@neurIST : informatique biomédicale intégrée pour la gestion des anévrismes cérébraux

Research legislation:	Ordinance on human research with the exception of Clinical trials (HRO) (1).
Type of Research Project:	Research project involving human subjects
Risk Categorisation:	Category A according to ordinance HRO Art.7
Project Leader:	Prof. Philippe Bijlenga, Médecin adjoint agrégé, Neurosurgery, Department of Clinical Neurosciences Hôpitaux Universitaire de Genève 4 rue Gabrielle-Perret-Gentil 1211 Genève 14 079 204 40 43 philippe.bijlenga@hcuge.ch

Hôpitaux Universitaires Genève

PROTOCOL SIGNATURE FORM

Study Title	@neurIST : informatique biomédicale intégrée pour la gestion des anévrismes cérébraux

The project leader (main center) and the investigator (at the local center/site) have approved the protocol version ***[6 (dated 16.05.2022)]***, and confirm hereby to conduct the project according to the protocol, the Swiss legal requirements (1, 2), the current version of the World Medical Association Declaration of Helsinki (3) and the principles and procedures for integrity in scientific research involving human beings.

Project leader (lead center/site)

Site *Geneva University Hospitals, Geneva*

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Date: 6.6.2022 Signature:

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GLOSSARY OF ABBREVATIONS

AUC	*Area Under the Curve*
CCU	*Critical Care Unit*
CFD	*Computational Flow Dynamics*
CI	*Confidence Interval*
CSF	*Cerebro-Spinal Fluid*
CT	*Computerized Tomography*
CTA	*Computed Tomography Angiography*
DAI	*Data Acquisition Identifier*
DALY	*Disability-Adjusted Life Year*
DoH	*Declaration of Helsinki*
DRA	*Digital Rotational Angiography*
EC	*Ethics Committee*
eCRF	*electronic Case Report Form*
EGEP	*Essentials of Good Epidemiological Practice*
E5Y	*Every 5 Years*
FOPH	*Federal Office for Public Health*
HRA	*Human Research Act*
HRO	*Human Research Ordinance*
GCP	*Good Clinical Practice*
IAs	*Intracranial Aneurysms*
ICU	*Intermediate Care Unit*
ISUIA	*International Study of Unruptured Intracranial Aneurysms*
ICP	*IntraCranial Pressure*
GCS	*Glasgow Coma Scale*
M3	*Month 3*
M6	*Month 6*
MMSE	*Mini-Mental State Examination*
MoCA	*Montreal Cognitive Assessment score*
MRA	*Magnetic Resonance Angiography*
MRI	*Magnetic Resonance Imaging*
mRS	*Modified Ranking Scale*
NIHS	*National Institute of Health Stroke*
OR	*Odds Ratio*
PKD	*Polycystic Kidney Disease*
rCBF	*regional Cerebral Blood Flow*
ROC	*Receiver Operating Characteristic*
SAH	*SubArachnoid Hemorrhage*
SE	*Serious Event*
ADB	*AneurysmDataBank*
UCAS	*Unruptured Cerebral AneurysmS*

UIAT	*Unruptured Intracranial Aneurysm Treatment*
W6	*Week 6*
Y1	*Year 1*
Y2	*Year 2*
Y5	*Year 5*
YLL	*Years of Life Lost*
YLD	*Years Lost due to Disability*

1 BACKGROUND AND PROJECT RATIONALE

1.1 Legal requirements

1) Ethical conduct of study:

The research project will be carried out in accordance to the research plan and with principles enunciated in the current version of the Declaration of Helsinki (DoH) (3), the principles of Good Clinical Practice, the Human Research Act (HRA) (2) and the Human Research Ordinance (HRO) (1) as well as other locally relevant regulations. The Ethics Committee (EC) and regulatory authorities will be informed about project start and termination.

2) Risk categorisation:

According to HRO Art. 7, this project comes under Category A because the planned measures for sampling biological material or collecting personal data entail only minimal risks and burdens:

- Biological samples taken for this project i.e. aneurysmal dome and cerebro-spinal fluid (CSF) are biological samples normally harvesting during surgery and are never used for diagnostics.
- Clinical information and images used for this project are not collected especially for this project but come from the patient clinical folder. During routine visits, the evolution of the intracranial aneurysm is monitored and the outcome of the patient is evaluated. As patients suffering from intracranial aneurysm have to go regularly to the hospital for the follow-up of their disease, enrolled patients in our study will not have to go to the hospital specially for the current project.
- Risk associated with this project are those associated with blood puncture i.e. low risk of infection and hematoma.
- Saliva and stool collection are without danger for the participant.
- Concerning data security, information will be transferred over networks and links will be made with electronic hospital patient records. It is a part of the project to control accesses, and comply to all clinical research good practice requirements (please see details on section 7)

3) Participant information and informed consent:

All participants will be informed about the research project by the clinician in charge of the patient or by research nurses or clinical researchers dedicated to the present project. Information letters and informed consents are the following:

- General information letter and associated informed consent (Annex 1);
- General information letter and associated informed consent for patient recruited in emergency (Annex 2)
- General information letter and associated informed consent for patient incapable of discernment (Annex 3)
- General information letter and associated informed consent for patient incapable of discernment and recruited in emergency (Annex 4)
- Genetic information letter and associated informed consent (Annex 5);
- Genetic information letter and associated informed consent for patient incapable of discernment (Annex 6);
- Declaration of informed consent for the re-use of biological data and samples in coded form (Annex 7);
- Declaration of informed consent for the re-use of biological data and samples in coded form for patient incapable of discernment (Annex 8);

- Declaration of Withdrawal of Consent (Annex 9);
- Declaration of Withdrawal of Consent for patient incapable of discernment (Annex 10).

Vulnerable participants will be recruited in normal and emergency settings by involving the next of kin as soon as possible as the patient's representative. The next of kin will be informed about the research project by the clinician in charge of the patient or by research nurses or clinical researchers dedicated to the present project. The next of kin will be invited to sign a temporary consent form. As soon as the patient recovers the ability to consent and within a delay of 3 months, a formal definitive consent will be obtained from the patient. All patients recruited before the age of 18 will be invited to confirm their consent within 3 months of their 18th birthday.
Agreement or refusal of each participant will be recorded in the eCRF "AneuX_Données Légales" (Annex 11).

4) Participant privacy and safety:
The Project Leader affirms and upholds the principle of the participants' right to dignity, privacy and health and that the project team shall comply with applicable privacy laws. Especially, anonymity of the participants shall be guaranteed when presenting the data at scientific meetings or publishing them in scientific journals.
Individual participant medical information obtained as a result of this research project is considered confidential and disclosure to third parties is prohibited. Participant confidentiality will be further ensured by utilising identification code numbers to correspond to medical information in the computer files.
For data verification purposes, authorised representatives of the Sponsor, a competent authority, or an ethics committee may require direct access to parts of the medical records relevant to the project, including participants' medical history.

1.2 Scientific background

Aneurysm is a disease of the vessel wall resulting in the deformation and enlargement of the vascular lumen. If the process of deformation remains active, the vessel wall may rupture and produce a hemorrhage, or a thrombosis and an ischemia may occur. All vessels can be affected but we are more particularly interested by Intracranial Aneurysms (IAs) (4). IAs are mostly quiescent and asymptomatic but when rupturing, potentially induce severe brain damage and death. The prevalence of IAs is high (2 to 5%) and affects young people (median at 50 years) (5). The major risk with IAs is their rupture, which results in a SubArachnoid Hemorrhage (SAH) (6). SAH occurs in 5 to 10/100.000 inhabitants per year. In Switzerland, SAH results in 24% death, 11% severely disabled patients and 64% patients recovering to a more or less independent life. Only 24% of the patients recover with no residual symptoms (7). Most of the IAs are asymptomatic and are rather incidentally detected. As image-based diagnosis is increasingly prescribed, the proportion of patients diagnosed with incidental IAs is likely to grow. Today, more and more patients face the extreme situation of taking a decision whether or not to risk an intervention (8-10). The complexity of decision-making regarding IA management has significantly increased since the last century. During the 80', all diagnosed aneurysms were considered at high risk and treated by microsurgical clipping. Nowadays, many technical innovations are regularly developed promoting less invasive interventions, but the risk associated with the surgery and the post-surgery disability for the patient are still elevated.

1) Current knowledge on IAs initiation, growth and rupture:

IA is a heterogeneous disease that results from the combination of multiple factors over time. The general consensus is that IAs progress through different stages associated with specific predisposing factors, injuries, repair mechanisms, and treatments that all influence the balance between healing and progression (11, 12).

A. Vessel conformations and IAs:

Observations suggest that abnormal cerebral vasculogenesis and suboptimal geometrical conformation may favor aneurysm formation. Once an aneurysm appeared, the complexity of local flow conditions is increased and wall shear stress gradients in time and space are steeper. Observation of the aneurysm vessel wall shows that impairment of the endothelial surface and of the elastic lamina is early sign of vessel wall disease. These damages lead to the exposition of the muscle cells to the vascular lumen inducing platelet aggregation, inflammatory cell infiltration and finally progressive de-cellularisation of the vessel wall.

As observed for many years, IAs develop on arterial feeders of arterio-venous malformations. In that specific situation, the treatment of the malformation is known to be sufficient to stabilize or shrink the aneurysms overtime (13-15). This observation leads to the hypothesis that aneurysm growth and rupture is driven by the vessel luminal hemodynamic.

Shape of bifurcation influences also hemodynamic forces on the vessel wall and may play an important role for the initiation of aneurysm formation. Studies showed an association between sub-optimal bifurcation geometries and presence of aneurysms (16, 17). Presently, aneurysm location on specific artery segments or bifurcations is the strongest factor associated with the risk of aneurysm occurrence and risk of aneurysm rupture (8-10, 18). Those observations lead to the hypothesis that vessel shape may induce hemodynamic conditions prone to induce aneurysm formation.

B. Aneurysm shape and risk of rupture:

Aneurysm size is well recognized to be the second strongest factor used to assess the risk of aneurysm rupture (8-10, 18). Aneurysm shape may also influence luminal flow patterns and future progression of the disease. A study published in 2011 describes the importance and benefit of studying the blood flow in patient specific vessel geometries to understand the mechanism of the disease and evaluate the risk of aneurysm rupture. The authors report that qualitative hemodynamic analysis of cerebral aneurysms by using image-based patient-specific geometries showed that concentrated inflow jets, small impingement regions, complex flow patterns, and unstable flow patterns are correlated with a clinical history of prior aneurysm rupture (19). Studies report a signature aneurysm wall shear stress profile associated with aneurysm rupture (20-23). Very recently, we showed that irregular lumen shape carries significant information on the aneurysm's disease status (24). Such irregularity constitutes a continuous parameter showing a strong association with the rupture status. Those observations lead to the hypothesis that aneurysm shape may induce hemodynamic or mirror biological conditions prone to inducing aneurysm growth or rupture.

C. Environmental and life style risk factors for IAs:

A variety of risk factors have been identified and their respective individual impact on the disease and patient outcome not fully investigated. Women are more affected than men, smokers more than non-smokers and hypertensive patients more than

normotensive subjects (7, 25, 26). Oral and gut microbiota emerged as critical environmental factors contributing to human physiology and pathology. Recently, oral bacteria derived DNA has been found in both ruptured and unruptured IA walls in surgically treated Finnish patients (27, 28), suggesting that dental infection could be a part of the pathophysiology of IA disease. Moreover, a mouse model of induced IA formation showed the relevance of gut microbiota for IA formation, and showed that exposure to gut microbiota affects the remodeling of cerebral artery wall through modulation of local immune response without local bacterial infection (29). Interestingly, IA patients have used more antibiotics than their age and gender matched population, suggesting that dysbiosis of the microbiota might be relevant in IA formation also in humans (30). While it remains to be studied whether gastrointestinal tract microbiota is relevant for IA formation in humans, it is important to note that oral microbiota dysbiosis can affect also the microbiota of the gastrointestinal tract (31), thus generating yet another possible explanation how periodontitis may predispose to IA formation. Oral and intestinal microbiota are strongly influenced by the local environment and eating habits. The association of oral and gut microbiota would represent a new factor influencing IA disease that might explain the currently unpredictable evolution of this disease. Importantly, identification of specific forms of oral and gut microbiota would serve as risk biomarkers for IA disease and rupture, and as a target for medical treatment. The clinical alteration, the amount of bleeding and the optimal choice of treatment management all impact independently on the long-term the patient outcome. New evidence appears showing that effects of combined factors vary according to different patient groups and need complex modeling (18, 32-34).

D. Genetics and IAs:

Genetic mechanisms for IA may be either mono-factorial (one single gene with a very strong effect present in the person's genome can cause the disease) or multi-factorial (multiple genes with mild effects present at the same time in the person's genome can predispose to the disease). For example, studies of cases with a familial history of IAs reveal that patients affected by Polycystic Kidney Disease (PKD) are by far the most prone to suffer from IA with a penetrance of approximately 20% (5, 35, 36). Vascular consequences of PKD seem to be due to a dysfunction of the endothelial cells in response to the wall shear stress induced by the blood flow on the vessel wall (37).
Studying the level of expression of a high number of different genes in circulating blood cells from healthy volunteers and patients affected with IAs lead to the identification of differentially expressed genes (38-40). The expression of forty-two genes is significantly modified in patients affected by non-ruptured IAs. Functional analysis shows immune system, inflammatory system and apoptosis to be the major biological processes implicated with aneurysm rupture whereas cell-cell communication and cytoskeleton seem to be implicated in aneurysm formation. Last year by performing a cross-ancestry, genome-wide association study in 10,754 cases and 306,882 controls of European and East Asian ancestry, we discovered 17 risk loci associated with IA disease, 11 of which are new (41). These results revealed a polygenic architecture and explained over half of the disease heritability. A high genetic correlation between ruptured and unruptured IAs has been shown. We also found a suggestive role for endothelial cells by using gene mapping and heritability enrichment. Drug-target enrichment shows pleiotropy between IAs and antiepileptic and sex hormone drugs, providing insights into IA pathophysiology. Finally, genetic risks for smoking and high blood pressure, the two main clinical risk factors, play important roles in IA risk, and drive most of the genetic correlation between IA and other cerebrovascular traits. Such results suggest that the multifactorial effects

extend out of genetics and involve interactions between environmental and genetic factors to cause the disease. Schematically, mono-factorial inheritance is responsible for familial cases while multi-factorial inheritance is mainly responsible for sporadic cases. Because roughly 10% of patients with aneurysmal SAH have first or second-degree relatives with SAH or non-ruptured IA aneurysms there is a likely genetic component to IA.

2) Current management of non-ruptured IAs:

Currently, the process of disease diagnosis, treatment planning and treatment development is compromised by the fragmentation of the underpinning data. Indeed, information is available from a wide range of sources at all levels from personal to population, and at all length scales from molecular through cellular and organ to system. Clinical decision making is usually performed by categorizing aneurysms as high or low risk of rupture considering:

- Location in a high or low risk segment of the cerebrovascular tree;
- Size smaller than 4 mm, 7 mm or larger;
- Overall aneurysm shape as saccular or fusiform;
- Already rupture status of the patient.

From this categorization, clinicians decide to observe or secure the aneurysm by an intervention exposing patients to risks that are difficult to balance. It appears that aggressive clinical treatment is not justified in all cases incidentally diagnosed with IA. Today, an increasing number of patients are monitored instead of being treated (9, 42-44). Clinicians have to extrapolate the individual risk of aneurysm rupture using observations made on cohorts of highly selected patients. Those cohorts are known to poorly represent the general population of subjects seeking medical advice for management of an IA. Due to the potential high impact of the decision, patients tend to refuse randomization regarding treatment, consequently, randomized controlled trials have failed to recruit (45-47). As a result, it appears very difficult to inform the patient on specific rupture *versus* treatment risks. Currently, the estimation of the aneurysm's rupture is based on the PHASES score (Table 1) (9). This is the best available tool but it only estimates the risk of rupture without prediction of death or disability associated with the treatment, and without estimation of the quality of life of the patient following the discovery of the IA and after the treatment.

PHASES aneurysm risk score	Points
(P) Population	
North American, European (other than Finnish)	0
Japanese	3
Finnish	5
(H) Hypertension	
No	0
Yes	1
(A) Age	
<70 years	0
≥70 years	1
(S) Size of aneurysm	
<7·0 mm	0
7·0–9·9 mm	3
10·0–19·9 mm	6
≥20 mm	10
(E) Earlier SAH from another aneurysm	
No	0
Yes	1
(S) Site of aneurysm	
ICA	0
MCA	2
ACA/Pcom/posterior	4

Table 1: PHASES aneurysm risk score (9)

Regarding the treatment of non-ruptured IAs, better understanding of the nature of IAs, and of the interaction between multiple and complex risk factors associated with aneurysm formation, growth and rupture, will allow us to create a decision support tool to assist the management of IAs.

1.3 Rational for the research project

As can be estimated from the discrepancy between the high prevalence of IAs (2-5% of the population) and the low incidence of rupture (5-10/100.000 inhabitants/year), 50% of the patients diagnosed with an IA will never suffer from a bleeding (5). Treatment of non-ruptured IA is associated to risky interventions that may induces patient's disability for several months and also death in the worst case. Financially, the average treatment and first year follow-up care costs for an IA patient is approximately CHF 40'000. Regarding the consequences of the treatment of non-ruptured IAs, better understanding of the nature of IAs, and of the interaction between multiple and complex risk factors relating to aneurysm formation, growth and rupture is needed to create a decision support tool for the management of IAs. To address this clinical challenge of obtaining a lifelong optimal patient health, we address to answer the following questions:

1) Who in the population should be screened for IAs?
2) Among patients diagnosed with IAs, whom should an intervention be offered?
3) Among patients diagnosed with IAs and initially observed, when should an intervention be offered?
4) Which intervention or management plan would offer the best outcome?

This project requires a holistic approach integrating information regarding:

- Genetics
- Environmental and life style factors, comorbidities and treatments
- Congenital factors (i.e. cerebrovascular anatomical variants)
- Shape of cerebral vessels and lesions
- Hemodynamic conditions in the cerebral vessel lumen
- Proteomic variants or profiles in blood, CSF or aneurysmal dome tissue
- Blood bacterial infection and inflammation
- Oral and gut microbiota
- Risk of disability and/or death associated with intervention undertaken to secure IAs
- Quality of life of the patient after discovery of the aneurysm and aneurysm surgery

1) Rational for genetic investigations

Several studies have highlighted genes that could be implicated in IAs initiation, growth or rupture but nowadays no definitive relationship has been demonstrated between one specific gene or a family of genes and IAs. Pursuing this research avenue more particularly in patients with a positive familial history of IAs would be a powerful complement because:

- Finding genetic linkage for familial cases will help in reducing the complexity of the genetics of IA.
- Genes responsible for familial cases may point out candidate genes for the sporadic forms of the disease.
- Some sporadic cases may actually belong to the familial group if for instance some members died before the disease has developed, nothing is known about the early death of a family member or whether there is only a single child in the family.
- Risk assessment in the context of a familial case may be substantially different as compared to sporadic cases.
- We may find new loci that could be specific to each sub-population.
- Screening for genetic markers of risk factors (like i.e. smoking or blood hypertension) may allow a better clustering of cases and associated with clinical information improve the precision of predictors.

Finding a genetic profile predisposing to IA formation or favoring IA rupture could result in a blood-screening test allowing a cheap and efficient selection of a population at risk.

2) Rational for information collection on environmental and life style factors, comorbidities and treatments

Currently, IAs have been described to be more present in women, smokers and hypertensive people (5), but the effects of this factors for IAs growth and rupture are not yet established and need more investigations. Oral and intestinal microbiota are strongly influenced by the local environment and eating habits. Recent work suggests a connection between IA and oral and gut microbiota, but a direct linked has never been proved. As IAs is a multifactorial disease it appears crucial to integrate all factors influencing patient's biology such as environmental and life style factors, co-morbidities and associated treatments. For details about all parameters that will be recorded, please see the electronic Case Report Forms (eCRFs) "AneuX_Antécédents" (Annex 12), and "Aneux_Microbiote" (Annex 13).

3) Rational for evaluation of congenital cerebro-vascular anatomical variants

People with arterio-venous malformations are known to be more prone for IAs formation as compared with people presenting a normal cerebro-vascular anatomy. As IAs growth and rupture seem to be influenced by hemodynamics flux in the parental artery and inside the aneurysm (22), presence of malformations could have additional effects on IAs growth and rupture (13, 14). In addition, existence of arterio-venous malformations increases risks during surgery (15). For these different reasons, more investigations are needed about the cerebro-vascular anatomy and IAs to better balance the risk between rupture and surgery.

4) Rational for cerebral imagery

As described above, aneurysm size and shape may induce hemodynamic or mirror biological conditions prone to induce aneurysm growth or rupture. Studying the differences between patients bearing anatomically stable lesion or in contrast lesions that do change in shape or size could provide information on the mechanism of disease activation or healing processes. Pursuing this avenue of research may allow the design of a better case classifier.

5) Rational for Computational Fluid Dynamics analysis

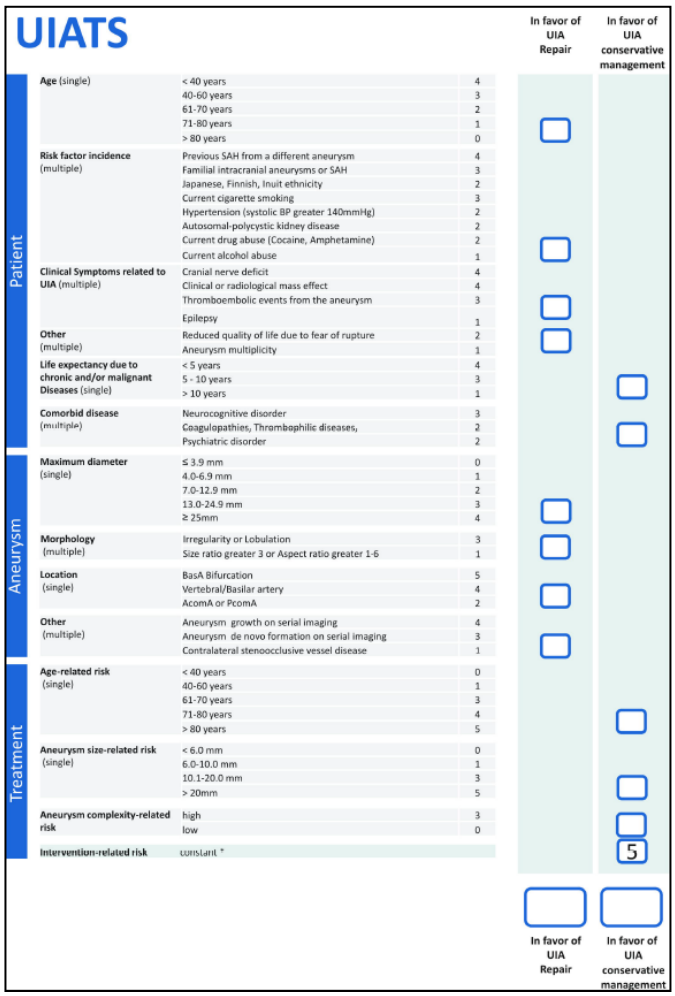
Increasing evidences allow researchers and neurosurgeons to consider that shear stress profile inside an aneurysm could define its growth and its risk of rupture (19-23). In this context, Computational Fluid Dynamics (CFD) analysis of Doppler, 3D-Digital Rotational Angiography (DRA) or 3D-Digital Subtracted Angiography (DSA) images performed during cerebro-vascular investigations for the characterizations of the IAs should provide qualitative measures aimed at assigning aneurysm risk of future rupture.

6) Rational for proteomics analysis

Following on the same track but one step down stream, differential protein expression and post-translational modification will be studied in blood, CSF and/or aneurysmal dome tissue. Searching for new biological markers of cerebral trauma and predictors of SAH complication such as vasospasm, will allow to identify markers for a better staging of the disease and hopefully to find prevention mechanisms or medications.

7) Rational for quality of life and surgery risk evaluations

Nowadays, the PHASES score is the best available tool for the prediction of IA risk of rupture (9), but it doesn't consider the risk of death or disability associated with interventions, and the impact of IA discovery and surgery on the quality of life of the patient. The type of treatment (i.e. surgical clipping, endovascular coiling, stenting or combination) offered to patients is decided on the basis of aneurysm and patient specific factors balanced by a multidisciplinary team. The level of risk for death and disability associated with intervention is estimated on the basis of the team's experience. There is currently a significant knowledge gap regarding the risk quantification as a function of aneurysm, patient and intervention factors. Intervention-related risk factors have been implemented in the Unruptured Intracranial Aneurysms Treatment (UIAT) score (Table 2) but no distinction between the different type of treatment has been made (48). It is therefore expected to improve decision making by quantifying risks integrating aneurysm, patients and intervention risk factors in a statistical and mechanistic disease model.



UIATS			In favor of UIA Repair	In favor of UIA conservative management
Patient	**Age** (single)	< 40 years	4	
		40-60 years	3	
		61-70 years	2	
		71-80 years	1	
		> 80 years	0	
	Risk factor incidence (multiple)	Previous SAH from a different aneurysm	4	
		Familial intracranial aneurysms or SAH	3	
		Japanese, Finnish, Inuit ethnicity	2	
		Current cigarette smoking	3	
		Hypertension (systolic BP greater 140mmHg)	2	
		Autosomal-polycystic kidney disease	2	
		Current drug abuse (Cocaine, Amphetamine)	2	
		Current alcohol abuse	1	
	Clinical Symptoms related to UIA (multiple)	Cranial nerve deficit	4	
		Clinical or radiological mass effect	4	
		Thromboembolic events from the aneurysm	3	
		Epilepsy	1	
	Other (multiple)	Reduced quality of life due to fear of rupture	2	
		Aneurysm multiplicity	1	
	Life expectancy due to chronic and/or malignant Diseases (single)	< 5 years	4	
		5 - 10 years	3	
		> 10 years	1	
	Comorbid disease (multiple)	Neurocognitive disorder	3	
		Coagulopathies, Thrombophilic diseases,	2	
		Psychiatric disorder	2	
Aneurysm	**Maximum diameter** (single)	≤ 3.9 mm	0	
		4.0-6.9 mm	1	
		7.0-12.9 mm	2	
		13.0-24.9 mm	3	
		≥ 25mm	4	
	Morphology (multiple)	Irregularity or Lobulation	3	
		Size ratio greater 3 or Aspect ratio greater 1-6	1	
	Location (single)	BasA Bifurcation	5	
		Vertebral/Basilar artery	4	
		AcomA or PcomA	2	
	Other (multiple)	Aneurysm growth on serial imaging	4	
		Aneurysm de novo formation on serial imaging	3	
		Contralateral stenoocclusive vessel disease	1	
Treatment	**Age-related risk** (single)	< 40 years	0	
		40-60 years	1	
		61-70 years	3	
		71-80 years	4	
		> 80 years	5	
	Aneurysm size-related risk (single)	< 6.0 mm	0	
		6.0-10.0 mm	1	
		10.1-20.0 mm	3	
		> 20mm	5	
	Aneurysm complexity-related risk	high	3	
		low	0	
	Intervention-related risk	constant *		
			In favor of UIA Repair	In favor of UIA conservative management

Table 2: UIATS aneurysm risk score (48)

2 PROJECT OBJECTIVES AND DESIGN

2.1 Hypothesis and primary and secondary objectives

Due to the multi-factorial nature of the disease, it is necessary to provide a holistic information platform covering all aspects of the vessel wall biology and clinical epidemiology to bridge between both worlds: biology and clinical epidemiology. In this context, the purpose of the AneurysmDataBank (ADB) (49) is to collect and harmonize information to allow more personalized and homogenous patient clustering associated with more refined disease management models to allow more accurate predictions according to all available options.

Estimation of the yearly aneurysm rupture risk using tables provided by the PHASES score (Table 1) (9), the International Study of Unruptured Intracranial Aneurysms (ISUIA) study (Table 2) (18, 48) or the Unruptured Cerebral Aneurysm Study (UCAS) (10) remains inaccurate with predictive power of less than 80% (43).

Risk associated with different treatment strategies is estimated on the basis of expert's opinion or analysis of single center case series, observational studies of high-volume centers and a few multicentric, industry supported, single arm studies that have not yet been meta-analyzed.

The purpose of the development of the information platform and associated decision support tools is to reduce the risk of bias by collecting information on a population basis and offer more accurate and personalized estimation of risks to support the disease management.

Recording of information concerning patients and aneurysms, and collection of blood, saliva, stool, CSF and aneurysmal dome tissue will allow interdisciplinary approaches to identify:

- Factors associated with an increased risk of aneurysm formation, such as genetic, proteomics, bacteriomics, anatomical, environmental and life-style factors, co-morbidities and treatments. Quantification of their respective impact on **disease initiation** will be done by comparing characteristics of IA patients with healthy controls.
- Factors associated with aneurysm growth or instability. Quantification of their respective impact on **disease progression** will be done by comparing characteristics of patients and aneurysms between patients presenting stable aneurysm and patients suffering of unstable aneurysms (i.e. new clinical symptoms, geometrical aneurysm dome modifications or vessel wall properties modifications).
- Factors associated with aneurysm rupture. Quantification of their respective impact on **rupture risk** will be done by comparing characteristics of patients and aneurysms between patients presenting stable aneurysm and patients diagnosed with ruptured aneurysm. Particular care will be taken to study characteristics of patients with long term aneurysm stability as compared to the rare patients that suffered aneurysm rupture during follow-up.
- **Prognostic factors** and to quantify their respective impact on outcome by comparing in groups of patients with similar initial characteristics, patients with the best outcomes to patients with the poorest outcome.

The primary objective of the project is to determine the disease burden of the presence of an IA and associated disease management on patient's life. To this aim, the modified Rankin Scale (mRS) will be repetitively measured to assess patient’s survival time and disability during the post diagnostic life duration.

The secondary objectives of the project are:

- To assess differences in the rate of disease associated significant adverse events and death following the diagnosis of an IA between different types of disease managements (medical, surgical, interventional).
- To evaluate the impact of the discovery of non-ruptured IAs and of the associated treatments and follow-up visits on the quality of life of the patients.
- To create a specific data base and a specific biobank on IAs to improve knowledge on initiation, growth and rupture of IAs.
- To create a decision-support tool for the management of non-ruptured IAs to reduce the risk associated with overtreatment of IAs, with poor treatment choices, with atypical follow-up of the patient, and to reduce significant clinical adverse events.
- To evaluate the use of the ADB on care improvement, cost-effectiveness, knowledge discovery and new product development and market promotion.

2.2 Primary and secondary endpoints

To determine the disease burden of the presence of an IA on patient's life, the **initial primary outcome** will be the disability and duration of disability after recruitment measured using the mRS.

Disability is defined as a score higher than 2 on the mRS (50, 51) specified as:

- 0= No symptom at all
- 1= No significant disability despite symptoms; able to carry out all usual duties and activities
- 2= Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
- 3= Moderate disability; requiring some help, but able to walk without assistance
- 4= Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
- 5= Severe disability; bedridden, incontinent and requiring constant nursing care and attention
- 6= Dead

The value of the mRS will be recorded initially assessing the disability prior to diagnosis and at diagnosis and later after treatment, discharge and at each follow-up according to the follow-up schedule (Table 4). mRS will be recorded using the following eCRFs: “AneuX_Antécédents”, eCRF “Aneux_Microbiote”, eCRF “Signes et Symptômes” (Annex 14), eCRF “AneuX_Evaluation de traitement” (Annex 15), eCRF “AneuX_Evaluation à la sortie” (Annex 16) and eCRF “AneuX_Suivi” (Annex 17).

To determine the overall impact of the IA disease on patient's life, we need to compare patients to a reference population not affected by IA. To our knowledge, no epidemiological study measuring the mRS and involving healthy volunteers have yet been performed in Switzerland, forcing us to enroll healthy volunteers in our project as done in other studies (52, 53). In addition, we are highly interested to enroll also family members because they are usually exposed to similar environment factors and will allow the distinction between environmental and genetic factors.

Ultimately the primary outcome will be Disability-Adjusted Life Year (DALY) for each relevant patient group. DALY will be the principal outcome factor to compare different management strategies. DALY is calculated as the sum of Years of Life Lost (YLL) due to premature mortality in the population and Years Lost due to Disability (YLD) for people living with the health condition or its consequences (54, 55):

$$DALY = YLL + YLD$$

YLL is calculated according to:

$$YLL = \frac{KCe^{ra}}{(r+\beta)^2}\left[e^{-(r+\beta)(L+a)}\left[-(r+\beta)(L+a)-1\right]-e^{-(r+\beta)a}\left[-(r+\beta)a-1\right]\right]+\frac{1-K}{r}(1-e^{-rL})$$

where K indicates age-weighting modulation factor; β, parameter from age-weighting function; *r*, discount rate; C, constant; a, age of death; L, life expectancy of general population at age a. Patient’s age-specific life expectancy without disease will be taken from the nation of residency life tables appropriate for gender.

YLD is calculated according to:

$$YLD = DW \{\frac{KCe^{ra}}{(r+\beta)^2} [e^{-(r+\beta)(L+a)} [-(r+\beta)(L+a)-1] - e^{-(r+\beta)a} [-(r+\beta)a-1]] + \frac{1-K}{r}(1-e^{-rL})\}$$

where DW indicates disability weight; K, age-weighting modulation factor; β, parameter from age-weighting function; *r*, discount rate; C, constant; a, age at diagnosis; L, duration of disability.

The secondary outcomes measured in this project will be separated in 4 categories to address to following points:

1) Evaluation of the impact of the discovery of non-ruptured IAs and of the associated treatments and follow-up visits on the quality of life of the patients. The measured outcomes will be:
   - Quality of life: evaluated with the EQ-5D survey (Annex 18).
   - Neuropsychological performance: evaluated with the Mini-Mental State Examination (MMSE™) assessment.
   - Neurological status: evaluated with the National Institute of Health Stroke (NIHS) scale.
   - Cranial nerves function evaluation.

2) Creation of a specific data base and a specific biobank on IAs to improve knowledge on formation, growth and rupture of IAs. The measured outcomes will be:
   - Aneurysm growth: Observation of the growth of an aneurysm after diagnosis: measurements are recorded in the eCRF "AneuX_Données d'imagerie" (Annex 19), the eCRF "AneuX_Anévrisme" (Annex 20) and in the eCRF "AneuX_Suivi".
   - Comorbidities: for details, please see the eCRF "AneuX_Antécédents".
   - Treatments: for details, please see the eCRF "AneuX_Antécédents".
   - Positive familial history of IAs: for details, please see the eCRF "AneuX_Antécédents".
   - Life style risk factors: for details, please see the eCRF "AneuX_Antécédents".
   - Environmental risk factors: for details, please see the eCRF "AneuX_Antécédents".
   - Food and drink habits: for details, please see the eCRF "AneuX_Microbiote".

3) Creation of a decision-making tool for the management of IAs to reduce the risk associated with overtreatment of IAs, with inadequate treatment choices, with inadequate follow-up of the patient, and with significant clinical events associated with IAs. The measured outcomes will be:
   - PHASES score: PHASES aneurysm risk score is described in table 1 (9). All data needed to calculate this score will be recorded in the eCRF "AneuX_Antécédents", in the eCRF "AneuX_Données d'imagerie" and in the eCRF "AneuX_Anévrisme".
   - Unruptured Intracranial Aneurysm Treatment Score (UIATS): UIATS is described in table 2 (48). All data needed to calculate this score will be recorded in the eCRF "AneuX_Antécédents", in the eCRF "AneuX_Données d'imagerie", in the eCRF "AneuX_Anévrisme" and in the

eCRF “AneuX_Signes et Symptômes”.
- Ability to completely and permanently exclude the lesion with the treatment.
- Recurrence or repermeabilisation of the aneurysm after treatment.
- Neo-aneurysm formation: identification of new aneurysm during follow-up.
- Number of significant adverse events observed after the diagnosis of an IA. Significant adverse events are defined as:
  - Rupture of IA after diagnosis leading to the death of the patient
  - Rupture of IA after diagnosis
  - Reintervention on a previously secured IA
  - New focal neurological deficits associated to the IA or intervention to secure the IA
- Occurrence of hydrocephalus.
- Occurrence of vasospasm.

All of these points will be recorded in the eCRF “AneuX_Anévrisme”, in the eCRF “AneuX_Traitement” (Annex 21), in the eCRF “AneuX_Evaluation du traitement”, in the eCRF “AneuX_Evaluation à la sortie” and in the eCRF “AneuX_Suivi”.

4) Evaluation of the use of the ADB on care improvement, cost-effectiveness, knowledge discovery and new product developments and commercialization. Measured outcomes will be:
   - Management cost per patient: number of imaging studies, type of interventions, numbers of hospital days in Critical and Intermediate Care Unit (CCU and ICU) needed to manage the patient due to IA disease.
   - Average disability pension per disease severity groups: national yearly costs in disability pension due to IA and aneurysmal SAH.
   - Number of scientific publications acknowledging the ADB.
   - Number of products or services provided by the ADB.
   - Number of products developed and sold by companies associated with the ADB.
   - Number of commercial entities having contracts with the ADB.

To reduce the confounding influence of baseline factors and to adequately estimate risks associated with the disease, it is important that the clinical sites are meticulous in identifying individuals known to have any of the conditions identified in Table 3. Such information will be recorded in the eCRF “AneuX_Antécédents” and in the eCRF “AneuX_Signes et Symptômes”.

Positive familial history for IA	Hypercoagulable disorders	Hypertension
ArterioVenous Malformation	Fear from IA	Hypercholesterolemia
Abdominal Aortic Aneurysm	Multiple aneurysms	Hypertriglyceridemia
Ehlers-Danlos Syndrome type IV	MoyaMoya disease	Myocardial infarction
Tuberous Sclerosis	Neurofibromatosis type I	Coronary Heart Disease
Former Meningitis	Pregnancy	Stroke
Cancer	Oral contraception	Carotid Stenosis
Sickle Cell Anemia	Hormone replacement therapy	Neurocognitive disorder
Atherosclerosis	Polycystic Kidney Disease	Psychiatric illness
Diabetes Mellitus	Coarctation of the Aorta	Epilepsy

Ethnicity (Caucasian/Japanese/Finnish)	Fibromuscular Dysplasia	Previous use of corticoids
Smoking History	Sturge-Weber Syndrome	Marfan syndrome
Alcohol History	Former Vasculitis	Recent brain ischemic lesion (less that 4 weeks)
Drug History	Alpha 1-antitrypsin Deficiency	Delivery
Migraine	Valvular Heart Disease	Infection disease
Bleeding disorders	Previous history of SAH	Elastic pseudoxanthoma

Table 3: Factors influencing decision making

All factors are compliant with the NIH Common Data Elements defined by the International Working Group (56-63) for patients suffering of SAH and patients diagnosed with IA, and with the proposed integrated disease model (49).

2.3 Project design

This project is an observational study where all decisions and interventions are taken according to international recommendations in the field and to the experience of the physician in charge and local multidisciplinary team. The observations made will serve as a baseline for the future evaluation of decision support tools, new management paradigms, treatments and interventions.

All information reported in the CRF are information routinely obtained or measured by the clinician in the context of IA discovery, treatment and follow-up.

Aneurysm dome removing is part of the surgical treatment process to safely exclude the aneurysm dome from the blood circulation. Aneurysm dome are removed to allow careful visual quality check of the clipping but have currently no relevant clinical value and are traditionally not analyzed. No intervention will be undertaken specifically for the purpose of this study.

The only surveys that the patient will have to complete in addition of usual questions asked in the context of this pathology is the EQ-5D survey for the evaluation of the quality of life of the patient, and the CRF AneuX_Microbiote to know the food and drink habits of the patients.

In addition, blood samples, saliva samples, stool samples and CSF will be harvested for genetics, proteomics or bacteriomics analysis.

For comparison, healthy volunteers and family members will be interviewed as it will be done for patient suffering from IAs. Blood, saliva and stool samples will also be taken from these people.

3 PROJECT POPULATION AND STUDY PROCEDURES

3.1 Project population, inclusion and exclusion criteria

1) Project population

Information will be collected prospectively and consecutively about all patients affected by IA, selected family members when two or more directly genetically linked members are affected and healthy volunteers. The rational is to obtain a minimally biased understanding of the affected population and burden of the disease on society. Special

care will be taken using information technologies to optimally select participants to screen (optimize prevention) and healthy volunteers to assess the reliability and representativeness of existing data to be used (subsidiarity).

There is no defined number of patients to be recruited. The accuracy and refinement of models will progressively be improved with growing number of patients. Based on the recent Swiss Study on Subarachnoid Hemorrhage (Swiss SOS) (7) in which 1787 patients suffering of SAH have been enrolled between 2009 and 2014, and based on the observation reported in the population based studies assessing the follow-up protocol and the PHASES score (43, 44), patients diagnosed with ruptured IA represent 1/3 of the patients affected by IAs. The expected number of patients to be enrolled every year in the HUG is estimated to be at least 150. Approximately 10% of patients are members of families affected by IAs and in each family usually 3 persons could be recruited as family members. Therefore, it is expected that 45 family members could be recruited each year in the HUG. To compare patients affected with IA with healthy controls and assess risk factors and the impact on patient's quality of life with a type I error of 5% and a power of 90%, setting the ratio between controls and patients at 0.7, it is calculated that 105 healthy volunteers should be recruited each year in the study. The relevance of recruiting healthy volunteers will be reassessed regularly (every 3 years).

2) Inclusion criteria

A participant is eligible as patient (IA or IA+SAH) if:

- he/she has an IA identified on the basis of angiographic appearance (3D-DSA, 3D-Magnetic Resonance Angiography (MRA), or 3D-Computed Tomography Angiography (CTA)) and of surgical documentation. SAH has to be verified by Computerized Tomography (CT) / magnetic resonance imaging (MRI) or by lumbar puncture;
  and
- he/she is older than 14 years;
  and
- he/she is able to provide consent. In the case of a patient incapable of providing consent, the consent has to be obtained from a person legally authorized to give it on behalf of the patient according to legal and ethical requirements of the country where the clinical center is located.

Participant eligible as healthy volunteer:

- any individual volunteering, responding to open advertisement or randomly selected in a defined population and accepting to be approached for recruitment;
  and
- he/she is not eligible as a patient or a family member;
  and
- he/she is older than 14 years;
  and
- he/she is able to provide consent.

A participant is eligible as family member if:

- he/she is selected on review of a patient's family tree where at least two directly linked members are affected by IA;
  and
- he/she is contacted by the patient;

and
- he/she is older than 14 years;
and
- he/she is able to provide consent.

3) Exclusion criteria

The presence of one of the following criteria will lead to the exclusion of the participant:

- He/she is younger than 14 years
- Refusal to provide informed consent
- Failure of the candidate to contribute to clinical data
- For patients only: Lack of angiographically proven IA on 3D-DSA, 3D-MRA or 3D-CTA on at least one occasion or a second occasion performed 1 or more weeks later, and absence of confirmatory CT/MRI or lumbar puncture in case of suspected SAH.

The verification that all inclusion and exclusion criteria are respected for all participant will be done automatically and documented on a recruitment form. At the moment of exportation of the data from the CRF to the data bank, the automated process will check the criteria and only export the data from participant filing all the criteria. If one of the criteria is not respected, the participant data will not be exported.

3.2 Recruitment, screening and informed consent procedure

The different participant groups are:

1) **IA**: Patients with one or more identified IA, none of which are believed to have ruptured.
2) **IA+SAH**: Patients with one or more identified IA, at least one of which has been radiologically or surgically determined to have ruptured.
3) **Healthy volunteers (Controls)**: Individuals, accompanying or contacted by a patient, or responding to open advertisement (Annex 22), or randomly selected in a defined population who agree to be approached for recruitment.
4) **Family Members**: Individuals selected on review of a patient's family tree and contacted by the patient, who agree to be approached for recruitment. In affected families, each member will be identified as proband, affected, unaffected, IA status unknown. Not genetically link family members may be recruited as healthy volunteers.

Participants will be recruited from the following sources:

1) **Patients** are people arriving at the clinical center either as newly diagnosed (incidental cases) or already known for the disease (prevalent cases).
   - Patient identification from medical records and ongoing practice has to be performed by the clinician responsible for clinical care of the patient, or a trained alternate who is a member of the patient's clinical care team.
   - A member of the patient's clinical care team, preferably one known by the patient, will introduce the project. The clinical care team member should screen the inclusion and exclusion criteria's, provide the participant's general information letter and the participant's genetic information letter and if there is no basis for exclusion or no unwillingness to participate, the two associated informed consents will be signed by the patient. Sufficient

time has to be given to the patient between information and signature of the consent (usually 72 hours but at the best convenience of the patient).
- The care team member performing this role must have received all information about the project and a training concerning the process of recruitment.
- In case of patients diagnosed with a ruptured IA, as the microbiota can be affected by the medical care, saliva and blood (17 ml) needed for the microbiota project will be collected just before IA treatment. In such cases, the anesthesiologist involved in the care of the patient, but not involved in the research project, will be consulted before any samples collection to defend the patient's interest. The patient or his/her representative will be informed about the project and will receive the informed consent for signature. If the patient or his/her representative refuses the sample to be used for this research, all the samples will be destroyed.
- Self-presentation as a potential patient is not a recognized pathway for identification.
- A patient cannot give consent to a care team member or a researcher on behalf of another.

2) **Healthy volunteers** are people answering a call, randomly selected subjects from a known population that consent to participate or non-genetically linked family members of patients that consent to participate. The initiation of the recruitment pathway for candidate healthy volunteers has to be identification through one of the following pathways (in order of preference for matching to the index patient thus to minimize the environmental effects):
   - The patient identifies the candidate on the basis of requirements of age, and ethnicity matching or analysis of the family history with the assistance of a trained clinician. The patient then introduces the @neurIST project to the candidate, provides the participant's general information letter and the participant's genetic information letter and asks the candidate to initiate contact with the trained clinician. The signing of the consent by a healthy volunteer contacted by a patient will not be done in presence of the patient to respect his/her freedom to accept or refuse to participate.
   - The candidate is known by the clinical researchers at the clinical center through having accompanied a patient at the time of the patient's recruitment, and is thus aware of the ADB, and is approached directly by the clinical researcher.
   - The candidate advances himself or herself in response to open advertisement or indirect publicity.
   - The candidate is randomly selected within a defined population and is directly approached by the clinical researcher.

3) **Family members** are people identified with a familial history of IA:
   - Each patient identified as being a familial case (i.e. having at least one other known family member affected by IA) will be asked to assist the clinical researchers in identifying affected and linking family members for involvement in the study. It will also be asked to perform the initial approach to candidate family members for involvement in the study unless prohibited by local legal or ethical requirements.

- The family member will be recruited only after he/she has agreed to be contacted for recruitment.
- The signing of the consent by a family member will not be done in presence of the patient to respect his/her freedom to accept or refuse to participate.

No compensation or payment will be given to the project participants.

3.3 Study procedures

Information to be collected and definition of patient groups as well as information used to classify patients, compare groups and outcomes for each stage of the disease have been defined by the International Common Data Elements for Subarachnoid Hemorrhage and Unruptured Intracranial Aneurysms Working Group (56-63) and the integrated disease model proposed by the @neurIST investigators (49).

The milestones for a participant recruited as "Patient" are:

- **Initial period**: Period between the initial diagnosis and the first management decision.
- **Treatment**: Period starting with the admission of the patient for the treatment of the IA and the end of the surgical or endovascular treatment (risk securing treatment of the IA).
- **Until 48h after treatment**: Time of clinical evaluation between the risk securing treatment of the IA until 48h after the treatment of the IA.
- **Discharge**: Time of clinical evaluation when patient is discharged from the specialized service to return home or to be transferred to rehabilitation or other secondary care institution.
- **Follow-up**: Scheduled follow-up visits are fixed according to initial condition at week 6 (W6), month 3 (M3), month 6 (M6), year 1 (Y1), year 5 (Y5) after diagnosis or treatment, and every 5 years (E5Y) thereafter.

The milestones for a participant recruited as "Family member" or "Healthy volunteer" are:

- **Initial period**: Period until 3 months following the agreement to participate to the study.
- **Follow-up**: every 5 years (E5Y).

For each milestone and participant group, a set of assessments will be recorded and samples could be harvested as described in the Annex 23 "Schedule of assessments" and in more details below.
Clinical history, imaging data, biological samples and information derived from are the main items to be captured to the ADB. No limits are set on the number of participants for whom data can be entered to the ADB.

1) Initial period:

A. Clinical evaluation:

For all participants, the following information (for details of each items see eCRF "AneuX_Antécédents", eCRF "Aneux_Microbiote" and eCRF "AneuX_Signes et symptômes") will be collected either directly or with help of relatives:

- Administrative information

- Demographic information
- Disability based on the mRS (prior to ictus for IA+SAH)
- Treatments
- Epilepsy
- Personal medical history
- Comorbidities
- Positive familial history for IA or SAH
- Systematic screening for risk factors according to list
- Quality of life using the EQ-5D survey
- Food and drink habits

For patients with IA and patients with IA+SAH, the following additional information will be collected:

- Neuropsychological performance using the MMSE™ assessment
- MMSE @neurIST scale
- Montreal Cognitive Assessment score (MoCA)
- Cranial nerve deficits evaluation
- Focal signs evaluation
- Type of IAs and characterization

For patients with IA, the specific additional following information will be collected:

- Fear of rupture

For patients with IA+SAH, the specific additional following information will be collected:

- WFNS and hWFNS scores
- Consciousness level on Glasgow Coma Scale (GCS)

The interview of the patient will be done by a clinician of the clinical care team via the use of computerized data entry of the hospital's patient records interface at the sites with suitable informatics infrastructure. For healthy volunteers and family members, interviews will be performed by a clinical researcher who has completed training in the interpretation of the questions and the use of the software.
The time to inform, answer questions and give the information sheets and consent forms is estimated to require 30 minutes.
The time required for completion of the EQ-5D survey should be around 15 minutes.
When possible, the data questionnaire should be administered prior to any planned or emergency treatment.
Completion of the questionnaire will take place within the clinical care institution, in a consultation room or similar location for ensuing privacy during the process.

B. <u>Imaging data (for patients only):</u>

Patients with IA or with IA+SAH will be assessed for;

- IA characterization by 3D-MRA, or 3D-CTA or 3D-DRA. Additional information consisting for example of bi-plane x-ray angiography, MR phase mapping flow maps, 4D-Xray angiography, transcranial Doppler ultrasound, or intravascular pressure measurements may be included.
- Hydrocephalus measuring ventricular size on imaging.

The imaging and angiographic data have to be derived from scans obtained in the course of routine clinical exams or from scans performed as part of other research projects.
On the basis of the imaging examinations, general observations about the intra-cranial vessels will be recorded and the aneurysms will be classified as to location, size and morphological features, consistent with clinical practice. Hemorrhage will be classified according to location, volume and mass effect. Presence of hydrocephalus will be reported as well as observation of vasospasm. These details are to be recorded as part of the radiological report for the patient. All information will be recorded is the eCRF "AneuX_Données d'imagerie" and in the eCRF "AneuX_Anévrisme".

Imaging and angiographic datasets will be incorporated into the ADB from IA and IA+SAH patients agreeing to have such data included. Angiographic data are to be provided to the ADB in DICOM format.
Acquisition parameters for routine angiographic studies are also known to vary between sites and changes over time are likely. To ensure the images obtained are optimal for both diagnostic and CFD modelling purposes, outline guidance on recommended parameters and practice are provided in the Annex 24: AneurysmDataBank regulation.

No specific exams will be performed in healthy volunteers and in family members for the project.
No requirement is made but it is routinely recommended that family members of IA or IA+SAH patients considered at risk undergo screening angiography for IA. However, these individuals should be asked whether they have had angiography, and if so, the angiogram findings should be verified, and consent requested to incorporate any 3D angiograms into the database.

C. <u>Blood samples:</u>

For all participants, a total of 56 mL of blood samples will be taken for:

- Genetics (17 mL), PAXgene DNA tube (2x8.5 mL) (ref: 761125)
- Gene expression profiling (5 mL), PAXgene RNA tube (2x2.5 mL) (ref: 762165)
- Protein marker profiling (17 mL), BD Vacutainer ACD-A (2x8.5 mL) (ref: 366645)
- Bacteriomic analyses on serum (6 mL), BD Vacutainer (ref: 367815)
- Bacteriomic analyses on whole blood (8.5 mL), PAXgene DNA tube (ref: 761125)
- Bacteriomic analyses on whole blood (2.5 mL), PAXgene RNA tube (ref: 762165)

Blood samples will be collected for genetics, gene expression profiling and protein marker profiling (Maximal blood volume collection: 39 mL) or for bacteriomic analyses (Maximal blood volume collection: 17 mL).
The time to take the blood sample is less than 20 minutes.

D. <u>Saliva sample:</u>

Saliva will be collected using the kit GeneFiX™ 2ml DNA/RNA Collector – GFX-02 (Isohelix).
Samples will be collected by rubbing saliva on the side of the back (molar) teeth with sheet swab and will be stored frozen until analysis.
The time to take the saliva sample is less than 5 minutes.

E. Stool sample:

Stool will be collected using the kit STF-S1/1/50, StoolFiX™ Tube Pre-Filled with 1ml Stabilization Buffer pk50 (Isohelix).
The time to take the stool sample is less than 5 minutes.

Collection of the samples have to be recorded in the eCRF "AneuX_Echantillons" (Annex 25).
Biological samples collection has to follow the AneurysmDataBank regulation.
Biological samples will be conserved in the Serotec of the Centre Médical Universitaire, Rue Michel-Servet 1, 1211 Geneva.

2) Treatments (for operated patients only):

A. Information about the treatment:

The type of treatment (surgery, endovascular interventions and supportive interventions) and the date of the intervention will be recorded in the eCRF "AneuX_Traitements".

B. Biological samples harvested for therapeutics, but not used in diagnostics:

For patients needing microsurgical clipping or the introduction of a cerebral ventricular catheter or intraparenchymal monitoring device, the CSF evacuated for treatment purposes will be stored. The patient will be asked for authorization of the storage and the use of CSF for research.
For patients treated by microsurgical clipping of the aneurysm it is standard procedure to cut the aneurysmal dome out to properly verify the complete exclusion of the aneurysm and preservation of all neighboring small perforator vessels. The patient will be asked for authorization of the storage and the use of the aneurysmal dome tissue for research.
For histological investigation, the aneurysmal dome will be conserved in formol. For bacteriomic analysis, the aneurysmal dome will be conserved in an RNA later solution (Merck R0901).

C. Blood samples:

For treated patient, four blood samples will be taken within the 48 hours following the treatment for gene (2x2.5 mL) and protein (2x8.5 mL) expression profiling analysis (Maximal blood volume collection: 22 mL).
For treated patient, 3 blood samples will be taken before any antibiotic treatment for the bacteriomic analysis (Maximal blood volume collection: 17 mL).
Blood samples will be collected for gene and protein expression profiling analysis or for bacteriomic analysis.

D. Saliva sample:

For treated patient, saliva will be collected before any antibiotic treatment following the same protocol as in the "Initial period" for the bacteriomic analysis.

E. Stool sample:

For treated patient, stool will be collected before any antibiotic treatment following the same protocol as in the "Initial period" for the bacteriomic analysis.

For detailed protocols, please see the AneurysmDataBank regulation.
Biological samples harvesting is not allowed to interfere with clinical care.

Collection of the samples will be recorded in the CRF “AneuX_Echantillons”.
Biological samples will be conserved in the Serotec of the Centre Médical Universitaire, Rue Michel-Servet 1, 1211 Geneva.

3) Until 48h after treatment (for operated patients only):

During the 48h after securing the aneurysm the following information will be collected for all operated patients and reported in the eCRF “AneuX_Evaluation Traitement” and in the eCRF “AneuX_Anévrisme”:

- Disability based on the mRS
- Epilepsy
- Neuropsychological performance using the MMSE™ assessment
- MMSE @neurIST scale
- Montreal Cognitive Assessment score (MoCA)
- Cranial nerve deficits evaluation
- Focal signs evaluation
- Consciousness level on Glasgow Coma Scale (GCS)
- Evaluation of IA treatment
- Complications
- New event
- Death (review of death certificates and autopsy reports may be requested to ensure completeness of the clinical history report. Of special interest is the date of death, the primary and contributing cause of death)
- Imaging data

4) Discharge (for operated patients only):

Before patients are discharged back home or to another institution or to a rehabilitation unit, the following information will be recorded in the eCRF “AneuX_Evaluation à la sortie” and in the eCRF “AneuX_Anévrisme”:

- Disability based on the mRS
- Treatments
- Epilepsy
- Neuropsychological performance using the MMSE™ assessment
- MMSE @neurIST scale
- Montreal Cognitive Assessment score (MoCA)
- Cranial nerve deficits evaluation
- Focal signs evaluation
- Consciousness level on Glasgow Coma Scale (GCS)
- Complications
- Destination of patient
- The number of days since admission
- The number of days in CCU
- The number of days ventilated
- The number of days in ICU
- Complains
- Death
- Imaging data (if not done at 48h post-treatment)

5) Follow-up:

On successive return clinical visits to the clinical care centre, a reduced version of the questionnaire will be used for clinical history follow-up data. The frequency of follow-up

visits recommended by the project varies with initial condition of recruitment (Table 4).

Participant groups	IA management status	Follow-up milestones
IA	Observation	Y1 / Y2 / Y5 / E5Y
	Treated by surgery	W6 / Y1 / Y5 / E5Y
	Treated by endovascular intervention	M6 / Y1 / Y5 / E5Y
IA+SAH	Treated by surgery	W6 / M3 / Y1 / Y5 / E5Y
	Treated by endovascular intervention	M3 / Y1 / Y5 / E5Y
Family members	Not applicable	E5Y
Healthy volunteers	Not applicable	E5Y

Table 4: Times for follow-up visits

To facilitate patient contacts, patients will be asked as part of the consent process to agree or disagree to being contacted on no more than an annual basis for follow-up purposes.
Different strategies may be evaluated for obtaining follow-up data from patients who do not attend annual follow-up visits as part of their clinical routine. These include postal questionnaire, telephone interview and a possible web-questionnaire.
The patients agreeing to participate in follow-up contact will be asked to provide the name and address of their primary care doctor and to sign a medical release form for use in the event that the patient cannot be contacted directly.

A. Clinical evaluation:

All patients will be evaluated regarding the following items and all of information will be collected in the eCRF “AneuX_Suivi” and in the eCRF “AneuX_Anévrisme”:

- Disability based on the mRS
- Treatments
- Epilepsy
- Comorbidities
- Risk factors according to list
- Neuropsychological performance using the MMSE™ assessment
- MMSE @neurIST scale
- Montreal Cognitive Assessment score (MoCA)
- Cranial nerve deficits evaluation
- Focal signs evaluation
- Consciousness level on Glasgow Coma Scale (GCS)
- Quality of life using the EQ-5D survey
- Complications
- New event
- Complains
- Death

For patients with untreated IA, the specific additional following information will be collected:

- Fear of rupture

For family members and healthy volunteers, only the following information will be collected:

- Disability based on the mRS
- Quality of life using the EQ-5D survey
- Death

B. Imaging data (for patients only):

To follow the evolution or the recurrence of the disease, 3D-MRA, 3D-CTA or 3D-MRA will be performed in patients. All information will be collected in the eCRF "AneuX_Anévrisme".
Modalities are the same as for images obtained during the initial period (see above and in the AneurysmDataBank regulation.

C. Blood samples (for treated patients only):

For treated patient, four blood samples will be taken within the 48 hours following the treatment for gene (2x2.5 mL) and protein (2x8.5 mL) expression profiling analysis (Maximal blood volume collection: 22 mL).
For treated patient, at least 6 months after the end of antibiotic treatment, 3 blood samples will be taken for the bacteriomic analysis (Maximal blood volume collection: 17 mL).
Blood samples will be collected for gene and protein expression profiling analysis or for bacteriomic analysis.

For detailed protocols, please see the AneurysmDataBank regulation.
Blood sample harvesting should not interfere with clinical care.
Collection of the samples have to be recorded in the eCRF "AneuX_Echantillons".
Biological samples will be conserved in the Serotec of the Centre Médical Universitaire, Rue Michel-Servet 1, 1211 Geneva.

D. Saliva sample:

For treated patient, at least 6 months after the end of antibiotic treatment, saliva will be collected following the same protocol as in the "Initial period" for the bacteriomic analysis.

E. Stool sample:

For treated patient, at least 6 months after the end of antibiotic treatment, stool will be collected following the same protocol as in the "Initial period" for the bacteriomic analysis.

5) Expected bias and taken measures:

A. Recruitment bias:

It is ethically and financially impossible to recruit all people affected by IA in Switzerland. It would need the screening of the full Swiss population and the risk/benefit balance has been shown beneficial only in specific subgroups of patients at high risk. Listing of recruited patients in the @neurIST project will be compared to listing of diagnostic and intervention codes in the HUG. All patients diagnosed with IA in the HUG should receive the information regarding the @neurIST project and should have the opportunity to be

enrolled in the project. Finally, particular efforts will be made concerning the recruitment of complex cases and deceased patients to reduce the risk of sample bias. Recruitment of deceased patient will be performed by the clinician who was in charge of the patient. One month following the death of the patient, the clinician contacts by phone a family member to find out about the family's experience of the tragic situation, to ensure that there is no outstanding issue, and to respond to concerns they could have. Then, the clinician will explain the study to the family member and will offer to send all the information about the project, and ask for consent.

B. Missing data bias:

To reduce the volume of missing data, CRF collecting data have been integrated within the Geneva University Hospital clinical information system and integrated to clinical practice and part of the necessary clinical documentation of cases. Such forms are part of the clinical patient files and are completed at each visit of the patients. Data extraction for the @neurIST project is performed automatically from these clinical forms limiting missing data and errors. Moreover, to favor the use of such forms in routine clinical practice, a clinical decision support tool will be added to the forms. To use such decision support tool, the forms have to be sufficiently documented reducing the quantity of missing data. At each follow-up visit, forms are checked and completed if data is missing. Once the data is extracted, presence of missing data will be inspected and information regarding missing data transferred to the clinician in charge for completion on the next patient visit.

C. Data quality bias:

The clinical file of each patients is discussed in multidisciplinary team meetings and signed by the clinician in charge of the patient limiting erroneous data. At each data extraction, outliers and incoherent data will be carefully inspected and if errors are identified after a careful file inspection and on a case by case basis corrected after discussion with the clinician in charge of the patient. The correction will be recorded in the case log.

3.4 Withdrawal and discontinuation

All participants retain the option of withdrawing from the study at any time. All participants are informed of the possibility to be withdrawn from the project and will be withdrawn on her/his demand.
When a participant indicates its desire to withdraw from the study to its contact at the clinical center, the participant will be provided the “Declaration of Withdrawal of Consent” (Annexes 9 and 10). The participant does not have to state their reason for withdrawal.
At withdrawal, two options are proposed to the patient: 1) All mechanisms for linking the information covered by the project to personal identifying information are removed and data are anonymized; or 2) Data and biological material are kept coded. Importantly, the collected data already recorded in the database will still be analyzed because once integrated into the database their destruction will become impossible.
The participant has also to choose whether his/her biological samples could be conserved or not.

4 STATISTICS AND METHODOLOGY

4.1 Statistical analysis plan

Statisticians and methodologists from the @neurIST project and later the ZHAW Institute (ZHAW Life Sciences und Facility Management, Einsiedlerstrasse 31a, 8820 Wädenswil) as well as statisticians and methodologists from the different clinical research centres of the different centres involved were and are integrated in the study when joining the effort.

1) Determination of Sample Size
There is no limited number of patients to be recruited. The accuracy and refinement of models will progressively be improved with growing number of patients. Based on the recent Swiss Study on Subarachnoid Hemorrhage (Swiss SOS) (7) in which 1787 patients suffering of SAH have been enrolled between 2009 and 2014, and based on the observation reported in the population based studies assessing the follow-up protocol and the PHASES score (43, 44), patients diagnosed with ruptured IA represent 1/3 of the patients affected by IAs. The expected number of patients to be enrolled every year in the HUG is estimated to be at least 150. Approximately 10% of patients are members of families affected by IAs and in each family usually 3 persons could be recruited as family members. Therefore, it is expected that 45 family members could be recruited each year in the HUG. To compare patients affected with IA with healthy controls and assess risk factors and the impact on patient's quality of life with a type I error of 5% and a power of 90%, setting the ratio between controls and patients at 0.7, it is calculated that 155 healthy volunteers should be recruited each year in the study. The relevance of recruiting healthy volunteers will be reassessed regularly (every 3 years).

2) Data processing
All clinicians involved in this project will be trained to adequately fill-up the eCRF. As data for this project will be collected in a multi-national clinical practice setting, it cannot be expected that the schedule of assessments will be respected accurately in all study sites. Therefore, for data to be analyzed by study visit, broad visit windows will be defined before database freezing, together with the definition of rules to determine the unique value to be used in case of multiple assessments within any given window.
Other data manipulation procedures will be documented in the statistical report.

3) Planned analysis
Intracranial aneurysm disease is defined by different phases :1) IA initiation; 2) IA growth characterized by modification of the IA geometry and/or change in the vascular wall composition; 3) IA rupture; 4) Vasospasm; 5) Hydrocephalus; 6) Recurrence defined as IA repermeabilisation or new IA formation on the same artery or new IA formation on a different artery.

For each stage, sets of factors and outcomes specific for each group of patients and stage transition have been determined in an integrated disease model proposed by the @neurIST investigators (49).

A. <u>Univariate analyses to compare basic characteristics of patient groups:</u>
    a. Comparison of dichotomic variables. Proportion will be compared using Fischer's exact test.

b. Comparison of categorical variables presented as median and quartiles or by absolute and relative frequencies. Comparison will be performed using Chi-Square or non-parametric Mann-Whitney U test.
c. Comparison of continuous variables reported as mean ± Standard Deviation (SD). Comparison will be performed using Student's t-test.

Two-sided P values of less than 0.05 will be considered as threshold for statistical significance and Bonferroni corrected for multiple testing if required.

B. Multivariate analyses to compare predictors of outcomes:

Multivariate analysis will be performed to determine the predictor factors of the different phases of the disease. For this purpose, parameters found to be significant ($P < 0.05$) in the univariate analysis will be analyzed using multivariate logistic regression to identify those parameters that retained significance when accounting for all relevant variables. Odds Ratios (ORs) will be reported with a 95% Confidence Interval (CI). Receiver Operating Characteristic (ROC) analysis will also be performed for all relevant parameters. The ROC curves will be plotted, and Area Under the Curve (AUC) values for each relevant parameter will be calculated and compared. The ROC curves and the AUC indicate the limits of a parameter's ability to discriminate between the subgroups. Thresholds for optimal sensitivity and specificity will also be calculated for parameters that were found to be significant.
Currently, some set of predictors are described in the literature but need to be confirmed such as cerebro-vascular shape, hypertension, and smoking for IA initiation; IA location, IA size, hypertension and gender for IA growth; IA location, IA size, IA shape, gender and age for IA rupture; Fisher grade or automated blood quantity assessment for vasospasm; Fisher grade, presence of acute hydrocephalus, atrophy and age for hydrocephalus.

As illustrated in recent publications involving investigators of the study, new advanced analysis tools based on statistical learning will be used to refine models specific to each stage of the disease (22, 23, 64-67).

As described previously, IA disease in a complex disease evolving through different stages and influenced by a lot of factors. To increase the clinical relevance and evolution of the models, Bayesian statistics will be used considering a priori predictor factors determined from our initial study and from the literature. The Bayesian's model that will emerge will be continuously updated by inferences of parameters or hypotheses as evidences will accumulate.

All statistical analysis will be performed using the statistical software R (68). To avoid or reduce data protection issues and accidental patient re-identification, analysis codes written in R will be developed on mock data sets. The R codes will be cross-checked by trusted parties before being run on the real data set and results based on less than 5 patients sensored. Only aggregated data will be provided back as results.

Datasets to be analyzed

Univariate analysis will include all patients who fulfill the selection criteria.
For the multivariate analysis, two-third of the patients who fulfill the selection criteria will be used to develop the model of each disease stage and one-third of the patients will be used to validate the model.

Ancillary analysis

Sensitivity analyses will be performed as described in the paragraph "Planned analysis".

Deviations from the original statistical plan
Deviations from the original statistical plan will be justified and documented in the statistical report.

4.2 Handling of missing data

To reduce the volume of missing data, CRF collecting data have been integrated within the Geneva University Hospital clinical information system and integrated to clinical practice and part of the necessary clinical documentation of cases. Such forms are part of the clinical patient files and are completed at each visit of the patients. Data extraction for the @neurIST project is performed automatically from these clinical forms limiting missing data and errors. Moreover, to favor the use of such forms in routine clinical practice, a clinical decision support tool will be added to the forms. To use such decision support tool, the forms have to be sufficiently documented reducing the quantity of missing data. At each follow-up visit, forms are checked and completed if data is missing. Once the data is extracted, presence of missing data will be inspected and information regarding missing data transferred to the clinician in charge for completion on the next patient visit.

In addition to the efforts for limiting missing data during data collection, standard inferring methods will be used to reduce missing data. However, data manipulation will be reduced as much as possible and most probably not necessary. It is expected that by promoting the interaction between patients and clinicians with the decision support tool, data collection of the most relevant information will progressively improve in quantity and quality avoiding the need of missing data handling.

5 REGULATORY ASPECTS AND SAFETY

5.1 Local regulations / Declaration of Helsinki

This research project will be conducted in accordance with the protocol, the Declaration of Helsinki (3), the principles of Good Clinical Practice, the Human Research Act (HRA) (2) and the Human Research Ordinance (HRO) (1) as well as other locally relevant regulations. The Sponsor and the Project Leader acknowledge their responsibilities.

5.2 Notification of safety and protective measures (HRO Art. 20)

The project leader is promptly notified (within 24 hours) if immediate safety and protective measures have to be taken during the conduct of the research project. The Ethics Committee will be notified via BASEC of these measures and of the circumstances necessitating them within 7 days.

5.3 Serious events (HRO Art. 21)

The risks associated with this study are those related to a blood test (low infectious risk, hematoma) and the use of a computer network for the transfer of data whose safety can never be fully guaranteed.

We will endeavor to make the blood tests as painless as possible and will put in place security measures for all our coded data transfers.

Assessment and documentation of unrelated and related serious events (SEs) will be done by expert clinicians. All SEs will be documented in the participant's file and on the SE report (Annex 26).
If a serious event occurs, the research project will be interrupted and the Ethics Committee notified on the circumstances via BASEC within 7 days according to HRO Art. 21[1].
The project leader will report any occurring SE to the responsible EC within 7 days. He will also submit a report which will evaluate the relationship between the event reported and the methods of collecting health related personal data or sampling of biological material within the project.
The project leader will notify the EC within 7 days of any immediate other safety and protective measures, which have to be taken during the conduct of the research project. In addition, the project leader will explain the circumstances, which necessitated the safety and protective measures.

5.4 Procedure for investigations involving radiation sources

NA

5.5 Amendments

Substantial changes to the project set-up, the protocol and relevant project documents will be submitted to the Ethics Committee for approval according to HRO Art. 18 before implementation. Exceptions are measures that have to be taken immediately in order to protect the participants.

5.6 End of project

This project is an observational study about a chronic disease whose purpose is to create a decision support tool for the management of intracranial aneurysms. The criteria for the termination of the project will be the creation of such a reliable tool. However, such a tool is a dynamic tool most probably requiring a constant evolution, in consequence the probability to terminate this project is quite low.

The Sponsor or the Project Leader may terminate the study prematurely according to certain circumstances, for example:

- Ethical concerns;
- Insufficient participant recruitment;
- When the safety of the participants is doubtful or at risk;
- Alterations in accepted clinical practice that make the continuation of a project unwise.
- Lack of funding or resources to continue the project.

[1] A serious event is defined as any adverse event where it cannot be excluded, that the event is attributable to the sampling of biological material or the collection of health-related personal data, and which:
a. requires inpatient treatment not envisaged in the protocol or extends a current hospital stay;
b. results in permanent or significant incapacity or disability; or
c. is life-threatening or results in death.

The premature end or interruption of the research project will be reported to the EC within 90 days upon completion of the project (HRO Art. 22).

5.7 Insurance

In the event of project-related damage or injuries, the Sponsor will be liable, except for damages that are only slight and temporary; and for which the extent of the damage is no greater than would be expected in the current state of scientific knowledge (Art. 12 HRO).

6 FURTHER ASPECTS

6.1 Overall ethical considerations

IAs which have a prevalence between 2 to 5% of the general population are mostly quiescent and asymptomatic, but once diagnosed they induce patient's fear to be the victim of SAH. In Switzerland, SAH results in 24% death, 11% severely disabled patients and 64% patients recovering to a more or less independent life. Only 24% of the patients recover with no residual symptoms (7). However, treatment of non-ruptured IA is a risky intervention inducing patient's disability for several months and death in the worst case. Today, more and more patients face the extreme situation to take the decision to live with their IA or to treat it. Regarding the consequences of SAH and of the treatment of non-ruptured IAs, better understanding of the nature of IAs, and of the interaction between multiple and complex risk factors relating to aneurysm initiation, growth and rupture is needed to create a decision support tool for the management of IAs.

This project is an observational study where all decisions and interventions are taken according to international recommendations in the field and to the experience of the physician in charge and local multidisciplinary teams. All participants will be informed about the research project by the clinician in charge of the patient or by research nurses or clinical researchers dedicated to the present project. This project is of minimal physical risk for the patient, indeed, all investigations that will be performed will be those routinely done to characterize and follow IAs or to follow the behavior of a ruptured IA with the exception of blood, saliva and stool samples for genetics, proteomics and bacteriomics.

The end result of the ADB is to provide a detailed assessment tool to monitor the aneurysmal disease burden and optimize patient care by developing and continuously up-dating a decision-support tool. It will support the collection of information and biological material to be investigated to better understand the patho-physiological processes involved in the disease. This databank and associated biobank will be beneficial to the overall aneurysm patient population. The original patient group will also profit from the study because IA is a life-long chronic disease that requires periodical re-evaluation. Decision making could be influenced in the future by the currently acquired information and biological samples.

6.2 Risk-Benefit Assessment

Presently, no precise and validated tool exists to balance the risk of rupture of an aneurysm with the risk of complications associated with the treatment option of this aneurysm. The end result of the ADB (49) is to provide a decision-support tool for the

management of IAs.

This project is of minimal physical risk for the patient. Indeed, all exams that will be performed will be those routinely done to characterize and follow the patients with IAs or to follow the behaviour of a ruptured IA with the exception of blood, saliva and stool sample collected for genetics, proteomics and bacteriomics investigations.
Concerning data security, information will be transferred over secured networks and links will be made with electronic hospital patient records (for details, please see section 7). It is part of the project to control data accesses, and comply to all clinical research good practice requirements as well as with EU General Data Protection Rules 2016/679. Despite the best use of methods for improving medical research using the latest information technologies, perfect data protection cannot be absolutely guaranteed, but all measures will be taken to ensure data protection. Data protection breaches will be reported and measures taken immediately to reduce the potential harm as much as possible.

A third risk lays in the return of clinically relevant details. The participants may receive individual research results, which could aid disease treatment and diagnosis. Participants will, as part of the informed consent process, have to choose whether or not they want to be contacted about any results relevant to their health. The return of individual research results will be reviewed by the Ethic and Legal Advisory Board, an internal ADB committee, which will consider whether results should be returned, the method of return, and whether counselling may be needed. In case of concerns caused by the study, psychological support will be offered to patients if wishes.

This database will be beneficial to the overall aneurysm patient population. The original patient group will also profit from the study because IA is a life-long chronic disease that requires periodical re-evaluation. Decision making could be influenced in the future by the currently acquired information and biological samples.

6.3 Rationale for the inclusion of vulnerable participants

Vulnerable participants are included in the present study. Rational for the inclusion of vulnerable participants is that the disease itself affects consciousness and judgement capacity in a high proportion of patients and exclusion would highly bias observations and result in clinically dangerously overoptimistic conclusions. Teenagers are rarely affected and medical management and treatments cannot be extrapolated from the adult population. It would be a discrimination to exclude this population from the project. Procedure to recruit and consent vulnerable participants in normal and emergency situations (incapable of judgment, under tutelage and capable of judgement, minor) is described in section 1.1. Legal requirements.

7 QUALITY CONTROL AND DATA PROTECTION

7.1 Quality measures

The interview of the patient will be done by a clinician of the clinical care team via the use of computerized data entry of the hospital's patient records interface.

For healthy volunteers and family members, interviews will be performed by a research nurse or a clinical researcher who has completed training in the interpretation of the questions and the use of the software.
The expert clinicians, research nurses and clinical researchers will only get access to the eCRF after specific training by the trial management. Information collected in these eCRF will permit the review of each particular case to check for data accuracy. The clinicians will have to sign a summary report that will be stored as a legally binding medical reports in the hospital archives. All this process should allow high data quality recording.

Health-related personal data captured during this project are strictly confidential. Data generation, storage and analyses of health-related personal data within this project will strictly follow the current Swiss legal requirements for data protection and will be performed according to the Ordinance HRO Art. 5. Only authorized personnel will have access to health-related data. Information about study subjects will be kept confidential and managed according to the requirements of the Authorities. For quality assurance, the Ethics Committee may visit the research sites. Direct access to the source data and all project related files and documents must be granted on such occasions.

7.2 Data recording and source data

All data will be recording in electronic CRF.

The eCRF “AneuX_Données Légales”, “AneuX_Antécédents”, “AneuX_Signes et Symptômes”, “AneuX_Evaluation de traitement”, “AneuX_Evaluation à la sortie”, “AneuX_Suivi”, “AneuX_Données d’imagerie”, “AneuX_Anévrisme”, “AneuX_Traitement”, “AneuX_Echantillons” are part of the « Dossier Patient Intégré » (DPI) system of the HUG.

The eCRF « AneuX_Microbiote » will be a Redcap® form.

To optimize resources and data collection quality, all information (primary and secondary outcomes) will be directly captured from expert clinicians during patient evaluation using eCRF adjusted to the clinical work flow. These expert clinicians will only get access to the eCRF after specific training by the trial management. Information collected in these eCRF will permit the review of each particular case to check for data accuracy. The clinicians will have to sign a summary report that will be stored as medical reports in the hospital archives. All this process should allow high data quality recording.

Only validated scores, scales and surveys commonly used for patients affected by IA will be recorded.

Source data collected in this project (with the exception of the data collected for the eCRF “AneuX_Microbiote”) are data routinely collected during the daily practice.

Source data collected in the eCRF “AneuX_Microbiote” are collected specifically for the project.

7.3 Confidentiality and coding

1) Confidentiality
Data generation, transmission, storage and analysis of health-related personal data, and the storage of biological samples within this project will strictly follow the current Swiss

legal requirements for data protection and will be performed according to the Ordinance HRO Art. 5.
Health-related personal data captured during this project and biological samples from participants are strictly confidential and disclosure to third parties is prohibited; coding will safeguard participants' confidentiality.
Project data will be handled with uttermost discretion and only be accessible to authorized personnel.
Information about study subjects will be kept confidential and managed according to the requirements of the Authorities. Direct access to source documents will be permitted for purposes of audits or inspections.

The ADB infrastructure (Figure 1) is divided in three zones as described by Kuchinke *et al.* (69, 70).

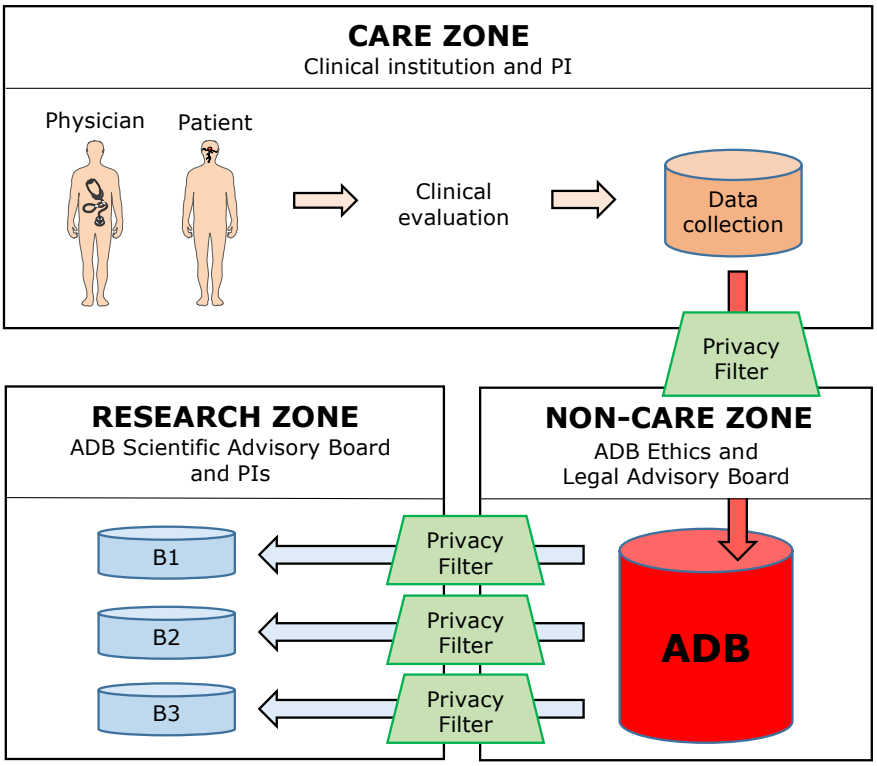


Figure 1: AneurysmDataBase (ADB) infrastructure

Although tools and services are provided to clinicians by the sponsor or other partners, the “Care Zone” is under the full responsibility of the clinical institution and principal investigator and comply with local medical practice and documentation regulations. Data stripped of all identifiable information and coded with a global unique pseudonym for each patient and transferred to the “Non-care Zone” managed by the ADB. The “Non-care Zone” is under the responsibility of the sponsor Geneva University Hospitals. The “Research Zone” contains different extractions (Bx) of the ADB where each case receives a new pseudonym for each extraction. Each extraction is limited to the necessary information required to answer the question addressed by the researcher. Researchers will be granted access to a mock of her/his requested Bx to code her/his analysis in R. The analysis code will be reviewed by the third party in charge of the “Non-care Zone” of the ADB to check it complies with the research agreement and sensors all results based on less than 5 patients to reduce the risk of accidental participant re-

identification. Only aggregated results are delivered to the researchers. It is not allowed and technically made extremely difficult to merged different extractions to avoid uncontrolled reconstruction of the original database. The “Research zone” is under the responsibility of principal investigators of each research project.
If relevant discoveries or errors are found by researchers, the information is transmitted to the Data controller of the ADB Management Office. After review and approval by the local ethics committees in clinical centers, information is re-identified and provided to physicians that inform patients according to what was agreed during the consent to participate to the project.

2) Coding
Project data will be handled with uttermost discretion and is only accessible to authorized personnel who require the data to fulfil their duties within the scope of the research project. On the CRFs and other project specific documents, participants are only identified by a unique participant number.

Biological material in this project is not identified by participant name but by a unique participant number. Biological material is appropriately stored in a restricted area only accessible to authorized personnel. For more details, please see the AneurysmDataBank regulation.

The measures to be taken to ensure patient privacy of digital data are:

1) Depersonalisation and Pseudonymization

The clinical data collection software generates a unique identifier, termed the Data Acquisition Identifier (DAI), for each individual participating in the Project. Before transfer to the ADB all the files are depersonalised by removing Identifying details except the DAI. The DAI is replaced by a pseudonym automatically generated by the system and information transferred to the ADB.
Data stored will be pseudonymized a second time with a new unique identifier different from the original one when a new data set is generated for the purpose of “*in silico*” research. The original pseudonym will be discarded from the new data set. This is done to avoid uncontrolled combination of multiple data sets.

2) Secure access, and defined access criteria

Data entry and access to the any ADB tools will require a non-repudiable means of access for each user as part of an end-to-end communication and information security. There is a separation of research and clinical accesses. From within a clinical centre, there will be no access to pseudonyms, or to any research findings attributed to an individual, or to results from other clinical centres.
From outside of the clinical centre, researchers will only be able access data depersonalised and pseudonymized.

3) Confidentiality, integrity and authenticity of communicated transmissions

All communications of data performed in the system will be encrypted, integrity-protected and authenticated, and all entities will have secure certificates.

4) Limitations on search criteria

Any tools developed or service provided by ADB will not support queries based on name, date of birth, address, or other possible identifiable details.

5) Logging of search requests and data entry

The identity of any person adding data to or requesting data from the ADB database will be logged together with the query expression.

6) Non-repudiation of search requests and data entry

The data collection and data query expression log will be protected at the hospital level and “Non-care zone” level.

7) Filter checking of response data

As a means of protecting against failure of the depersonalization processes, and to ensure uniformity between hospitals depersonalization processes data being transferred in response to queries will be filtered for information in the strip list of potentially identifiable information. No query result will be provided if representing less than 5 patients.

8) Monitoring and alerts

The completeness of data in the ADB databases will be checked, individual participant consent options will be recorded and followed in relation to participation and re-contact, and the system will be monitored for any attacks made on the data, and an appropriate notification mechanism for such an eventuality will be implemented.

9) Data origin authentication and provenance

Mechanisms are in place to ensure the information is verifiable and traceable including means to unambiguously identify the origin of a data set and of subsequent updates.

10) Confidentiality agreements

Confidentiality provisions are built into ADB project documentation. External collaborators on the project will be asked to sign a specific confidentiality agreement, as any other parties accessing the ADB data sources.

11) Removal of identifying facial features (imaging data)

Where 3D MRI imaging data encompasses more than 5 cm of the head in the three-orthogonal axis, a required step is that a bounding box is defined that contains the intracranial compartment, but excludes the nose and eyes. This bounding box has to be applied before imaging transfer. An automated facial features remover will be used for all radiological imaging before transfer to the ADB.

7.4 Retention and destruction of study data and biological material

At final analyses, data files will be extracted from the database into statistical packages to be analyzed. The status of the database at this time will be recorded in special archive tables. The study database with all archive tables will be securely stored by the Swiss Institute of Bioinformatics for at least 10 years. The sponsor will also keep the Trial Master File and interim and final reports both in electronic and in hard copy form for at least 10 years.
Destruction is not envisaged.

8 FUNDING / PUBLICATION / DECLARATION OF INTEREST

8.1 Funding

The ADB infrastructure is proposed to be maintained indefinitely.
The Sponsor Geneva University Hospitals will raise funds from all possible sources as well as from commercial exploitation of the ADB and services offered to different stakeholders.
Currently the project is funded by the “Fond de Service de Neurochirurgie (HUG)”, and financial support are regularly submitted to private foundations and public funding agencies.

8.2 Publications of results

Results will be disseminated via several ways:

- Research reports for the financial supporting foundations
- National and international community meetings
- Peer-reviewed articles
- Hospitals website

All data or biological samples collected from patients in this study are public but remain protected and access gated under the responsibility of the Geneva University Hospital and the project leader. All data resulting from the processing of information remains the intellectual property of the individual or group of individuals that developed the data processing method and remain under the responsibility of the individual or group of individuals that generated the processed data. Commercial use of processed data or services processing data is authorized if complying with Swiss ethical and legal requirements or any country where the processed data or service processing data is to be sold. Patients and collaborators not involved in the development of the data processing or service processing data cannot claim any financial reward regarding the commercial use of processed data or services processing data involving their data or biological sample.

8.3 Declaration of interest

The sponsor and the investigators have no conflict of interest to declare.

8.4 Data sharing

Eventual queries regarding access to study data will be addressed to the project leader. Access will only be provided to third parties fulfilling Swiss Federal Data Protection Act, Swiss Human Research Act and EU data protection standards according to EU GDPR 2016/679 and performing research in the field of medicine complying with ethical and legal standards.

9 REFERENCES

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10 APPENDIX

- Annex 1: General information letter and associated informed consent
- Annex 2: General information letter and associated informed consent for patient recruited in emergency
- Annex 3: General information letter and associated informed consent for patient incapable of discernment
- Annex 4: General information letter and associated informed consent for patient incapable of discernment and recruited in emergency
- Annex 5: Genetic information letter and associated informed consent
- Annex 6: Genetic information letter and associated informed consent for patient incapable of discernment
- Annex 7: Declaration of informed consent for the re-use of biological data and samples in coded form
- Annex 8: Declaration of informed consent for the re-use of biological data and samples in coded form for patient incapable of discernment
- Annex 9: Declaration of Withdrawal of Consent
- Annex 10: Declaration of Withdrawal of Consent for patient incapable of discernment
- Annex 11: eCRF “AneuX_Données Légales”
- Annex 12: eCRF “AneuX_Antécédents”
- Annex 13: eCRF « AneuX_Microbiote »
- Annex 14: eCRF “AneuX_Signes et Symptômes”
- Annex 15: eCRF “AneuX_Evaluation de traitement”
- Annex 16: eCRF “AneuX_Evaluation à la sortie”
- Annex 17: eCRF “AneuX_Suivi”
- Annex 18: EQ-5D Survey
- Annex 19: eCRF “AneuX_Données d’imagerie”
- Annex 20: eCRF “AneuX_Anévrisme”
- Annex 21: eCRF “AneuX_Traitement”
- Annex 22: Advertisement for healthy volunteers
- Annex 23: Schedule of Assessments
- Annex 24: AneurysmDataBank regulation
- Annex 25: eCRF “AneuX_Echantillons”
- Annex 26: Serious Event Report