE 21
DAY TO DAY MANAGEMENT 21

SECTION 4: GUIDELINES 22

DELTA TREATMENT PLAN 22
CENTRE REQUIREMENTS 23
APPENDIX 1: REFERRAL CENTER DETAILS 24
APPENDIX 2: INVESTIGATOR DECLARATION AND AGREEMENT 25
APPENDIX 3: ADJUDICATION OF OUTCOMES 27

REFERENCES 30

SECTION 1: BACKGROUND

Endovascular treatment

Endovascular treatment with platinum coils is safe and effective in preventing rebleeding of intracranial aneurysms in the acute phase after subarachnoid haemorrhage; it is now the preferred method of treatment in many centers, because it can improve the outcome of patients as compared to surgical clipping.[2-6] While treatment of ruptured aneurysms is imperative to prevent rebleeding, the management of unruptured aneurysms remains controversial, because of a low annual risk of haemorrhage and a high surgical risk.[7-8] An effective endovascular treatment could offer a less morbid alternative to surgical treatment of unruptured aneurysms and thus prevent the morbidity associated with SAH.[7, 9-11] Unfortunately, endovascular treatment of aneurysms with coils has been associated with incomplete occlusion at initial treatment (remnant) or at follow-up (recurrence). This in some studies has been as high as 20%-33%. While many such aneurysm remnants or recurrences exhibit benign behavior, many require retreatment to prevent future hemorrhage. This has been rare so far (in less than 1% of patients).[12-19] A multicenter registry has reported up to 15% retreatment rates 2 years after coiling of ruptured aneurysms, but a yearly re-rupture rate of only 0.20% after the first year. [2, 20]

Packing Density

Previous attempts at decreasing recurrences include second-generation coils with surface modification or bioactive moiety.[21-24] The HELPS trial revealed that aneurysms between 2 and 9.9 mm diameter were more likely to have an improved angiographic and composite clinical outcome when treated with hydrogel-coated coils, an improvement inferred to result from the higher packing density afforded by hydrogel expansion.[1] New, bare platinum 15-caliber coil systems[25] are now available which may achieve consistent high packing density compared to previously available coils. Aneurysm packing density[26], an oft argued surrogate marker for coiling efficacy[26-32], has not been proven however to equate to angiographic or clinical long-term efficacy, although the data, at least for small aneurysms with satisfactory packing densities, is compelling.[33-37] Given the lack of scientific evidence that these new voluminous coils improve the clinical outcome of patients with small aneurysms (≤12mm) treated endovascularly, we propose a randomized trial to address this question.

Mission Statement

The DELTA trial is a large multicentre prospective randomized trial of endovascular management of aneurysms comparing voluminous coils to standard, commercially available platinum coils. It aims to recruit 564 patients with ruptured or unruptured small and medium sized aneurysms (≥4 and ≤12 mm). The clinical impact will be of major significance if substantial differences are found in the outcome according to a randomized procedure.

SECTION 2: THE PROPOSED TRIAL

Design

Delta is an investigator-initiated multicenter randomized, single-blind controlled trial comparing 15-caliber coils to standard 10-caliber coils in patients harboring small to medium size aneurysms. All patients with aneurysm ≥ 4 and ≤ 12 mm or with a recurrence will be eligible. Adjudication of angiographic results will be done by a committee blinded to treatment allocation in an independent core laboratory. The study will be conducted in 10-25 centers. The study aims to enroll 564 patients equally divided between the two groups (15-caliber platinum coils vs. standard 10-caliber platinum coils), to obtain statistical significance in the primary endpoint, the occurrence of a recurrence at follow-up. The forecast duration of the study will be 6 years, the first 4 years for patient recruitment and accrual plus 12 months of follow-up.
The pivotal trial will be preceded by a pilot phase of approximately 165 patients, over approximately 3 years, designed to confirm the feasibility of the coiling strategy, its safety, the enrolment rates, as well as to compare packing densities between the 2 groups.

Hypotheses

The use of 15-caliber platinum coils will lead to a decrease in the number of patients that reach the primary endpoint from 33 to 20% at 12 ± 2 months.

The pilot phase has been powered to test the hypothesis that the use of 15-caliber platinum coils will lead to an increased packing density as compared to caliber 10 coils from an expected mean of 25% to 28% (95% power; alpha 0.05).

Interventions

The goal of the study is to assess if the use of voluminous 15-caliber coils could reduce the number of patients reaching the primary endpoint with little if any additional risk compared to standard caliber 10 commercially available platinum coils. Thus the interventions will consist of either:

A/ Standard, commercially available 10-caliber coil embolization of aneurysms, using standard or adjunct techniques.

Or

B/ The use of the highest safely achievable proportion of 15-caliber coils, including Deltamaxx, the operator being unrestricted in the use of the coil he/she believes is appropriate at any time during the procedure using standard or adjunct techniques.

The aim of treatment is the complete angiographic exclusion of the aneurysm, or, as complete an exclusion from circulation as is feasible while minimizing risks of the procedure as per practice standards.

The interventionist and therefore the clinical and interventional research team cannot be blinded to the nature of the coils used. However, the imaging center (core lab) that will determine the success of the procedure will be blinded during its evaluation.
Although the mechanism evoked to support the potential benefit of 15-caliber coils is an increase in 'packing density', the trial does not require the use of a minimal number or length of coils of either nature, nor to reach a certain packing density. To attempt to introduce more coils, even after angiographic exclusion of the lesion, to increase packing density, could be seen as taking unjustified additional risks. The use of balloon assistance for coil deployment or stents deployed after coiling is authorized but will be recorded. Parent vessel occlusion concomitant to endosaccular coiling can be performed as long as it was not the procedure's primary intent.

Selection criteria

Inclusion criteria

- At least one ruptured or unruptured aneurysms with a dimension ≥4 mm and ≤12 mm (longest axis)
- For ruptured lesions, patients should be in WFNS grade < IV.
- The anatomy of the lesion is such that endovascular treatment is possible with both types of coils (not necessarily certain or probable)
- Patient is 18 or older
- Life expectancy is more than 2 years

Exclusion criteria

- Patients with planned treatment of an associated cerebral arteriovenous malformations
- When parent vessel occlusion, without simultaneous endosaccular coiling of the aneurysm, is the primary intent of the procedure
- Any absolute contraindication to endovascular treatment, angiography, or anaesthesia such as severe allergies to contrast or medications

Treatments

Patients allocated to caliber-15 coiling will preferably receive caliber-15 coils (perhaps including a caliber-15 framing coil (or not), as many Deltamaxx filling coils as safely achievable, but the procedure can be completed with caliber-10 or smaller finishing coils, in order to achieve as complete an occlusion as possible, keeping the procedure as safe as possible.

Patients allocated to caliber-10 coiling will preferably receive caliber-10 coils (perhaps including a caliber-10 framing coil, caliber-10 filling and finishing coils), once more to achieve as complete an occlusion as possible, keeping the procedure as safe as possible.

Both groups will receive platinum coils only. Balloon-assisted or stent-assisted coil embolization is permitted, but should be noted in the procedure CRF.

Technical freedom

The goal of the endovascular procedure is (as usual) to realize the most complete exclusion of the lesion that is judged to be possible, while keeping risks as small as possible, using the randomization algorithm's assigned embolization material. At any time during the procedure the interventionist is unrestricted in the use any device, technique or drug judged important to the safety and success of the endovascular procedure.

If a patient is randomized to 15-caliber coils but the operator prefers, for strong clinical reasons not initially thought of at the time of recruitment, not to deploy predominantly voluminous coils in this particular case, he should proceed using appropriate coils in the best interests of the patient. The converse is also true. In any such case, the operator details reasons on the endovascular treatment case report form. Analysis will be on an intention to treat and per-protocol basis.

Randomization

DELTA is designed with 1:1 randomization.

A minimization algorithm will be used whether the aneurysm is ruptured or unruptured and previously treated or not (major recurrence).

Type, frequency and duration of follow-up

For the analysis of the safety data, clinical examinations will be recorded at end of procedure, at discharge, and at the time of follow-up imaging (to 12 ± 2months). Follow-up CT-scan or MRI will be performed at 24 hrs or before discharge to detect silent periprocedural events, as standardly performed in each institution. In certain cases, when patients are unable or unwilling to come to the hospital for follow-up visits information may be collected via telephone. Also, Rankin scores may be obtained through phone interviews (using a standardized questionnaire) by the study coordinator or the Principal Investigator.

Adverse events will be recorded immediately after the procedure and during the 12-month follow-up period. First, the number and nature of adverse events for each patient is recorded. Then the relation to the aneurysm itself, to the endovascular coil embolization (not possibly or probably related) will be recorded. Clinical assessments will include the modified Rankin scale (mRS) at 6-12 months. Follow-up imaging studies will be performed at 12 (±2) months by either catheter angiography or non-invasive vascular imaging according to the preference of the participating center. The commonly recommended 6 month follow-up angiogram may not be sufficient to detect most recurrences.[38]

Table 1: Schedule of Evaluation

Evaluation	Pre-entry	Entry	Treatment	Discharge	6 months	12 ± 2 months
Informed consent		x				
Documentation of Disease/disorder	x					
Medical/treatment history	x					
Clinical assessment	x		x	x	x	x
Neurological exam	x			x		x
Vascular imaging	x		x			x
Brain imaging	x			x*		
WFNS (for HSA patient)		x				
mRS		x		x	x	x

** According to standard of care of participating centre*

Outcomes

Primary outcome

The primary outcome determines the size of the population to be studied to reach statistical significance. Although the clinical significance of angiographic recurrences remains to be determined, the primary outcome cannot be limited to hemorrhagic events, estimated to be quite rare, in the range of 0.1-1% per year. New coils or embolic agents are meant to improve long-term results, including a reduction in the recurrence rate.

Primary endpoint:

The primary efficacy endpoint will mainly consist in the occurrence of a major recurrence or a residual aneurysm at the time of follow-up angiography at 12 (±2) months.

An independent committee will adjudicate, for each patient, whether he or she has reached the endpoint. In the absence of follow-up imaging, the committee will adjudicate other potential cases of treatment failures (expected to be rare) such as:

- Hemorrhage during the follow-up period
- Retreatment of the same lesion by endovascular or surgical means during the follow-up period
- Occurrence or progression of a mass effect in relation to the treated aneurysm
- Morbidity and mortality that precludes follow-up

The pilot phase of the study was powered to detect a difference of 3% in mean packing density between the 2 groups.

Secondary outcomes:

Secondary outcomes include other indices of immediate treatment success as well as standard safety outcomes:

- Procedure-related serious adverse events
- Initial technical success of the coiling strategy
- Use of adjunct devices.
- Number and total length of coils implanted for each type
- Packing density (core-lab measured)
- Time of fluoroscopic exposure
- Immediate angiograhic results according to the Montreal scale

- mRS at 1 year follow-up
- Major recurrence on follow-up angiography
- Morbidity and mortality that precludes angiographic follow-up

Concerning radiographic evidence of recurrence, the angiographers at each participating center will ensure that best projections showing residual necks at the time of treatment are repeated during follow-up evaluations. For the purpose of this study, only major recurrences or residual aneurysms that are of a size that would ideally necessitate retreatment, as judged by the core lab, will be counted. Angiographic results will also be scored according to a previously published classification system[12] as complete obliteration, residual neck or residual aneurysm and groups will be compared initially and at follow-up at 12 ± 2months.

Recurrences will be recorded (present or absent) as they are discovered, at the routine follow-up assessments as clinical symptoms appear any time during the 12 months that follow the intervention. The independent core lab will determine the presence of angiographic recurrences.

Initial technical success

For the patients allocated to 15-caliber coils, the interventionists will have a choice to use 15-caliber coils only and/or other coils during the embolization procedure, in order to guaranty the same safety and immediate efficacy as the standard procedure. A study protocol deviation will be considered to have occurred if < 30% of coil length is 15-caliber coils. The initial technical success or failure of the procedure will be determined after treatment by the adjudication committee by reviewing core lab independent result of procedural angiogram and coils uses as recorded in the data collection sheets.

Mortality

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

Adverse events

Adverse events will be recorded immediately after the procedure and during the 12-month follow-up period. Serious adverse events (SAEs), those that are life threatening, leading to hospitalizations or prolonged hospitalizations, as well as unexpected events will all be reported within 48 hours to the data coordination centre that will transmit the information to the DSMC. The number and severity of all reported adverse events will be recorded for each patient and for each treatment group.

Morbidity

The number and the severity of morbid events per patient will be recorded for each patient. The modified Rankin scale will be measured at follow-up appointments. This scale classifies the patients according to their neurological outcome.[39]

Sample size

A decrease in the recurrence rate from 33 to 20% would be clinically significant. Based on Fisher's Exact test, a total sample size of 512 patients would allow detecting such a difference with a power of 90% and an alpha error of 0.05 (Table 2). A sample size of 564 patients for DELTA is sufficient to detect a decrease in the recurrence rate from 33 to 20% with an alpha error of 5% and a beta error of 10%, allowing 10% of losses at determination of the primary endpoint

Table 2: Log Rank Survival Power Analysis – Simple – Primary Hypothesis

Two Independent Proportions (Null Case) Power Analysis
Numeric Results of Tests Based on the Difference: P1 - P2
H0: P1-P2=0. H1: P1-P2=D1<>0. Test Statistic: Fisher's Exact test

	Sample Size Grp 1	Sample Size Grp 2	Prop|H1 Grp 1 or Trtmnt	Prop Grp 2 or Control	Diff if H0	Diff if H1	Target	Actual	
Power	N1	N2	P1	P2	D0	D1	Alpha	Alpha	Beta
0.9009	256	256	0.2000	0.3300	0.0000	-0.1300	0.0500		0,0991

Summary Statements
Group sample sizes of 256 in group one and 256 in group two achieve 90% power to detect a difference between the group proportions of -0.1300. The proportion in group one (the treatment group) is assumed to be 0.3300 under the null hypothesis and 0.2000 under the alternative hypothesis. The proportion in group two (the control group) is 0.3300. The test statistic used is the two-sided Fisher's Exact test. The significance level of the test was targeted at 0.0500.

Recruitment rate and centres

The targeted lesions are the most frequent lesions treated in endovascular centres; thus we expect at least 10-20 patients per year per center. We need to recruit 20-25 centers that will recruit 10-20 patients/year for 2-3 years to reach the necessary sample size. Centers will be experienced in endovascular treatment of aneurysms (at least 100 aneurysms will have been treated previously).

Duration of the trial

We plan a 3 to 4 year recruitment phase, followed by a follow-up period of 12 months for all patients. If we add a 6-month catch-up period the trial should be completed within 5-6 years, including data analysis.

Planned analyses

Descriptive statistics will be done on demographic variables and pre-operative and peri-operative data to compare the two groups at baseline. Means, standard deviations and range will be presented for quantitative variables and frequency tables for categorical variables. Those statistics will be broken down by treatment arm. Comparability of the groups will be assessed through independent ANOVAs (quantitative data) or Mantel-Haentzel and chi-square tests (categorical data). For the pilot phase, the number of patients with satisfactory immediate angiographic results, as well as the mean packing density, will be compared between the 2 groups. The primary outcome of the pivotal phase, recurrence rates (for both intent-to-treat end per-protocol populations) will be compared between groups through a z-test for independent proportions at 6 months and 12 months. Secondary outcomes and safety data will be compared between groups through independent t-tests (quantitative variables) or chi-square statistics (categorical data). The analyses of neurological data at follow-up will control for baseline data when possible (for tests done before discharge and at follow-up) using logistic regression, ANCOVA or Cox regression multivariate models. All tests will be interpreted with adjustment for the interim analysis to have the 0.05 level of confidence at 12 month only. Finally, a logistic regression will be used to find variables capable of predicting recurrences. The method planned is a stepwise forward with alpha < 0.05 to enter a predictor. Possible predictors include the type of the aneurysm, location, size of the aneurysm, size of the neck of the aneurysm as well as other baseline characteristics.

Pilot phase

The pivotal trial will be preceded by a pilot phase of approximately 165 patients designed to verify the feasibility of the coiling strategy, compliance to treatment group allocation, the safety of an 15-caliber platinum coil embolization strategy, recruitment rates, and the capacity to improve packing density with a standardized effect size (E/S) of 0.60, with a power of 95% and a two-sided alpha error of 0.05 (assuming the packing density of the control group will be approximately 25%). The data will be reviewed and analyzed by the DSMC and recommendations will be forwarded to the Steering Committee regarding continuation into the pivotal phase of the study.

Protection against bias

Classic biases such as selection bias or information bias will be dealt with by randomizing patients and blinding in the assessment of the primary outcome. Random allocation of treatment is best for insuring internal validity and is the best approach to control for confounding and selection bias.
Finally, control variables will be measured and compared between treatment groups in order to ensure group comparability (initial angiographic success, periprocedural events, and disease characteristics). Protocol compliance will be carefully monitored in every centre.

Publication of research findings

Publication of the results of this trial will be governed by the policies and procedures developed by the Steering Committee (SC). Any presentation, abstract, or manuscript will be made available for review by the SC prior to submission.

Regulatory considerations

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

> ** The Declaration of Helsinki (Document 17.C) is an official policy document of the World Medical Association, the global representative body for physicians. It was first adopted in 1964 (Helsinki, Finland) and revised in 1975 (Tokyo, Japan), 1983 (Venice, Italy), 1989 (Hong Kong), 1996 (Somerset-West, South Africa) and 2000 (Edinburgh, Scotland). Note of clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002.*

Trial management and coordination

DELTA is meant to be a clinical research project within the ICONE framework.[40] Trial management will be transparent, fully independent, and aims at preserving the scientific integrity of the research enterprise and the welfare of the participants. The industry has no control over the design or conduct of the trial, and no access to the data will be granted until publication; the results will be published whether they are favorable or not, and publications will be fully independent and autonomous, but as authorized by the

steering committee. The steering committee will have full responsibilities regarding the conduct and progress of the trial, as well as reporting of results. The steering committee will not have access to the unmasked data before completion or interruption of the trial. The clinical events committee, the endpoint review committee, and the adverse event committee, once nominated, will work independently from the steering committee. These committees will regularly send progress reports, notices and warnings when appropriate, to the independent data and safety and monitoring committee (DSMC). The committees that will have access to unmasked data are limited to the adverse event committee, responsible for reviewing each adverse event, and the DSMC, any time members judge that unmasking of groups is mandatory to protect the safety of participants, or once they are convinced that significantly different results have occurred. The DSMC will follow the progress of the trial, results and events being masked (tagged as group A and B) at all times, but with the possibility of unmasking results in case of necessity. The DSMC will inform the steering committee if the trial should be interrupted if any concern arises during the trial. The steering committee will act according to the DSMC recommendations.

SECTION 3: TRIAL MANAGEMENT

Investigators

Principal Investigators Jean Raymond M.D., Neuroradiologist, Montreal, Canada

Core Lab: TBD

Steering Committee

Dr Jean Raymond, M.D., Neuroradiologist
Centre hospitalier de l'Université de Montréal Hôpital Notre-Dame, Montreal, Canada

Dr David Kallmes, M.D., Neuroradiologist
Mayo Clinic, Rochester, Minnesota

Dr Jai Jai Shiva Shankar, M.D., Neuroradiologist
Queen Elizabeth II Health Sciences Centre, Dalhousie University, Halifax, Nova-Scotia, Canada.

DELTA Steering Committee terms of reference (SC)

The role of the SC is to provide overall supervision of the trial. In particular, the SC will concentrate on the progress of the trial, adherence to the protocol, patient safety and consideration of new information. Day to day management of the trial is the responsibility of the PI. The PI may set up a separate trial management group to assist with this function.

Data Safety and Monitoring Committee (DSMC)

Dr Pascale Lavoie, M.D., FRCSC
Centre hospitalier affilié universitaire de Québec - Hôpital de l'Enfant Jésus, Québec, Canada

Miguel Chagnon, MSc (statistician)
Université de Montréal, Montreal, Canada

Dr Thanh Nguyen, M.D., FRCPC
Boston University Medical Centre

Data Safety and Monitoring Committee terms of reference

- To consider the interim data for the trial and relevant information from other sources;
- To assess the progress of recruitment after 1 year.
- To safeguard trial participants and trial integrity;
- To determine how frequently interim analysis of trial data should be undertaken;

Note: Members of the DSMC will remain independent of the trial staff and Steering Committee.

Imaging Center (core lab)

Philip White, MD
Department of Neuroradiology Western General Hospital, Edinburg, UK.

Other committees to be determined by decision of Steering Committee

Day to day management

The steering committee will be responsible for overseeing the administrative progress of the protocol. The steering committee will meet to monitor patient accrual, non-compliance with the protocol at individual centers, to act upon recommendations of the data and safety monitoring committee (DSMC).

An independent DSMC will be led by a neurologist not involved in the conduct of the trial. He will be assisted by 2 members: an interventionist and a statistician. The DSMC will be notified of all SAE reported by the clinical adjudication committee. Based on safety data, the DSMC may recommend that the steering committee modify or stop the trial.

The clinical adjudication committee will review all clinical events and use the criteria from Appendix 3 to evaluate if they correspond to the clinical primary outcome definitions (hemorrhage, retreatment or progressive mass effect) and secondary outcome definitions. It will communicate these results to the DMSC.

The imaging center (Core Lab) will be blinded. This committee will determine the angiographic success of the initial procedure as well as the presence of angiographic recurrences shown by follow-up studies. The committee will be composed of two neuroradiologists.

The coordinating centre will be in Montreal (Centre de Recherche du CHUM, Hôpital Notre-Dame). Periodic monitoring visits will be conducted all along the trial, or as needed. Data management will be done using a web-based application (Medscinet AB). The application is fully compliant with good clinical practice guidelines regarding electronic data transfer (US-FDA 21 CFR, part 11).

SECTION 4: GUIDELINES

DELTA treatment plan

1. Confirmation of an aneurysm ≥ 4mm and ≤ 12mm
2. The aneurysm must be suitable for endovascular treatment by catheter or non-invasive angiography (catheter angiography required if any doubt).
3. There is uncertainty over the best method of treatment.
4. For elective cases, outpatient visit for baseline medical and neurological examination, including modified Rankin scale (mRS).
5. Patient meets selection criteria.
6. For elective cases, during this visit, the physician and/or assistant explain treatment options, uncertainty over the best option, the trial, rationale for the trial and goals to the patient and family. If there is interest, documents and consent forms are handed to patient. Standard blood tests and a pregnancy test in women of childbearing age will be performed to exclude potential contraindications to endovascular treatment. Following verification that inclusion and exclusion criteria are met, the consent form and voluntary nature of participation into the study will be explained to the patient. The patient and family will be offered to sign the consent form. At this time, the recruitment form is filled and randomization can proceed online.

   For ruptured aneurysms, the physician will explain the treatment options including surgery to the patient and relatives. If endovascular treatment is to be offered, the physician will explain the potential benefits of using voluminous coils in terms of reducing the recurrence rate. Following verification that inclusion and exclusion criteria are met, the consent form and voluntary nature of participation into the study will be explained to the patient and relatives. The patient and family will be offered to sign the consent form. At this time, the recruitment form is filled and randomization can proceed online.
7. Randomization is automatic after the registration form is entered.

8. Elective patients are scheduled for treatment (within 1-2 months). Ruptured cases are treated as soon as possible as generally done. Images are sent to the coordinating centre.
9. For all patients, a procedure form is completed following treatment. Pre and final images, as well as 24 hour or at discharge CT scan, are sent to the coordinating centre.
   Discharge assessment form completed at the time of discharge.
10. Severe adverse events are entered online or faxed within 48 hours to the coordinating centre. The coordination center will transmit the information to the clinical adjudication committee which will relay it to the DSMC. These events include haemorrhages, strokes related to the aneurysm, deaths, or further treatments of aneurysm.
11. All patients will be followed at 6 and 12 months. Follow-up visits are crucial to assess any change in medical condition and to answer questions.
12. For all patients, follow-up visits at 6 and 12 months and vascular imaging 12 (±2) months. Follow-up angiography, catheter or non-invasive, is required. Images are sent to the coordination centre.

Centre requirements

1. Participating centres will be regional referral centre for the treatment of intracranial aneurysms. They will have demonstrated a large experience in endovascular treatment of aneurysms (at least 100 patients treated with safety records within acceptable limits (< 8% overall treatment-related complications; < 4% poor outcome at follow-up).
2. The names of operators in each centre should be submitted to the coordinating centre. The years of experience and number of aneurysms treated will be kept in a confidential centre log.
3. The centre will identify a local coordinator who will be responsible for all data collection. This person will also be responsible for ensuring maintenance of the ascertainment log. A monthly return will be expected to the trial office.
4. Investigators are committed to provide an appropriate environment and quality care that will minimize losses to follow-up.
5. The approval of the local ethical committee must be obtained and copies of approval must be lodged with the trial office.
6. Participants must sign the investigator agreement form.

APPENDIX 1: REFERRAL CENTER DETAILS

Complete name of the centre:	
City	
Country	
Contact name	
Email (or phone/fax information)	
How many aneurysms were treated by endovascular coiling last year?	☐☐☐

Please fax to :

DELTA Coordinating Centre
CHUM
Fax: (514) 412-7621

Thank you

APPENDIX 2: INVESTIGATOR DECLARATION AND AGREEMENT

We wish to participate in the clinical study mentioned above.
We have obtained approval from appropriate committees at our institution.
We agree to conduct the investigation in accordance with the agreement, the investigational plan, the protocol included, other applicable regulations and conditions of approval imposed by the reviewing IRB.
We will ensure that the requirements for obtaining informed consent are met.
We will offer participation to all eligible patients, follow all randomized patients until the end of the study.
We expect to randomize ☐☐☐ patients/year.

Centre name: _____

Centre address: _____

_____

_____

Signed on behalf of the Centre: _____

Name (Block capitals): _____

Participating interventionist names and signatures:

Name (Block capitals)	Signature	Date (mm/dd/yy)

Name of the local coordinator: _____

Telephone: _____ Fax: _____

Email: _____

APPENDIX 3: ADJUDICATION OF OUTCOMES

Primary outcome:

An independent Committee will adjudicate, for each patient, whether he or she has reached the endpoint. In the absence of follow-up imaging, the committee will adjudicate other potential cases of treatment failures (expected to be rare) such as:

- Hemorrhage during the follow-up period
- Retreatment of the same lesion by endovascular or surgical means during the follow-up period
- Occurrence or progression of a mass effect in relation to the treated aneurysm
- Morbidity and mortality that precludes follow-up

The pilot phase of the study was powered to detect a difference of 3% in mean packing density between the 2 groups. This will be measured by the Core lab.For both types of treatment, the packing density (PD) will be calculated as the volume of coils (VC) over the volume of the aneurysm (VA): PD = VC/VA with VA = $(4/3)\pi(\text{length}/2)(\text{width}/2)^2$

Safety

A. Safety data

Safety endpoints

- Mortality
- Morbidity (mRS ≥ 3)
- Combined Mortality & Morbidity(M&M) (mRS ≥ 3 at 12 months)
- Serious Adverse Event

Endpoint assessment

- For all DELTA patients
- Separately for ruptured and unruptured DELTA patients

Causality attribution

- Treatment-related
- Strictly treatment related: any M&M associated with a procedural event or complication or hemorrage
- Possibly related: any M&M occurring within 30 days
- Not treatment related (> 30 days)
- Related to aneurysm
- Unrelated

Safety data will be adjudicated by an independent committee.

Example of a table supplied to the DSMC:

Mortality and Morbidity (mRS $\geq$ 3)

All patients	Group A	Group B
DELTA ruptured	☐	☐
DELTA unruptured	☐	☐
Treatment-related (within 30 days)		
Strictly	☐	☐
Possibly	☐	☐
Aneurysm-related (> 30 days)	☐	☐
Not related (> 30 days)	☐	☐

This pattern will apply to mortality, morbidity, morbi-mortality and SAEs.

B. Definitions

Adverse Event

- Any procedural event (thromboembolic, hemorrhage, complication).
- During follow-up, any symptomatic event.
- During follow-up, any imaging finding secondary to investigation of symptom.
- Adverse Events will be categorized into: minor or moderate and serious

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

End of study

- Death
- No coils deployed during procedure or additional procedure
- 12-months follow-up completed.

REFERENCES

1. White PM, Lewis SC, Gholkar A, 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
2. Molyneux A, Kerr R, Stratton I, et al. International Subarachnoid Aneurysm Trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised trial. *Lancet* 2002;360:1267-1274
3. Roy D, Raymond J, Bouthillier A, et al. Endovascular treatment of ophthalmic segment aneurysms with Guglielmi detachable coils. *AJNR American journal of neuroradiology* 1997;18:1207-1215
4. Raymond J, Roy D, Bojanowski M, et al. Endovascular treatment of acutely ruptured and unruptured aneurysms of the basilar bifurcation. *Journal of neurosurgery* 1997;86:211-219
5. Raymond J, Roy D. Safety and efficacy of endovascular treatment of acutely ruptured aneurysms. *Neurosurgery* 1997;41:1235-1245; discussion 1245-1236
6. Guglielmi G, Vinuela F, Dion J, et al. Electrothrombosis of saccular aneurysms via endovascular approach. Part 2: Preliminary clinical experience. *Journal of neurosurgery* 1991;75:8-14
7. Roy D, Milot G, Raymond J. Endovascular treatment of unruptured aneurysms. *Stroke; a journal of cerebral circulation* 2001;32:1998-2004
8. Wiebers D. Unruptured intracranial aneurysms: natural history, clinical outcome, and risks of surgical and endovascular treatment. *The Lancet* 2003;362:103-110
9. Johnston SC, Dudley RA, Gress DR, et al. Surgical and endovascular treatment of unruptured cerebral aneurysms at university hospitals. *Neurology* 1999;52:1799-1805
10. Johnston SC, Gress DR, Kahn JG. Which unruptured cerebral aneurysms should be treated? A cost-utility analysis. *Neurology* 1999;52:1806-1815
11. Murayama Y, Vinuela F, Duckwiler GR, et al. Embolization of incidental cerebral aneurysms by using the Guglielmi detachable coil system. *Journal of neurosurgery* 1999;90:207-214
12. Raymond J, Guilbert F, Weill A, et al. Long-term angiographic recurrences after selective endovascular treatment of aneurysms with detachable coils. *Stroke; a journal of cerebral circulation* 2003;34:1398-1403
13. Raymond J. Counterpoint: has the last word been said? *AJNR American journal of neuroradiology* 2009;30:1649-1652
14. Byrne JV, Sohn MJ, Molyneux AJ, et al. Five-year experience in using coil embolization for ruptured intracranial aneurysms: outcomes and incidence of late rebleeding. *Journal of neurosurgery* 1999;90:656-663
15. Cognard C, Weill A, Spelle L, et al. Long-term angiographic follow-up of 169 intracranial berry aneurysms occluded with detachable coils. *Radiology* 1999;212:348-356
16. Gupta S. To clip or to coil? Today patients with cerebral aneurysms face a difficult choice: brain surgery or a less proven alternative. *Time* 2002;159:78

17. Hayakawa M, Murayama Y, Duckwiler GR, et al. Natural history of the neck remnant of a cerebral aneurysm treated with the Guglielmi detachable coil system. *Journal of neurosurgery* 2000;93:561-568
18. Ng P, Khangure MS, Phatouros CC, et al. Endovascular treatment of intracranial aneurysms with Guglielmi detachable coils: analysis of midterm angiographic and clinical outcomes. *Stroke; a journal of cerebral circulation* 2002;33:210-217
19. Thornton J, Debrun GM, Aletich VA, et al. Follow-up angiography of intracranial aneurysms treated with endovascular placement of Guglielmi detachable coils. *Neurosurgery* 2002;50:239-249; discussion 249-250
20. CARAT I. Rates of delayed rebleeding from intracranial aneurysms are low after surgical and endovascular treatment. *Stroke; a journal of cerebral circulation* 2006;37:1437-1442
21. Fiorella D, Albuquerque FC, McDougall CG. Aneurysm embolization with Matrix detachable coils: Assessment of durability at 6-month follow-up. *American Society of Neuroradiology 43rd meeting*; 2005
22. Niimi Y, Song J, Madrid M, et al. Endosaccular treatment of intracranial aneurysms using matrix coils: early experience and midterm follow-up. *Stroke; a journal of cerebral circulation* 2006;37:1028-1032
23. Molyneux AJ, Clarke A, Sneade M, et al. Cerecyte Coil Trial: Angiographic Outcomes of a Prospective Randomized Trial Comparing Endovascular Coiling of Cerebral Aneurysms With Either Cerecyte or Bare Platinum Coils. *Stroke; a journal of cerebral circulation* 2012;43:2544-2550
24. Hetts SW, Turk A, English JD, et al. Stent Assisted Coiling versus Coiling Alone of Unruptured Intracranial Aneurysms in the MAPS Trial: Safety, Efficacy and Midterm Outcomes. *SNIS 9th annual meeting*. San Diego, CA; 2012
25. FDA. Deltamaxx 18 microcoil system 510(k) summary. In: Department of Health and Human Services.; 2012: http://www.accessdata.fda.gov/cdrh_docs/pdf12/K120274.pdf
26. Sluzewski M, van Rooij WJ, Slob MJ, et al. Relation between Aneurysm Volume, Packing, and Compaction in 145 Cerebral Aneurysms Treated with Coils1. *Radiology* 2004;231:653-658
27. White PM, Lewis SC, Nahser H, et al. HydroCoil Endovascular Aneurysm Occlusion and Packing Study (HELPS trial): procedural safety and operator-assessed efficacy results. *AJNR American journal of neuroradiology* 2008;29:217-223
28. Chalouhi N, Dumont AS, Hasan D, et al. Is Packing Density Important in Stent-Assisted Coiling? *Neurosurgery* 2012;71:381-386
29. Kadirvel R, Ding YH, Dai D, et al. Proteomic Analysis of Aneurysm Healing Mechanism after Coil Embolization: Comparison of Dense Packing with Loose Packing. *American Journal of Neuroradiology* 2012;33:1177-1181
30. Morales HG, Kim M, Vivas EE, et al. How Do Coil Configuration and Packing Density Influence Intra-Aneurysmal Hemodynamics? *American Journal of Neuroradiology* 2011;32:1935-1941
31. Piotin M, Spelle L, Mounayer C, et al. Intracranial aneurysms: Treatment with bare platinum coils - Aneurysm packing, complex coils, and angiographic recurrence. *Radiology* 2007;243:500-508
32. Slob MJ, Sluzewski M, van Rooij WJ. The relation between packing and reopening in coiled intracranial aneurysms: a prospective study. *Neuroradiology* 2005;47:942-945

33. Cloft HJ, Kallmes DF. Aneurysm packing with HydroCoil Embolic System versus platinum coils: initial clinical experience. *AJNR American journal of neuroradiology* 2004;25:60-62
34. Cloft HJ. HydroCoil for Endovascular Aneurysm Occlusion (HEAL) study: periprocedural results. *AJNR American journal of neuroradiology* 2006;27:289-292
35. Cloft HJ. Have you been smoking something that is biologically active? *AJNR American journal of neuroradiology* 2006;27:240-242
36. Cloft HJ. HydroCoil for Endovascular Aneurysm Occlusion (HEAL) study: 3-6 month angiographic follow-up results. *AJNR American journal of neuroradiology* 2007;28:152-154
37. Gaba RC, Ansari SA, Roy SS, et al. Embolization of intracranial aneurysms with hydrogel-coated coils versus inert platinum coils: effects on packing density, coil length and quantity, procedure performance, cost, length of hospital stay, and durability of therapy. *Stroke; a journal of cerebral circulation* 2006;37:1443-1450
38. Raymond J. Reflections on the TEAM trial: why clinical care and research should be reconciled. *The Canadian journal of neurological sciences Le journal canadien des sciences neurologiques* 2011;38:198-202
39. Quinn TJ, Dawson J, Walters MR, et al. Reliability of the modified Rankin Scale. *Stroke; a journal of cerebral circulation* 2007;38:e144; author reply e145
40. Raymond J, White P, Kallmes DF, et al. ICONE: An International Consortium of Neuro Endovascular Centres. *Interventional neuroradiology : journal of peritherapeutic neuroradiology, surgical procedures and related neurosciences* 2008;14:203-208