Virchows Arch
DOI 10.1007/s00428-010-0998-1

ORIGINAL ARTICLE

# Quality management and accreditation of research tissue banks: experience of the National Center for Tumor Diseases (NCT) Heidelberg

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Received: 26 August 2010 / Revised: 6 October 2010 / Accepted: 8 October 2010


**Abstract** Tissue banks are key resource and technology platforms in biomedical research that address the molecular pathogenesis of diseases as well as disease prevention, diagnosis, and treatment. Due to the central role of tissue banks in standardized collection, storage, and distribution of human tissues and their derivatives, quality management and its external assessment is becoming increasingly relevant for the maintenance, acceptance, and funding of tissue banks. Little experience exists regarding formalized external evaluation of tissue banks, especially regarding certification and accreditation. Based on the accreditation of the National Center of Tumor Diseases (NCT) tissue bank in Heidelberg (Germany), criteria, requirements, processes, and implications were compiled and evaluated. Accreditation formally approved professional competence and performance of the tissue bank in all steps involved in tissue collection, storage, handling as well as macroscopic and histologic examination and final (exit) examination of the tissue and transfer supervised by board-certified competent histopathologists. Thereby, accreditation provides a comprehensive measure to evaluate and document the quality standard of tissue research banks and may play a significant role in the future assessment of tissue banks. Furthermore, accreditation may support harmonization and standardization of tissue banking for biomedical research purposes.

**Keywords** Tissue bank · Quality management · Accreditation · DIN/ISO 17020:2004

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## Introduction

Tissue banks represent essential resources and platforms for biomedical research [1–4] serving basic, translational, and clinical research projects by providing human tissues and their respective derivatives as well as offering access to key technologies. Research tissue banks require reliable and sustainable solutions for several key issues to provide high-quality material based on optimized procedures for acquisition, storage, documentation of specimens, expert evaluation according to the specific project needs, and standardized material transfer procedures. Furthermore, some biobanks additionally offer project management as an essential component, including advice and support in project planning, support in the use of bioresources-associated technologies, and even project tracking and recall procedures [1]. Especially the expert evaluation of tissue specimens for research projects represents an essential tissue bank function and is a key element of good scientific practice in research projects based on human tissues [5]. The failure to provide expert evaluation of tissues is a frequent cause for incorrect data in biomedical research based on human tissues, causing considerable

Published online: 27 October 2010

damage to the respective projects, the scientific community, and also companies relying on these results.

To guarantee a consistent level of quality and good scientific practice, it is mandatory for research tissue banks to provide quality management systems that ensure correct performance. Furthermore, a defined and transparent quality management system within research tissue banks is increasingly expected by funding organizations and even researchers and cooperating industrial partners. Several attempts have recently been made to formulate the requirements for research tissue banks and to set standards for their procedures [6–8]. In contrast, specific quality management and its external evaluation have attracted far less attention and systematic consideration. Only recently authorized external assessments by a third party, i.e., certification and accreditation, have become accessible for tissue banks.

Based on the experiences of the Tissue Bank of the National Center of Tumor Diseases in Heidelberg (Germany), the accreditation process with respect to research tissue banks was critically evaluated.

## Quality management components in tissue banks

Tissue banks have been established to provide high-quality samples of normal and diseased human tissues for the purpose of biomedical research. Thus, a tissue bank must provide optimized technical solutions for the acquisition, storage, documentation, and transfer of specimens that comply with national and international standards and legal requirements [6–11]. Additionally, expert evaluation of the tissue samples according to the specific needs of a given project is mandatory and standardized material transfer procedures should be established [5,12]. Expert evaluation includes an entry control, in which the type of tissue sample is examined and verified with regard to anatomical origin, tissue status (normal or diseased), and general tissue condition (vital, necrotic, or autolytic). It also includes an exit control, which confirms that tissue taken from the repository fulfills all of the requirements (e.g., histologic tumor type, tumor grade, percentage of tumor cells) requested by the recipient. Furthermore, a tissue bank should provide active project management including specific advice and support in project planning, support in the use of bioresource-associated technologies, and even project tracking and recall procedures. To guarantee good scientific practice and to meet the interests of all participants—especially cooperating scientists—in a transparent manner, it is mandatory for a tissue bank to establish a quality management system. The NCT tissue bank's quality management system represents a set of coordinated procedures and activities that guide and control the performance of all persons involved with regard to their specific responsibilities, positions, and interactions [13]. Therefore, the NCT tissue bank's quality management system has been implemented to address all of its structures and procedures (Table 1; Figs. 1 and 2).

*Structural components* of the NCT tissue bank include the rights, responsibilities, and obligations for members and partners of the tissue bank as well as for patients providing tissues and researchers using tissues and technologies provided by the tissue bank:

- Agreed upon "rules of procedures" that clearly define policy and aims, organizational structure, and regulations of the tissue bank.
- Guarantee of independence, impartiality, and integrity of the tissue bank and its personnel.
- Legal status of the tissue bank, including its affiliations and the specification of actions to be taken in case of a change in status or even termination of its activity and a financial disclosure of the tissue bank (e.g., non-profit organization, commercial institution).
- Sustainability of the tissue bank as guaranteed by a long-term financing plan based on full-cost estimates addressing all of its activities.
- Clearly defined interfaces to the clinical and diagnostic units, especially those regarding patient care and routine diagnostics.
- Internal (e.g., tissue bank advisory board) and/or external reviews of the tissue bank to evaluate its performance.

*Procedural measures* are those that directly affect the quality of the provided specimens as well as good scientific

**Table 1** Most important standard operating procedures (SOPs) of the NCT tissue bank Heidelberg

| |
|---|
| Structural standard operating procedures |
| Responsibilities of leadership |
| Definition of politics |
| Definition of aims |
| Organizational structure |
| Description of functions |
| Training schedules |
| Training plan |
| Scientific/procedural standard operating procedures |
| Patient consent |
| Entry controls of fresh tissue and other materials |
| Asservation of fresh tissues |
| Storage of fresh frozen tissues |
| Processing of tissues/materials |
| Project coordination |
| Pathological and anatomical evaluation of tissues (exit control) |
| Tracking of projects |

**Fig. 1** Quality management components of NCT tissue bank

| Quality Management System | |
|---|---|
| **Structural components** | **Procedural/scientific components** |
| 1. Organizational structure | 1. Project assessment |
| 2. Regulations | 2. Tissue evaluation and characterization (exit control) |
| 3. Internal and external review system | 3. Project tracking |
| 4. Patient consent modalities | |

practice in handling of tissues, project management, and even project tracking and recall procedures:

- Standard operating procedures (SOPs) for all technical procedures within the NCT tissue bank such as acquisition, storage as well as preparation, examination, and re-evaluation of tissues including reporting the results in the case of a request according to national and international standards and guidelines [6–10], including documentation.
- Standard regulations detailing how projects are handled starting from the application up to the material transfer and project tracking. This includes standardized application forms and definition of procedures for reviewing and decision making (Fig. 2).
- Professional evaluation by board-certified surgical pathologists of the tissues prior to material transfer to the respective research project (exit control) as the core element of tissue banking that significantly contributes to good scientific practice. It is protocolled and included into the standard Material Transfer Agreements.
- Project tracking and appropriate recall procedures, including sanctions in case of non-compliance. Results of project tracking are documented in order to improve handling and quality management.

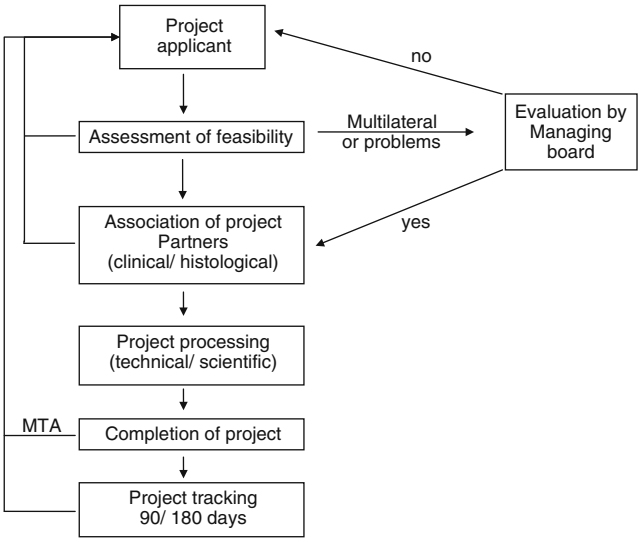


**Fig. 2** Standard project management in NCT tissue bank. Every application for project support to the NCT tissue bank is assessed and specified together with the project leader (required number, type, and quality of materials) and for feasibility; bilateral projects (involving only material from one institution) are directly processed if there are in accordance with all regulations; multilateral projects or specific problems arising require approval by the managing board (rejections are communicated to the project leader). All projects mandatorily involve an expert scientific, clinical, and histopathologic project partners as nominated by the tissue bank. After completion of project, processing pseudonymized materials and data are handed over to the project leader together with a Material Transfer Agreement (MTA). Every project is tracked after 90 and 180 days regarding initiation of experiments and material quality and all project management data are documented

An effective quality management system requires the documentation of all of these parameters in a manner amenable to reviewing procedures. The results of these reviewing procedures and measures to improve deficiencies are protocolled and followed-up.

## External reviewing and documentation of quality management: accreditation vs. certification

Evaluation of quality management performance is increasingly expected by funding organizations, researchers, and even cooperating industrial partners. Different measures such as internal reviews or reports to an advisory board are used (Table 2). Although they may meet all practical needs, these measures lack standardization and comparability. Thus, an objective evaluation of quality management systems has been increasingly considered and has recently entered realm of tissue banks.

External objective evaluation of the quality management system can be provided either by certification or by accreditation. Certification addresses adherence to designated standards or defined requirements for products, persons, or attendances. It does not include the validation of the examination procedures and the results regarding their correctness or the level of professional competence in accordance with the current state of the art for scientific and technical knowledge. In contrast, accreditation addresses result-oriented performance by authorized and adequately trained personnel providing the required professional

**Table 2** Internal and external controls of the quality system

| Measure | Characteristics | | |
|---|---|---|---|
| | Control by | Control mechanism | Aims |
| Internal and external review | Internal/ external | Regular report of head of tissue bank | Information and internal control |
| Advisory board meeting | Internal | Regular report of head of tissue bank | Information of tissue bank partners |
| Certification | External | Internal and external audits; user trainings; quality management handbook | Confirmation of operational sequences with standards or requirements |
| Accreditation | External | Internal audits and external assessments; user trainings; quality management handbook | Confirmation of operational and technical sequences with an international standard; confirmation of professional competence and quality |

competence. Thus, accreditation formally recognizes the competence to carry out all procedures in tissue banking including sampling, handling, storage, examination, evaluation, and reporting of results as well as transfer to third parties (individual researchers, institutions, or industrial partners).

Certification of tissue banks is undoubtedly possible. However, important key indicators for the quality of a tissue bank such as the evaluation of tissue specimens by competent histopathologists, the competent performance of entry and exit controls of tissues and the reporting of the results, which represent essential elements of good scientific practice, are not addressed by the certification process. In contrast, professional competence in tissue banking, especially in terms of tissue evaluation, is only assessed by accreditation. Therefore, the National Center of Tumor Diseases tissue bank in Heidelberg (Germany) had decided to use accreditation due to "ISO/IEC17020:2004 General criteria for the operation of various types of bodies performing inspection" as its measure for external and independent evaluation of its quality management [14].

## Conditions for the accreditation of tissue banks

Since the NCT tissue bank was the first institution of its kind to aspire accreditation, the accreditation body had to verify whether the activities of a tissue bank were eligible for accreditation and which standards should be applied in the process. No respective international experiences or examples existed. Over the past 10 years, more than 70 institutions for pathology have been accredited in Germany according to the ISO/IEC 17020 standard. Therefore, the first step was to question whether this international standard was applicable for the accreditation of a tissue bank. Firstly, a sector committee (advisory expert panel for the accreditation body) already existed for the subject of pathology, which had developed subject-specific criteria for accreditation that could be applied to the work of pathologists for a tissue bank. Secondly, pathologists generally possess the professional experience and expertise in the sampling, storage, diagnostic evaluation, and distribution of human tissue samples. Thirdly, experts of the field (board-certified pathologists and neuropathologists) as well as an independent expert review board of pathologists within the sector committee were available for the assessment within the realm of the accreditation process for the tissue bank.

The ISO/IEC 17020 establishes the internationally standardized competence criteria for areas that perform expert evaluations (=diagnosis) based on examinations (=findings). These competence criteria had to be interpreted by the sector committee of the accreditation body with respect to the specialty at hand in order to be able to apply them for the accreditation, e.g., in the field of pathology. An accreditation according to these standards mandatorily requires that activities of a tissue bank include the evaluation of findings and consequent diagnoses. This would not be the case if a tissue bank would be solely involved in the sampling, storage, and distribution of tissue samples. This includes tissue banks that are run independently of institutions for pathology (e.g., by clinical institutions or some biotechnology companies). The certification of such tissue banks is possible as the result of a lack of standards and regulations; however, the accreditation according to the ISO/IEC 17020 is excluded under these circumstances.

The analysis of the activities, processes, and expertise in the NCT tissue bank showed that it compares to the activities and expertise of a department of surgical pathology. The sampling of tissues designated for the NCT tissue bank and the histological evaluation of the type, quality, and composition of the samples was performed by either a board-certified surgical pathologist or a trainee under the direct supervision of a board-certified pathologist. The selection and sampling of tissues for the NCT tissue bank were performed in accordance with the principles applied to patient material under clinical diagnostic conditions. The only difference was, e.g., for the production of a tissue microarray that the "sampling" in this case was taken from a pre-existing paraffin block instead of a sample taken from resection material. In both cases, the

specific expertise of a pathologist was applied. This process always culminated in the formulation of a diagnosis, which was communicated in the form of a report at the time of sample delivery (exit control), in this case for a researcher instead of a clinician. Clinical data, blood, and serum products as optional, additional, and project-specific components provided by the clinical cooperation partners were not included in the considerations of the accreditation process. Based on this assessment, the accreditation body decided that the NCT tissue bank performs a service that can be accredited according to the ISO/IEC 17020 standard because expert evaluations (=diagnosis) of tissues are based on examinations (=findings), which are communicated to a researcher (instead of a clinician) at the time of material delivery (tissue sample, TMA, etc.).

## Accreditation of the National Center of Tumor Diseases Tissue Bank, Heidelberg

Accreditation requires a systematic approach and the stepwise implementation of a quality management system including several stages: preparation, the review process, and the post-reviewing period (Fig. 3).

*Preparation* Since the foundation of the NCT tissue bank in 2005, standard operating procedures for all relevant procedures have been defined (Table 1, Fig. 1) and were constantly improved and adapted to national and international regulations. In consequence, in 2006 the NCT tissue bank stratified all existing workflows regarding organizational structures, responsibilities, procedures, processes, and resources, including all activities that directly or indirectly contribute to quality, and tested them for weak points and practicability. For tissue bank processes not previously listed, new SOPs were implemented in the NCT tissue bank's quality management system. Interfaces to interacting institutions (e.g., German Cancer Research Center, hospital facilities) and especially the Institute of Pathology were reviewed, documented, and formalized. In 2007, the first quality management manual covering all working processes related to the NCT tissue bank (Table 1, Fig. 1) was finished and implemented in daily practice. From that time point on, regular internal audits were performed to evaluate the quality management system.

*Accreditation process* After formalization of the quality management system was completed, the NCT tissue bank applied for accreditation according to ISO/IEC 17020:2004. The quality management system was adapted to the standards [15,16] set forth by one of the predecessors of the national accreditation body DAkkS, and the application was filed in mid-2008 to the "Deutsches Akkreditierungs-

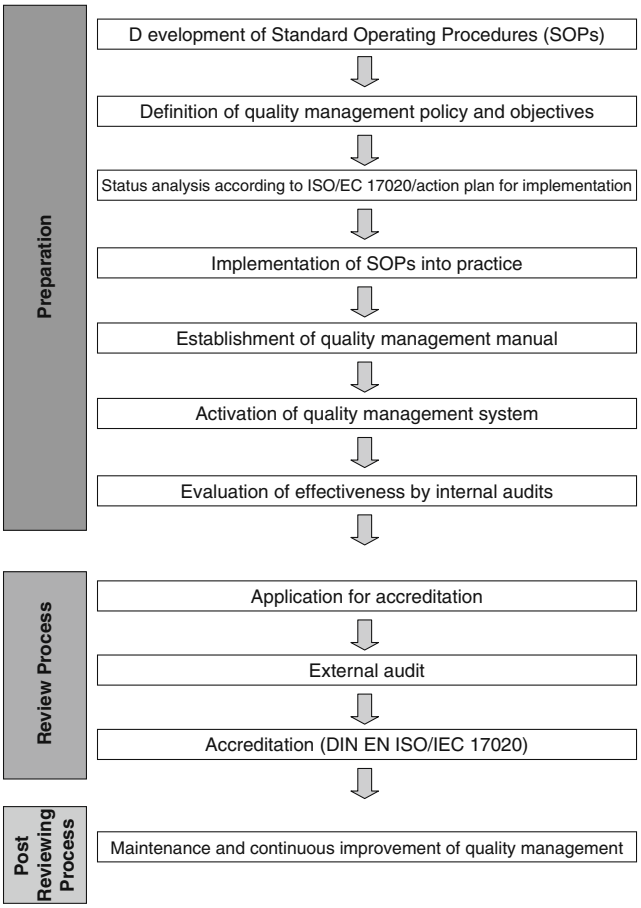


**Fig. 3** Systematic approach to tissue bank accreditation

system Prüfwesen GmbH (DAP)" [now the national accreditation body "Deutsche Akkreditierungsstelle GmbH (DAkkS)"], which initiated the accreditation of the NCT tissue bank. At the end of 2008, the NCT tissue bank was subjected to a 3-day on-site review by an authorized and independent external assessor team of the DAP [lead assessor for the management system and a technical assessor (senior board-certified surgical pathologist with special training in accreditation)]. By this assessment of the NCT tissue bank, the following aspects were evaluated in accordance with the standards set forth by the ISO/IEC 17020:

- the quality management system including its documentation,
- the structure and the legal status,
- the procedures for sampling, storage, handling, examination, and evaluation of requested material including records and reports,
- the fulfillment of legal requirements including all ethical issues,
- the responsibilities of the top management of the tissue bank and the scientific advisory board,

- the competence of the head of the tissue bank and the laboratory as well as the medical experts involved and the procedures for the maintenance of competence of all personnel including the pathologists, and
- the performance of effective and target achievement of the NCT tissue bank's quality management system.

After the successful review, the NCT tissue bank was accredited In April 2009 according to ISO/IEC 17020 by the DAP as the first research tissue bank in Europe.

*Post-reviewing process* After successful accreditation in April 2009, the quality management system was further improved; internal audits and regular education and training programs were performed. In February 2010, the NCT tissue bank successfully completed the first external surveillance assessment by the DAkkS (former DAP).

## Discussion and future developments

The National Center of Tumor Diseases tissue bank in Heidelberg, Germany, was the first tissue bank to subject its quality management system to external evaluation by an accreditation body. This process had revealed several aspects (Table 3) that should be considered prior to decision making.

With regard to staff members, accreditation (as well as certification) is an important tool for communication and to promote adherence to regulations by staff members because all procedures and working processes are defined in the quality management documentation. Instructions for all staff members are likely to be followed more strictly as they are controlled continuously by audits and reviews and are improved regularly if necessary. All staff members are necessarily and actively involved into the design of the quality management system and the review process so that there is continuous incentive for further education. Although initially an adverse attitude towards certification or accreditation may occur as it may be considered to be a form of supervision, this process holds significant potential to strengthen the identification of all participants with the tissue bank, to increase the feeling of responsibility, and to offer staff members greater visibility. Thus, over time the staff's attitude towards accreditation is likely to develop in a positive manner, especially when it becomes more and more familiar with the accreditation procedure.

**Table 3** Aspects of tissue bank accreditation

| Positive | To be considered |
|---|---|
| Induces comprehensive system analysis | High effort (personnel, time, costs) |
| Higher internal and external acceptance (confidence, "marketing") | Difficulty to acquire specific funding for accreditation |
| Relevant for industrial interactions ("label"; quality assurance) | |
| Integrates performance of all participants | |
| Transparent workflows for all participants; facilitates incorporation of new staff members | |
| Fixes tight link to expert histological analysis, i.e., pathology | |
| Relevant tool to justify and gain funding for tissue banks | |

The increased work load—especially during the preparation and accreditation process and its specific documentation— as well as the resulting direct and indirect costs have to be seen as the main aspects to be considered. Only institutions that are able to provide these resources (personnel and finances) will be able to successfully complete the accreditation process; therefore, planning of the accreditation process should include a critical review of the available resources. The required specific effort depends on the pre-existing level of quality management, documentation, and experience in accreditation procedures.

With regard to external partners, positive aspects dominate; accreditation documents quality in an official and visible manner. This will increase confidence in the performance of the tissue bank, especially for cooperating scientists and funding institutions; it may even become an important argument for funding and sustainability of the tissue bank as well as unifying tissue banking efforts at a given location. Furthermore, since the performance of tissue evaluation within the tissue bank, especially the exit control, is linked to the specific qualification level, it closely links tissue banking with the professional expertise of board-certified surgical pathologists. Therefore, it is a good, indirect measure to eradicate "wild", uncontrolled tissue collections, which represent a major threat to good scientific practice. On a long-term basis, it may be discussed whether accreditation may be one of the means to guarantee tissue bank quality on a national or international level. This is an important aspect with regard to large cooperative projects or grant applications based on significant decentralized tissue resources. Due to the increasing impact of translational research and especially targeted therapy, the importance of developing specific and individual targets and predictive markers is rising. Investigating subgroup-specific targets implicates that tissue collectives may be too small in a local research unit. Since accreditation according to ISO/IEC 17020 represents an international standard, it may be helpful to harmonize national and international tissue banking and support the generation of large and comparable tissue collectives even of small

subgroups for translational research and targeted therapy [17]. Accreditation is likely to become increasingly relevant for cooperating projects involving industrial partners. Industrial research also depends on high-quality tissue resources for drug development and the identification of novel targets and biomarkers [18]. On the other hand, industrial partners will ask for objective confirmation of the tissue bank's high-quality performance. In light of all of these aspects, accreditation offers an attractive perspective to improve quality management, transparency, and external acceptance of competent tissue banks.

**Conflict of interest statement** We declare that we have no conflicts of interest.

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