Registry and Biobank of the
European Network for the Study of Adrenal Tumours (ENS@T)

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1. Background, hypothesis and aim of the scientific project

1.1. Background

**Adrenal tumours**

Tumours of the adrenal glands arise from the cortex or the medulla part of the adrenal gland. Clinical manifestations arise because of symptoms from excess secretion of hormones by the tumours. The tumours from the adrenal cortex can produce excess of steroid hormones including cortisol and aldosterone and tumours from the adrenal medulla can produce excessive amounts of catecholamines. Malignant adrenal tumours can also manifest through local mass effects or symptoms related to distant metastatic spread. Adrenal tumours can be benign or malignant. Often this separation is difficult to make and long-term close follow up is necessary after surgical removal to detect recurrences early in patients who have adrenal cancer. While malignant tumours of the adrenal gland are rare, up to 3.5% of the population have so called adrenal incidentalomas - tumours of the adrenals found incidentally during investigation for an unrelated condition. The majority of these do not secrete hormones (1).

*Aldosterone Producing Adenoma*

Primary aldosteronism is the most frequent form of secondary hypertension accounting for more than 11% of referred hypertensive patients (2). Although it is usually held to be caused by bilateral idiopathic hyperplasia in approximately two-thirds of cases and aldosterone-producing adenoma (Conn’s syndrome) in one-third, these relative rates are reversed when adrenal vein sampling is systematically used (2). Hence, primary aldosteronism due to adrenal tumours is likely the most common form of the disease. However, many experts now contend that there could be a continuum between bilateral adrenocortical hyperplasia and unilateral aldosterone-producing adenoma. Of note, notwithstanding the high prevalence of primary aldosteronism the molecular mechanisms underlying excess aldosterone production in this continuum remain totally unknown. Therefore, the availability of a large collection of aldosterone-producing tumours would be instrumental for allowing investigating these molecular mechanisms through application of novel techniques for the analysis of the whole transcriptome (3), the microRNA profile and the proteome.

In its classical form, primary aldosteronism presents with aldosterone excess, low plasma renin activity, while hypokalemia, once assumed to be a hallmark of the syndrome lacks in most cases. Patients with aldosterone producing adenomas have more severe hypertension, more frequent hypokalemia, higher plasma and urinary levels of aldosterone, and are younger than those with bilateral disease. Once primary aldosteronism is confirmed, the
subtype needs to be determined to guide treatment. Computed tomography or magnetic resonance imaging are required to detect the adenoma or aldosterone-producing carcinoma, but give misleading results in terms of identifying the unilateral or bilateral source of excess aldosterone (4, 5). Hence, to pose the indication for adrenalectomy most patients require adrenal vein sampling (5). Optimal treatment for aldosterone-producing adenoma or unilateral hyperplasia is unilateral laparoscopic adrenalectomy.

**Pheochromocytomas and Paragangliomas**

Catecholamine-producing tumours may arise in the adrenal medulla (pheochromocytomas) or in extra-adrenal chromaffin cells (paragangliomas). Their prevalence is about 0.2% in patients with hypertension (6-8) and 4% in patients with a incidentally discovered adrenal mass (9).

These tumours may be sporadic or may present as part of any of several genetic syndromes: familial pheochromocytoma-paraganglioma syndromes, multiple endocrine neoplasia type 2, neurofibromatosis 1, and von Hippel-Lindau disease. Familial cases are diagnosed earlier and are more frequently bilateral and recurrent than sporadic cases. The most specific and sensitive diagnostic test for the tumour is the determination of plasma or urinary metanephrines. The tumours can be located by computed tomography, magnetic resonance imaging and metaiodobenzylguanidine scintigraphy. Treatment is resection of the tumour, usually by laparoscopic surgery.

About 10% of tumours are malignant either at first operation or during follow-up, malignancy being diagnosed by the presence of metastases at sites where chromaffin cells should be normally absent (i.e., bones, liver, lungs, lymphnodes). Recurrences and malignancy are more frequent in cases with large or extra-adrenal tumours. Treatment for malignant recurrence includes surgery, therapeutic embolization, chemotherapy and metabolic radiotherapy (10). Patients, especially those with familial or extra-adrenal tumours, should be followed-up indefinitely.

**Non-aldosterone cortical adrenal adenomas**

Non-aldosterone secreting cortical tumours represent the most common benign adrenal tumour. These may be truly non-functioning, that is not associated with any hormonal excess, and are usually detected incidentally in patients undergoing radiological investigations (ultrasound, CT, MRI scanning) for other reasons. Indeed, autopsy studies have shown that up to 5% of the population may harbour so-called adrenal "incidentalomas". Malignancy rate in these lesions is very low - the majority of lesions are less than 3cm in diameter and can be treated conservatively (11).
Rarely the tumours may secrete cortisol. In the most florid example, Cushing's syndrome results because of severe hypercortisolism resulting in central adiposity, muscle wasting, thinning of the skin with bruising, osteoporosis, hypertension and diabetes mellitus. Removal of the adenoma is required to cure the condition. More rarely patients may have a genetic problem that results in autonomous production of cortisol from adenomas within the adrenals (e.g. McCune Albright syndrome or Carney's complex). The adrenals may also become hyperplastic or tumorous when the adrenal glands develop an unusual pattern of receptor expression over and above the normal receptor that controls cortisol production - the ACTH-receptor.

"Sub-clinical" Cushing's syndrome can also be found in patients harbouring adrenal incidentalomas occurring in up to 10% of all cases. These patients may have an increased risk of hypertension, obesity and diabetes.

**Adrenocortical Carcinomas**

Adrenocortical carcinoma (ACC) is a rare malignancy with incompletely understood pathogenesis and poor prognosis. Patients present with hormone excess (e.g. virilization, Cushing's syndrome) or a local mass effect (median tumour size at diagnosis > 10cm). Tumours typically appear inhomogeneous in both computerised tomography and magnetic resonance imaging with irregular borders, and differ from benign adrenal tumours by their low fat content. Hormonal analysis reveals evidence of steroid hormone secretion by the tumour in the majority of cases, even in seemingly hormonally inactive lesions. Histopathology is crucial for the diagnosis of malignancy and may also provide important prognostic information. In stages I -III open surgery by an expert surgeon aiming at complete resection is the treatment of choice. Local recurrence is frequent, particularly after violation of the tumour capsule. Surgery plays also a role in local tumour recurrence and metastatic disease.

In patients not amenable to surgery, mitotane as a substance with adrenolytic properties remains the treatment of choice (12). Monitoring of drug levels is mandatory for optimum results. In advanced disease, the most promising therapeutic options (etoposide, doxorubicin, cisplatin plus mitotane and streptozotocin plus mitotane) are currently being compared in an international phase III trial. Adjuvant treatment options after complete tumour removal (e.g. mitotane, radiotherapy) are urgently needed, as postoperative disease free survival at five years is below 50% (13).

**European Network for the Study of Adrenal Tumours (ENS@T)**

With the exception of endocrine inactive adenomas adrenal tumours are rare. Therefore, progress in diagnosis and treatment of these tumour entities can only be achieved by
combining the efforts of researchers and clinicians from several countries. To overcome these difficulties and to achieve significant progress benefiting the affected patients a Network on Adrenal Tumours at a European-wide level has been created.

The European Network for the Study of Adrenal Tumours (ENS@T) aims to improve the understanding of the genetics, tumourigenesis and hormonal hypersecretion in patients with adrenal tumours and associated familial syndromes. It intends to improve the prediction of recurrence and the management of malignant adrenal tumours, which are particularly rare. The study of adrenal tumours is likely to reveal new molecular mechanisms of tumour growth and provide insight into the role of hormones as the cause of hypertension.

ENS@T was founded in 2002 by putting together three already existing National Adrenal Networks (COMETE in France, GANIMED in Germany, and NISGAT in Italy) and teams from the United Kingdom all dedicated to the study of adrenal tumours. In 2009, ENS@T became a membership-based society with statutes and bye-laws (www.ensat.org).

1.2. Scientific aims

A core part of the scientific efforts of ENS@T researchers bases on the establishment of a common registry and associated collection of biomaterials. Patients with adrenal tumours prospectively included in the ENS@T registry will be asked to provide blood and urine samples and – as available – tumour material collected during surgical resection.

The scientific aims of the proposed project can be summarized as follows:

1) Improvement of networking in the field of adrenal research in Europe through integration of local and national research efforts
2) Implementation of an European adrenal tumour registry and associated biobank
3) Improvement of differential diagnosis and risk stratification of adrenal tumours
4) Identification and validation of tools for follow-up of patients with adrenal tumours
5) Identification of novel biomarkers for evaluating treatment response in patients with adrenal tumours
6) Screening for molecular mechanisms as the basis to improve treatment response in patients with adrenal tumours

2. Type of scientific project

European multi-central retrospective and prospective register study and associated biobank.
3. Study population and study protocol

- **study design:** European multi-central retrospective and prospective register study and associated biobank.

- **study duration:** In a first step, patient enrolment and biomaterial collection is planned for 10 years. However, in case of positive interim analysis this timeframe will be extended. The registry will be maintained for at least 20 years.

- **proposed number of patients:** Participating European Centers will aim to enrol as many patients with adrenal tumours as possible. An upper limit of patients included in the registry is not defined.

- **participating centers:** The following centers are already part of the ENS@T network:
  - **Germany:** University Hospital Munich, University Hospital Wuerzburg, University Hospital Dresden, University Hospital Duesseldorf, Charité Berlin
  - **France:** Institut Gustave Roussy Villejuif, Groupe hospitalier Cochin Paris, Hôpital Européen Georges Pompidou Paris,
  - **Italy:** University Clinic Turin, University Clinic Padova, University Clinic Florence
  - **U.K.:** University of Birmingham, University Clinic Glasgow, University Clinic Dundee
  - **Netherlands:** Radboud University Nijmegen Medical Center, Erasmus Medical Center Rotterdam
  - **Austria:** University Clinic Wien, University Clinic Graz
  - **Sweden:** University Clinic Uppsala
  - **Poland:** Centre for Postgraduate Medical Education Warsaw

In addition, it is foreseen that further centers will be included in the ENS@T network upon application and positive review by the ENS@T steering committee.

- **inclusion criteria:** patients with adrenal tumours who have provided written informed consent.

4. Research methods

Clinical parameters pertaining to signs and symptoms of hormone excess or mass effects from adrenal tumours will be collected. During initial diagnosis and follow-up examination additional blood (10ml serum and 10ml whole blood) and urine samples (spot urine and
Collection of biomaterial will be performed to provide the basis for the identification of novel biomarkers to improve individualized therapeutic regimens. Specifically, the following parameters will be taken into account:

1. **Prognostic markers**: An increasing number of adrenal masses are detected incidentally during imaging (“adrenal incidentalomas”), but the assessment of the malignant potential of these tumours by imaging procedures is difficult. Even in patients operated on, both adrenocortical carcinoma and malignant pheochromocytoma can often not be definitely distinguished from benign adrenal tumours based on histomorphological features alone, and within both entities a phenotypic range exists that impairs consistent prognostic classification. Reliable and sensitive screening tools for early detection and risk stratification of adrenal cancers are currently lacking, which makes the development of such tools a clinical priority. Similarly, benign adrenal tumours can be associated with significant morbidity and mortality due to their endocrine activity. Definition of patient subgroups with increased cardiovascular risk profile would enable initiation of close follow-up and justify more aggressive treatment.

Newly applied genomic techniques including expression analysis, microRNA profiling, methylation pattern, chromosomal gains and losses, proteome techniques and exon sequencing will refine a set of markers that identify subgroups of tumours with defined biological behaviour. Lymphocytic DNA will be utilized for comparison of genetic markers identified during mutation analysis. Validation of identified marker genes will be performed by immunohistochemical approaches on paraffin embedded and frozen tumour material. Secreted markers will be assessed by metabolome techniques in blood and urine samples. In all cases correlation with disease free survival and overall survival as most significant clinical endpoints will be included.

2. **Markers of treatment response**: Similarly, markers that would predict outcome after a specific therapeutic intervention are being sought. Based on molecular, genetic and biochemical analyses as described above markers will be defined that are associated with a beneficial or unfavourable response after specific therapy. Examples for malignant tumours (adrenocortical carcinoma and malignant pheochromocytoma)
include markers of recurrence free survival after complete surgical resection (R0) or treatment response in patients without resectable disease after chemotherapy, radiotherapy or targeted therapy. In patients with benign hormone secreting tumours markers will be identified that correlate with treatment response (e.g. surgery or medical therapy) and cardiovascular endpoints.

3. **Follow-up markers**: A significant problem in the follow-up of patients with malignant adrenal tumours is the timely detection of persistent or recurrent disease following an apparently complete surgical resection. Delay in detection can often translate into postponed initiation of treatment and, thus, worsening of prognostic outlook. Biomarkers for detection of persistent or recurrent disease will be identified on the basis of the above defined –omic technologies.

5. **Risks, side effects and ethical aspects**

The proposed project comprises a European multi-central retrospective and prospective register study and associated biobank. Centralization of information regarding diagnosis, prognosis and management, together with the availability of a common scoring system for homogenized assessment of tumours will improve patients’ access to Best Clinical Care. The benefit (optimized grading and management and potentially better treatment decisions based on biomarker results) to burden (providing clinical information, blood and urine samples and surgical tissue specimens) balance is in agreement with ethical principles and favours (at least in the long-term perspective) the benefits. Implementing standardized collections of tumour samples and annotations is necessary to achieve the proposed scientific objectives. Enrolment of patients into the registry and associated biobank will start only upon positive appraisal by the appropriate ethical committee and after agreement of the patient through documented provision of informed consent.

5.1 **Education and written informed consent**

Each individual patient with an adrenal tumour at risk of malignancy (suspected adrenocortical tumour, pheochromocytoma or paraganglioma) and/or with proven endocrine activity (aldosterone or cortisol secreting adenoma) will be given information concerning their condition with regard to Best Clinical Practice for management and follow-up. Information will specifically mention that the decision to perform tumour or metastatic resection, using surgery or alternative ablative methods, will be taken by the physician(s) clinically in charge independently of the patient participation in the study. This information will be provided
verbally by one of the physicians in charge of their clinical care. Following this procedure the purpose, design, procedures and duration of the ENS@T registry and biobank will be presented verbally and in the form of a written patient information leaflet, carefully observing the balance between burden (need for collecting, processing and preserving genetic material and biological samples and for supplying participating laboratories with biological material and associated annotations) and personal benefits to the patient including further optimisation of best clinical care. Separate information documents will be prepared for patients with adrenocortical tumours and with pheochromocytoma/paraganglioma.

Written information and the consent form will specifically mention:

- The overall objective of the study, i.e. the search for a better understanding, grading and management of the condition through progress in the knowledge on the pathophysiology of tumour growth and hypersecretion, and the search for indexes of tumor recurrence or progression and disease-free or progression-free survival

- The duration of individual patient participation, i.e. the time for the collection of blood and urine samples and for recording the corresponding annotations. In addition to preoperative bio-specimens and annotations, patients who had undergone a previous resection of a primary tumour or a metastasis will be asked permission to access archival pathological specimens; those who will undergo the resection of a primary tumour or metastasis will be asked to permit, after selection of tumour samples by a pathologist for diagnostic purposes, the collection of frozen tumour samples for research purposes.

- The overall duration of the study, i.e. 10 years of patient recruitment plus 10 years for the follow-up of the last included patient. After completion of the study, patients will be approached whenever possible to decide whether they want their biological samples and annotations destroyed or accept their use for future research in the same domain.

- The collection of serum, urine and lymphocyte DNA preoperatively, the collection of tumour samples during surgery, the collection of relevant pseudonymised\(^1\) data, and the organization of subsequent follow-up. In compliance with EU and national regulations, the consent form will mention that the choice to enter the study is entirely voluntary, and that if a patient decides not to participate, their enrolment in any other protocol will not be affected; that they are free to withdraw from the study at any time; and that all data will be used in an anonymous\(^2\) manner. The patient will be asked to share clinical data and biomaterial within Europe with scientific partners participating in the ENS@T initiative.

5.2 Premature study interruption by the patient

\(^1\) This terminology is inconsistent and ambiguous; one can use the term coded (see the glossary in the recent OECD guidelines attached), or an eventual alternative used by the EU, for instance by the EMEA.

\(^2\) See above
The patient will be informed that he/she is free to interrupt and/or withdraw from the study at any time without stating the reasons. Importantly, the patient will be reassured that their clinical management will not be affected by their decision to take part or not to take part in the study.

5.3 Assessment of benefit to risk balance

The benefits of optimized grading, management and potentially better patient treatment decisions based on biomarker results needs to be balanced against the patient burden including providing clinical information, blood and urine samples and surgical tissue specimens. This balance needs to be cognisant of the ethical principles underlying such scientific research. Our belief is that the benefits to the patient (at least in the long-term perspective) far outweigh the burden imposed. Implementing standardized collections of tumour samples and annotations is necessary to achieve the proposed scientific objectives.

6. Statistics

Results will be expressed as the median of individual data points. Comparison between patient groups or different therapies will be evaluated by Wilcoxon’s test for paired and by Mann-Whitney U test for unpaired data sets. Multiple testing will be corrected by Holm-Bonferroni. Kaplan–Meier survival analysis will be carried out to compare different subgroups (e.g. defined by biomarkers or different therapies) using log-rank tests. Multivariate regression analysis are performed by the Cox proportional hazards regression model including all the variables with a p value < 0.1 in the uni-variate analysis to identify those factors that might significantly influence survival. A p value < 0.05 will be considered as significant.

7. Privacy and data protection

Data collection:
Throughout the European Union, numerous institutions that are involved in clinical service delivery, as well as clinical research commonly hold local registers of clinical cases and associated biological data sets. The EU Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 (along with numerous national initiatives such as the UK Data Protection Act 1998) focuses on the protection of individuals with regard to the processing of personal data and on the movement of such data. These efforts provide an overarching framework for how the collection and sharing of such information between
member states for research purposes can be achieved in an individual, privacy-protecting manner. Many countries support further refinements to personal privacy and data usage especially in a clinical context. For example, Section 33 of the UK Data Protection Act 1998 and the Data Protection (Processing of Sensitive Personal Data) Order 2000 allows research to be conducted on non-identifiable data – this needs to be recognised explicitly when dealing with data that is unique and identifying by its very nature, e.g. DNA.

Many of these directives and acts, including the UK Freedom of Information Act 2000 make it clear that subjects that are included on any clinical research systems have a right to know of their inclusion on those systems and a right to access the data. In addition, they have a right to have their data removed from those systems. The practice of informing subjects of inclusion on clinical systems varies across the EU. In the UK, a system of opt-out consent is often used. In other countries opt-in models of consent are in place. Contributing sites for ENS@T need to ensure that they adhere to nationally defined data sharing policies. Where necessary, applications will be made to relevant authorities, e.g. in the UK to PIAG, and the NHS Security and Confidentiality Advisory Group to enable appropriate access to confidential datasets. Other countries will have their own ethics committees that they will apply to, to ensure that data entry is driven by patient consent. The software systems that allow for such exchange of information will be designed to enforce such checks by contributors. Thus the first part of adding a case to the registry will be to advise the clinical contributor that they must have written consent to do so, and the final part of completing the addition of a case to the registry confirming that this is in accordance with local ethical arrangements regarding data sharing.

To comply with the directive 02/58/EC of the European Parliament and of the Council of 12 July 2002 concerning the processing of personal data and the protection of privacy in the electronic communications sector (Directive on privacy and electronic communications), the ENS@T project will adhere to the highest standards of data security in the development of the registry. Under the directive 96/9/EC of the European Parliament and of the Council of 11 March 1996 on the legal protection of databases, users of the ENS@T registry will have specific privileges depending on their role within the project. These roles will be used to restrict access to data and tools into the registry. The default model will be to deny access, i.e. only individuals with authentic and valid credentials, i.e. digitally signed credentials recognised by the ENS@T registry service components, will be able to access and use the registry. It is important to note that the ENS@T registry will not hold the names or addresses of any individuals or any direct information which can be used to identify an individual. Instead cases shall be identified for the purposes of communication with an automatically
generated identifier that is unique within the registry. This identifier will be coded to include the country, partner and a generated patient number only, e.g. FRPA1-3 for a patient from France, at Paris Centre number 1 and patient number 3. Local centres, e.g. Paris Centre number 1 will keep a local track of this record on their own patient management systems and how it relates to an individual patient record in the ENS@T registry. At no time will they ever be asked to reveal the identity of individual FRPA1-3 to any ENS@T or other researcher outside of their immediate clinical care environment.

Furthermore, the linkage between the patient identifiers in the registry and identifiers used for biomaterials will be both distinct and completely separated, i.e. it will never be possible to directly identify (through a given software query or direct observation of a particular software system) that a particular sample comes from a particular patient through use of the registry or other related IT system. To address this, software systems will be used to generate unique identifiers for actual physical biomaterials/genetic samples from individuals that are to be stored at clinical partner sites for ENS@T clinical studies. These identifiers will include the study number, subject group, the country, centre and a unique patient number, e.g. 1VFRP1001 can be used to identify a patient sample for study 1, from a voluntary control group (V), from France (FR), Paris centre 1 (P1) with local number 001. Where appropriate this identifier can be used directly on the registry for direct tracking and location of biosamples. However, in some countries it is often the case that further separation of identifiers used on biosamples to identifiers used for collaboration is made. In this case, a unique local identifier will be generated (e.g. XYZ123) to associate the biosample identifier (e.g. 1VFRP1001) with the patient identifier used on the registry (e.g. FRPA1-3). Thus a user of the registry would see a patient FRPA1-3 with biosamples XYZ123. Only the Paris centre would be able to establish which particular biosample this refers to through local translation of XYZ123 to 1VFRP1001 for patient FRPA1-3. The VANGUARD system (15, 16) has been developed to supports such levels of indirection between identifiers used and their linkages and will be deployed in the course of the ENS@T project.

Whilst data collected by the participating clinical centres will be shared under the above legal framework to select cases and case materials for research by ENS@T participants any research that is carried out on these data or resources will be subject to the Declaration of Helsinki, 1964 and the Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine Oviedo, 4.4.1997 and Strasbourg 25.1.2005 and will need to be approved by the ethics committees of the clinical centre that contributes the case and the centre that is performing the research study. As access to the ENS@T registry will depend
on the nature of the study being performed by the investigator, the latter will submit a case or requirements including ethics approval status to the steering committee.

In developing IT systems for previous clinical research studies, the consortium partners have had to address a number of important security and data privacy considerations. The project partners have direct experience in working to UK and international standards (including ISO 17799, and US 21 CFR part 11), and have extensive experience of using healthcare data in the context of privacy and data protection legislature (including the Data Protection Act 1998, EU Data Protection Directive 95/46/EC, and the US Health Insurance Portability and Accountability Act [HIPAA] 1996). Such experience is directly shaping the IT security of numerous on-going clinical projects with advanced security at their heart, and we leverage this expertise directly. This includes major on-going European projects in the area of disorders of sex development and clinical trials in the brain trauma domain amongst numerous others.

We emphasise that no data concerning sexual lifestyle, ethnicity, political opinion, religious or philosophical conviction will be collected in the registry and only those data sets directly relevant to research into adrenal tumours will be incorporated in the registry. Information regarding past history, presentation, biological parameters, imaging tests and interventions will be provided with a unique and non-patient identifying identification number of the biological material. The data set associated locally with the collection of biological material will also include the identification of the depositor and the identification number of the donor, but this information will not be provided to users. Given the diversity of regulations concerning data protection within the EU as outlined previously, contact will be taken in France with the Comité National Informatique et Libertés, in Italy with Garante per la Protezione dei Dati Personali, in Germany with der Bundesbeauftragte für den Datenschutz und die Informationsfreiheit, and in the UK with the Information Commissioner's Office, to obtain permission to use the ENS@T registry.

**Biomaterial:**
The main factors associated with longer survival in patients with adrenal cancer include early diagnosis and complete resection of the primary tumour, and, whenever possible, aggressive resection of any recurrence or soft-tissue metastases, making surgery the cornerstone of management. Tumours are usually large, leaving a sufficient amount of tumour mass for biomarker research after the pathologist has set apart tumour samples required for diagnosis and grading. Although we aim at developing animal and cell culture models for adrenal
cancer, there is currently no alternative to using human tumour specimens following tumour resection that is necessary.

The collections will comply with the OECD best practice guidelines for human-derived material (OECD, Marc 7th 2007). Specifically, no deposit will be accepted by any of the ENS@T partners without written informed consent from the patient (see above). Further information derived from this data, e.g. related to non-paternity will not be disclosed. To support this, provision of samples will require a material transfer agreement mentioning that the recipient must use the research material solely in connection with the ENS@T registry, in compliance with all applicable laws and government regulations of the recipient's country. When biological material is exchanged between two countries, the national laws of both countries will be respected. Biological material will not be released to any person other than the laboratory personnel under the direct supervision of the person designed in the material transfer agreement as the recipient.

8. Insurance

Registry and bio-sampling does not require therapeutic or diagnostic interventions. Sample collection is done as part of clinical routine procedures. An additional insurance is, thus, not required.

9. References