- VASCULAR -
- INDEPENDENT RESEARCH AND EDUCATION -
EUROPEAN ORGANISATION

REGULATION

REGULATION OF THE VAS-EUROPEAN BIOBANK ON VASCULAR DISEASES (VAS-EBVD)

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1. INTRODUCTION

Biobanks (called also "biological material banks") have come to constitute a body of central importance in current medical reality, and as "deposits" of biological samples, data, images, and as research facilities.
In parallel with developments in medicine, Biobanks have also taken a leading role in contemporary ethical and legal landscape, becoming the subject of laws, regulations and ad hoc recommendations to national and international level.
These documents enshrine respect for human rights and the fundamental freedom of patients and research subjects participating in studies using human biological material and acknowledge, on one hand, the need for information and consent to these studies, on the other hand, the guaranteed respect for confidentiality of those involved.
The invocation of such rights is not impeding scientific research but it rather guarantees its development while respecting the fundamental rights of patients / subjects of research and, where relevant, of their family members.
In light of the considerations mentioned above, this document describes the Regulations of the Biobank of VAS - Vascular - Independent Research and Education European Organisation Vascular- of which the first enabled project is the European Biobank on PAD patients.
This document is based on the principles, ethical standards and legal regulations at national and international level to which biomedical research and, specifically, research involving the use of human biological material inspire to.
This document was submitted to the VAS – European Ethics Committee and to the VAS European Guarantors Committee and approved by those in the Official Session of 14/11/2008 as official regulation of the European Biobank on Vascular Diseases constituted at the VAS' headquarter.

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Signature of the Scientific Coordinator of VAS - Vascular - Independent Research and Education - European Organisation and Director of Biobank

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Signature of Head of the Biobank

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Signature of Director of European Ethic Committee and the European Committee of Guarantors VAS - Vascular - Independent Research and Education - European Organisation

2. BIOBANKS

2.1. Definitions and acronyms

According to the literature, the term "Biobanks" are identified as "service units dedicated to the collection and preservation of biological material of human origin (as, for example, tissues, cells, DNA, blood, semen) for the purpose of diagnosis, biodiversity studies and research (1).

There are currently different types of Biobanks, characterized according to their nature (commercial vs. non-profit), the type of biological samples stocked (eg. exclusively human or human and animal), the objectives pursued (diagnosis, research, maintenance).

Biobanks operate in accordance with national and international laws and regulations, aimed at ensuring respect for human rights and fundamental freedom of patients / subjects of research.

Specifically with regard to confidentiality, Biobanks operate according to procedures and programs to ensure the reliability of analytical data. These structures are, in this respect, subject to certification and accreditation, to determine and control every stage of their operational flow.

For the purposes of this Regulation, "Biobank" means a facility that collects and retains biological samples of various nature and origin and the data associated with them in order to make diagnostic studies, clinical association and / or research (epidemiological, medical , biomedical).

By the term "Biobank" and by the acronym VAS-EBVD we refer to VAS' European Biobank on Vascular Diseases (and to its sub-projects).

2.2. The Biobank: characteristics and purposes

The VAS-EBVD is a valuable source of human biological material, the potential is expressed specifically with regard to the storage of biological samples and data relating to vascular disease, it is well known how the collection of biological material on these diseases is still today, very complex, with the effect of making it very difficult to study and understand. The possibility to have, through a structured collection, biological samples and data for these diseases available can, therefore, deepen and expand scientific knowledge in this field.

The VAS-EBVD operates in compliance with ethical and legal national and international reference and in accordance with this Regulation, which implements these provisions.

The VAS-EBVD also operates on information systems and computer software that ensure that the storage, use and distribution of human biological samples deposited in it and its associated data are treated according to the confidentiality of patient / research subject and / or family members.

The VAS-EBVD is non profit-seeking.

3. ETHICAL AND LEGAL ASPECTS OF HUMAN BIOLOGICAL MATERIAL IN THE BIOMEDICAL FIELD

3.1. Information concerning consent and Biobanks: general profiles

A number of Government instruments regulate the activities of Biobanking. These documents derive on one side from the transposition of international standards (2-5) and specifically European (6-8), on the other side from the adoption of national guidelines and advice (9-12). There are also regulations made locally by individual Biobanks to regulate their internal activities (13).

Common to these provisions is the forecasting of a consent *ad hoc* for the Biobank's activities. Which requirements must obtain consent is a question now open. To make the definition of an appropriate consent to the collection, storage and use of human biological material for purposes of diagnosis and / or research controversial is, first, the difficulty of applying legal and ethical principles that govern the issue of the "Informed consent" to the primary field of Biobanking (14-19). It is, secondly, the existence of many ethical and legal standards governing such matters, both internationally and nationally (20).

As reported in the document prepared by the National Bioethics Committee in collaboration with the National Committee for Biosafety, Biotechnology and Life Sciences - titled "Collection of biological samples for research: informed consent" - in the current international literature four standard information and consent to use of Biobanks can be identified: Broad Consent, Partially Restricted Consent, Multi-option Consent, Specific Informed Consent (12).

Models of informed consent	Definition
Broad Consent	allows the use of samples and their associated data and future research of all kinds (except the restrictions referred to in this Regulation or in additional specific agreements)
Partially Restricted Consent	allows the use of samples, and data associated with them, an immediate search for specific investigations and in the future directly or indirectly associated with these samples
Multi-option Consent	requires a lot of options that must be explained to the donor subject in detail
Specific Informed Consent	allows the use of samples and data associated with them for an immediate specific research, prohibits any future study that was not foreseen in the original consent.

3.2. The information and consent models adopted by the VAS-EBVD

The VAS-EBVD adopts a model of information and consent to storage and use of human biological material and / or data associated with value of guideline for the OU / Organisations that require to preserve biological material (and / or associated data) in Biobank.

This model of consent has been prepared in compliance with the requirements of laws and regulations applicable to national and international level and approved, together with this Regulation, by VAS' European Ethics Committee and European Guarantors Committee

This model provides the necessary requirements for the conservation and use of biological samples (and / or associated data) for diagnostic purposes and / or research. It does not provide the necessary requirements for the removal of biological material, which is an indication of competence and responsibility of the participant OU / Organisation that directly implements the levy.

The requirements of the information and consent model for storage and use of human biological material (and associated data) for diagnostic purposes and / or research may, at the discretion of the participant OU / Organisation, be incorporated into the informed consent normally in use at the OU / Organisation itself or be included in a separate informed consent (see appendix).

Regardless of the procedure, consent to storage and use of biological material that the OU / Organisation shall submit to the Biobank's staff must meet the following conditions:

a) Informative

- Inform the patient / research subject of the intention to maintain at the VAS-EBVD the biological material / additional to that collected in the context of diagnostic study / research study and / or store the data associated.
- Inform and clearly express that both storage and future use of biological material and / or associated data is possible only if and insofar as the patient / research subject gives his consent to storage and future use and that any decision not to allow storage and / or the use of biological material and associated data will have no negative consequences with respect to medical care and attention to the person of the patient / research subject.
- Indicate the storage of biological material and associated data modality and, where applicable, identify the risks associated.
- Indicate the storage times of biological material and / or associated data.
- Specify whether the secondary uses are related either directly or indirectly to the primary.
- Indicate whether secondary uses are probable or merely possible.

- Indicate that VAS – Vascular – Independent Research and Education – European Organisation will use the biological material and / or associated data for the purposes indicated.
- Clarify that the results obtained during / after studies will not be communicated personally to the patient / research subject but will be used, in anonymous form, for publications, congresses and scientific presentations.
- Specify whether the study will lead to the creation of patent medicines, and other state explicitly that the patient / research subject and / or his family will not receive economic compensation because the provision of biological material is a useful gift for developing scientific research and thus oriented to the improvement of current knowledge on diseases and the development of new therapies and / or diagnostic and therapeutic methods.
- Clarify that the results of the study will be used anonymously in scientific publications, conferences, or for educational purposes.
- Indicate that the biological samples and data will be used in anonymous form which allows the identification of patient / research subject only when necessary
- Specify that the consent to storage and / or future use can be modified and revocable at any time by the patient / research subject and indicate the consequences of that withdrawal.
- In case of withdrawal of consent, ask the patient / research subject to indicate what he wants done with the personal samples and / or associated data: destruction or irreversible anonymity

b) Informed Consent Sheet
- Provide options for consent / refusal to the preservation of biological material and / or associated data
- Provide options for consent / refusal to use the samples and / or data and specify the purposes for which you intend to use the biological material and / or data. Immediately provide the possibility of further use of residual biological material and / or associated data
- Provide options for consent / refusal to use the biological material by VAS - Vascular - Independent Research and Education - European Organisation that will use samples and / or data in the event of any collaborative research projects with other research bodies, after approval by VAS - Vascular - Independent Research and Education - European Organisation: if Biobank, if Biobank and / or other OU / Organisations
- Provide options for consent / refusal for the development of patent medicines, and other use of the results achieved during the study in scientific publications, conferences, lectures

- Provide in the declaration by the patient / research subject, that he is aware that the samples and / or data will be processed in anonymized form
- Provide in the declaration by the patient / research subject, of being aware of the possibility to modify or withdraw consent at any time and options available in case of withdrawal: destruction of samples and / or data or irreversible anonymization of samples and / or data

3.3. Further requirements and specific consent to the collection, storage and use of biological samples and genetic data

In compliance with applicable regulations (21-24), as implemented by these Regulations, the conservation and use of biological samples that contain information specific to an individual genotype (also called, for the purposes of this paragraph, biological samples) and data genetic treatments are carried out according to the directives of the Guarantor for the protection of personal data and on the basis of informed consent of the person concerned.

The processing of biological samples and genetic data must be anonymized manner, separating the identifying data from the moment of collection of biological material.

Compared to the request for Biobank preservation of biological samples and genetic data in view of future studies, the OU / Organisation must adopt an informed consent which meets the requirements of the regulations and specific authorization of the Guarantor for the protection of personal data

3.4. Exceptions to requesting consent

Exceptions to the general rule of application for consent to storage and use of biological material and / or associated data are allowed in the following cases:

a) biological samples and associated data are anonymous *ab initio* or were being irreversibly anonymized with the patient/research subject's consent. Secondary studies may be carried out without a new individual informed consent by the patient/ research subject, after the approval of Ethics Committee;

b) the biological samples and associated data have been anonymized in a non-reversible way, with patient/research subject's consent. Secondary studies may be carried out without a new individual informed consent by the patient/ research subject, after the approval of the Ethics Committee;

3.5. Situations of incapacity and consent to the collection, storage and use of human biological material

Where the patient / research subject lines in a state of legal incapacity to act for minor age, prohibition or disqualification, the informed consent to the collection, storage and use of his

biological material and associated data with a view to future studies, diagnostic and / or research, must be signed by his legal representative.
Where the person concerned, without being in a formal legal status of inability to act, is anyway not able to give his consent, as in fact incapable of understanding and volition (eg., Unconsciousness, impaired ability to make decisions due to neurological disorders, and / or psychiatric and / or psychological) and the incapacity is permanent, consent must be signed by his legal representative.
If, however, the condition is of temporary incapacity, consent to the collection, storage and use of his biological material and associated data in view of future studies will be required personally to him once that the condition of incapacity has failed.
In any case, in both situation of failure to act formally recognized and in situation of natural incapacity of fact, the will and the opinion expressed by the person and any document in writing (cd declaration of intention in advance) must be taken , where possible, into account.

3.6. The properties of biological material deposited in Biobank
At present, the matter of definition of "property" of human biological material collected in the context of surgery, medical examination, research project and subsequently deposited into a Biobank is not uniquely regulated (25, 26). However, the prevailing trend in Italy, as in some other European countries, is to consider "owner" of biological material, the patient / research subject from whom it originates and to describe the act of making available the material in terms of "donation", in the same way as when blood or organs are donated for diagnostic purposes and / or treatment. Underlying this position is an intention and a precise orientation to enhance the provision of the biological material as an act of solidarity, aimed to develop better treatments and therapies for the community. There is, consequently, a clear justification for not making provision of the biological material, of the development of Biobanks and of Research based on Biobanking an economic trade.
In accordance to those positions, for the purposes of these Regulations, the biological material be stored in the VAS-EBVD is considered "property" of the patient / research subject, unless he expressly waives. Only in this case, the biological material is considered to be owned by VAS - Vascular - Independent Research and Education - European Organisation.

3.7. The protection of confidentiality, general profiles
According to regulations at national and international level on the processing of biological samples and personal data (21-24), the VAS-EBVD deals with the biological samples and associated data in ways which ensure the confidentiality of patient / research subject and / or family members.

In particular, except in cases of anonymity *ab initio* or acquired, the VAS-EBVD treats the biological samples and associated data in anonymous form, so as to permit identification of patient / research subject only in case of medical necessity and / or in other cases provided by law.

3.8. The protection of confidentiality and management of biological samples

The VAS-EBVD contains the following types of biological samples of human origin:

- Whole human blood
- Blood components (eg., Serum, Plasma, Buffy Coats)
- Cell extracts (eg., DNA, RNA, proteins)
- Other tissues related to Vascular Diseases

As a general principle, the procedure for coding the samples taken from the VAS-EBVD will ensure that the identity or other identifying information of the patient / research subject does not appear on labels, cards or on other instrumental material which use is not specifically aimed to the maintenance of identification data.

In particular, the Biobank stocks the samples in an anonymized way.

Anonymized: the personal data of the patient / research subject are stored in a database separate from the one reserved for storing data samples. The single sample will be identified by a code and only the collecting Centre will be able to relate the unique code of the sample data to the patient. This code then determines the matching between the patient/ research subject 's personal medical records and specific data of the sample. Only the Head of the VAS-EBVD will be allowed access to two data sets (clinical and genetic) where necessary to protect the health of the patient / research subject and / or their family members and / or in case of a primary interest of collective nature, while the BioRepository where samples are stored and any other Centre or researcher will not have access to any sensitive data of the patient.

3.9. Protection of privacy and personal data

Access to personal data of the patient / research subject concerns only the information and consent forms as the biological sample is treated in a manner dissociated from the personal data.

The paper forms are collected in special bins, in alphabetical order, cabinet lockable at the collecting Centre and managed according to security procedures by the same collecting Centre.

Clinical data are processed through a special online questionnaire that allows you to manage separately the identification data and medical history of the patient / research subject.

Data storage will be performed by special computer software for coding developped by a quality certified IT society. The Biobank uses two different databases:

- ï one for entering data on biological material, visible externally via a website to allow sharing by authorized entities);
- ï - one to keep in separate files, the data of the sample. This database is not visible outside.

4.ORGANISATION AND OPERATION 'OF THE BIOBANK

4.1 Structure

The VAS-EBVD is based at the Headquarters of VAS - Vascular - Independent Research and Education - European Organisation while the storage is carried out at a separate Biorepository using dedicated facilities commissioned and certified suitable for Biobanking on behalf and in accordance to VAS - Vascular - Independent Research and Education - European Organisation's rules and regulations.

4.2 Staff

Resources related to the VAS-EBVD are identified on the basis of CONTINGENTE availability of personnel from VAS - Vascular - Independent Research and Education - European Organisation. Consequently, the operating staff varies according to the volume of business that must always be guaranteed continuity.

Currently the staff of the Biobank, which manages both the biological and administrative parts, identifies:

- a responsible manager biologist;
- a dedicated technical staff
- a legal consultant

4.3. The organs of the Biobank

VAS-EBVD counts on 2 specific organs and refers to 4 already existing organs of VAS - Vascular - Independent Research and Education - European Organisation (Scientific Team; Ethic Committee; Guarantors Committee; Management Team).

4.3.1 EBVD-DAC (European Biobank on Vascular Diseases' Data Access Committee). The Biobank's Data Access Committee has been established to objectively and systematically review the requests for data submission and access to VAS-EBVD resources. Collectively, the EBVD-DAC has overall responsibility for ensuring compliance with the VAS Policy. They are appointed for 5 year renewable terms. Each Member of the EBVD-DAC is required to supply the name of one Deputy who will be acting in his place in case the Member is not able to attend a meeting.

The EBVD-DAC includes: VAS Scientific Coordinator; one VAS Management Team's Referees; the VAS Management Team's legal Expert for Biobanking; the VAS-EBVD's Quality Manager and the Coordinators of any single sub-project of the VAS-EBVD.

4.3.2. EBVD-CT (European Biobank on Vascular Diseases' Coordinating Team). The EBVD-CT coordinates the enacting activities of the whole VAS-EBVD and of each sub-project (separate meeting can be arranged for any sub-project). In particular each CT is charge for the development of the protocols for the collection of data and biological samples for each sub-project of the VAS-EBVD. It details the samples to be collected, the preliminary processing and storage temperatures, the transport of samples to the central processing facility, and the processing, aliquoting and storage of each sample (which is summarised below). When a geographical location has been identified based on eligible population and one or more suitable assessment centre(s) facility needs to be established, the specific CT will be responsible for sourcing and securing each of the centre-facilities that are required. A mixed facilities model is intended: where suitable cost-effective academic facilities are available then these may be used, but otherwise it is up to the CT to find out the best solution for each Centre to collaborate. It also controls the activities of the centres working on any specific sub-project.
The VAS-EBVD-CT is composed by: the members of the EBVD-DAC; the National project-coordinators; the representatives from the Biorepository and the Database (these private partners have no rights to vote).

4.3.3. VAS-ST (VAS - Vascular - Independent Research and Education - European Organisation's Scientific Team). It is responsible for screening and defining new proposals, monitoring the progress of current projects and defining development strategies for VAS. It is the decision-making body (subject to the limitations detailed elsewhere in this section) with regard to the single projects and the development of VAS. In particular, referring to the VAS-EBVD the VAS-ST:

a) approved the institution of the VAS-EBVD and the general criteria listed in the VAS-EBVD's Regulation (later approved by the Ethic and Guarantors Committees);

b) approves any new sub-projects;

c) defines the diffusion and implementation strategies;

d) plans the integration of the VAS-EBVD and the other existing and planned projects from VAS - Vascular - Independent Research and Education - European Organisation (e.g. educational, patient-organisation, awarness, etc…);

e) ratifies the general criteria of collaboration and of data-exchange (included in the VAS-EBVD's Regulation).

4.3.4. VAS-Guarantors Committee. It consists (like VAS-Ethics Commitee) mainly of researchers, teachers, representatives of the scientific and clinical community well-known for their intellectual independence and even if retired. It also includes a member from outside the scientific/cultural world (representative of patients' organisation or similar). It judges whether the proposals are in line with the aims and the ethical premises of VAS.

4.3.5. VAS-Ethic Committee. It consists (like VAS-Guarantors Commitee) mainly of researchers, teachers, representatives of the scientific and clinical community well-known for their intellectual independence and even if retired. It evaluates each single project, in line with the aims of European Ethics Committees.

4.4. Relations with the Ethics Committee

Diagnostic studies and / or researches involving the use of human biological material stored at the Biobank will be subject to evaluation and approval of VAS' European Ethics Committee and of the Ethics Committees of each Centre in the cases provided by law.

4.5 Project/Proposal-acceptance path

When a Research Institution/Centres asks to access the VAS-EBVD Data or Samples the following path will be carried out.

The Institution/Centre must apply to VAS - Vascular - Independent Research and Education - European Organisation providing:

- the complete project;
- the fully detailed Institution/Centre description;
- the Main Investigator's CV;

The application and all the attached documents will be forwarded by VAS' Secretariat to the EBVD-DAC which will evaluate the proposal and make a decision based on the following criteria (also called "Access Criteria":

- No re-identification of participants;
- Limited to uses stated in approved application;
- No third-party data or sample sharing/selling;
- No contact is allowed with the participants.
- Primary data must not be patented;
- That the use of the material has medical, public health or research objectives;
- Details of how the data will be used and handled;
- Compliance with original consents and applicable laws and institutional policies;
- Access granted for a limited time period (e.g., 6 months or a year), after which the recipient must reapply.

In case of positive answer by the EBVD-DAC, the project will be sent to:

- the VAS-ST for the evaluation of the relevance of the scientific content and methodologies,
- the VAS' Ethic and Guarantors Committees

for the final approval.

Once the project is approved the applicant will be asked to sign the Material Transfer Agreement to which the following further documents:

- a letter (on official paper) signed by Main Investigator declaring:
  - that the Research is totally independent from any economic interest (no-profit) and
  - that any publication related to the sample/data supplied by VAS-EBVD will carry the origin of the data/samples and VAS - Vascular - Independent Research and Education - European Organisation must be listed among the authors of the publication.

5. SERVICES AND ACTIVITIES OF THE VAS-EBVD

5.1. Offered services

The VAS-EBVD, within VAS - Vascular - Independent Research and Education - European Organisation's Network offers the following services:
- Stocking and storage of biological samples and associated data
- DNA processing
- Use of biological samples and associated data for research

5.2. Terms of use of services
a) The VAS-EBVD offers services to all members of VAS - Vascular - Independent Research and Education - European Organisation's Network and to structures that cooperate officially with VAS - Vascular - Independent Research and Education - European Organisation in research projects.
Each facility participating in research projects is responsible for:
- Joining and respecting VAS - Vascular - Independent Research and Education - European Organisation's ethical principles;
- Adhering to the project in written form;
- Obtaining the patient's informed consent (both the one proposed by VAS - Vascular - Independent Research and Education - European Organisation or another form containing the elements described in paragraph 3
- Following the procedures for collecting and shipping detailed in the individual Sub-project
- Filling out the patient's anonymized online questionnaire (www.vas-int.org) after obtaining an ID, password and login from VAS - Vascular - Independent Research and Education - European Organisation's headquarters
b) The VAS-EBVD may establish, within VAS - Vascular - Independent Research and Education - European Organisation, cooperation agreements with other agencies who have their own blood samples, after checking the certified quality of the samples and the consistency with the requirements.

For samples from Institutions / foreign Organisations, the Responsible of that Biobank verifies that the Informed Consent was acquired from the patient / research subject, in accordance with the requirements of the regulations in the country of origin. To this end, the head of VAS-EBVD may ask for the transmission of the documentation.

5.3. Acquisition of samples in the VAS-EBVD
Acquiring samples, the personnel in charge at the collecting Centre checks:
- the suitability of the sample (appropriateness of collection and preservation);
- the correct labelling;
- the presence of appropriate forms (application form, data sheet, informed consent).
- the suitability of packaging;

5.4. Procedures for ensuring the quality of the samples

The VAS-EBVD provides strict control procedures to guarantee the different phases of the service. As far as instruments and equipments, the maintenance and periodic inspections are carried out.

The Biobank adopt standardized procedures for the processing of samples and quality control available to the collecting Centre online. There are, thus, guidelines that ensure sterilization methods, purity and stability of the deposited biological material.

5.5. Use and distribution of samples

The use of samples stored in the Biobank is in accordance with the Informed Consent of the patient / research subject and in accordance with the provisions of this Regulation.

On the basis of and within these conditions, the stored biological samples, can be used for purposes of diagnosis and / or research but, in any case and under any condition, the use of the samples will never be allowed for:

- clonation;
- genetic manipulation;
- any use not in accordance with the European Guidelines provided by BBMRI;
- any use not in accordance with the National guidelines provided by the competent Organ for the Country where the research is based (for Italy the competent Organ is the *Nodo Consultivo delle Biobanche* at the *Istituto Superiore di Sanità* and the referring Guidelines are those by BBMRI-ERIC);
- profit.

Thanks to the anonimisation process the samples will always be shared without any sensitive data attached.

5.6. Responsibility of the VAS-EBVD

The VAS-EBVD is responsible for the know-how, support and material offered to collecting Centre, and for the use of the samples for diagnosis and /or research.

The Biorepository is responsible for the handling, characterization, conservation, and the withdrawing of biological samples deposited in it.

6. OPERATING COSTS OF THE VAS-EBVD

6.1. Costs related to services and activities of the VAS-EBVD

Each cost is centrally covered by VAS - Vascular - Independent Research and Education - European Organisation or by *ad hoc* funding received under the rules adopted by VAS - Vascular - Independent Research and Education for research.

7 ACCESS TO VAS-EBVD

Access to the Bioreporitory is controlled and limited only to authorized personnel.

8. UNINTENDED AND ACCIDENTAL EVENTS

8.1. Natural disasters

The VAS-EBVD and VAS - Vascular - Independent Research and Education - European Organisation are not liable for damages occurring to biological samples and associated data stored in case of natural disaster.

8.2. Unpredictable events

The VAS-EBVD and VAS - Vascular - Independent Research and Education - European Organisation are not liable for damages occurring to biological samples and associated data stored in case of unforeseen and unforeseeable events.

9. EMERGENCY PLAN

9.1. Evacuation of the Biobank

In case the need to evacuate Biorepository arises, the samples are transferred to a special place according to specific procedures based on priority criteria linked to the value of biological samples under the responsibility of the certified facility for storage.

10. PROVISIONS CONCERNING THE REGULATION OF VAS-EBVD

10.1. Changes and revisions

The Rules of the VAS-EBVD is effective from the date of its approval by Vas' European Ethic Committee and VAS' European Guarantors Committee.

It is subject to revision if changes and / or updates are needed after the approval of VAS' Scientific Committee, VAS' European Ethic Committee and VAS' European Guarantors Committee

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12. APPENDIXES

1. Material Transfer Agreement
2. VAS-European Biobank on vascular Diseases: Standard Operating Procedure (SOP)
3. Template of Informed Consent
4. Template of Informative to the Informed Consent

APPENDIX 1

MATERIAL TRANSFER AGREEMENT

VAS - Vascular - Independent Research and Education - European Organisation welcomes collaborations finalised to improving of human life.
VAS - Vascular - Independent Research and Education - European Organisation, European Scientific non-profit Association considers mandatory the subscription of this MTA related to the European Biobank on Vascular Diseases (and to its Sub-projects) in order to guarantee the respect of VAS - Vascular - Independent Research and Education - European Organisation's vision and aims and to respect the Patients'/Research Subjects' Informed Consent.
Each project (or sub-project) requiring the transfer of samples must be attached to this Agreement and both the project (or Sub-project) and this Agreement must be signed by both (or more) parties involved.

The parties to this Transfer Agreement (this "Agreement") are VAS - Vascular - Independent Research and Education - European Organisation with headquarter at the Research Centre on Vascular Diseases and Angiology Unit, University of Milan – "L. Sacco" Hospital, Via G.B. Grassi 74, 20157 Milan – Italy, and _____ herein after TRANSFEREE.

VAS - Vascular - Independent Research and Education - European Organisation does hereby grant TRANFEREE permission to use MATERIAL solely for the pur pose of conducting a study _____ as agreed between VAS - Vascular - Independent Research and Education - European Organisation and _____

1. The MATERIAL that is covered by this agreement includes: a) whole blood samples; b) plasma; c) serum.

2. TRANSFEREE shall not distribute or release the MATERIAL to any person other than to TRANSFEREE employees in order to carry out this Agreement, and shall ensure that no one will be allowed to take or send this MATERIAL to any other location, or to beach an other covenant of this Agreement applicable to the parties, unless prior written permission is obtained from VAS - Vascular - Independent Research and Education - European Organisation. TRANSFEREE agrees that neither the MATERIAL, nor any biological materials treated therewith, will be used in human beings, and that the MATERIAL will not be used for any purpose inconsistent with this Agreement.

3. TRANSFEREE agrees that nothing herein shall be deemed to grant to TRANSFEREE any rights under any intellectual property rights of VAS - Vascular - Independent Research and Education - European Organisation that may arise from the activities covered by this Agreement.

4. TRANSFEREE shall have no rights in the MATERIAL except for the permission provided for in this Agreement

5. TRANSFEREE agrees to provide all research results related to the MATERIAL to VAS - Vascular - Independent Research and Education - European Organisation. TRANSFEREE agrees to use the same degree of care to maintain the confidentiality of any information respecting the MATERIAL as

TRASFEREE would if the MATERIAL and information were proprietary information of TRANSFEREE.

6. If the research involving the MATERIAL results in a further innovation which may be academically useful, TRANSFEREE will promptly disclose the existence of the further innovation to VAS - Vascular - Independent Research and Education - European Organisation. The Parties hereby agree to negotiate in good faith the terms under which the information can and should be disseminated to the wider scientific community.

7. In no event shall VAS - Vascular - Independent Research and Education - European Organisation be liable for any use by TRANSFEREE of the MATERIAL, or any loss claim, damage or liability, of whatsoever kind of nature, which may arise from or in connection with this Agreement or the use, handling or storage of the MATERIAL, except for that VAS - Vascular - Independent Research and Education - European Organisation shall be responsible for liability which is directly attributable to its gross negligence.

8. TRANSFEREE will refrain from use of the MATERIAL or any parts thereof in or for the production of products for sale or for any commercial use.

9. VAS - Vascular - Independent Research and Education - European Organisation may terminate this Agreement at any time in the event that TRANSFEREE is in breach of any of the covenant contained herein, provided that TRANSFEREE is unable to cure such breach within thirty (30) days upon receipt of a written notice by VAS - Vascular - Independent Research and Education - European Organisation addressing such breach.

10. Any MATERIAL remaining in the possession of TRANSFEREE upon termination of this Agreement, and in absence of any further agreement between the Parties will be destroyed or, at request of VAS - Vascular - Independent Research and Education - European Organisation, returned to VAS - Vascular - Independent Research and Education - European Organisation and all of TRANSFEREE's rights to use the MATERIAL shall end.

11. The TRANSFEREE agrees that use of the MATERIAL shall be in compliance with all applicable laws, European and local governmental guidelines and regulations pertaining to research with the MATERIAL.

12. If any of the provisions of this Agreement shall become or be held invalid or unenforceable all other provisions hereof shall remain in full force and effect. The invalid or unenforceable provision shall be deemed to be automatically amended and replaced by a valid and enforceable provision which accomplishes as far as possible the purpose and the intent of the invalid or unenforceable provision.

13. As VAS - Vascular - Independent Research and Education - European Organisation has its headquarters in Milan (IT), this Agreement shall be construed and interpreted in accordance with the laws of Italy and the Parties hereby submit to the non exclusive jurisdiction of the Courts of Italy.

APPENDIX 2

STANDARD OPERATING PROCEDURES (SOP)

1.0 Purpose

To describe the procedures used to pack and ship biological samples frozen with dry ice. In accords with:

- UN recommendations of the Transport of Dangerous Goods.
- IATA Regulations and Packaging Instructions (PI650) related to diagnostic samples, for samples delivered by air.
- ADR regulation
- Communication n.3 (8th of May 2003) – Recommendation for the safe shipment of biological samples.

2.0 Scope.

This procedure must be followed by all individuals who must be trained and competent in performing the procedures described in the document.

3.0 Specific Safety Requirements

3.1 Care must be taken when handling dry ice and samples at subzero temperatures.

4.0 Reference Document

4.1 International Air Transport Association (IATA) Dangerous Goods Regulations, current edition and ADR regulation

5.0 Procedures

5.1 Place the biosamples into a biohazard bag tested in accordance with IATA packing instruction.

5.2 Place bag in a Polyfoam shipper completely surrounded by dry ice pellets. Use at least 2.5 Kg (~ 5 pound) of pellets for each day the box is expected to be in transit.

5.3 Attach the following labels to the outside of the box:

5.3.1 Mailing address of recipient

5.3.2 The dry ice hazardous materials label with the weight of dry ice reported according with the current regulatios.

5.4 Place air waybill forms and the material transfer, proforma invoice (required for delivery in NON European Countries) and shipper's declaration (if required) in plastic envelopes on the outside of the package and ship priority overnight.

5.5 Deliver package for carrier pickup. Before the delivery it is required to call the carrier in order to have a confirmation that they can deliver dry ice packaging into the country where the delivery can be done. Because of the frequent regulation change this check has to be done for any kind of delivery done with the courier.

5.6 Notify the appropriate recipient contact person by fax or e-mail and provide a tracking number for the shipment, the date of shipment and number of subjects and tubes enclosed.

APPENDIX 3

Informed consent for collection and conservation of biological and genetic material

"VAS – European Biobank on Vascular Diseases (VAS-EBVD)"

Subproject: _____

The undersigned …… Born in …….. on …. / … / …….. and resident in ……. Country …… Postal code …….. address …… tel ……. Email: ……..@…….

After being properly informed of the Sub-project …….. by means of visit by dr. …….. from the centre [name of the collecting centre] and informative material from VAS that:

- the blood collection will cause no harm to my health,
- the collected biological material can be stocked at the VAS-EBVD-Biobank's biorepository or, also, at other biorepositories according with the necessities of the research;
- the samples can be used for further investigations for a goal which must be exclusively diagnosis and research, in any case it can never be use for-profit;
- anonymity and reservation on the origin of the samples and its investigations will be granted;
- every useful action will be taken to grant the sample's anonymity, however VAS and the EBVD-Biobank cannot be considered responsible for every damage or accident which could happen to the stocked samples;
- my consent to the sample storage and their use can be withdrawn at any time and for any reason. My samples and related data can be destroyed on request and will not be used for any investigations after the date of the receipt of my communication by the Biobank. These choices will have no negative outcome to my medical assistance;
- the results of the study will be made accessible, as scientific and statistic articles, by the scientific community even to investigate new drugs, techniques of investigation, diagnosis and therapy;

- the results of the surveys can be shared with the population and patients' groups in anonymous form;
- My samples and the related clinical and personal information will be treated by researchers and personnel in charge respecting my privacy and can be shared in anonymous form with other researchers, based on my consent, according to the law and based on VAS' authorisation.

In complete liberty and without any constriction

declares

to:

1. [ ] authorise [ ] not authorise
the conservation, according to the previously specified modalities, of the biological sample

2. [ ] authorise [ ] not authorise
the possible use of this material for studies and researches

3. [ ] authorise [ ] not authorise
that my samples and the related clinical and personal information will be treated by researchers and personnel in charge respecting my privacy and can be shared in anonymous form with other researchers, based on my consent, according to the law and based on VAS' authorisation.

4. [ ] have been [ ] have not been
informed about the possibility to withdraw my consent at any time and for any reason

5. [ ] have had [ ] have not had
enough time to properly read and understand the supplied information

6. [ ] have had [ ] have not had
the opportunity to ask for details and explanations regarding the project and its methodologies

7. [ ] have received [ ] have not received
detailed and exhaustive information regarding the project and its methodologies by dr. ……

8. [ ] have been given [ ] have not been given
the opportunity to ask any questions I considered necessary

9. [ ] have received [ ] have not received
detailed and exhaustive answers to any question I have asked

10. [ ] have asked [ ] have not asked
the opinion of my GP or of any other person I trust (if answer is "have asked" skip to n. 12)

11. I did not ask for any other person's opinion because I considered it not necessary. [ ] true [ ]false

12. [ ] have been told [ ] have not been told
that I can ask information regarding the progress of the project at any time

13. [ ] have been given [ ] have not been given
the name of dr. …….. as my referee for any question and/or clarification concerning the project.

14. [ ] have been given [ ] have not been given
copy of the Informative and of this Informed Consent

15. [ ] have had [ ] have not had
the time and the information to make an informed and conscious decision

Date …… Signature ……..

The undersigned …… explicitly confirms to be taking part in the project freely, without any constriction, and having fully understood the risks and benefits that it implies.

Date …… Signature ……..

The undersigned …… also explicitly declares to:
[] authorise [] not authorise
the researches on familiarity.

Date …… Signature ……..

I, undersigned dr. ……, certify that Mr/Mrs …… at the moment when he/she read the here attached Informative sheet and affirmatively answered to the here above questions and accepted to take part in the project had clearly understood the information provided and was able to make an aware and fully conscious decision.

Name of the doctor collecting the consent ……
Signature of the doctor collecting the consent ……..

APPENDIX 4

Informative to the Informed Consent

Dear Patient,

the collected blood-samples, after being properly treated, will be stored at the European Biobank on Vascular Diseases called VAS-EBVD (property of VAS – Independent Research and education European Organisation) for the project _____. VAS-EBVD is a no-profit biological bank finalized towards research on vascular diseases. The samples, after your consent, can be used for future scientific surveys regarding vascular diseases according to VAS' politics and philosophy as detailed in the attached technical sheet (*ATTACHMENT 1 to the "Informative to the Informed Consent"*) and on VAS's website www.vas-int.org.

Your blood will be collected by the personnel of the Centre _____, authorised by VAS with deliberation of _____

Such a blood-collection will cause no harm to you health.

Your samples and the related clinical and personal information will be treated by researchers and personnel in charge respecting your privacy and can be shared in anonymous form with other researchers, based on your consent, according to the law and based on VAS' authorisation.
The accomplished results by such surveys can be used in anonymous form in scientific publications and/or can be shared with the interested population and with patients' groups. They can also contribute to the development of new technologies for diagnosis, survey or treatment of vascular diseases.
Your consent to the sample storage and their use can be withdrawn at any time and for any reason. Your samples and related data can be destroyed on request. These choices will have no negative outcome to your medical assistance.