Title:	**Biobanking**	
Version:	02	
Effective date:	01-MAR-2016	
Author name	*Signature*	*Date*
P. Westveer		21-Mar-2016
Approver name	*Signature*	*Date*
Prof Dr J.J. Cornelissen		26 February 2016

References:

Human tissue and medical research: code of conduct for responsible use, Federa, 2011

Biobanking policy of the department of hematology, Radboud UMC, 2013

AMC biobank policy, 2013

UMC Utrecht biobank policy, 2013

VUMC Biobank policy 2015

Erasmus MC research code (no date)

SAKK biobank regulations as adapted for HOVON 132 AML trial, 2014

Belgian law on the collection and use of human tissue for medical application or scientific research, 2008

Scope of this policy

This policy applies to samples collected for biobanking by HOVON from patients that are included in a HOVON clinical trial. The scope is limited to clinical trials that were first approved by an Ethics Committee after the effective date of version 01 of this policy (15AUG2015) It does not apply to samples collected from earlier trials, unless the records from the trial state that this policy does apply (meaning it is mentioned in the protocol or another document in the Trial Master File).

Definition of biobanking

Biobanking is the storage of human tissue, cell and body fluid samples for the purpose of future scientific research. The objectives and methods of this research may or may not have been defined at the time of collection and storage.

Studies on human tissue, cell and body fluid samples under HOVON Biobanking Policy

Several types of studies may be performed on tissue, cell and body fluid materials stored in the HOVON Biobanking system. In general, these are all directed towards biomarker identification, biomarker validation and other correlative studies. Three situations can be defined:

1) planned and integrated in the study protocol and mandatory for inclusion
2) planned and integrated in the study protocol, but not mandatory for inclusion
3) not planned and not integrated in the study protocol and not mandatory for inclusion

The objectives and methods of type 1 and 2 studies are defined and recorded as part of the clinical trial protocol or as an appendix with the protocol. These studies may generate one or more secondary endpoints in the clinical trial and are generally performed during or shortly after the execution of the clinical trial. The tissue, cell or body fluid sample based studies are submitted to the Ethics Committee as part of the clinical trial application, and can only be performed after the clinical trial including the correlative study is approved.

For type 1 and 2 studies, the patient information letter of the clinical trial should include a (brief) explanation of the study, collection and biobanking of samples for this purpose and refer to the HOVON Biobanking Policy document.

Type 3 studies concern all studies using tissue, cell or body fluid samples that are not fully described as part of the clinical trial protocol. Informed consent is required. The patient information of the clinical trial should include a generic description of the intended use of the samples, on collection and biobanking of samples and refer to the HOVON Biobanking Policy document. Consent to collect tissue samples for the exclusive purpose of biobanking (type 3 study) should always be completely voluntary. Not giving consent for such biobanking cannot be a reason to exclude a patient from participation in the clinical trial. Type 3 studies have no relation to the clinical trial endpoints and therefore can never be a mandatory part of the clinical trial. It is allowed to take into account the willingness of the local investigator or hospital board to cooperate in the collection of type 3 biobank samples during the process of site selection for a clinical trial.

For release of samples see page 6. For informed consent requirements see page 9.

Sources of samples for biobanking

The first source of samples for biobanking is so-called residual material after primary use. This primary use can be a diagnostic procedure or a planned research procedure according to protocol within a clinical trial. The second source of tissue samples for biobanking is tissue that is obtained exclusively for the purpose of storage in a biobank. This collection can either be performed in a separate procedure or as supplemental material during a regular procedure

scheduled for other purposes. It should be noted that any extraction of samples for the single purpose of storage is considered to be an intervention for the purpose of scientific research, and is therefore subject to the conditions of the “WMO” (Medical Research Involving Human Subjects Act)

Requirements for biobanking under HOVON governance

Lymphoma tissue samples

The HOVON Pathology Facility and Biobank, (HOP) has been installed as the central storage facility for tissue samples and derived materials thereof of patients treated within HOVON clinical trials for malignant lymphoma. The HOP is responsible for the timely collection of diagnostic tissue samples and processing of such material for pathology review purposes and for processing and storage of tissue samples, DNA and RNA for future research according to protocol as well as for timely returning tissue samples to the original pathology laboratories.

Tissue samples are only allowed to be collected and stored after confirmation of informed consent for these purposes as included in the clinical trial protocol. Informed consent information is reported to the original pathology laboratories in all instances.

HOP is responsible to keep complete records of storage in a restricted database under complete anonymization and is responsible to keep complete registration of material localization. All activities are performed within the context of the “Requirements for the handling and storage of human tissue samples” (Code Goed Gebruik).

At the time of the current effective date, HOP does not include samples other than related to HOVON lymphoma trials. All other tissue samples are liable to the procedures for “cell samples and body fluids”.

Cell samples and body fluids

For HOVON, biobanking of residual material is restricted to samples that were extracted for a HOVON clinical trial procedure , and collected at a central laboratory for that primary use. This means no residual samples will be collected for biobanking from primary assessments that were performed locally at investigational sites.

For HOVON, the collection of samples exclusively for the purpose of biobanking is restricted to taking samples from patients included in a HOVON clinical trial, or patients who are screened for participation in a HOVON clinical trial.

Samples may only be extracted and/or stored at the biobank after written informed consent for biobanking by the patient. This means that HOVON does not allow storage and further use of samples using a “no objection” or “opt-out” model. There always needs to be written informed consent, so HOVON follows the “opt-in” model in all cases of biobanking.

HOVON biobank coordination

HOVON Pathology Facility (HOP) and Biobank Coordinator

HOP is physically located at the Department of Pathology, VUMC, Amsterdam, the Netherlands as an independent organization. HOP acts as the central point of contact for all matters involving pathology review and research involving tissue samples of patients within the context of HOVON malignant lymphoma trials. HOP is coordinated on a daily basis by a HOP laboratory technician and supervised by a central pathologist as appointed by the HOVON Lymphoma Working Group after approval by the HOVON Executive Board. The central pathologist reports regularly to the HOVON Pathology Group and HOVON Lymphoma Working Group.

Biobank coordinator for cell samples and body fluids

The HOVON executive board will appoint a biobank coordinator. The biobank coordinator serves as a central point of contact and advice for all biobank related matters and liaises between all parties involved: biobanks, researchers, local investigators, principal investigators, working groups, HOVON board, HOVON management, HOVON Data Center.

The HOVON biobank coordinator keeps an overview which samples from which trials are biobanked and at which location(s). The coordinator also keeps a record of all requests and decisions for the release of samples.

Requirements for the handling and storage of human tissue samples

HOVON Pathology Facility and Biobank

Pathology samples will be shipped between pathology labs by registered post only (e.g. FEDEX, DHL or other courier service).

Storage is performed according to standard procedures for archiving in pathology laboratories within the restrictions of safety and privacy regulations.

The HOP database information is anonymized using the HOVON trial number and sequential patient study number as identifiers only as received upon registration in the HOP system by the HOVON Data Center. All identifying information such as full name, initials, address, partial address (zip-code, city), BSN (citizen service number), hospital record number should be removed. Also all material (blocks, slides, DNA, RNA) is physically labelled with the HOVON trial number and HOVON sequential patient study number only.

Biobank for cell samples and body fluids

Samples should be packaged and transported in such a way that there is no safety risk for people handling the samples and that the quality of the sample is safeguarded.

Samples and the data associated with the samples need to be stored in such a way that they are protected from unauthorized access, loss, unintended destruction or deterioration.

Within the privacy regulations, samples and accompanying documents may not contain any identifying personal data, such as full name, initials, address, partial address (zip-code, city), BSN (citizen service number), hospital record number.

Sample labels and accompanying documents should be coded using the HOVON trial number and the patient study number in the trial. The sample label should also include a description of the contents (bone marrow, EDTA blood, etc.) It is allowed to add the following data for administrative purposes: date and time of sample extraction, gender of the patient, year of birth of the patient, hospital where sample was collected.

In some trials samples may need to be collected and shipped after informed consent (possibly using a “pre-study ICF”) but prior to enrolment in the trial and therefore prior to assignment of a patient study number. In those trials patients should be issued a screening-number by HOVON at the time that the samples are collected. The screening-number should be recorded on the sample label. If and when the patient is enrolled in the trial, the link between screening-number and patient study number should be recorded and shared with the biobank. If it is not possible to issue screening-numbers in a trial, it is allowed to record the full date of birth, to ensure that samples can be attributed to the correct patient after inclusion in the trial. At inclusion of a patient in such a trial, the date of extraction of samples that have been sent in prior to inclusion may be recorded in the enrolment database as an additional safe-guard for correct attribution of samples.

Clinical data from patients in the trial are collected on the CRF and in the clinical trial database. The biobank will not collect clinical data with the samples, unless it concerns limited data necessary for the proper handling and storage of the sample. The clinical data collected by the biobank are not used for analysis of trial results.

The biobank may re-code samples according to their own procedures. However, a link between the samples and the HOVON clinical trial number and patient study number or screening-number must remain intact.

An exception to the coding and privacy requirements described above, is allowed for samples that are not collected solely for research purposes, but are also used to generate test results that are of significance for the treatment of the patient. The sample is tested at the central facility and the result is returned to the site, where it is used to make a decision regarding the patient's treatment. In this situation, any risk that the test result cannot be reliably attributed to the correct patient by the site, is unacceptable. In a trial where this is the case, study specific measures should be taken to mitigate this risk. The chosen procedure still has to comply with privacy laws, and should be described in the trial protocol.

Requirements for assignment as HOVON Biobank

The biobank facility needs to be part of a university medical center in the Netherlands or Belgium, or a part of a non-academic HOVON regional coordinating hospital (such as Haga ziekenhuis, Medisch Spectrum Twente)

A biobank located in Belgium needs to be a FAGG accredited biobank.

The biobank has procedures safeguarding the quality of receipt, storage, release, shipping, destruction, management and documentation of samples.

The biobank is compliant with its institution's biobank policy (if applicable) and with the principles outlined in the Federa Code of Conduct for responsible use of human tissue in medical research.

The biobank is willing and able to comply with all relevant requirements as outlined in this HOVON policy.

The biobank has sufficient resources (people and equipment) available to provide the biobank services requested by HOVON.

The biobank is willing and able to provide to HOVON an annual report of the samples from HOVON trials that were received, released and destroyed.

The biobank is willing and able to provide to HOVON upon request an overview of all currently stored samples from a specific HOVON trial.

HOP serves as the single central biobank for tissue samples from HOVON lymphoma trials and is responsible for full compliance to all requirements as listed above. Standard procedures as formulated by the VUMC Pathology Biobanking protocol with the exception of governance issues are followed.

Contracting a HOVON Biobank

HOP serves as the single central biobank for tissue samples from HOVON lymphoma trials under a generic Material Transfer Agreement (VUMC registration …).

For each trial related to trials other than lymphoma and that includes biobanking the Principal Investigator together with the relevant HOVON working group decides which facility or facilities will function as biobank for samples from that particular trial.

The Principal Investigator should inform the HOVON biobank coordinator about the intended use of a biobank as soon as possible, to ensure sufficient time to draw up a contract with the biobank prior to any shipment of samples to the biobank.

HOVON needs to draw up a contract with the biobank prior to any shipment of samples to the biobank. This will be arranged by the HOVON manager at the HOVON Central Bureau, in collaboration with the Principal Investigator and the biobank coordinator.

HOVON will draw up a standardized framework agreement with the biobank facility. The framework agreement will address the general rights and obligations of biobanking for HOVON,

based on the contents of this HOVON policy document. It will also include general conditions regarding legal and financial aspects.

In addition to the framework agreement, a trial specific addendum will be drawn up. This includes a description of the type and number of samples to be stored, storage conditions, and any trial specific requirements. It also includes a trial specific budget and payment agreements.

Governance of HOVON Biobanks

The functional management of the samples from HOVON trials is delegated to the biobanks, to be performed according to their own procedures with the exception of governance, which remains under the final responsibility of HOVON. Decisions regarding the management and use of samples are delegated to the HOVON executive board. Any unusual situations or when disagreement arises, the decision will be brought forward to the full HOVON board by the executive board.

This means that samples cannot be released for use, transferred to another facility, or destroyed for any other reason than outlined in this policy document or the contract, without approval of the HOVON executive board. Therefore, the biobank will only release, transfer or destroy any sample as requested by the HOVON executive board within the restrictions of the Code of Conduct.

Release of materials from HOVON Biobanks

Researchers with a direct relation to HOVON Working Groups are allowed to apply for the use of HOVON Biobank samples for research purposes according to procedures set by the HOVON Working Groups. In all instances, the Primary Investigator(s) of the trial will be involved as (co-)applicant(s).

HOVON Pathology Facility and Biobank

To apply for use of pathology tissue samples as stored in HOP, a brief description of the research project, including background, objectives, methods, preliminary data, anticipated results and appropriate power calculations (not more than 3xA4) will be submitted to the HOVON Lymphoma Working Group via the secretary. The proposal will be presented (if needed) and discussed during the first coming group meeting for approval. If needed, the HOVON Pathology Group and/or other laboratory experts will be consulted for expert advice prior to decision. All proposals are to be finally approved by the HOVON Executive Board.

HOP is responsible for submitting the requested material to the research group, for timely return of the remaining materials and re-storage. Material Transfer Agreement (MTA) will be drawn and signed by the researcher and HOP prior to the release of samples.

After completion of the project, the researchers are required to deliver a full report to the HOVON Lymphoma Working Group in all instances. Principle investigators and other members of the HOVON Lymphoma Working Group will be co-authors on any publication or presentation according to regulations of the HOVON Lymphoma Working Group unless otherwise agreed. HOVON as an organization should be mentioned as a sponsor in all publications and presentations.

HOVON Biobank for samples other than tissue

Investigators can submit a request to receive samples for their research project. HOVON will provide a form for this purpose. Requests are sent to the biobank coordinator, who will forward it to the chair of the relevant HOVON working group(s) The research proposal will be discussed with the biobanking committee of the working group which will advise the members of the working group. The biobanking committee of the working group consists of the chair and at

least 5 representatives of different HOVON centers. The chair then sends the request together with an advice to the HOVON executive board.

The HOVON executive board decides if the samples can be released as requested. They inform the biobank coordinator of their decision. The coordinator informs the researchers and the applicable biobank(s), ensures that the necessary practical arrangements for shipment are made between biobank and researchers, and ensures that a Material Transfer Agreement (MTA) is signed by the researcher prior to the release of samples.

The decision if samples are released or not, should be based on the following criteria:

- The researcher should be actively involved in HOVON and HOVON biobanking.
- The researcher has provided a research proposal outlining the objective(s) and the methods of the project.
- It concerns scientific research with an objective that is in line with the HOVON objective "To promote optimum treatment of adult patients with malignant hematological diseases", meaning the project aims to contribute to a better understanding of hematological disease or to the improvement of diagnostic procedures or treatment options.
- The HOVON working group is of the opinion that the research as proposed would indeed result in a sufficiently relevant contribution to this HOVON objective that justifies the use of the requested samples.
- The available tissue samples are suitable for the purpose of the research project.
- The research objective must fall within the scope of the consent given by patients who donated the samples.

In case of doubt if the use of the samples for the proposed research would be compliant with applicable laws and regulations, such as the Code of Conduct, the HOVON executive board can request an advisory review by an Ethics Committee from the researcher.

In addition, the researcher needs to be willing and able to comply with the following conditions:

- The researcher will publish the results in a scientific journal and/or at a congress, or will otherwise make the results available to the scientific community.
- The Principal Investigator and the Co-investigators of the trials that generated the samples, and those persons who have made a significant contribution to the published results, are included as authors of manuscripts based on research of biobanked material.
- The researcher will only use the samples for the purpose of the research as outlined in the research proposal.
- The researcher needs to report any other party or individual who will be involved in the research project when making the request for the release of samples. The researcher will not transfer any samples to a party or individual that was not included in the request as approved by HOVON.
- The researcher will either return or destroy unused samples at the end of the research project, depending on the agreement made with HOVON upon release of the samples.
- The researcher is willing and able to report significant findings on individual samples to the HOVON biobank coordinator (see below)
- The researcher is willing and able to pay the costs made for the delivery of the samples as charged by HOVON, if applicable.

The researcher needs to sign a Material Transfer Agreement (MTA) to confirm compliance to these conditions before samples are released.

Release of clinical trial data associated with materials from HOVON Biobanks

The researcher can submit a request for the use of clinical trial data associated with the samples. The procedure and conditions are outlined in the HOVON policy Data Confidentiality.

Both data and samples are coded with a corresponding combination of HOVON clinical trial number and patient study number, so data and samples can be linked.

Duration of storage of materials from HOVON Biobanks

HOVON Pathology Facility and Biobank

Storage of samples in HOP will be done according to the guidelines for achieving diagnostic human pathology samples as set by the Nederlandse Vereniging voor Pathologie (www.pathology.nl , advies bewaartermijnen) i.e. at least for 30 years except if otherwise specified within the HOVON clinical trial protocol.

HOVON Biobank for samples other than lymphoma tissue

The storage duration for tissue samples needs to be specified in the protocol and Informed Consent Form. HOVON informs the biobank of the storage duration of samples from a trial. After that time, the sample is destroyed by the biobank. The recommended storage duration is between 15 years and 30 years. Tissue samples received by the biobank without a patient study number and without a screening-number, will be stored for a maximum of 6 months after receipt of the sample by the biobank. If no screening-number or confirmation of enrolment with a patient study number has been provided by that time, the sample is destroyed by the biobank. Prior to destruction of such “unassigned samples”, the biobank should inform the HOVON biobank coordinator, so an attempt can be made to retrieve the missing information.

The biobank will keep track of the expiry date of the samples and ensure timely destruction.

Destruction will be executed and recorded according to the biobanks own procedures.

Withdrawal of consent

The consent to donate tissue for biobanking is entirely voluntary. The patient can withdraw this consent at any time. The patient should make this known to his/her physician at the investigational site.

The local investigator will inform HOVON of the consent withdrawal immediately. The investigator can either contact the HOVON biobank coordinator, or the trial manager at the HOVON Data Center who will in turn inform the coordinator.

The biobank coordinator will inform the appropriate biobank(s) where the patient’s tissue is stored.

The biobank will destroy the stored samples. Destruction will be executed and recorded according to the biobank’s own procedures.

Samples that have already been used or released for use, will not be re-called or destroyed. Neither will data from analysis of the samples be withdrawn or destroyed.

If the patient is deceased, the prior consent given will remain valid.

Findings from research with tissue samples from the biobank

It is possible that the scientific analysis of a sample leads to a finding that is of direct medical importance for the patient who donated the sample, or for the patient's relatives if it concerns genetic information. Such occasions are rare and difficult to assess.

However, should a researcher come across a finding that can be reasonably assumed to be of medical importance for the individual patient or for the patient's relatives, the researcher should immediately inform the HOVON biobank coordinator.

The coordinator will ensure that the local investigator at the patient's investigational site is informed. The investigator will inform the patient's current treating physician (assuming they are not the same person). If the patient indicated on the ICF that he/she does not want to be informed of such findings, the investigator will inform the physician about this.

It is up to the physician to decide whether or not the patient and/or the patient's relatives should be informed. He/she will make this decision in accordance with the relevant guidelines of standard medical practice, such as the "WGBO".

Requirements for the protocol and informed consent form of the clinical trial

Procedures for pathology review and biobanking should be described in HOVON clinical trial protocols and in the patient information documents. Separate informed consent is required for biobanking procedures for future research, but not for pathology or other diagnostic reviews.

The procedures for collection, handling, labelling and shipping of samples need to be included in the protocol or in a lab manual that is referred to in the protocol. The guidelines in the protocol and/or lab manual should be in accordance with the Code of Conduct ("Code Goed Gebruik") and reflect the privacy conditions as described in the paragraph "Requirements for the handling and storage of human tissue samples" from this policy.

The patient information should refer to "Requirements for the handling and storage of human tissue samples" (Code Goed Gebruik) and explicitly include information on anonymization (coding), tracebility, biobanking and duration of storage. For type 1 and type 2 studies, a brief description of the research should be included. For type 3 studies, a generic description of prognostic, predictive and correlative studies is included.

Written informed consent is in all instances obtained together with the written informed consent for participation in the clinical trial or together with the written informed consent for participation in screening procedures for the clinical trial (e.g. pre-study ICF).

Consent for trial (screening) participation and consent for trial associated biobanking can be obtained on a single informed consent form (ICF) or on two separate forms. Either way, the ICF should provide the opportunity to indicate consent for biobanking separately from consent to participate in (screening for) the trial.

Consent for biobanking in the ICF should include a "broad consent" for the use of stored samples for future research that is in line with the conditions described in the paragraph "Release of tissue samples" from this policy.

The patient information and ICF need to include a statement that consent to donate tissue for biobanking is voluntary, that consent can be withdrawn, how consent can be withdrawn, and that used samples and data cannot be withdrawn. See the section on "Withdrawal of consent" in this policy.

The patient information and ICF need to include a statement that the patient will be informed of important medical findings, and given the opportunity to indicate on the ICF that they wish not to be informed.