Article

REXIC project: retrospective cross-sectional study of documentation of informed consent for research biobanking in a public research and teaching hospital

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Significance for public health

Biobanks collect and store human and non-human biological material for diagnostic and research purposes. These biobanks keep sensitive data and biological samples also for long periods of time, and such data and samples can be used for research even many years after they have been deposited. Therefore, a well-designed and carefully applied informed consent is an essential document to help research purposes. There has been a continuous growth in the activities of the biobanks yet a definitive informed consent model is still not available. So, it is important i) to make a systematic evaluation of the models of consent used, and this should also include a survey of public opinion in order to develop guidelines which can be shared in an international setting and ii) to improve the quality of research projects.

Abstract

Background. The Center for Transfusion Medicine, Cell Therapy and Cryobiology, Milan, Northern Italy, is the headquarter of the POLI-MI biobank. It co-ordinates the biobank activities of the Fondazione Ca' Granda Ospedale Maggiore Policlinico of Milan. Such activities require specific safeguarding of donors' rights and protection of sensitive and genetic data. The Fondazione Ca' Granda Ospedale Maggiore Policlinico has set up a project on informed consent with the aim of developing awareness and understanding of this issue. Within this project, it has been decided to evaluate how consent for biobanking material is expressed.

Design and methods. The aim of the study was to evaluate the quality and completeness of consent to biobanking in the POLI-MI biobank. This was a retrospective study carried out in 2012 on samples of consent declarations collected by biobank units in 2011. Some units used a single, standard consent model available from a previous POLI-MI biobank workgroup. Other units used models which had been previouly formulated. Evaluation was made using a form that indicated the essential elements of consent.

Results. A total of 48 consent declarations were collected using the single, standard model and 84 were collected using other models. The consent declarations that used the single, standard model were found to be the most complete and were filled in better than other models.

Conclusions. Progressive adoption of a simple, standard consent model is expected to improve the quality of consent acquisition. Regular audit of the compliance of consent practices with ethical and legal requirements is mandatory to improve the quality of research biobanking.

Introduction

Biobanks collect and store human and non-human biological materials for diagnostic and research purposes. Some countries have identified their ideal operative context to be within institutes known as Biological Resource Centers (BRC).[1,2]

The creation of biobanks has required, among the various critical issues involved, the definition of adequate privacy protection systems to safeguard donors. In fact, biobanks collect and hold sensitive data and biological samples also for long periods of time. These can be used for research purposes even many years after their collection. Furthermore, since biobanks often operate through the internet, biological samples and their related data are often used for multicenter studies and can even be exchanged between BRCs in different countries.[3] There is little homogeneity in the legislation regulating the exchange of biological materials and their documentation between countries. For example, even within the European Union there is no shared regulatory system concerning biobanking. This means that the same kind of activity is allowed in some Member States but not in others.[4] For this reason, some countries are starting to standardize their legislation and to share regulations concerning research and working methods.[5-9] Between 1999 and 2001, the European Commission set up the EUROGENEBANK, a project which involved six countries and aimed to define the types of existing biobanks and the critical issues related to their regulation. This has opened the debate on several issues, such as the methods used to collect biological samples, the objectives of biobanking, how the samples and related data should be managed and the access procedures.[4] In 2009, the German BMB-EU Coop project analyzed the legal and ethical consequences of international biobanking, underlining how similar theoretical principles are applied in different ways in different countries.[10] One of the aspects to which legislators should pay attention is the issue of consent. The American Society of Human Genetics (ASHG) has identified some essential items that must be covered by the donor's consent declaration for collecting samples for a specific research project: i) the objective of the research, ii) the limitations and possible consequences, iii) risks and benefits, iv) the type of information expected from the research, v) how results will be made available, vi) methods of maintaining confidentiality. According to the ASHG, it is unacceptable to request informed consent for any possible research carried out using the samples at a later date. In cases of deceased donors, the indiscriminate use of samples and data is not allowed, since this could put relatives at risk.[11]

Italian law concerning the donation of biological materials and treatment of personal data is presented in legislative decrees.[12-17]

The Legislative Decree n. 196 of 30th June 2003 (Code for the protection of personal data) guarantees […] *that the treatment of personal data is carried out with respect for the fundamental rights and liberties, and the dignity of the person concerned, with particular reference to confidentiality, personal identity and personal data protection rights.*[12]

The Legislative Decree n. 191 of 6th November 2007 (bringing into force of the 2004 EC directive 2004/23/EC on the definition of the regulations concerning donation quality and safety, the supply, control, processing, preservation, storing and distribution of human tissues and cells) lists the essential information that must be given to donors, *[…] that is the objective and nature of the supply, its consequences and risks, analytical tests (if carried out), registration and protection of donor data, medical confidentiality, therapeutic objective and potential benefits, together with information on guarantees that can be given to safeguard the donor*.[13] In order to validate the consent documentation, there is some essential information that the donor must receive. Guidelines regarding this information have been published on the Official Journal n. 159 of 11th July 2011.[9] Recently, Lombardy Region has developed guidelines for the correct institution and regulation of biobanks, suggesting a possible organizational model and emphasizing the importance of the informed consent; however, operative instructions are not provided.[17]

The problems involved in informed consent were also examined at the POLI-MI biobank of the Fondazione Ca' Granda Ospedale Maggiore Policlinico of Milan. This is part of the Center for Transfusion Medicine, Cell Therapy and Cryobiology. The POLI-MI biobank offers a service of cryopreservation of biological material collected for research purposes by all the Departments in which the Fondazione is divided, the Operative Units (OU).

The Center for Transfusion Medicine, Cell Therapy and Cryobiology is made up of 4 sectors:

i) The Milano Cord Blood Bank which performs characterization, storage and distribution of placental blood for hemopoietic transplantation; the Cell Manipulation Laboratory is responsible for the cryopreservation of hemopoietic stem cells from peripheral blood and bone marrow.
ii) The Franco Calori Cell Factory, which is a certified laboratory compliant to the regulations and standards of Good Manufacturing Practices (GMP). It is authorized to produce cell therapy products, and to carry out translational research on stem cells for transplantation and tissue repair.
iii) The Interdepartmental Flow Cytometry Center carries out research and services for cell immunophenotyping and sorting; the Experimental Hepatology Laboratory studies cancer stem cells.
iv) The POLI-MI Biobank preserves around 100,000 human biological samples (serum, plasma, cells, DNA, tissue) collected for research purposes from 24 internal and external groups.

In 2005, the Fondazione set up a workgroup with the aim of revising the methods of attaining informed consent relating to biological samples collected for research purposes on the basis of the Italian legislation in force and in consideration of the international experiences reported so far.

The evaluation of the consent documentation used by the Fondazione identified a variety of models. On the basis of the models in use, and taking into account the requirements reported in the literature, the workgroup drew up a single, standard model.[18] This model was proposed to all OU of the Fondazione and was used experimentally from 2009 to 2011. This model was formally adopted by the Fondazione on 22nd November 2011.

Research objective

Since the immediate adoption of the new model by all OU in the Fondazione who use the biobank services is unlikely, through 2011 it was decided to carry out a survey to evaluate its use by the various OUs and at the same time to verify the completeness and the correct compilation of the old models that may still be in use.

All original consent documents collected at the Fondazione are archived in the patient's case sheet. The physician in charge provides the patient with information about the collection, preservation and use of human biological materials for research and obtains the patient's consent. The physician presenting the consent form to the patient is responsible for its correct compilation in all its parts.

Design and methods

The REXIC project is a retrospective study that aims to verify the adoption of the single, standard consent model proposed for experimental use in 2009, and to check the correct compilation and archiving of the informed consent documentation relating to biological samples deposited in the bank during 2011.

The study protocol was drawn up together with the directors and staff of the Center for Transfusion Medicine, Cell Therapy and Cryobiology (CTMC) and the Post-graduate School of Hygiene and Preventive Medicine in Milan. For the study, we selected the OUs or sectors which sent samples to the POLI-MI biobank during 2011. All consent documentation was examined by those OUs or sectors that collected at least 50 samples; otherwise a 10% random sample of documents was examined.

In order to collect data relating to the completeness and correct compilation of the consent documentation, an *ad hoc* evaluation form was provided based on the single, standard consent model proposed by the CTMC and established in November 2011. Researchers confirmed the OU (or sector) on the form and a number code was used to identify the type of consent examined if this was not already identified by a quality control system code assigned by the Fondazione. The form included various items subdivided into sections. The researcher had to verify whether each of these issues had been filled in and whether compilation was correct and/or complete.

In the first section we checked the presence of information relating to the OU where the samples were taken and its contact details (telephone number and e-mail address).

This information is useful for the accountability of donors.

In the second section we verified the presence of 5 items: i) the reasons why and the methods by which the sample was taken; ii) information on the methods of preservation used for the biological samples; iii) information on the management of the documentation related to the samples deposited in the bank (*e.g.* results of tests carried out, sensitive donor data, etc.); iv) information on the risks related to the collection and preservation of the biological material; v) information on the disposal of the stored material.

This kind of information is needed to justify the type of the collected sample and to explain the aim of the research. We also examined whether the consent documentation included a note confirming that the donor may, at any time, withdraw consent to the use of his/her samples and data by writing to the Director of the OU where the samples were taken, and if collected data were treated with the needed confidentiality and in respect of the donor's privacy.

Lastly, the protocol set out the expression of consent for: i) additional sample collection; ii) the preservation of samples; iii) the manipulation of biological material; iv) the management of sensitive data; v) the sharing of anonymous data; vi) the use of data for scientific publication; vii) the possible use of samples and data for further research; viii) the disposal of the samples once the research has been completed.

The collection of consent for future research is fundamental since the use of biological materials is not always immediate, and samples

can be stored for an undefined time. Each consent document was checked to evaluate whether the following data had been provided: date, name, surname and signature of the person responsible for obtaining consent and of the donor. For those OUs which had still not adopted the single, standard model, evaluation of consent was made through a comprehensive checklist of all the above-listed items.

The project was presented by the Directors of the involved OUs during several meetings and in the presence of a specialist in Public Health and post-graduate Public Health students, who had been previously instructed on to how to fill in the evaluation form and who subsequently checked the consent documentation.

The Public Health specialist and 4 students were asked to verify whether the patients' case sheets contained the consent documentation; they also had to report the type of consent model used and to evaluate whether it had been filled in correctly and fully by those responsible for obtaining the patient consent. A pilot evaluation was made on 10 patient case sheets at one of the OUs, where the single, standard consent documentation adopted in November 2011 was already in use to test the evaluation method and to examine the level of agreement between the researchers. The same 10 patient case sheets were evaluated separately by all the researchers and the results were then compared in order to establish if the level of agreement was acceptable. A level of agreement of over 95% was considered sufficient to then assign 2 researchers to each OU for subsequent evaluation of the patient case sheets: the 10 case sheets and consent forms obtained the same evaluation from all the researchers of the examination group.

Results

A total of 172 patient case sheets were examined (Table 1). Consent documentation was included in 132 (76.7%) cases. In the remaining 40 (23.3%) patient case sheets, the absence of any consent documentation meant that no evaluation of content could be made. Two OUs adopted the single, standard consent model: OU1 and OU2.

The researchers identified that 48 consent declarations were obtained using the single, standard model adopted in November 2011 and other 84 consent documents were obtained using other models. The consent declarations, obtained using the single, standard model were shown to be the most complete and were filled in better than the other models used. In fact, the standard consent model always included information relating to the OU and the physician responsible for obtaining consent while the other items were filled in in 85-90% of cases. The missing items were: use of the information for scientific publication and possible sharing of data acquired anonymously from other research centers. Furthermore, items relating to taking additional samples and their preservation were only included in less than 20% of the consent documents. Finally, 7 consent documents were not signed and/or the date was missing (Table 2).

As far as the 84 consent documents obtained using other models are concerned, only items relating to the reason for the sample collection and the use of material for research were nearly always included and filled in fully and correctly (95% and 98% of cases, respectively). Compilation of items relating to consent for the sample to be taken was also satisfactory (99%), while consent to sample preservation and data availability was compiled in 64% of cases. Compilation of other sections was missing or incomplete. Some types of consent models had sections that were preprinted and were, therefore, already filled in, such as information relating to the physician responsible for obtaining consent (Table 3). Finally, it should be noted that examination of the patient case sheets and, therefore, evaluation of the consent were carried out directly at each individual OU. This allowed researchers to meet those responsible for obtaining consent in person. This provided an opportunity to meet the staff involved and to raise their awareness as to how important it is to correctly and fully fill in and archive the documentation.

Discussion

Before discussing the results of our study, we feel appropriate to point out its main limitations, due to the relatively limited number of forms that could be examined. In this regard, it was disappointing to note that, independently from the type of informed consent form, in several instances the form was missing or partially filled. However, although disappointing and negative in its nature, this finding is itself an interesting result of our investigation, which stresses the importance of regular staff education and careful auditing of informed consent practices related to the collection of biological materials for research biobanking. In spite of the above limitations, an analysis of the results shows that the adoption of the single, standard consent model improved the quality of consent collection. The only information missing from this type of consent model was the expression of consent, while the items relating to taking and preserving additional samples was included in only 20% of cases. Given the retrospective nature of the study, it was not possible to clarify whether in the majority of cases

Table 1. Number of patient case sheets examined at the Operative Units selected for the study.

Operative unit	Case sheets examined
1	40
2	45
3	19
4	28
5	40

Table 2. Results of checklist of the standard consent model.

Item	Included n. (%)	Incomplete n.	Not included n.
Operative units and contact details	48 (100)	0	0
Physician responsible for obtaining consent	41 (85)	7	0
Reason for sample collection	46 (96)	2	0
Information on sample collection	46 (96)	2	0
Use of the information	18 (37)	30	0
Risks	46 (96)	2	0
Disposal	45 (94)	3	0
Sample collection	8 (17)	0	40
Preservation	7 (14)	1	40
Use of materials for research	46 (96)	2	0
Management of sensitive data	46 (96)	2	0
Sharing of anonymous data	46 (96)	2	0
Use for publication	46 (96)	2	0
Use for research and development	7 (14)	1	40
Disposal	46 (96)	2	0
Date, signature, name and surname	41 (85)	7	0

these items were missing because they were not relevant and this will be discussed with the OUs involved. However, critical issues still remain and it is hoped that these problems will gradually be resolved by more OUs adopting and using this standard model, and by its subsequent revision and improvement.

The model currently being used was drawn up on the basis of the European Masters in Bioethics. Over the last decades, questions have been raised concerning which type of informed consent should be considered the gold standard from an ethical point of view, and this is of particular concern in fields such as biobanking. Some authors emphasize that consent to biobanking can never cover everything and can not, therefore, be *informed*. This is because at the moment in which consent is obtained, it is probably not known for what type of future research the data will be used. It is, therefore, often impossible to inform the donor as to the detailed objectives, methodology, risks and financial sources of subsequent research. One example of a good organizational model is provided by the United Kingdom Biobank that has been set up in such a way as to offer an important resource capable of sustaining a wide range of research aimed at the prevention, diagnosis and treatment of diseases and promotion of health issues across all social groups. This biobank uses a consent model that is fairly general in format. The biobank does, however, encourage much greater participation on the part of donors in its operations, also through the creation of a specific interactive website.[19] Another question, which is often discussed in the scientific community, is the possibility of having the patient consent model renewed each time it is proposed that the preserved samples are used for a new research project. There is a general agreement on the fact that blank consent is not acceptable, even though this is still used in some centers. In many cases, the option of asking consent for a wider use of material and data although providing little specific information on the project is being considered. This allows the researcher to carry out a wide range of activities but the consent is too vague to be considered *informed*.[20,21]

Various institutions are wondering how to draw up a consent model that respects those issues identified as essential. It is interesting to mention the experience of the S. Giovanni di Dio Center in Brescia, Northern Italy. Here they have revised the main criteria related to the preservation and use of human-derived material from an ethical point of view; sixteen critical areas were identified that must be respected by the consenting individual.[22] These regard the type of material taken, the location and duration of preservation, the reasons for the biobanking, the consequences on donor health, the voluntary nature of the donation, donor privacy, control of access to the deposited material and any possible transfer.

Conclusions

Defining the requirements for giving consent to the collection, storage and use of biological samples and related information for research is still a subject of controversy at international level.[18] Samples preserved in biobanks represent an important resource for future research, but their use can raise ethical questions regarding the consent obtained.[23,24] Some groups are developing regulatory systems for the biobanks using a self-administered questionnaire to evaluate the attitudes and perceptions of potential donors of biological samples; the majority of those interviewed have shown a positive attitude towards genetic research.[18] In spite of rapid expansion of the biobanks and their related activities, a definitive consent model is still not available. This can probably be achieved by modifying and adapting the models in current use and by taking into consideration the perceptions and attitudes of donors. Indeed, general population's confidence in research is essential in order to achieve important benefits for society at large. It is to be hoped, therefore, that other experiences of this type are reported in the literature by those who are involved with ethical, legal and social issues related to research biobanking. It can be expected that larger studies could provide useful information to improve the quality of current practices of research biobanking.

Recently, critical aspects of the above issues have been thoroughly discussed in an editorial on HeLa and WI-38 cells recently published in Nature, that invites for a rethinking of the ethical issues concerning the use of human tissue in research.[25]

Table 3. Results of the checklist of other consent models.

Item	Included n. (%)	Incomplete n.	Not included n.
Operative units and contact details	65 (77)	0	19
Physician responsible for obtaining consent	29 (35)	41	14
Reason for sample collection	80 (95)	1	3
Information on sample collection	51 (61)	1	32
Use of the information	51 (61)	1	32
Risks	36 (43)	0	48
Disposal	0 (0)	36	48
Sample collection	83 (99)	1	0
Preservation	54 (64)	1	29
Use of materials for research	82 (98)	2	0
Management of sensitive data	51 (61)	1	32
Sharing of anonymous data	51 (61)	1	32
Use for publication	1 (1)	1	82
Disposal	0 (0)	0	84
Date, signature, name and surname	34 (40)	50	0

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