

Provision of diagnostic material for research purposes

The Health Research Act requires that an internal quality assurance system be established for medical and health research. We will describe our experience of the establishment and application of such a system for provision of human diagnostic material for research purposes. In our experience, a systematic review of project documentation will in many cases reveal errors or deficiencies.

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The Health Research Act (Act on medical and health research), which was adopted by the Storting in May 2008, contains a separate chapter on the requirements for organisation and conduct of medical and health research. For example, Section 6 states that internal quality assurance must be carried out in a manner that is adapted to the size, nature, activities and risk factors of the research (1). The implications are described in a separate set of regulations (2), with explanatory notes (3). These documents, as well as the underlying public report *God forskning – bedre helse* [Good research – better health] from 2005 (4), focus on the responsibility held by the institution and the project manager conducting the research.

As regards the use of human tissue for research purposes, this will often involve material collected in the course of regular diagnostic work. Such diagnostic tissue material is examined and stored in departments of pathology. The largest collections of human tissue are thus found in diagnostic biobanks in these departments (5).

Research on such human tissue can be subdivided into two categories:

- Retrospective studies, which conjoin clinical follow-up data and/or registry data with results from new examinations of previously collected tissue.
- Prospective studies, in which clinical follow-up data are also collected.

The organisation storing the diagnostic tissue material may not invariably participate in the research project that wants to make use of the material. The project manager may be employed by a different organisation, but wants to gain access to material located in various departments of pathology. In this case, the question arises

as to what kind of internal quality assurance systems need to be present in departments that provide diagnostic biological material to external research projects. In this article, we will describe the process and the experience associated with the establishment and application of such an internal quality assurance system at the Department of Pathology, Akershus University Hospital.

Appropriateness and permissions

After the Health Research Act had come into force in the summer of 2009, the department wished to prepare practical guidelines for provision of diagnostic material to research projects. It was agreed that the efforts should be based on recognised principles for quality improvement (6), and that the guidelines should be incorporated into the department's internal quality assurance system. A draft mandate for a research committee and a biobank coordinator was prepared. The latter was to assess the requests before they were submitted to the research committee. Once approved by the head of department, the mandate was entered into the department's electronic quality manual. Since September 2010, all requests for provision of diagnostic material have been assessed using these guidelines. Since the routines were new, systematic evaluation and necessary amendments were part of the process. The timeline for this process, from October 2009 until February 2013, is illustrated in Figure 1.

With regard to what should actually be assessed in the case of requests, two key questions were identified: Is provision of the diagnostic material appropriate? Is the requester in possession of the required permits?

When requests for provision of material are received, due consideration should be given to whether such access will make the execution of statutory duties as regards storage and processing of the material, as well as safeguarding the interests of the donor of the material difficult or impossible (7). In our opinion, the pathology depart-

ment's primary task is to provide adequate health care. As a general rule, provision of diagnostic material should thus not come into conflict with ongoing or future diagnostics. This accords with the guidelines prepared by the International Society for Biological and Environmental Repositories (8). In practice, this means that material should not be retrieved and/or provided to research projects in cases where such retrieval may impede ordinary diagnostics, or whenever there is only a minimum of relevant diagnostic material left.

The commission that investigated the Sudbø affair criticised several organisations for having provided research projects with human biological material and data without prior assurance that the required permits were in order (9). Our conclusion was therefore that whoever requests access to diagnostic material must submit a copy of the approval provided by a Regional Committee for Medical and Health Research Ethics (REK), the project protocol, and a copy of the consent form to be signed by the project participants included in the study.

New findings in old material

During the first five months, the department received three requests. In one case, one of the department's staff members had given the green light for participation in a biobank project involving prospective retrieval of tissue without prior assessment of the request by the biobank coordinator and the research committee. In a subsequent review of relevant documentation, all formalities were assessed and found to be satisfactory. In another case, it turned out that the project did not have all the required approvals, and the material was therefore initially not provided. One year later all required permits had been obtained, and the material was released. In a third case, new tissue slides were to be produced for an evaluation undertaken by pathologists in order to ensure uniform inclusion criteria. In such cases, new clinically relevant find-

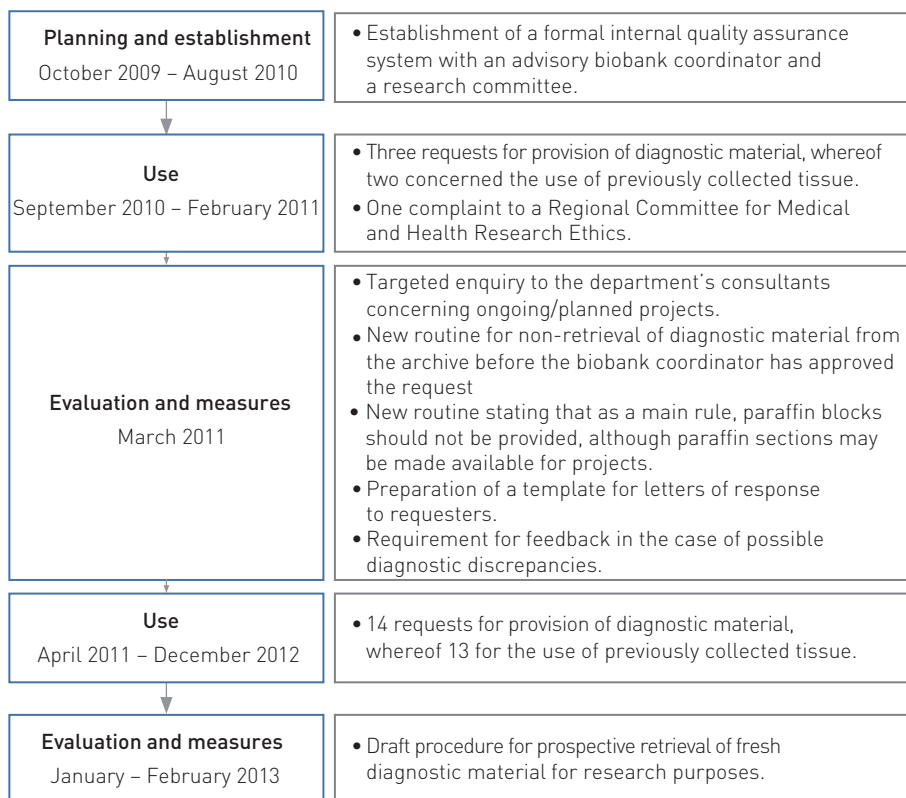


Figure 1: The various stages associated with establishment, evaluation and revision of the internal quality assurance system for provision of diagnostic human tissue material for research purposes at the Department of Pathology, Akershus University Hospital.

ings may come to light, but this issue was not discussed either in the protocol or in the approval granted by the research ethics committee. When reviewing the consent form, the department also discovered formulations that were deemed to erroneously limit the rights of the project participants. These issues were pointed out in a written feedback note to the project management. After several exchanges of viewpoints, a complaint against the department was filed to the Regional Committee for Medical and Health Research Ethics. In its response, the committee confirmed that there was an error in the consent form, and requested that a new consent form be sent to all project participants. Moreover, the committee noted that an approval does not imply that organisations are obligated to provide material. Following the receipt of a revised consent form, the department supplied material to the project.

In March 2011, the first evaluation was undertaken, and a number of formal and practical measures were implemented on the basis of experience from the first six months (Figure 1). The department currently requires feedback to be provided on findings of possible clinical relevance to the project participants in question (10).

Absence of documentation

From April 2011 to December 2012, the department received 14 requests for provision of material. In five of these cases the required project documentation was not supplied, even after a reminder had been sent. Furthermore, the department declined to provide material to one project as this would require an excessive use of resources. In two cases, the request was rejected because the desired material had been collected outside the time period specified by the protocol, or because the protocol did not refer to material collected at Akershus University Hospital. A fourth request was initially rejected since it referred to another type of material than what was described in the protocol. After an amended request had been submitted to and approved by the Regional Committee for Medical and Health Research Ethics, the material was provided. In a fifth case, the project has undergone so many changes since the original approval that the department is still assessing the request. In the remaining four cases provision of material was approved without comments.

A second evaluation was undertaken in January 2013. Based on a number of informal inquiries concerning prospective provision of fresh material for research

projects based on diagnostic tissue material, a draft procedure for this was prepared.

Discussion

The Health Research Act authorises the Norwegian Board of Health Supervision to monitor medical and health research as well as the management of research biobanks. In 2012, this inspectorate therefore undertook an assessment of the vulnerability involved in such research (11). The report by the Norwegian Board of Health Supervision states, *inter alia*: «The risk assessment did not reveal any major risk that research participants could be inflicted with serious physical harm in Norway. The risk is to a greater degree associated with inappropriate management of health information and biological material, with consequent violations of the research participant's integrity.»

In the period from October 2010 to December 2012, the department received 17 requests for provision of diagnostic biobank material for research projects. In five cases, required project documentation was missing. In five of the 12 remaining cases, significant errors or omissions were detected, and one further project had undergone so many changes that no real assessment was possible. In none of these cases did the project manager or the ethics committee address the issue of how to handle new findings of possible clinical significance emerging as a result of a re-investigation or a new examination of the diagnostic material. For example, if new sections are taken from paraffin blocks in which severe dysplasia was detected in the initial diagnostic examination, invasive cancer may be detected. In our opinion, such issues must be addressed in a transparent and predictable manner, thus to safeguard the interests of the project participants (10). The project manager should explicitly discuss this issue in the project protocol and the application form to the ethics committee. The committee should similarly address this issue in their decisions.

Quality improvement is a continuous process, in which systematic evaluations should entail adjustments of procedures as required. In addition to formal administrative measures, the first revision included information efforts targeting the department's consultants, since many of them maintain contact with internal as well as external research groups. During the second revision, a stronger focus was placed on routines associated with prospective retrieval of tissue for research purposes. As regards the administrative management of tissue requests, the biobank coordinator has seen it as an advantage that the routines have been included in an internal quality assessment system which has

been approved by the head of department. In situations involving occasional vehement exchanges of opinion with researchers who strongly object to what they regard as interference in their projects, it was opportune to be able to refer to the internal quality assurance system. In our experience, very few project managers contacted the pathology departments from which they planned to acquire their material before elaborating the project protocol and submitting it to the regional ethics committee.

In cases where the project manager receives feedback indicating a need for changes regarding the collection and use of the biological material, a project protocol amendment must occasionally be submitted to the regional ethics committee. In the second revision of the internal quality assurance system, attention was therefore paid to guiding project managers at the planning stage, to ensure that the protocol describing the collection and use of diagnostic material will be realistic and comply with the department's operational routines.

The establishment of the internal quality assurance system described above has been resource-intensive and occasionally conflict-ridden. In our opinion, however, such an establishment has been organisationally necessary. The quality assurance system has raised the quality of the department's routines, and has also introduced more predictability in the department's requirements to requests for tissue. We also believe that at least in some cases, project managers have received feedback that has helped improve the quality of the projects.

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