

Histology review process and/or biological material collection within EORTC clinical trial(s)

POL017

Version 1.0

(Always refer to the Intranet to check the validity of this document)

Author

Ivana Teodorovic Signature: _____ Date: _____
Paolo Dei Tos Signature: _____ Date: _____

Co-author

Martin Isabelle
Alain Spatz
Wolter Oosterhuis
Wolter Mooi
Marc van de Vijver
Martin Cook
King Lam

Approved by

Françoise Meunier Signature: _____ Date: _____
Patrick Therasse Signature: _____ Date: _____

Distribution

Everybody

REVISION HISTORY			
Version	Brief Description of Change	Author	Issue Date
1.0	Initial Release	Ivana Teodorovic Paolo Dei Tos	April 15, 2005

Table of contents

1. OBJECTIVES	4
2. RESPONSIBILITIES	4
3. DEFINITIONS	4
4. PROCEDURES	6
4.1. Histology Review	6
4.1.1. Histology review not involving EORTC Tumor Bank	6
4.1.2. Histology review involving EORTC Tumor Bank	7
4.2. Biological material collection	8
4.2.1. Prospective material collection	9
4.2.2. Retrospective material collection	9
4.3. Anonymisation	10
5. LIST OF ABBREVIATIONS	10
6. APPENDICES AND REFERENCES	10

1. Objectives

The objective of this Policy (POL) is to describe the functioning and workflow of histology review and/or biological material collection within the scope of an EORTC clinical trial.

2. Responsibilities

The Policy will mainly focus on the responsibility and workflow between the investigators (usually clinicians), pathologists, Tumor Bank Administrator (TBA), Data Center Team and translational research project scientists. The clinician and pathologist role may be combined with that of scientist.

3. Definitions

Biological Material (BM) – “tissue” obtained from patients, used to investigate how cancer cells develop and behave, in order to adapt and improve treatment of cancer and help patients. Biological material can include: tumor tissue, other tissues, serum, blood, etc.

Data Center Team – Coordinating Physician (CP), Data Manager (DM) and Statistician (Stats) involved in a particular clinical trial.

Case Report Form (CRF) – paper documents (forms) used to collect relevant trial data for individual patients

Investigator(s) - physicians administering treatment to patients and authorized to randomize patients in EORTC clinical trials

Histology review (HR) – histological investigation of slides by the review/reference pathologist(s) and/or panel members, in order to assess tumour type or any other parameter relevant to the inclusion of the case in a particular trial.

Local Pathologist (LP) - the pathologist deciding the pathology diagnosis at the local hospital/centre where the patient will receive protocol treatment

Originating Pathologists (OP) - the pathologist who first diagnosed the case at the originating hospital and/or centre (may not be the same institute where protocol treatment takes place).

Panel committee (PC) – group of expert pathologists reviewing difficult diagnostic cases or all cases, depending of the clinical group’s policy.

Panel Member (PM) – pathologist, member of the panel committee

Panel Chair Person (PCP) – chairperson of the panel committee, in charge of approving the panel committee diagnosis (full agreement or conciliation)

Review/reference pathologist (RP) - the expert pathologists who will review (provide second opinion) the slides and confirm or disagree with the local pathologist’s diagnosis

Representative images - are standard universal jpeg images produced by a telepathology system or a system consisting of a digital camera mounted on a microscope. These images are usually between 0.5 - 5MB in size. They are images representative of a particular field of view of a tumour at a particular magnification and therefore can only be produced by a trained pathologist. The virtual tumor bank system has been designed so that once the pathologists have created these representative images (in their laboratories) in preparation for pathology review they can use the VTB to upload/send online these images to the patient case record. Once in the virtual tumor bank system, other pathologist experts can then view the patient case record online and view these representative images as well. These images will also be stored on the EORTC Tumor Bank image file server.

Tumor Bank Unit (TB) – unit within the EORTC Data Center facilitating the histology review (diagnostic) process, collection (real and virtual) of biological material and making biological material available within the scope of EORTC translational research projects.

Real tumor bank: centralized storage facility (at the Tumor Bank Unit) of slides and/or paraffin blocks.

Virtual tumor bank (VTB) system: collection of digital images and related information (including information on decentralized collection of slides, paraffin blocks and frozen material) stored in the tissue central database at the Tumor Bank Unit and accessible via the Internet.

Tumor Bank Administrator (TBA) - person responsible for the management and access of data and material in the Tumor Bank Unit.

Tumor Bank Coordinator (TBC) – person responsible for the functioning of the Tumor Bank Unit and supervising the work of Tumor Bank Administrator.

Tumor Bank forms- special case report forms designed to facilitate the work of the TBA and the whole TB process. Use of the below listed forms will be protocol specific and discussed upfront. Every effort will be made to make these forms available electronically (to be completed on-line via the VTB system) in order to facilitate pathologists work and minimize their time on form completion.

Tumor Bank Slide Form- Tumor Bank CRF for collecting information on histological slides sent to the EORTC Data Center for pathology review and/or storage. Information includes: date of arrival at the EORTC, glass slide code, date, type and time of biopsy/sampling, pathology report number (if applicable) , and whether glass slide will be stored at EORTC Tumor bank or returned after pathology review, i.e. current location.

Tumor Bank Paraffin Block Form - Tumor CRF for collecting information about paraffin blocks sent to the EORTC Data Center for pathology review and/or storage. Information includes: date of arrival at the EORTC, paraffin block sample code, date, type and time of biopsy/sampling, pathology report number (if applicable), and whether paraffin block will be stored at EORTC Tumor bank or returned after pathology review, i.e. current location .

Tumor Bank Frozen Material Form - Tumor CRF for collecting information about any frozen material sent to the Institutional Pathologist (Frozen material is NOT stored at the EORTC Data Center). Information includes: date of receipt by the Cancer Centre Pathologist, frozen material sample code, tissue type (i.e. primary tumor, metastasis, or both), date, type and time of biopsy/sampling, pathology report number (if applicable).

Tumor Bank Material Transfer Form – In cases not using the VTB on-line system, this paper form will be used by pathologists when material is transferred to the original laboratory or other laboratory for further analysis or central pathology review. Information includes: paraffin block and glass slide sample codes, date of transfer from EORTC TB/Pathology laboratory. A copy of the TB paraffin block/slide form(s) will accompany this form. Otherwise, the on-line tissue records associated with the patient should be updated with the new material location.

Translational Research (TR) - Translational research studies are integrated clinical-laboratory investigations designed to improve the prevention, diagnosis and/or treatment of cancer. These studies involve both clinical and laboratory investigations or laboratory investigations on clinical material collected during clinical trials. Generally, translational research is disease-specific. Creative proposals for translational studies should emerge in EORTC groups from multidisciplinary collaboration between clinicians, pathologists and basic scientists.

Translational Research Scientist (TRS) – principal scientist in charge of the translational research project

Virtual microscopy system (VM) - allows a pathologist to microscopically examine a slide-mounted biopsy specimen at a remote location using an internet-connected computer. This is done by scanning the specimen on a computer-controlled scanning microscope, and loading the images onto an internet server computer. Once the microscope slide is digitized, the remote personal computer connected to Internet now becomes a “microscope” for the reviewer (pathologists or researcher). By moving a cursor on the overview image, a magnified image of the selected field can be shown at any required “objective magnification”.

Virtual slide images - are produced via a virtual microscope system, which scans the entire slides in strips and then re-assembles these together to create a complete virtual slide image. These images (mostly scanned at x10 magnification) are usually between 100-300 MB in size when compressed. Special software installed on the web server will allow a user/client to view these virtual slide images online and navigate/zoom through the entire slide. If a slide is scanned at an objective of 40X, the user can view the virtual slide image at various magnifications (40, 20, 10, 5, 2, 1X). The software will also allow a user to store, within the patient case record, selected field of views ('screen captures') from the virtual slide. These virtual slides have to be produced by the virtual microscope system installed at the EORTC and so glass slides must be sent to the EORTC for digitization. The slides can then either be stored at the EORTC or returned to the original laboratory after digitization.

4. Procedures

4.1. Histology Review

Pathology review performed by an expert pathologist represents an essential component of quality control in oncologic clinical trials. It has become crucial with the advent of targeted therapies, in which the most accurate determination of both the tumour type and the selected target is mandatory. It has to be recognized that the process of pathology review, by allowing optimal selection of individuals to be enrolled in clinical trials, represents a clinical action that is undertaken in the patient's best interest.

Ideally, all patients entering a clinical trial should have pathologic diagnoses reviewed, preferably upfront. Nevertheless, patients are included in EORTC clinical trials on the basis of a (local) pathologic diagnosis.

Since practicalities may preclude the review of all cases, it is proposed that for each EORTC trial, the pathology group subcommittee of the involved disease-oriented EORTC group rules whether pathology review should be regarded as mandatory. This decision should be taken on the basis of the following considerations:

- ◇ Pathology subspecialty:
 - ◇ Some areas of tumour pathology such as hematopathology or bone and soft tissue pathology are intrinsically complex ("difficult") as are most rare tumours usually.
 - ◇ Some areas of tumour pathology require not only assessment of tumour type but also parameters such as grading and pathologic staging, which are subject to significant inter-observer variability (i.e. Gleason's score in prostate cancer, measurement of thickness of malignant melanoma, etc).
- ◇ Necessity to determine prognostic and/or predictive parameters such as ER/PGR, HER2, EGFR, c-KIT...
 - ◇ In general, immunohistochemical staining results and their interpretation are prone to inter-laboratory variations, which may preclude the pooling of data. . Any immunostain utilized for patient selection should be repeated in a reference laboratory. Reference laboratories should participate in External Quality Control Programs (i.e. UK-NEQAS ICC, NordiCQ).

If the clinical protocol requires histology review, details of this process must be clearly stated in the protocol.

4.1.1. Histology review not involving EORTC Tumor Bank

The flow of material (slides and/or paraffin blocks, original pathology reports, etc) is performed directly by the local pathologist and review pathologist(s) and/or panel review committee, according to the current practice of the group. It is absolutely mandatory for the local pathologists to assure that slides/paraffin blocks are correctly labeled and that original pathology reports/trial local pathology form correspond to the correct material (slides/paraffin blocks). This process must be clearly explained in the protocol.

After the review is completed, the materials can be returned directly from the reviewing pathologist to the local pathologist. Or, if agreed otherwise in advance, and explicitly stated in the protocol, between the Group and EORTC Tumor Bank, material (slides/paraffin blocks) and related Tumor Bank forms can be sent from the reviewing pathologist to EORTC Tumor Bank for cataloging and further central storage. At the same time, the case report form(s) related to the review process (i.e. trial pathology forms) will be returned to the trial data manager. A copy of the form related to the review process will be given to the Tumor Bank Administrator.

The Group should refund the Tumor Bank for the provided services (material storage/slide digitization/tissue tracking/return of material to local pathologists, etc). In case of academic studies, budget might be provided through the EORTC Translational Research Funds. This will be discussed and agreed for each academic trial separately.

The cost of the review process should be refunded by the group to the reviewing pathologist(s). To this end, it is strongly advised to involve the review pathologist as early as possible in writing and developing the protocol, i.e. relevant chapters.

4.1.2. Histology review involving EORTC Tumor Bank

The involvement of the Tumor Bank Unit and the Tumor Bank Administrator will be clearly explained in the final protocol. Tumor Bank Administrator will be involved in development of protocol chapter(s) relevant for the histology review process.

In order to monitor the review process for every patient entered in a trial, the TBA will receive an automated e-mail notification (as TBA is appearing on the EORTC Data Center trials ManaRand list) after each patient has been randomized in the trial. Following this notification, TBA will contact the respective local pathologist (at the institute for which the patient has been randomized) to request slides and/or paraffin blocks, the trial local pathology form and the original pathology report. The local pathologist will complete (paper forms or on-line via the VTB system) a Tumor Bank slide and/or paraffin block form for any slides and/or paraffin blocks being sent.

After receiving material (slides/paraffin blocks/forms) the TBA will label each of them:

- ◇ For slide: VTB/protocolnumber/institution number/patient seqid/Sno. of slide
- ◇ For paraffin block: VTB/protocolnumber/institution number/patient seqid/PBno. of p. block
- ◇ For form (CRF/original report): VTB/protocolnumber/institution number/patient seqid

The TBA will give the original of the trial local pathology form and copy of the original pathology report to the responsible trial's data manager for placing these documents in the patient file. A set of copies of these documents will remain within the Tumor Bank. Request for missing /inconsistent data, from the trial local pathology form, is the responsibility of the trial data manager (this also means that in case of a query, done by the DM, an updated form should be passed to TBA). The Tumor Bank Slide/Paraffin Block forms are entered into the tissue central database (if not already entered on-line by the local pathologist). The VTB system will automatically allocate the relevant VTB slide/paraffin block codes based on the above structure. Any query regarding the data on these Tumor Bank forms (Slide/Paraffin block) will be done by the TBA.

The TBA will also scan and digitize the pathology report, if available, and this digital (PDF) copy will be entered into the VTB system so the pathologists can view electronically online via the VTB system along with the other tissue and pathology data.

The TBA will create digital/virtual slide image for each slide received, using the VM system. These images will be transferred onto the 1TB Tumor Bank Image file server and the server location will be stored in the Database. The images will be designated a VTB image code based on their respective VTB slide code:

VTB protocolnumber/institution number/patient seqid/Sno_no.jpg

The TBA will send the slides/paraffin blocks, copies, of the Tumor Bank Slide/Paraffin block forms (unless available on-line), copies of the trial local pathology form and pathology report (if any) and a Tumor Bank Material Transfer Form (unless available on-line) to the review pathologist/panel committee chairperson, depending on how the review system is organized in the particular group/trial, and as specified in the protocol. It is remarked that, if desired, panel review on the basis of representative images can be done electronically. This process is than described in the histology review chapter of the final protocol.

Once the review system (including the screen capture of representative images using the VM web software) is concluded, the review pathologist /panel committee chairperson will return the material (as well as the trial central pathology form/slides/paraffin blocks/completed Tumor Bank Material Transfer Form or otherwise completed on-line via the VTB) to the EORTC Tumor Bank. In order to inform the local pathologist about the review diagnosis, Tumor Bank Administrator will send to the local pathologist instructions on how to access the patient record online with the final diagnosis, and the residual material when requested.

Whenever there is a need for a direct contact between the reviewer pathologist and the local pathologist (for example, require more identifiable patient data to allow correct diagnostic review or comparison with an earlier diagnosis), the former will receive full coordinates of the local pathologist. In case the Tumor Bank Material Transfer Form is not returned (or the tissue record is not updated on-line via the VTB system), the TBA will contact review pathologist /panel committee chairperson to request the missing form or information. The material (slides/paraffin blocks) will remain centrally stored, within EORTC Tumor Bank Unit, unless the local pathologist has requested that some/all material is to be returned. The TBA will give the trial central pathology form to the trial data manager. A copy of this form will remain with the Tumor Bank Unit. At the end of the review process, the material location will be updated within the tissue record on-line.

The TBA will monitor the whole review process by the so-called TBAtool (software program based on interactions between TBA and pathologists). The system is automatically updated after a step in the review system is finalized and will therefore alert the TBA to take appropriate actions in case of delay, or proceed to further steps within the review system.

The level of Group's compensation to the EORTC Data Center will depend on the service provided by the Tumor Bank Unit (material transfer/material storage/slide digitization/tissue tracking/return of material to local pathologists, etc). This will be (during protocol development) discussed upfront and agreed upon.

4.2. Biological material collection

The main purpose of biological material collection (tumor samples, healthy tissues, blood, etc.) is to use it for laboratory analysis and correlate them to clinical findings, and to apply these results in developing future therapeutic strategies. Such tissue banking is considered to be important by all EORTC Groups.

Thus, the EORTC Tumor Bank will constitute the central repository (real and/or virtual) for biological material collected from patients entered in the EORTC clinical trials. It will facilitate the translational research in the context of EORTC clinical trials by allowing rapid identification (by using the online search engine) of the tumor tissue needed for side – studies.

Presently, comprehensive physical storage of tissue (slides/paraffin blocks), from patients entered in the EORTC trials, at the Data Center is not considered a feasible option. Therefore, all efforts from EORTC will be focused on the development of the Virtual Tissue Bank.

Material (slides/paraffin blocks) storage at the Data Centre should be discussed and organized on a specific request (for particular projects) by the groups. This can be done prospectively, while the trial is running. In that case material collection should be mentioned and explained in the protocol itself. Material collection can also be done retrospectively, i.e. on samples that have already been collected in the hospitals where patients received their treatment.

In either case, the Tumor Bank costs for the provided service (material transfer/material storage/slide digitization/tissue tracking/return of material to local pathologists, etc) should be reimbursed either from the Group or the specific project funds. The Group (or specific project funds) should reimburse the efforts of pathologist(s) for sending material and performing the analysis.

4.2.1. Prospective material collection

The description of material collection and the flow and completion of forms is explained in the PRC approved protocol. Prior to the actual collection of materials, the TBA will check with Regulatory Affairs Unit (RAU) if all institutional regulatory documents and approvals are met with. In addition, the TBA will ensure, for every patient, that he/she has agreed to the collection of materials and to which extent (by checking answers from Randomization checklist/ORTA program). This will be possible as TBA will receive an automated e-mail through ManaRand. After these checks, if the patient consented for providing the biological material, TBA will contact the respective local pathologist to request the materials, as described in the protocol. Depending on the protocol:

- ◇ materials (paraffin blocks and /or slides) and corresponding CRF (also available on-line via the VTB) can be sent and stored at the Tumor Bank Unit until forwarding the material to laboratory for the research process
- ◇ materials (paraffin blocks and /or slides) and corresponding CRF (also available on-line via the VTB) can be sent to the Tumor Bank Unit for immediate forwarding to laboratory for the research process
- ◇ materials (paraffin blocks and /or slides) and corresponding CRF (also available on-line via the VTB) can be sent to the laboratory for the research process (however, Tumor Bank Unit is kept informed, in order to keep track of material flow)
- ◇ materials (frozen samples, blood, serum...) and corresponding CRF (also available on-line via the VTB) are always immediately sent from the local institute to central laboratory for the research process (however, Tumor Bank Unit is kept informed, in order to keep track of the materials).

In order for the Tumor Bank to keep track of material location during the entire process, the local institute's personnel must either:

- ◇ complete the of CRFs on-line via the VTB system
- ◇ or, complete the paper CRFs (Tumor Bank Paraffin Block Form/ Tumor Bank Slide Form/ Tumor Bank Frozen Material Form/Tumor Bank Material Transfer Form) and send them to the Tumor Bank Unit

After laboratory analysis has been completed, the remaining material (paraffin blocks/slides) will be returned to the Tumor Bank Unit for central storage for further cancer research, if the patient has consented to this. If the local pathologist has requested to have some or all of the materials returned (or the patients did not consent for future cancer research), they will be returned to him/her through the Tumor Bank Unit (in order to keep the track of material location). Alternatively, the material may be returned directly by the research laboratory. However, Tumor Bank Unit must be informed either by receiving a copy of the form that accompanied material as well as a Tumor Bank Material Transfer form, or by updating the forms on-line via the VTB. The same procedure applies for the frozen material, i.e. Tumor Bank Unit must be kept informed as material transfer will be done directly between research laboratory and local pathologist.

4.2.2. Retrospective material collection

This corresponds to central material collection, through Tumor Bank Unit, of material already stored in the institutes where patients received their (protocol) treatment. In certain cases, especially older EORTC trials, protocols did not foresee any organized material collection or research on these samples. However, in daily practice, surplus biological samples are still kept after therapeutic procedures (biopsies, resection specimens, frozen blood, etc). Therefore, these samples can, after adequate scientific and ethical review and approval (and, when feasible, after re-consenting patients), be used for research purposes.

For the purpose of retrospective material collection and distribution, the following steps are anticipated:

- ◇ approval of the research project (see also Policy "EORTC Tissue Research Policy" (Ref.:POL015))
- ◇ after approval, handling of material by the Tumor Bank Unit as specified in the project (see also Policy "EORTC Tissue Research Policy" (Ref.:POL015))
- ◇ laboratory analysis of collected material

- ◇ returning of unused material to the Tumor Bank or to the local institute, depending on the type of material and agreement with the local pathologist (and as specified in the project).

4.3. Anonymisation

No full names are collected, only patients codes. The labeling of material and forms follows the rule explained in 4.1.1.

5. List of abbreviations

Abbreviation	Full name
BM	Biological Material
CP	Coordinating Physician
CRF	Case Report Form
DM	Data Manager
HR	Histology review
LP	Local Pathologist
OP	Originating Pathologists
PC	Panel committee
PCP	Panel Chair Person
PM	Panel Member
POL	Policy
RAU	Regulatory Affairs Unit
RP	Review/reference pathologist
Stats	Statistician
TB	Tumor Bank Unit
TBA	Tumor Bank Administrator
TBC	Tumor Bank Coordinator
TR	Translational Research
TRS	Translational Research Scientist
VM	Virtual microscopy system
VTB	Virtual Tumor Bank

6. Appendices and references

Document title	Reference (file name)
EORTC Tissue Research Policy	POL015