

# Unruptured Intracranial Aneurysms

## A Critical Review of the International Study of Unruptured Intracranial Aneurysms (ISUIA) and of Appropriate Methods to Address the Clinical Problem

J. RAYMOND<sup>1</sup>, F. GUILLEMIN<sup>2</sup>, F. PROUST<sup>3</sup>, A.J. MOLYNEUX<sup>4</sup>, A.J. FOX<sup>5</sup>,  
J.S. CLAIBORNE<sup>6</sup>, J.-F. MEDER<sup>7</sup>, I. ROULEAU<sup>8</sup>, THE TRIAL ON ENDOVASCULAR  
ANEURYSM MANAGEMENT (TEAM) COLLABORATIVE GROUP

<sup>1</sup> Interventional Neuroradiology Research Unit, Department of Radiology, Université de Montréal, CHUM Notre-Dame Hospital, Montréal; Canada;

<sup>2</sup> Épidémiologie et Évaluation Cliniques, Hôpital Marin, Nancy; France;

<sup>3</sup> Service de Neurochirurgie, CHU de Rouen, Rouen; France;

<sup>4</sup> Neurovascular Research Unit, Nuffield Dept of Surgery, University of Oxford, Radcliffe Infirmary, Oxford; United Kingdom;

<sup>5</sup> Department of Medical Imaging, Sunnybrook and Women's College Health Sciences Centre, Ontario; Canada;

<sup>6</sup> Department of Neurology, University of California, San Francisco; USA;

<sup>7</sup> Département d'Imagerie morphologique et fonctionnelle, Centre Hospitalier Sainte-Anne, Paris, France;

<sup>8</sup> Centre de Neurosciences de la Cognition, Département de Psychologie, Université du Québec à Montréal and Service de Neuropsychologie, CHUM Notre-Dame Hospital, Montréal; Canada

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### Summary

*The preventive treatment of unruptured aneurysms has been performed for decades despite the lack of evidence of a clinical benefit. Reports of observational studies such as the International Study of Unruptured Intracranial Aneurysms (ISUIA) suggest that preventive treatments are rarely justified. Are these reports compelling enough to guide clinical practice?*

*The ISUIA methods and data are reviewed and analysed in a more conventional manner. The design of the appropriate clinical research program is approached by steps, reviewing potential problems, from the formulation of the precise research question to the interpretation of subgroup analyses, including sample size, representativity, duration of observation period, blinding, definition of outcome events, analysis of*

*cross-overs, losses to follow-up, and data reporting. Unruptured intracranial aneurysms observed in ISUIA ruptured at a minimal annual rate of 0.8% (0.5-1%), despite multiple methodological difficulties biased in favour of a benign natural history. Available registries do not have the power or the design capable of providing normative guidelines for clinical decisions. The appropriate method to solve the clinical dilemma is a multicentric trial comparing the incidence of a hard clinical outcome events in approximately 2000 patients randomly allocated to a treatment group and a deferred treatment group, all followed for ten years or more.*

*Observational studies have failed to provide reliable evidence in favour or against the preventive treatment of unruptured aneurysms. A randomized trial is in order to clarify what is the role of prevention in this common clinical problem.*

### Abbreviation list:

CI: Confidence intervals

ISUIA: International Study

on Unruptured Intracranial Aneurysms

M&M: overall mortality/morbidity

RR: relative risk

SAH: subarachnoid hemorrhage

UIA(s): unruptured intracranial aneurysm(s)

RCTs: randomized controlled trials

### Introduction

The preventive treatment of unruptured aneurysms has been a common clinical practice for decades, despite the absence of a clinical proof of its benefits. In our view, this stems from a combination of understandable human

factors: the sobering realization that the outcome of patients with ruptured aneurysms remains dismal despite advances in neurocritical care and neurosurgical techniques; a favourable but spurious comparison of the outcome of patients treated electively as compared to patients treated after rupture, as opposed to the necessary comparison between active treatment and conservative management; the dreadful fear of being at risk of intracranial hemorrhage and the temptations of the illusion of control of future events.

These factors, combined with an inflated evaluation of what can be done, commonly lead to an irresistible urge to act. Hence the systematic treatment of small unruptured aneurysms may perhaps do more harm than good, and some reports support this possibility by showing a very small hemorrhagic risk in patients that were observed and comparatively high complication rates in other patients that were treated<sup>4,20</sup>. However preventive treatment of unruptured aneurysms may still be sound<sup>4,11</sup>.

There are two aims to this paper. First ISUIA data will be reviewed and re-interpreted in a more conventional manner. This will allow us to observe that results are in fact no different from the background knowledge on unruptured aneurysms available before its publication.

The conclusions reported from ISUIA that stirred so much controversy were unwarranted because they were based on data-driven post-hoc reconstructions of artificial subgroups too small to be reliable.

If after more than ten years we are still in want of pertinent information and entangled in controversies it is because the clinical problem calls for an entirely different approach from a desperate search for an illusory 'natural history' of species of aneurysms. Clinical research must resolutely take another direction to provide valuable answers to clinically relevant questions regarding patients with unruptured aneurysms. Thus we will thoroughly review methodological pitfalls of observational studies, and propose better means to meet the challenge posed by unruptured aneurysms. Hence we will finally propose that the randomized trial methodology is the appropriate method to deal with the pervasive, longstanding clinical dilemma regarding preventive actions in the management of unruptured intracranial aneurysms.

## Material and Methods

### *The data*

We will limit our source to what is included in the article reporting the results of the prospective phase of ISUIA<sup>1</sup> and the recently published metanalysis by Wermer et Al.<sup>18</sup>.

### *Methods*

*Principles:* Canons of clinical research methods were taken from two basic textbooks on clinical research<sup>5,6</sup>.

*Statistics:* Calculation of confidence intervals was according to Pr Hossein Arsham<sup>1</sup>.

## Results and Discussion

### *Re-analysing ISUIA*

#### *Critical reading of ISUIA*

A prospective cohort study on 1692 patients with unruptured aneurysms that were managed in a conservative fashion was conducted. Two other cohorts were simultaneously followed, one treated using surgical (1917 patients), the other endovascular means (451 patients)<sup>20</sup>.

Ideally the subjects should have been appropriate to the research question, available for follow-up, and representative of the population to which the results would be generalized<sup>5</sup>. However, the conservative cohort was built around the beliefs of the expert investigators, who tended to exclude of the conservative group patients selected for treatment. The result was a population irrelevant to the question of the appropriateness of preventive treatment: patients were older, had a high incidence of cerebrovascular diseases, and a high mortality rate that precluded long-term follow-up (five year mortality rate of 12.7 % while the yearly mortality of the corresponding age group should have been 0.7%)<sup>16</sup>. Still, many patients (32%) ended up being censored for having treatment, although the reasons justifying treatment were not recorded (sentinel headaches, third nerve palsies, warning leaks, enlarging lesions?). These factors culminated in a poor follow-up rate of patients selected to define the 'natural history of aneurysms', with less than 22% of patients being followed for four years or more.

Results are summarized in table 1. We have included in table 1 the minimal number of events, but also what would be the incidence of ruptures in a worst-case scenario, if deaths from intracranial hemorrhages and from un-

known causes were included as outcome events.

Although the number of subjects and minimal duration of the observation period should be planned to provide adequate precision and power (and control type I and type II errors), subgroups, relative risks, or number of subjects needed to convincingly demonstrate the influence of risk factors for hemorrhage were not pre-specified.

A data-driven attempt to identify patients in whom risks of rupture were so low that no treatment could be justified, or in whom risks were so high as to mandate treatment posed many difficulties. A multivariate analysis identified three risk factors for hemorrhage: size (7-12 mm maximum diameter, relative risk [RR]: 3.3 [95% CI 1.3-8.2],  $p=0.01$ ), and two specific locations: posterior communicating ([RR]: 2.1 [1.1-4.2],  $p=0.02$ ) and basilar bifurcation aneurysms ([RR]: 2.3 [1.1-4.8],  $p=0.025$ ). On the other hand complications from treatment may also be more frequent in basilar bifurcations aneurysms, or in larger aneurysms, so in effect treatment cannot formally be recommended for any category of patients<sup>4</sup>.

A surprising finding emerged when authors looked for optimal cut-off points to relate lesion size to rupture risks: the absence of event associated with anterior circulation aneurysms less than 7 mm in size. This result was obtained provided that

a) posterior communicating aneurysms were excluded from the anterior circulation, to be lumped with basilar bifurcation aneurysms to construct a high risk 'posterior circulation' category<sup>2</sup>,

b) patients with a history of hemorrhage from another lesion were excluded and

c) patients with more than one lesion (40% of patients), such as a larger or a 'posterior circulation' aneurysm in combination with the small anterior lesion, were also excluded from the lower risk category to be classified in higher risk categories. Hence this tentative finding should be regarded with caution and at best calls for confirmation, since many sources of sampling errors, bias, and data driven selection could have artificially created this conjuncture. Major limitations of methods are summarized in Table 2 and reviewed in<sup>3,9,19</sup>.

The outcome event concerned patients, but important risk factors were defined using aneurysm characteristics. One problem is that

Table 1 **Actual ISUIA results.**

Observational case study	
Number of patients:	1692
Followed for 4 years or more	21%
Patient-years	6544
Minimal number of SAH:	51
Minimal incidence of rupture:	3% (2.3-4%)
Mean follow-up	4 years
Annual incidence	0.8%/year (0.6-1%)
Mortality from proven ruptures:	33 (2%; 1.4-2.7%)
Overall 5 year mortality:	12.7% (11.7-13.7%)
Worse case scenario (WCS)*:	81 (4.8%; 3.8-5.9%)
WCS annual incidence:	1.2%/year (0.9-1.5%)
* Ruptures, deaths from intracranial hemorrhages or unknown causes	

40% of patients harboured multiple aneurysms. The method for allocating patients to particular subgroups was not reported, but one may speculate that a hierarchy taking into account 'dominant' lesion size and/or location (both determined post-hoc) was arbitrarily fixed. This procedure will by definition, before any observation, attribute the outcome event to the higher level of the hierarchal group the patient can match (large aneurysm or posterior circulation). This in turn causes an a priori relative paucity of possibilities of events for patients that are members of the lower level of the hierarchy of risk factor groups. In addition, groups were then either split or lumped according to other criteria, such as a history of hemorrhage from another lesion, according to the authors' whim (in<sup>20</sup>). All these categories and their combinations are now too numerous (15 reported ones) for the small number of outcome events that were observed ( $n=51$ ).

#### *Conservative conclusions drawn from ISUIA*

Once a clinical behaviour has become entrenched compelling arguments based on hard facts are needed to alter the practice that has become custom to the field. To guide prudent and appropriate clinical decision-making is the main goal of clinical research. The rigour and prudence that characterize the scientific me-

Table 2 **Methodological difficulties and factors decreasing apparent rupture risks in ISUIA.**

1. Poorly defined objectives and indeterminate hypotheses	
2. Irrelevant population of patients excluded from treatment	
3. Selection bias at entry manifest by: (all $p < .001$ as compared to treated cohorts)	a. age b. Size of lesion c. History of hemorrhage from another lesion d. Location e. Multiplicity f. Symptoms
4. Undefined observation period	
5. Error rates and sample size not pre-specified	
6. Excessive losses to follow-up (21% of patients followed at 4 years)	a. Excessive loss by unrelated (?) mortality (12.7%) b. Excessive loss by cross-over (32% eventually treated; reasons?)
7. Assessment of outcome events was not blind	
8. Exclusion of events when other potential causes for intracranial bleeding (n=31)	
9. Exclusion of other intracranial hemorrhagic deaths (n= 19)	
10. Exclusion of deaths of unknown cause (n= 11)	
11. Post-hoc definition of subgroups	
12. Arbitrary relocation of P. Com aneurysms	
13. Inclusion of extradural lesions (cavernous lesions)	
14. Systematic attribution to large or posterior location categories when lesions multiple (40%)	
15. Incomplete reporting:	a. Actual numbers not provided b. Confidence intervals not provided c. Methodological obscurities

thod of assessing the pertinent facts, allegedly designed to reach closer to 'true results', must be followed by a critical review of all potential sources of bias to minimize risks of erroneous conclusions. When the observations contradict the typical actions of the community of experts, a classical approach to argumentation is to use a 'principle of charity', conceding every point that remains in doubt, to come up with the most conservative interpretation of the data. It is only when results of rigorous methods are followed by conclusions that survive such a sceptical interpretation can one hope to have an impact on the entrenched beliefs of clinical experts. Available reports on unruptured aneurysms do not pass muster for these requirements.

The rupture risk of unruptured aneurysms is at least 3% in four years (95% CI: 2.8-5.1%). Given the disparities between the populations reported, results do not differ significantly from other publications on unruptured aneurysms, such as the one by Rinke<sup>13</sup>, that reported a 0.8% (0.4-1%) annual rupture for group I patients, the one by Juvela<sup>7</sup> reporting 10.5% (5.3-15.8%) at ten years, and the one by Wermer<sup>18</sup> (0.5-1.3% annual rupture risk). Exploratory analyses revealed basilar bifurcation and posterior communicating aneurysms were at higher risk of rupture; single (<7 m) small anterior circulation aneurysms, without a history of hemorrhage from another lesion, if posterior communicating aneurysms are arbitrarily subtract-

ed, may be at lower risk, but these post-hoc findings need confirmation by trials with more rigorous methodology.

#### **Foundations of a more reliable method to provide pertinent answers to the clinical dilemma**

There are numerous methodological flaws in ISUIA; many are common to all cohort studies, but some are specific to the way it was designed and reported. Observational studies are often chosen because they are easily performed, relatively inexpensive and do not question the clinical habits of physicians or preferences of participants. However they are so frequently misleading that they are often considered exploratory phases to more definitive experiments such as randomized trials that must be performed to prevent large scale error. Hence we will review classical principles of clinical research that will guide us on the path to the resolution of our clinical dilemma.

##### *a) The relation between the research question and the method*

The goal of clinical research is to draw inferences from the study results to help guide our actions for future patients we encounter in daily practice. Certain principles must be respected for these inferences to be valid. The process includes first and foremost the formulation of a precise research question and the construction of the most appropriate design that will provide the correct answer<sup>5,6</sup>. A fatal error is to design a study that provides 'surprise' findings after asking the wrong question to the wrong population.

If we go back to ISUIA's project description<sup>15</sup> we read:

*The International Study of Unruptured Intracranial Aneurysms (ISUIA) 'was designed to define the natural history of UIAs'; determine the risk factors associated with the development and rupture of UIAs; and assess the morbidity and mortality associated with repair of UIAs among UIA patients with and without a history of subarachnoid hemorrhage from a separate aneurysm. The primary hypotheses of this study are as follows.*

*1) Among patients without a history of SAH with UIA, there is a critical size above which there is a significant risk of subsequent aneurysmal rupture, with accompanying neurologic morbidity and mortality.*

*2) Among patients with UIAs and a history of SAH from another source, the risk of future rupture of UIA, disability, and death is greater than in patients without a history of SAH and varies directly with aneurysmal size.*

*3) The risk of death and significant disability from surgery to isolate UIAs from the intracranial circulation varies according to the size and the location of the aneurysm, history of SAH from another source, and confounding variables such as age and co-morbid conditions.*

There are at least three fundamental problems with this description:

A) There is nothing natural about a so-called 'natural history' of UIAs. Unruptured aneurysms are most frequently discovered incidentally, at the time of imaging for some other reasons; the 'natural history' is a ratio of the number of events (that are unlikely to go unnoticed) divided by the number of patients identified with the disease and observed for a certain period. However this denominator will drastically change with imaging developments, the local circumstances justifying the clinical use of imaging modalities, and equipment availability. Thus we are in fact studying 'man-made' numbers that reveal more about referral patterns for imaging and co-morbidities than about 'natural kinds' of aneurysms.

B) The hypotheses are vaguely phrased, the clinically significant differences that are expected undefined, the population size and follow-up periods undetermined (Table 2). This condemns the authors to data-driven exploratory analyses, which by definition cannot be used reliably by clinicians if they are not confirmed by appropriate studies<sup>5</sup>. Statistical instruments do not perform normally when post hoc analyses are carried out, because their basic assumptions are not respected<sup>10</sup>. Any observation in this context runs the risk of being a chance finding, a sampling error, a bias or a post-hoc creation<sup>8</sup>.

C) The project description is ambiguous, with an implicit comparison between conservative management and treatment, but the groups that will be studied are divorced, and thus any comparison will be invalid.

Clearly the investigators wished to look for clinically pertinent information. But clinical pertinence here regards patients in whom treatment is a possibility. Had a clear and focused question been formulated, many errors

would have been prevented. Leaving details for a later part of this review, the initial formulation of a pertinent question could start with: Should unruptured aneurysms be treated preventively?

*b) Population representativity, spectrum of the disease, and the need for randomization*

All observational clinical research is based, philosophically and practically, on the use of a sample to represent a population. The advantage is efficiency, by relieving the investigators from investigating everyone with the disease, an impossible task. The price to pay is the bias that is introduced: the findings may not apply to all patients and in particular to future patients if the sample is not representative of the population that we are asked to treat in clinical practice<sup>5</sup>. We must remember that our primary goal is not to accurately represent a series of patients of the past. Our primary goal is to find the appropriate treatment of the future patient that we will encounter in our practice.

In many diseases there is a spectrum of severity. In UIAs, this spectrum of severity may concern the hemorrhagic risk, but there is no reason to suppose that there is a single one-dimensional spectrum of severity organized along a single criterion. Any individual patient can be described by multiple characteristics (age, sex, number of lesions, sizes, locations, morphology, previous history etc...). and be a member of various classes of patients defined according to their combinations. Hence the observational study could be analyzed and dissected into an infinity of classes of aneurysms that could be designed to show a 'zero risk' for a particular conjunction of characteristics, especially if these classes are determined once the results are known (table 2). Even if we could separate various groups with significantly different rupture risks, this would not solve our clinical dilemma since we would then need to compare this multitude of 'natural histories' with another spectrum, the spectrum of treatment risks, and perhaps with a third, the spectrum of treatment efficacy. But now all these comparisons are invalid, since they concern different groups of patients.

If a spectrum of aneurysm risks exists, then the so-called natural history of patients selected for observation may significantly differ from the one of patients selected for treatment, and then findings from one group cannot apply to the

other. As long as we first arbitrarily decide what should be done for each patient, act, and then observe the outcome of our actions, systematic bias is introduced. Not only does this procedure lead to invalid comparisons between groups, but it also systematically leads to a distorted picture of the 'reality' of the consequences of harbouring an aneurysm, by selectively exempting from evaluation of the so-called natural history those patients that are precisely the ones we desperately need to know more about, perhaps the ones most likely to rupture. One can safely speculate that ISUIA centres offered surgical clipping or coiling to patients with a favourable risk/benefit ratio, and observation to unfavourable patients, according to clinical judgement... This speculation is supported by the characteristics of patients that vastly differed for the three cohorts in ISUIA, for all factors that are believed to have a significant effect on rupture rates, such as lesion size, location, aneurysm-related symptoms, and history of SAH from another lesion ( $p < .0001$  for each factor; table 2)<sup>4</sup>. The fundamental question regarding UIAs is to determine if preventive treatment of unruptured aneurysms, when treatment is possible and actually considered, is in general beneficial, because we want this knowledge to apply to the future patient considered for treatment.

Hence the only way out of this systematic bias is randomization, a difficult but inescapable method if we are to come out of the current scientific and clinical dead-end. Randomization assures that only pertinent patients are recruited in the study, that the information given by the study results concerns the same patients who are eligible for the intervention, since any patient observed within the randomized trial had no reason whatsoever not to be in the treated group (beside treatment being allocated according to the randomization procedure). We are not in fact interested in finding a universal truth about natural species of aneurysms that may not be of clinical relevance. We are interested in the value of two treatments that must be tested in a diversified variety of patients. We want to know what is the outcome of two different approaches that are actually permissible decision choices in future patients of our clinical practice, when and only when a choice is possible. In such a perspective, the randomized trial design is the most appropriate method, and the research question should be articulated

around: 'Is the outcome of patients with unruptured aneurysms improved with treatment as compared with observation?'

*c) Sample size*

ISUIA is our largest prospective effort in the study of unruptured aneurysms to date. But it is actually quite small when one considers the ambitions of the study, the retention of patients and length of follow-ups, and the intention to analyse numerous subgroups. Now sample size is neither a virtue, nor a goal in itself. A large sample can only be useful to minimize random error (errors due to distortions caused by chance alone). Size has no effect on systematic error due to bias (sources of distortion that affect the results of the study in one direction only). In fact an increase in the size of a biased sample can only increase the magnitude of erroneous conclusions.

The sample size must be predetermined and tailored to a precise research question<sup>5,6</sup>. Clinical subgroups are more likely to produce random findings just through the aggregation of events. In the absence of specification of subgroups and error rates in advance, there is no way to control the error which rapidly rises above acceptable levels with multiplying post-hoc analyses<sup>10</sup>.

What actually determines the size of the population to be studied is the number of outcome events, which must be estimated a priori. The smaller the number of events, the larger the population required for meaningful results. For example, if one wishes to prove that one group carries a 1% risk, the other 0.5%, more than 4670 patients per group must be recruited (using 80% power and 5% alpha). Between ten to 25 events per risk factor are required for a meaningful analysis<sup>5</sup>. ISUIA was clearly too small to offer reliable estimates regarding the subgroups that were targeted.

Sample size determination is often performed in a pragmatic fashion; a number of patients that is feasible to recruit is first estimated. Then the investigators evaluate what difference between two groups would be clinically relevant. This procedure can only determine the size necessary to prevent differences likely to be caused by chance alone. If the research question cannot be answered with this population, the investigators are encouraged to look for more feasible endeavours. This crucial step often turns out to be a humbling experience, as

one is forced to realize the limits of clinical research. Sample size determination must be performed early during the planning phase of clinical research, whether we are contemplating an observational study or a randomized trial.

*d) Observation period*

The duration of a meaningful follow-up period must also be chosen with care, and the analysis of the outcome should take into consideration the number of patients that have completed the observation period. This is obvious when one studies 'cures' after cancer treatment. There are a number of illicit assumptions that are hidden behind selection of an observation period in research concerning aneurysms. Is the risk of rupture constant with time, age, concomitant diseases? Are a thousand patients followed for one year without hemorrhage to be counted as equivalent to a hundred patients followed for ten years without hemorrhage? Of course there is no 'true' answer to this problem, but we should think in this way: what would be clinically meaningful once we want to apply our new knowledge to our clinical decisions?

A thought experiment may help: imagine we designed an experiment in which premortem imaging in a million patients within a week of death were performed. We identified ten thousand patients with aneurysms, none of whom bled before dying from an unrelated cause. Would this be equivalent evidence of a natural history showing the absence of any rupture in 192 individuals each followed for ten years?

Since the knowledge we want is one that could apply to individual patients, for whom the clinical dilemma exists, a safe choice is an observation period that is long, ten or 15 years, since it is in patients with relatively long life expectancy, in good health, that treatment would be considered.

*e) Blinding and outcome events*

That it is vital to conceal assignment of patients to treatment in clinical research has been repeatedly stressed<sup>5</sup>. Blinding of both subjects and investigators is essential to eliminate differential bias, and in assuring that outcome measurements will not have different degrees of accuracy in the two groups. What is less obvious is the bias introduced by open allocation of events in registries. There is a high risk of error in the interpretation of outcome events in a study in

which there are more deaths from cerebrovascular diseases and 'unrelated' intracranial hemorrhages than primary outcome events<sup>4</sup>.

Because it may be considered unethical to perform sham operations, blinding is almost impossible in surgical trials. A less reliable but useful compensation is to resort to masked evaluation of the primary outcome, if it must be causally interpreted (such as morbidity or mortality caused by the disease or its treatment), the assessors being ignorant of group allocation at the time of the evaluation<sup>5</sup>.

It is appropriate to choose cause specific mortality as an outcome event only when the specific cause of death accounts for most of the deaths that occur among study patients.

The fact that individuals with other causes of intracranial hemorrhage could be included in ISUIA, but excluded from primary analysis once hemorrhages occurred could only result in dilution of the frequency of primary events. Designating any events that occur after randomization as 'ineligible' is a very risky strategy. A fair procedure that could have been used to convince readers that events had a very low frequency was to include all events in the primary analysis.

When blinding is not possible, it is judicious to choose a 'hard' outcome, less sensible to bias, such as overall mortality. The difficulty lies in the fact that with a sufficiently long trial, eventually everyone dies. In addition, many patients fear dependency more than they fear death, and there are reasons to think that treatment may cause more morbidity than mortality<sup>12</sup>. Thus alternative possibilities for choosing the outcome events of a trial is overall morbidity and mortality (M&M), or M&M caused by the lesion or its treatment, but blind adjudication becomes mandatory.

*f) Losses to follow-up and analysis of cross-overs*

The treatment of patients that cannot complete the entire duration of the observation period is a problem. Results are drastically influenced by the manner in which this problem is addressed. Bias becomes likely if there is a trend to enrol patients with concomitant diseases that a) may, physiologically or through unknown factors (such as physical activity) influence rupture rates, and

b) will statistically show that aneurysms are less relevant in the life of the population than

in healthy patients who are candidates for surgery. The systematic inclusion of months or years of 'non ruptures' of patients that can no longer bleed because they were treated (32%) or died from unrelated causes can only weigh in favour of a 'benign natural history'<sup>4</sup>.

The gravity of this problem can be estimated in any given study by examining the ratio of missing patients to events. If it is in the 1% range, this is not too worrisome; but as this ratio grows, validity of the event rate becomes questionable<sup>5</sup>. Not unexpectedly given the population and methodology, this problem became overwhelming with time in ISUIA. Patients lost to analysis or censored came to outnumber patients retained for analysis, undermining the credibility of an alleged low event rate<sup>20</sup>).

Deciding how to handle missing data in the analysis is crucial: It is tempting to treat patients that are lost as if they were lost at the end of the study, and 'censor' anything that might have happened afterwards. But this could bias conclusions; ignoring them would lower credibility of the study. In therapeutic trials, it is safest to arbitrarily assign lost patients the outcome that will make it harder for your study question to be answered by a 'yes'. This is 'the worst case scenario' method, assigning death to experimental patients, and survival to the end of the trial to control patients. In the case of ISUIA, the argument is reversed. The authors wish to show that small anterior circulation aneurysms do not rupture. The worst case scenario would have called for attributing a rupture to all cases lost to analysis, but also to attribute rupture in any patients with two aneurysms to the smallest, anterior circulation aneurysm if it were present in the patient. There are many less harsh methods to model and assign outcomes to lost patients, but all are 'fictitious' constructions that depart from a pure observational truth<sup>5</sup>.

*g) Explanatory or management research*

Trials are often described as 'explanatory' or 'management' trials. Explanatory trials are designed to discern any potential benefit of treatment in ideal circumstances. Explanatory trials call for tight eligibility criteria that select patients who are most likely to benefit, restriction of outcome events, and analysing just those outcome event that answer the precise research question. Explanatory trials allow a novel therapy to be rapidly abandoned in the face of negative results<sup>5</sup>.



Once a therapy has become common practice it is no longer a useful option. Only an ambiguous conclusion could come from an explanatory trial that shows clear benefits, while a management trial would prove that it is clearly worthwhile to adopt the treatment. If we keep in mind the purpose of our investigation ('Is the outcome of patients with unruptured aneurysms improved with treatment as compared with observation?'), we shall opt for the 'management' type of trial. This calls for a large, simple trial, looking for a pragmatic answer

1) with loose eligibility criteria based on uncertainty, 2) taking all comers; 3) retaining every admitted patient in the analysis; 4) proceeding with non-obstructive monitoring; 5) ascertaining a range of hard outcome events 6) counting every event and charging it against intervention (in<sup>5</sup>).

#### *h) Reporting results*

The rigorous and standardized fashion of reporting study results is beyond the present discussion but can be found in the Consort publications<sup>14</sup>. We only wish to mention here that conclusions should not be exaggerated, especially about subgroups. Many advocate rejection of any conclusion about subgroups, even in RCTs, unless they are 'big, highly statistically significant, specified before analysis, replicated in other trials and supported by other evidence'<sup>5</sup>.

#### *i) The appropriate research*

Summing up the result of this discussion, what needs to be done is a research that can lift the current uncertainty regarding the clinical management of patients with unruptured aneurysms. This is a large multicentric randomised controlled trial comparing a relatively hard outcome such as mortality or severe morbidity of a treated group with a group managed in a conservative fashion. The population studied must be appropriate, inclusive of all patients considered for treatment, but eligible to both options, and all patients should be followed for a fixed time period, ten years for example. If possible, the trial could be powered to show a difference in overall mortality or morbidity. Alternatively, cause-specific endpoints, such as morbidity and mortality related to the aneurysm or its treatment, can be used, provided this adjudication is performed by a committee blinded to treatment allocation. The sample size must be feasible, perhaps in the range of 2000

patients, a size necessary to prove a relatively large difference between the two groups. Since previous series, including ISUIA, are all compatible with a 1% yearly event rate for conservative management, such a sample size could prove a decrease in related M&M from 7-9% to 3-5% at ten years with treatment. Subgroup analyses can be performed but should ideally be pre-specified, limited to one or two, and results interpreted in a very conservative fashion.

The precise research question becomes: Is the clinical outcome, as judged by a committee blind to treatment allocation, in patients with unruptured aneurysms eligible to both treatment options, and in whom there is a clinical dilemma, all followed for at least ten years, significantly better with intervention or with observation?

This endeavour may appear a formidable task, but it is in our view the only option available to rationally justify the treatment of patients with unruptured aneurysms. We do not do clinical research because it is easy, but because it is necessary.

#### **Conclusions**

The appropriate management of individuals with unruptured aneurysms is a clinical dilemma that can only find a resolution through clinical research.

The most reliable findings of ISUIA concern the general incidence of rupture of patients with unruptured aneurysms, which remain, despite many methodological difficulties that all tend to lower the frequency of events, within the previously published 0.5-2%/year range. Observational studies do not possess the power or the methodology to provide safe and reliable conclusions about subgroups. Our previous endeavours to estimate the truth about a 'natural history' were ill-advised; numbers on unruptured aneurysms are man-made, and depend on our use of technology and our clinical decisions. Patients with unruptured aneurysms are treated everyday throughout the world. It is time to evaluate in a rigorous fashion if this is beneficial or harmful. This calls for a randomized trial.

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## References

- 1 Arsham Hossein: Business statistics web site. <http://home.ubalt.edu/ntsbarsh/business-stat/otherap-plets/ConfIntPro.htm>.
- 2 Clarke G, Mendelow AD, Mitchell P: Predicting the risk of rupture of intracranial aneurysms based on anatomical location. *Acta Neurochir (Wien)* 147(3): 259-263, 2005.
- 3 Da Costa LB, Gunnarsson T, Wallace MC: Unruptured intracranial aneurysms: natural history and management decisions. *Neurosurg Focus* 17(5): E6, 2004.
- 4 Donnan GA, Davis SM: Patients with small, asymptomatic, unruptured intracranial aneurysms and no history of subarachnoid hemorrhage should be treated conservatively. *Stroke* 36: 407, 2005.
- 5 Haynes RB, Sackett DL et Al: *Clinical epidemiology: how to do clinical practice research*. 1<sup>st</sup> edition. Philadelphia, PA: Lippincott Williams & Wilkins, 2005.
- 6 Hulley SB, Newman TB et Al: *Designing Clinical Research: An Epidemiologic Approach*. 2<sup>nd</sup> Ed Philadelphia: Lippincott Williams & Wilkins, 2001.
- 7 Juvola S, Porras M, Heiskanen O: Natural history of unruptured intracranial aneurysms: a long-term follow-up study. *J Neurosurg* 79(2): 174-182, 1993.
- 8 Mills JL: Data torturing. *N Engl J Med* 329(16): 1196-1199, 1993.
- 9 Mocco J, Komotar RJ et Al: The natural history of unruptured intracranial aneurysms. *Neurosurg Focus* 17(5): E3, 2004.
- 10 Moye LA, Deswal A: Trials within trials: confirmatory subgroup analyses in controlled clinical experiments. *Control Clin Trials* 22(6):605-619, 2001.
- 11 Proust F, Derrey S et Al: Unruptured intracranial aneurysm: possible therapeutic strategies? *Neurochirurgie* 51(5): 435-454, 2005.
- 12 Raaymakers TW, Rinkel GJ et Al: Mortality and morbidity of surgery for unruptured intracranial aneurysms: a meta-analysis. *Stroke* 29(8): 1531-1538, 1998.
- 13 Rinkel GJE, Djibuti M et Al: Prevalence and Risk of Rupture of Intracranial Aneurysms. *Stroke* 29(1): 251-256, 1998.
- 14 Stroup DF, Berlin JA et Al: Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 283(15): 2008-2012, 2000.
- 15 The International Study of Unruptured Aneurysms. Background. May 9<sup>th</sup>, 2007. <http://www.isuia.org/isuia/Background.htm>.
- 16 US death statistics: Disaster Center. May 9<sup>th</sup>, 2007. [www.disastercenter.com/cdc](http://www.disastercenter.com/cdc).
- 17 Weir B: Patients with small, asymptomatic, unruptured intracranial aneurysms and no history of subarachnoid hemorrhage should be treated conservatively: Against. *Stroke* 36: 410-411, 2005.
- 18 Wermer MJ, van der Schaaf IC et Al: Risk of rupture of unruptured intracranial aneurysms in relation to patient and aneurysm characteristics: an updated meta-analysis. *Stroke* 38(4): 1404-1410, 2007.
- 19 White PM, Wardlaw J: Unruptured intracranial aneurysms: prospective data have arrived. *Lancet* 362(9378): 90-91, 2003.
- 20 Wiebers DO, Whisnant JP et Al: Unruptured intracranial aneurysms: Natural history, clinical outcome, and risks of surgical and endovascular treatment. *Lancet* 362: 103-110, 2003.

Dr Jean Raymond, MD  
 CHUM - Notre-Dame Hospital  
 Interventional Neuroradiology  
 Laboratory (NRI)  
 1560 Sherbrooke east, suite Z-12909  
 Montreal, Quebec, CANADA H2L 4M1  
 Email: dr\_jean\_raymond@hotmail.com  
 (www.TEAMstudy.org)

### \* Trial on Endovascular Aneurysm Management (TEAM) Collaborative Group

#### *Principal investigators:*

Jean Raymond (CHUM Notre-Dame Hospital, Montréal, Canada), Andrew J. Molyneux (Oxford Radcliffe Hospitals NHS Trust, Oxford, UK), Allan J. Fox (University of Toronto, Canada), Claiborne S. Johnston (University of California, San Francisco, USA), Jean-Paul Collet (CHII, University of British Columbia, Vancouver, Canada), Isabelle Rouleau (CHUM Notre-Dame Hospital, Montreal, Canada).

#### *TEAM Steering Committee:*

Jacques Moret (Fondation Rothschild, Paris, France); Alejandro Berenstein (INN Beth Israel, New York, USA); Herman Zeumer (University Hamburg-Eppendorf, Hamburg, Germany); Gabriel Rinkel (University Medical Centre, Utrecht,

the Netherlands); Cameron G. McDougall (Barrow Neurological Institute, Phoenix, USA); In Sup Choi (Lahey Clinic, Burlington, USA); Jean Raymond (CHUM Notre-Dame Hospital, Montreal, Canada); Andrew Molyneux (Oxford Radcliffe Hospitals NHS Trust, Oxford, UK); Claiborne S. Johnston (University of California, San Francisco, USA); Allan Fox (University of Toronto, Canada); Isabelle Rouleau (CHUM Notre-Dame Hospital, Montréal, Canada); Jean-Paul Collet (University of British Columbia, Vancouver, Canada); Yvan Lepage (University of Montreal, Montreal, Canada).

#### *Data Monitoring Committee:*

Luc Picard (Chairman, CHU Nancy, France), Michael Eliasziw (University of Calgary, Canada); Louise-Hélène Lebrun (CHUM Notre-Dame Hos-

pital, Montréal, Canada); Gerald R. Winslow (Loma Linda University, California, USA); James Hosinec (patient representative, Montréal, Canada).

*TEAM Clinical events Committee:*

Charles Strother (University of Wisconsin, Madison, USA); Karl-Fredrik Lindegaard (University of Oslo, Norway); Daniel Roy and Sylvain Lanthier (CHUM Notre-Dame Hospital, Montréal, Canada).

*TEAM EndPoint Review Committee:*

Robert Coté (McGill Health Centre, Montréal, Canada); Jeffrey Minuk (SMBD-Jewish hospital, Montréal, Canada); François Guilbert (CHUM Notre-Dame Hospital, Montréal, Canada).

*TEAM Expert Committees:*

Imaging Centre: Allan Fox (University of Toronto, Canada); Alain Weill (CHUM Notre-Dame Hospital, Montréal, Canada). Data Preparation and Blinding Centre: Philip White (Western General Hospital, Edinburgh, UK). Neuropsychology: Isabelle Rouleau (CHUM Notre-Dame Hospital, Montréal, Canada). Patient support group: Maria Angeles de Miquel (Hospital Universario de Bellvitge, Barcelona, Spain).

*TEAM Executive Group:*

Jean Raymond (CHUM Notre-Dame Hospital, Montréal, Canada); Andrew Molyneux (Oxford Radcliffe Hospitals NHS Trust, Oxford, UK); Claiborne S. Johnston (University of California, San Francisco, USA); Allan Fox (University of Toronto, Canada); Yvan Lepage (University of Montréal, Montréal, Canada).

*Central Coordinating Team:*

Guylaine Gevry (Trial Manager), Ruby Klink (Assistant Trial Manager), Julia Yarnold (European Coordinator and Co-trial Manager). Coordination Team for France: Christophe Cognard (principal investigator for French centres).

**Participating Centres and Investigators**

**FRANCE**

Paris, Centre Hospitalier Sainte-Anne: Jean-François Meder, Denis Trystam, Sylvie Godon-Hardy; Toulouse, Hôpital Purpan: Christophe Cognard, Anne Christine Januel, Philippe Tall; Nancy, CHU de Nancy - Hôpital Central: Serge Bracard, René Anxionnat; Creteil, Hôpital Henri Mondor: André Gaston, Raphael Blanc; Paris, Fondation Rothschild: Jacques Moret, Michel Piotin, Laurent Spelle, Charbel Mounayer; Lille, Hôpital Roger Salengro: Jean-Pierre Pruvo, Xavier Leclerc; Paris, Pitié Salpêtrière: Alessandra Biondi, Fabrice Bon-

neville, Béatrix Jean, Nader Sourour, Louis Puybasset; Paris, Hôpital Lariboisière: Emmanuel Houdart; Reims, CHU Reims - Hôpital Maison-Blanche: Laurent Pierot; CHU Tours, Hôpital Bretonneau: Sophie Gallas, Denis Herbretreau; Clermont Ferrand, CHU Clermont-Ferrand - Hôpital Gabriel Montpied: Emmanuel Chabert; Caen, CHU Côte de Nacre: Patrick Courtheoux; Besançon, CHU Jean Minjoz: Jean-François Bonneville; St-Etienne, Hôpital Bellevue: Luis Manera; Nantes, Hôpital Laennec: Axel de Kersaint Gilly, Hubert Desal; Colmar, Hôpital Pasteur: Alain Tournade; Lyon, Hôpital Pierre Wertheimer: Francis Turjman, Bernadette Lamy, Florence Tahon; Suresnes, Hôpital Foch: Georges Rodesch; Limoges, Hôpital Dupuytren: René Chapot; Grenoble, Hôpital Albert Michallon: Jean-François Le Bas; Angers, Hôpital Larrey: Anne Pasco-Papon.

**UK**

Bristol, Frenchway Hospital: Andre Molyneux; Nottingham, Queens Medical Centre: Robert Lenthall; Oxford, Radcliffe Infirmary: James Byrne, Richard Kerr; Salford, Hope Hospital and Manchester Royal Infirmary: David Hughes, Roger Laitt, Herwadkar, A.; Newcastle, General Hospital: Anil Gholkar; London, Kings College Hospital: Martin Jeffree; West Sussex, Brighton and Sussex University Hospital: Jonathan Olney; Edinburgh, UK, Royal Infirmary: Philip White, Robin Sellar; Birmingham, University Hospital: S. Lamin; Cardiff, University Hospital of Wales: Shawn Halpin; Liverpool, Walton Centre for Neurology and Neurosurgery: Hans Nahser, Donald Shaw; Plymouth, Derriford Hospital: William Adams; Essex, Centre for Neurological Science: Sanjiv Chawda, M. Pfeiffer; London, University College Hospital: J. Grieve, N. Kitchen; Southampton, Wessex Neurological Centre: J. Millar.

**CANADA**

Montreal, Notre-Dame Hospital: Jean Raymond, Daniel Roy, Alain Weill, François Guilbert; Montréal, Neurological Institute: Donatella Tampieri, Gerard Mohr; Quebec, Hôpital Enfant-Jésus: Geneviève Milot, Jean-Luc Gariépy.

**USA**

New York, INN Beth Israel: Alejandro Berenstein, Y. Niimi; New York, Cornell University: Pierre Gobin; New York, Presbyterian Hospital Columbia University Medical Center: John Pile-Spellman; Phoenix, Barrow neurological Institute: Cameron McDougall; San Francisco, Moffitt-Long and San Francisco General Hospitals: Claiborne Johnston; Burlington, Lahey clinics: In Sup Choi; Houston, Methodist Hospital: Michel Mawad; Honolulu, Queen's Medical Centre: Cherylee Chang; Wichita,

Via Christ Medical Centre: As'ad Ehtisham; Maywood, Loyola University Medical Centre: Michael Schneck.

#### GERMANY

Hamburg, Universitätsklinikum Hamburg-Eppendorf: Herman Zeumer, J. Fiehler; Dresden, Universitätsklinikum Carl Gustav Carus: R. Von Kummer; Freiburg, Universitätsklinikum Freiburg: Martin Schumacher; Wuerzburg, Universitätsklinikum Wuerzburg: Laslo Solymosi; Mainz, Universitätsklinikum Mainz: P. Stoter, Kurt Ringel.

#### ITALY

Bologna, Ospedale Bellaria: Marco Leonardi; Milano, Ospedale San Raffaele: F. Scomazzoni, C. Righi, F. Simionato, G. Scotti; Aquila, Università degli Studi dell'Aquila: M. Gallucci.

#### OTHERS

Beijing, China, Capital University of Medical Sciences: Ling Feng; Shanghai, China, Second Military Medical University: Bo Hong; Ankara, Turkey, Hacettepe University Hospital: Saruhan Cekirge, Isil Saatci; Istanbul, Turkey, Cerrahpasa Medical School: Civan Islak; Perth, Australia, Royal Perth Hospital: C. Panthouros; Brno, Czech Republic, Masarykova Univerzita V Brné: Peter Krupe; Oslo, Norway, Rikshospitalet University Hospital: S.J. Bakke, KF Lindergaard; Athens, Greece, Henry Dunant Hospital: George Magoufis; Warszawa, Poland: Przemyslaw S. Richter; Barcelona, Spain, Hospital Bellvitge: Maria A. De Miquel; Berne, Switzerland, Universitatsspital: G. Schroth; Zwolle, Netherlands: Frits de Beer; Santiago de Chile, Chile, Hospital Clinico Pontificia Universidad Catolica: J. Tevah.