ETOP·IBCSG PARTNERS
Foundation for International Cancer Research

IBCSG

ETOP IBCSG Partners Foundation

Biobank and

Translational Research

Policy (Breast)

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ETOP IBCSG Partners Foundation
Effingerstrasse 33 · 3008 Bern · Switzerland · +41 31 511 94 00 · TranslationalResearch@etop.ibcsg.org · www.etop.ibcsg.org

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1 Scope and Introduction

1.1 Scope

This policy outlines the key principles that must be followed within the framework of ETOP IBCSG Partners Foundation (herein referred to as 'Foundation' or 'ETOP IBCSG') when collecting and banking biological material, ethical considerations, such as consent, confidentiality, data protection, and governance. It also describes the organization, purpose, operational processes of the ETOP IBCSG Foundation Biobank (Breast). It describes the requirements for collecting, storing, and distributing biological material and their associated data (i.e., biological resources) and the access for translational research.

1.2 Introduction of ETOP IBCSG Partners Foundation

In 2022 the ETOP IBCSG Partners Foundation was formed by the merger of two highly respected clinical and translational cancer research foundations, the European Thoracic Oncology Platform (ETOP) and the International Breast Cancer Study Group (IBCSG). Biobanking for thoracic and breast cancer research within the ETOP IBCSG Partners Foundation is addressed in two separate policies. This biobank policy focuses primarily on the breast biological material and associated research data. Commonly referred to as 'IBCSG Biobank', as the biological material is collected within the 'IBCSG' clinical trials.

IBCSG was formed in 1977 as the "Ludwig Breast Cancer Study Group". When the Ludwig Institute of Cancer Research decided in 1985 to focus on laboratory research, the Group continued with a new name and structure - the International Breast Cancer Study Group (IBCSG). It was legally established as a not-for-profit foundation in 1992. IBCSG and its investigators are renowned for their clinical and translational research in breast cancer. In particular, the group pioneered the research in combined hormone- and chemotherapy, timing and duration of adjuvant therapies, as well as improvement of quality of life. IBCSG stands for a number of practice-changing studies in the breast cancer field.

The specific aims of the Foundation in breast cancer research are:

- To pursue and maintain the leading role in scientific research in breast cancer
- To conduct clinical and translational cancer research at the highest level of knowledge in cancer medicine, trial methodology, data and biomaterial handling, and ethical principles.
- To serve as a meeting platform for international study groups and institutions that research on cancer, and to foster inter-group studies.

- To continue to provide and encompass all expertise needed to develop and coordinate clinical and translational cancer research on an international level.
- To continue to have the global reach for the conduct of collaborative projects in Europe, North and South America, Asia, Africa and Australia
- To be open to promote and conduct international clinical research and translational research on other topics.

1.3 Definitions

Biological Material - Any type of human tissue, fluids or derivative thereof, collected within the trials or studies.

Derivatives - means substances created, which constitute an unmodified functional subunit or product expressed by the original biological material. Some examples include purified or fractionated subsets of the original biological material, proteins expressed by DNA/RNA.

Biobank - A biobank is a facility for the collection, preservation, storage and supply of biological samples and associated data, which follows standardized operating procedures and provides material for scientific and clinical use. It is a international cancer research associated biobank. Participating institutions in clinical trials transfer the protocol-defined biological material to the biobank and laboratory for testing and long-term banking.

BIMS – Biobanking information management system

DFexplorer- the remote data entry system used to capture clinical data, including pathology reports, and some information on biological material from patients entered to IBCSG trials or studies**.**

PMTS – Pathology Material Tracking System, the remote data entry system used to capture information on biological material from patients entered to IBCSG trials or studies**.**

General Data Protection Regulation (GDPR) – Regulation (EU) 2016/679 of the European Parliament and of the Board of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data.

Human Research Act (HRA) – The Swiss Federal Act on Research involving Human Beings of 30 September 2011, CC 810.30. This act defines the general requirements for research involving persons, including the regulations on: informed consent, consent to further use of biological material and health-related data, transfer / export / storage of biological material, financial gain, research ethics committees as well as transparency and data protection.

Long-Term biobanking - Biological Material increases in scientific value with longer follow up clinical data. The Foundation foresees long-term biobanking for all biological material that has appropriate patient consent and/or Ethics Committee approval to have available for translational research.

World Medical Association (WMA) – International organization providing ethical guidance to physicians and researchers through its Declarations, Resolutions and Statements to promote the highest possible standards of medical ethics. The WMA Declaration of Taipei addresses ethical considerations regarding health databases and biobanks (revised in October 2016).

2 Description of the ETOP IBCSG Partners Foundation Biobank (Breast)

The Foundation maintains a centralized Biobank of formalin-fixed, paraffin-embedded tissue specimens, fresh-frozen tissue, biofluids, including blood, plasma, serum, and derivatives thereof, including digital images. It contains specimens from the majority of patients included in clinical trials conducted by the group since 1981. This high-quality material is being used for correlative studies that relate markers to clinical outcomes documented during the conduct and follow-up of our clinical trials. The purpose of such research is to improve our knowledge on the prevention, diagnosis and treatment of breast cancer.

2.1 Purpose of ETOP IBCSG Partners Foundation Biobank

The Foundation maintains the centralized breast cancer biobank with associated patient specific information (baseline information and outcomes), histology, genetic test results, biological material, as a resource for research and hypotheses generation for future diagnostic platforms and marker driven clinical trials. The objectives are:

a) *Hypothesis Generation:*
   Generate biological hypothesis for personalized treatment approaches and link

them to available/new treatment options.

b) Establish a flexible clinical trial platform for Hypothesis Testing

c) Studying the molecular epidemiology of breast cancer, by coordinating and harmonizing the procedures of a group of breast cancer specialists working in translational research across Europe and globally, and facilitating analysis of larger series of cases.

d) Expedite knowledge of the prevalence and context of current and emerging molecular biomarkers with clinical significance.

e) Facilitate more rapid translation of biomarker knowledge to the clinic, and provide a platform/mechanism for future molecular correlative studies conducted in randomized trials of novel therapeutics.

f) Establish molecular testing and diagnostic algorithms for personalized medicine

2.2 Scope of the ETOP IBCSG Partners Foundation Biobank

2.2.1 Scope of the ETOP IBCSG Partners Foundation Biobank (Breast)

The Foundation maintains the biobank of formalin-fixed, paraffin-embedded biological material, fresh frozen tissue and biofluids, including blood, plasma or serum, samples, and derivatives thereof, from patients included in IBCSG Trials. Biological material collections are integral components to IBCSG trials.

All FFPE blocks, tissue micro array blocks, frozen or fluid samples, or derivatives thereof, are logged in the Foundation informatics system, IBCSG Pathology Material Tracking System (PMTS), or another protocol-designated system. The biological material is centrally collected and banked in the IBCSG Biobank.
Participating institutions transfer the samples to the IBCSG Biobank and Laboratory for testing and banking. Collection, handling, processing, banking, and research are done under strict observation of patients' rights and confidentiality.

The specimens are used for Central Pathology Review by the reference pathologist appointed for the trial, and for any translational research specified in the trial protocol. Central pathology review, which includes immunohistochemical characterization and in situ hybridization testing is integral to the IBCSG trials. From the formalin fixed paraffin embedded blocks transferred to the IBCSG Central Pathology Office, cores may be punched to construct Tissue Micro Arrays (TMA) and nucleic acid extraction is performed

This high-quality material is kept for future research/ translational research that is not yet specified at the time of collection.
This Biobank and the IBCSG Central Pathology Office and Laboratory are located at the European Institute of Oncology, in the Division of Pathology, in Milan, Italy.

2.3 Custodianship

The material collected is, in principle, regarded as donated by the patients for research. There is no international consensus on the issue of ownership of material. The Foundation therefore has custodianship of the samples. The Foundation oversees that custodianship is respected by all involved parties and entities.

The material is used in research projects proposed by Foundation investigators or scientists outside of the Foundation. Collaboration with commercial companies is not excluded, but no material will be sold for profit. All institutions who receive specimen samples or resources for research projects must adhere to the same ethical standards as the Foundation (see section 4).

2.4 Storage Duration

The biological material, and derivatives thereof, are stored in the biobank for an indefinite length of time.

2.4.1 Storage Duration at Centralized Trial Biobanks

Biological material, and derivatives thereof, are kept in the Biobank for an indefinite length of time. No biological material is destroyed without prior Foundation consultation.

Biological material centrally collected within an ETOP IBCSG Partners Foundation Trial is to be solely used for research to answer the objectives of the Trial, and for translational research that is under the auspices of the Foundation and approved by the Foundation's Translational Research Working Group (TRWG).

2.4.2 Termination of the Biobank

In the unlikely event that the Foundation should decide to stop pursuing the Biobank, it would pass the Biobank on to a non-profit research organization adhering to the same ethical standards, but would not sell it.

It is possible that biomaterial that is banked elsewhere then the central IBCSG Biobank (e.g. Blood samples from IBCSG 48-14 POSITIVE), may be handled case by case, after consultation with the relevant Trial Steering Committee, the Translational Research Working Group (Breast), and in accordance with the Foundation Board decisions.

3 Governance

The Biobank is under the ultimate responsibility of the ETOP IBCSG Partners Foundation Board.

3.1 Establishment and Legal Status

The breast cancer biobank of the ETOP IBCSG Partners Foundation was formed as part of the first trials of IBCSG. The breast cancer biobank is bound to ETOP IBCSG Partners Foundation and is not an independent legal entity.

3.2 Structure

The ETOP IBCSG Partners Foundation conducts translational research as defined by the Translational Research Working Group (breast).

Access to IBCSG biological material is based on scientific excellence, involving a rigorous competitive scientific review. The Translational Research Working Group – Breast (TRWG-B) of the ETOP IBCSG Partners Foundation serves as an advisory committee to the Scientific Committee (Breast) and is in charge of assessing the scientific merit, feasibility and the priority of each research proposal and the proper use of the biological material or resource for translational research. The TRWG-B serves as the Biobank Access Committee. The TRWG-B decides on all submitted projects. It may involve the Scientific Committee, Foundation Board or respective Trial Steering Committees if deemed appropriate.

Any research project using biological material, or related resources, from the Biobank of the Foundation must be compliant with the ethical framework of the Foundation for use of human biological material (see section 4) and with local Ethics Committees.

The Principal Investigator of any research facility to which tissue material, or any derivatives thereof, is shipped for a specific translational research project signs a written agreement, such as a Material Transfer Agreement, with the Foundation stating the use of the material and the rules applicable for surplus material. Material which can be used for further projects must be shipped back to the IBCSG Biobank.

All publications arising from such projects will follow the Foundation Guidelines for Presentation and Publication.

3.3 Intellectual Property Rights

In rare cases, intellectual property may arise from a research project. The intellectual property rights will remain with the ETOP IBCSG Partners Foundation and any financial gain will be reinvested in research of the ETOP IBCSG Partners Foundation.

4 Ethical and Regulatory Considerations

ETOP IBCSG Partners Foundation is the custodian of all patients' biological material. The Foundation will make optimal use of the material for research purposes, while guarding the patients' interests.

The protection of the patients' rights and safety are the basis for the management, collection, storage, and use of the biological material collected as part of the Foundation trials and studies.

The collected biospecimens, and derivatives thereof, are used for research according to the written consent obtained from the patient.

The specimens are used according to local ethics committee approvals and in accordance with the written consent obtained from the patient at the time the biosample is taken, or retrospectively if required by national legislation.

4.1 Consent

The collection, storage, and use of biological material is based on a specific study consent or on a previously given general board consent allowing further use of these biological materials.

For prospective collections, the Patient Information Sheet and Informed Consent (PIS/IC) are developed according to Foundation standards and Good Clinical Practice, and must be adapted to local laws and regulations.

For retrospective collections, the basis for further use of data and biological material is Ethics Committee approval that allows further use of data and biological material (see section 4.4).

There will be local, regional and country specific differences in the regulations concerning the use of biological samples for research. Each centre is expected to notify the Foundation of the local regulations and seek the relevant approvals.

4.2 Re-Consent

Re-consent of the individual patients for a new research project will not be sought, except if declared mandatory by the responsible ethics committee.

4.3 Withdrawal of Consent

Consent can be revoked at any time and without justification by the patient. In case a patient revokes the prior consent for future use of the material, all biological material will be marked accordingly in the Foundation database. Further use of the biological material is halted; however, data derived from previous research with the biological material will continue to be used. Any remaining FFPE tissue bocks are returned to the originating center and fluid samples are destroyed.

4.4 Institutional Review Board (IRB) and/or Ethics Committee (EC) Approval

Approvals are asked of the IRB and/or EC responsible for the institution by which the patient or biological material was included in the biobank. The decision of the IRB/EC will also cover patients who are deceased, in accordance with local legislation.

The Foundation or the collaborating investigator takes all measures that the research, that accesses the biological material and data, is conducted in full conformance with the applicable laws and regulations.

If the requirements for informed consent are not met, the Foundation refers to the responsible ethics committee, which may in exceptional circumstances authorize the use of biological resources for research purposes under the conditions provided in article 34 of the Swiss Human Research Act (HRA), or article 9(2) of the EU General Data Protection Regulation (GDPR), or any other applicable laws.

The Foundation will only grant access to its biological material for studies or projects that have been approved by the responsible ethics committee or equivalent authority, or are in accordance with applicable laws or regulations.

4.5 Confidentiality and Data Protection

The confidentiality of the patients is maintained by coding all material specimens with a unique patient identifier at the participating center, even before the material is provided to the Biobank. The patient identifier corresponds to the one used in the clinical database of the trial. This unique identifier is assigned by the EDC system used for IBCSG trials. This number effectively inhibits the identification of patients and only permits the correlation between the biological material and the clinical data in the EDC systems and BIMS used. Research data is marked exclusively with this identifier and cannot be linked to the patient's name within the EDC systems.

Centres are responsible to keep a patient identification log locally in order to be able to link the unique identifier to the record of the patient. Foundation personnel cannot identify or contact patients.

No identifiable / personal data will be stored in the biomaterial tracking database or biobank. When biological material and/or associated data are transferred to a researcher, who fulfils the access conditions to the biobank resources, no identifying information from the participant is given.

If a research project requires samples and data transfer to external laboratory or research facility, all measures will be taken to ensure data protection, and having a GDPR compliant data processing agreement in place.

Results generated from research projects will be coded only by the IBCSG patient identifier.

All samples and derivatives thereof are being provided to researchers as pseudo-anonymized, or if required, double coded, with a Translational Research Identifier (TRI), a laboratory reference number. This TRI effectively inhibits the identification of patients and only permits the correlation with clinical data through a separate key. All samples shipped from the IBCSG Central Pathology Office, or other designated trial biobank, to a research facility is marked exclusively with the trial patient identifier and cannot be linked to the patient's name or origin by the recipient. Access to patient identification is restricted to personnel at the treating institution. Personnel of the ETOP IBCSG Coordinating Center, the IBCSG Central Pathology Office, the IBCSG Data Management and Statistical Centers can link the specimen to the patient's data with the key, in the clinical database, but not to the patient's name (see also section 5).

4.6 Incidental Findings

In case of incidental findings with immediate clinical relevance for the patient, the treating physician will be informed. Together with the local Ethics Committee, the treating physician will be charged to assess whether to contact the patient, while taking into account local regulations and availability of genetic counselling.

5 Operational Procedures

5.1 Organization and management

The ETOP IBCSG Partners Foundation Executive Committee presides over the Biobank. The Director of the IBCSG Central Pathology Office and the Head Translational Research Coordination manage it. Standard Operating Procedures regulate the work of IBCSG Central Pathology Office and ETOP IBCSG Translational Research Coordination personnel.

The Translational Research Working Group (Breast) is consulted to decide on and prioritize research proposals seeking access to biomaterial and derivatives thereof.

The biobank personnel manage the operation under the oversight of the Head Translational Research Coordination.

Standard Operating Procedures or study protocols and guidelines regulate the work of the IBCSG Central Pathology Office, research laboratory and biobank.

5.1.1 Storage of Biological Material and Associated Data

The biobank personnel manage the biological material in accordance with Foundation requested standards. These standards are based on international best practices.

The EDC and BIMS systems are set up as an informatics system. The clinical trial database assigns the unique patient identifier to guarantee pseudoanymization. The unique patient/trial identifier is the only key providing the link with the demographic and clinical data of the patient.

5.2 Requirements for third-party based Trial Biobanks (Breast)

The biobank and laboratory for a particular trial is designated in the Trial Protocol. For most IBCSG trials this is centralized at the IBCSG Central Pathology Office, Research Laboratory, and Biobank in Milan, Italy. For some trials, such as IBCSG 48-14 POSITIVE, the blood samples will initially be banked, processed, and analyzed in two separate institutions in Belgium. The institute hosting the Trial Biobank is subject to meeting the following criteria:

- Meet objectives per trial protocol requirements.
- Meet objectives per scope of work, this includes, but is not limited to, tracking biological material and any relevant information on processing, analysis and the results.
- A primary contact person shall be designated at the Trial Biobank and Laboratory to ensure smooth communication flow with the Foundation and the participating centers. Status and progress reports must be provided to the Foundation upon request.
- Biobank may be subject to an audit or peer-review by the Foundation or a Foundation designated person.
- A collaboration agreement must be set in place between the institute hosting the Trial Biobank and the Foundation.
- The personnel of a Trial Biobank and laboratory must adhere to any international, national or other applicable legislation.
- In case of changes in personnel, the Foundation must be informed in advance to ensure continuity to meet the defined requirements.

5.3 Technical and operational guidelines

Generally, all aspects related to the Foundation Biobank operations will be supported by the designated EDC and BIMS systems to ensure reliable tracking of:

- biological material handling and processing,
- related consent,
- specimen designation
- annotated data collection,
- biological material use and correlation to research data.

The ETOP IBCSG Partners Foundation Biobank Policy (Breast) and guidelines regulate all these activities. Biological material is collected according to criteria set in the study or trial specific protocols relevant to the biological material of interest.

A central or peer-review of FFPE tumor tissue will be instituted by participating pathologists when deemed necessary, to ensure that biological material, and results thereof, being included in the Foundation Biobank and data capture system is of high quality, and well annotated. If a Foundation trial has a centralized biobank, then it is this designated centralized Foundation Trial Biobank, laboratory or pathology division that is charged with central review, in accordance with trial protocol requirements.

When participating in collaborations with other groups, other systems and policies may apply according the respective protocols.

5.3.1 Banking Conditions and Criteria

Biological material either will be permanently banked at local centers, and designated for use in collaborations by the Foundation or is sent to a centralized Trial Biobank. It may be possible that for medical or legal reasons or wish of the patient a portion or all of the biological material will be removed from a Foundation Biobank. However, in these cases, the Foundation must be informed beforehand, and documentation specifying the reason for this removal must be provided to the Foundation.

All biological material is kept in secure and controlled appropriate conditions, without any identifiable patient information.

5.3.2 Subject to Audit or Peer Review

The Foundation reserves the right to audit centers or institutions that perform decentralized or centralized biobanking, also by peer review visits. Banking conditions, processing and handling of biological material that is included in the Foundation Biobanks may be subject to audit or peer review.

6 Access to Biological Material

6.1 Translational Research proposals

The Foundation supports excellence in translational research by facilitating researchers who are members of the Foundation, or collaborators of the Foundation, to access biological material that has been ethically collected and approved for research, under the condition that the primary translational research objectives of a trial are not jeopardized. Foundation members may submit translational research proposals asking to access biological material collected as part of a Foundation study.

The 'IBCSG' Translational Research Working Group (TRWG) was established to ensure that projects using the IBCSG biological material resources address fundamental and relevant biological questions. They are put in charge of assessing the scientific merit, scientific aspects and the priority of each project, which includes assessment of originality, methodology, priority, feasibility. The biological material is a finite resource and should be used in the best possible way. Therefore, use of Foundation biological material is carefully assessed with respect to the amount of material to be allocated for a certain project.

For approved projects, the principal investigator of the research facility, which will examine the specimens allocated for the project, will have to sign a Material Transfer and Collaboration Agreement with the Foundation.

Research proposals must use a Foundation specific template, and be submitted in Word or pdf format to Head Translational Research Coordination
Rosita.Kammler@etop.ibcsg.org

6.2 Consent Control

The Head Translational Research Coordination is responsible to undertake a consent control prior to giving access to any sample and/or associated data.

7 References:

International Society for Biological and Environmental Repositories (ISBER) (2018), ISBER Best Practices: Recommendations for Repositories, Fourth Edition.

National Cancer Institute (NCI) (2016) NCI Best Practices for Biospecimen Resources (2016) Available from https://biospecimens.cancer.gov/bestpractices/2016-NCIBestPractices.pdf. [Accessed on 18th May 2022].

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8 Revision and Approval History

Version	Effective Date	Details of revision
1.0	March 24, 2006	Initial Release Approved by: IBCSG Executive Committee IBCSG Ethics Committee IBCSG Foundation Council
2.0	June 2010	Updated to the new location of the biobank at the European Institute of Oncology, Milan, Italy.
2.1	21 December 2022	Updated to ETOP IBCSG merger and reference to GDPR Approved by: Chair Translational Research Working Group (Breast) and Director IBCSG Central Pathology Office, Research Laboratory and Biobank, Professor Giuseppe Viale Updated by: Head Translational Research Coordination, Rosita Kammler