STUDIA UBB BIOETHICA, LX, 2, 2015 (p. 85-93)
(RECOMMENDED CITATION)

ETHICAL ASPECTS OF USING BIOSPECIMENS IN RESEARCH

ANTOANELA NAAJI[1]

REZUMAT. Aspecte etice privind folosirea probelor biologice în cercetare. Lucrarea prezintă câteva consideraţii privind aspectele bioetice în utilizarea şi depozitarea probelor biologice. Una dintre cele mai importante preocupări este modul în care consimţământul informat general este adaptat la această problemă specifică, ţinând seama de principiile etice. Un alt aspect este legat de provocările ridicate de obţinerea unui consimţământ informat valid. Pentru o mai bună abordare a acestor probleme specifice, pe baza experienţei din SUA în acest domeniu, este prezentată, din punct de vedere juridic, situaţia din România cu privire la utilizarea probelor biologice, în scopul de a determina unde ne aflăm şi ce este necesar de făcut pentru a îndeplini standardele bioetice internaţionale.

***Cuvinte-cheie**: probe biologice, etică în cercetare, bioetică, aspect legale, consimţământ informat*

ABSTRACT. The paper presents some considerations regarding bioethical aspects in using and storing biospecimens. One of the most important concerns is the way the general informed consent is adapted to this specific problem, taking into account ethical principles. Another aspect is related to the challenges raised in obtaining a valid informed consent. For a better approach to these specific issues, building on the experience of USA in this field, the situation in Romania concerning the use of biospecimens is presented from a legal point of view, in order to determine where we are and what is needed to meet the international bioethical standards.

***Keywords**: biospecimens, ethics in research, bioethics, legal aspects, informed consent*

[1] *Assoc. Professor, "Vasile Goldis" Western University of Arad, Bd. Revolutiei nr. 94-96, 310025 Arad, Romania. Email: anaaji@uvvg.ro*

Introduction

The collection, storage and usage of biospecimens for research, especially in future studies, raise a lot of controversies and introduce complex legal and ethical issues. Each investigator should consider carefully how to safeguard the rights of study participants, as well as ensure the privacy and confidentiality of personal data.

Key ethical issues include respect for autonomy of research participants, protecting research subjects from breaches of privacy and confidentiality, developing appropriate policies for biospecimen use, and ensuring that biospecimens are used in scientifically sound research. Legal issues include the need for biospecimen resources to adhere to relevant regulations related to the collection, storage, dissemination, and use of biospecimens [7].

According to the National Cancer Institute, "biospecimens are materials taken from the human body, such as tissue, blood, plasma, and urine that can be used for cancer diagnosis and analysis. When patients have a biopsy, surgery, or other procedure, often a small amount of the specimen removed can be stored and used for later research. Once these samples have been properly processed and stored they are known as human biospecimens" [8]. Even if the definition refers for biospecimens collected for research concerning cancer disease, it can be extrapolated to other types of clinical studies.

For example a single biopsy could provide several biospecimens, including multiple paraffin blocks or frozen biospecimens. A biospecimen can comprise subcellular structures, cells, tissue (e.g., bone, muscle, tissue, and skin), organs (e.g. liver, bladder, heart, and kidney), blood, gametes (sperm and ova), embryos, foetal tissue, and waste (urine, feces, sweat, hair and nail clippings, shed epithelial cells, and placenta). Parts of a biospecimen are referred to as samples. Each sample may contain DNA, proteins, and other molecules important for understanding disease evolution [7]. The biospecimens are usually recorded with information about the patient from whom the biospecimen was taken, including data about their medical conditions and history. The biospecimens are stored in biorepositories (or biobanks). They are "libraries" where biospecimens are stored and made available for scientists, for therapeutic or research purposes. There are thousands of biorepositories in the United States, which vary widely by size, the type of biospecimens collected, and the categories of studies for which they are intended [8].

The next sections of the paper will address the following aspects: the ethical implications of informed consent in the process of collecting, storing and using biospecimens and how it must be adapted to these purposes, presentation of the most important ethical and legal issues in this matter in the USA, and a short presentation of regulations in Romania. In the conclusions, a few considerations regarding the challenges for biospecimens-based research are mentioned, in order to improve Romanian legislation in the field.

Aspects Regarding Informed Consent for the Collection, Storage and Usage of Biospecimens

Informed consent is considered to be a cornerstone of the ethical conduct of research involving humans. Based on the ethical principle of respect for persons (the concept that all people deserve the right to fully exercise their autonomy), the goal of informed consent is to ensure that subjects are aware of the risks and potential benefits and make a voluntary decision about participating in the research [9]. The philosophical justification of informed consent is that in research where humans are involved, respect for the autonomy implies that the patient has the capacity to act intentionally, with understanding, and without controlling influences that would lower against a free and voluntary act. As D.W. Brock mentions, "the rule that with a few exceptions, research with humans should not take place without participants' informed consent is a settled ethical and legal principle" [3].

Throughout the history of bioethics, the necessity of informed consent appears in different documents through some simple statements such as: "The voluntary consent of the human subject is absolutely essential" [1]; "Respect for persons requires that subjects, to the degree that they are capable, be given the opportunity to choose what shall or shall not happen to them" [2]; "After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent"[10]; "Except as provided elsewhere in this policy, no investigator may involve a human being as a subject in research covered by this policy unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative" [11].

Thus, the main characteristic of a valid inform consent is that a participant in a study must have the capacity to make an autonomous decision regarding three aspects: to have and to understand the information needed so that the act of accepting to participate in the study/research be well-documented (informed), the information must be given by a competent person and the decision has to be a voluntary one. In a simple representation, a valid informed consent is based on information, the competence of the person who gives the information and voluntariness (Fig.1).

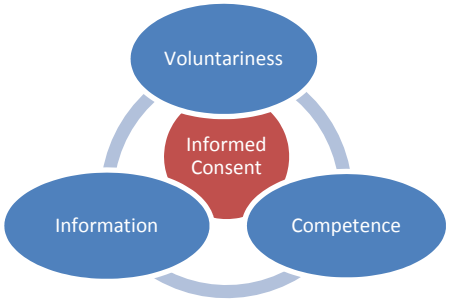

Fig. 1. A valid informed consent

In order for the subject to be informed, it is important to give him/her a detailed description of the research, adapted to his/her level of understanding, to present the effects, including the risks involved, and to give the possibility to ask any question related to that trial, so that the information to answer such questions as 'What?', 'Why?', 'How?', 'By whom?' would be provided; what will happen to the participant, the possible risks and discomforts, as well as the benefits, are issues which must also be addressed. The study subject should understand that participation is completely voluntary and he/she can withdraw at any time without loss of any benefits.

When we are talking about what consent means, we have to take into account that the participant has the capacity to decide and that the consent is voluntary and non-coerced.

Considering the content of the informed consent, there is some general required information, but in some cases there is a need for specific information, such as in research involving children, people with disabilities or mental diseases. Also specific informed consent is necessary for genetic and genomic research requiring access to human DNA from biological specimens, which can be used in multiple research studies. Some templates of informed consent, adapted to specificities of these types of studies, are available on the WHO web page [12].

Regarding the informed consent for researches dealing with the collection, acquisition, storage, use, and disbursement of biospecimens, the document should describe the planned and potential future uses of the collected biological specimens. In addition to the general data, such as the description of research in terms of stages and activities, the possible risks as well as the benefits, the extent of confidentiality, the existing medical treatments in case of injuries or disabilities, etc., the informed consent should also contain some specific data. The difficulty of introducing this specific information is due to reasons such as impossibility to describe in detail the future research for which the biospecimen might be used at the time when it is collected; uselessness of samples after donors' death in absence of generalized

consent for future use; privacy/confidentiality risks if samples are not anonymized, but these can be minimized by appropriate coding precautions. Also if samples are anonymized, they are potentially less useful for research [4]. There are other aspects regarding future researches connected with cultural issues which are relevant to informed consent in terms of the collection, storage and use of biospecimens, but these will not be approached in this paper [6].

Considering all these aspects, from a theoretical point of view, the investigators conducting the researches where biospecimens are used have some options related to the way informed consent is obtained for covering the ethical aspects. Some of them are:

- researchers should re-contact participants to obtain specific consent for each additional use, but in this case difficulties might appear in terms of what it means to contact the participants, or they might even change their minds, preventing the subsequent use of biospecimens;
- the informed consent should contain a statement that stored materials will be used in future research, some details regarding the diseases that may be studied, and at least some goals of the research project;
- participants could provide general (blanket) consent for all future uses of their biospecimens at the time when they are collected.

In most of the cases, the last option is considered more appropriate [5].

Legal Aspects Related to the Collection, Acquisition, Storage and Use in Research of Biospecimens

In this section I will present a few legislative documents regarding the regulation of these activities, with reference to US and Romanian legislation.

As far as US regulations are concerned, the issues regarding the collection of biospecimens during the course of medical care, the timing of consent, the storage, and the future use of biospecimens for research are very well documented. Most of these aspects are regulated, with rules which include ethical guidelines and logistical constraints.

The NCI Best Practices for Biospecimen Resources Office of Biorepositories and Biospecimen Research, developed by the National Cancer Institute, National Institutes of Health and the U.S. Department of Health and Human Services in 2011 contain a chapter regarding biospecimen collection, processing, storage, retrieval, and dissemination. There is additional information regarding data management, inventory control and tracking. The general best practices mentioned in this document apply to all types of biospecimens, such as wet tissue, frozen tissue, paraffin-embedded tissue, glass slides, blood, serum, urine, etc. [7].

In Romania, ethical aspects regarding the obtainment of informed consent are comprised in the Guide on good practices in clinical studies, but this refers more to the organization and conduct of clinical studies regarding the use of pharmaceutical drugs on human subjects. This guide (approved by Res. No. 39/27.10.2006), in chapter V – The investigator, subchapter V.8. – Informed consent expressed by study subjects, in addition to rules regarding the obtainment of informed consent, provides at Art. 64:

(1) "In order to obtain and record informed consent, the investigator must comply with legal regulations in force, good practices in clinical studies and ethical principles originating in the Declaration of Helsinki regarding human rights.

(2) Before initiating the study, the investigator must obtain the written approval/favourable opinion of the EC regarding the informed consent form and any other information conveyed to subjects" [13].

Likewise, Art. 65. Para. (2) provides that: "Any revision of the informed consent form and written information must obtain the written approval/favourable opinion of the EC before being used" [13].

In Romania, legislation regarding the collection, storage and use of biospecimens in research is still inadequate. There are, however, a few laws and resolutions partly regulating these activities from an ethical point of view. Here we might mention:

- Law no. 282/2005, republished and featured in the Official Gazette no. 188 of 17 March 2014, on the organization of blood transfusions, human blood and blood component donation, as well as quality assurance and safety in healthcare, for therapeutic use, but which does not refer to the use of blood samples in research, only to the blood donation process, and the way in which privacy and data protection are ensured so that the donor could not be identified, while only considering the therapeutic component [14].

- Law no. 95 of 14 April 2006 on healthcare reform, republished in the Official Gazette no. 652 of 28 August 2015, Title VI – Harvesting and transplanting organs, tissues and cells of human origin for therapeutic purposes, which establishes, in Chapter II, the rules regarding donation and organ donors, tissues and cells of human origin, but only for transplantation purposes. For example, Art. 144 stipulates the methods and conditions in which organs, tissues and cells of human origin are harvested from living donors, such as:

- at paragraph a): "organs, tissues and cells of human origin can be harvested, for therapeutic purposes, from living adult persons, with full capacity of exercise, after having obtained their prior, free, express and written informed consent, according to the form template approved by order of the minister of health. It is prohibited to harvest organs, tissues and cells from undiscerning persons" [15].

- at paragraph c): "the donor can withdraw their consent until the moment of harvesting" [15].

Article 146 provides, at Para. (6), regulations regarding how donation should be approved by the committee established to this end, as well as the fact that: "Harvesting blood, skin, sperm, femur head, placenta, umbilical cord blood, and amniotic membranes from living donors, for therapeutic purposes, is done in compliance with bioethical rules comprised in the regulation of the committee approving donation from living donors, without requiring the approval of this committee" [15].

Consequently, none of the legislative regulations makes direct reference to how biospecimens are collected, stored and used in research, as defined in the law, but only to how they are harvested, stored and used for therapeutic purposes (e.g. for blood transfusions, for transplants). Nevertheless, Romania, as an EU member, must comply with all European directives related to the topic approached in this paper.

Conclusions

The way biospecimens are used in research, especially in future studies, is an issue which entails numerous ethical and legal problems. There are still questions that are quite difficult to answer and which often pose difficulties for ethics committees or IRBs. Such questions are: How to obtain an autonomous decision about future use of biological samples?; Is the informed consent really informed?; How to evaluate the risks for future researches?; How to ensure confidentiality (security of computer files)?; Who owns or has the custody of biospecimens?; Who has access to biospecimens and data? Who has the intellectual property?

Of considerable importance is the way in which these aspects are regulated from a legislative point of view and the ethical norms imposed in each country. While in the USA legislation concerning ethical aspects related to the collection, storage and use of biospecimens in research is covered, even if the patients' consent to future use of biospecimens is further complicated by the discrepancies between relevant federal regulations, in Romania, and even in some countries in Europe, several efforts are under way to address informed consent, privacy, ownership, and access issues with respect to biospecimen collection and use. Consequently, further discussions are needed among stakeholders within the biospecimen research community in order to make these processes as transparent as possible.

Acknowledgement

This paper was realized with the support of NIH Research Grant # R25 TW008171, Research Ethics Education in the Balkans and Black Sea Region, funded by the Fogarty International Center, U.S. National Institute of Health, PI: Prof. Rosamond Rhodes, Ph.D.

REFERENCES

[1] George J. Annas, Michael A. Grodin - *The Nuremberg Code*, in Oxford Textbook of Clinical Research Ethics, Emanuel EJ, Grady C, Crouch RA, Lie RK, Miller FG, Wendler D (eds). New York, NY: Oxford University Press, pp. 136-140, 2008

[2] Tom L. Beaucham - *The Belmont Report*, in Oxford Textbook of Clinical Research Ethics, Emanuel EJ, Grady C, Crouch RA, Lie RK, Miller FG, Wendler D (eds). New York, NY: Oxford University Press, pp. 149-155

[3] Dan W. Brock - *Philosophical Justification of Informed Consent in Research*, in Oxford Textbook of Clinical Research Ethics, Emanuel EJ, Grady C, Crouch RA, Lie RK, Miller FG, Wendler D (eds). New York, NY: Oxford University Press, pp. 606-612, 2008

[4] Joseph Goldfarb – *Informed Consent*, PowerPoint Lectures, 2014

[5] Amy L. McGuire, Laura M. Beskow - *Informed Consent in Genomics and Genetic Research*, Annual Review of Genomics and Human Genetics, Vol. 11, Mc Guire, p. 361-381, 2010, available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3216676/

[6] Jimmie B. Vaught, Nicole Lockhart, Karen S. Thiel, Julie A. Schneider - *Ethical, Legal, and Policy Issues: Dominating the Biospecimen Discussion*, in Cancer Epidemiology Biomarkers Preview, December 2007, issue 16 (12), American Association for Cancer Research, p. 2521-2523, available at: http://cebp.aacrjournals.org/content/16/12/2521.full

[7] *** - *National Cancer Institute Best Practices for Biospecimen Resources*, National Cancer Institute, National Institute of Health, US Department of Health and Human Services, 2011, available at: http://biospecimens.cancer.gov/bestpractices/2011-NCIbestpractices.pdf

[8] *** - *What are Biospecimens and Biorepositories*, National Cancer Institute, Biorepository and Biospecimen Research Branch, available at: http://biospecimens.cancer.gov/patientcorner/

[9] *** - *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research,* National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research, Washington, DC: Dep. Health Educ. Welfare, 1979, available at: http://videocast.nih.gov/pdf/ohrp_appendix_belmont_report_vol_2.pdf

[10] *** - *WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects*, World Medical Association, available at: http://www.wma.net/en/30publications/10policies/b3/
[11] *** - *Code of Federal Regulations, Title 45 – Public Welfare*, US Department of Health and Human Services, Part 46, Protection of Human Subjects, 2009, available at: http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html
[12] *** - *Informed Consent Form Templates*, World Health Organization (WHO), available at: http://www.who.int/rpc/research_ethics/informed_consent/en/
[13] *** - Hotărârea nr. 39/27.10.2006 referitoare la aprobarea Ghidului privind buna practică în studiul clinic, Agenția Națională a Medicamentului/Resolution no. 39/ 27.10.2006 on the approval of the Guide on good practices in clinical studies, National Agency of Medicines, available at: http://www.anm.ro/anmdm/med_studii_legislatie.html
[14] *** - *Legea nr. 282/2005 privind organizarea activităţii de transfuzie sanguină, donarea de sânge şi componente sanguine de origine umană, precum şi asigurarea calităţii şi securităţii sanitare, în vederea utilizării lor terapeutice*, *republicată în M. Of. nr. 188 din 17 martie 2014 / Law no. 282/2005 on the Organization of Blood Transfusions, Human Blood and Blood Component Donation, as well as Quality Assurance and Safety in Healthcare, for Therapeutic Use, Republished in the Official Monitor no. 188 of 17 March 2014,* available at: http://www.clr.ro/rep_htm/L282_2005_Rep1.htm
[15] *** - *Legea nr.95 din 14 aprilie 2006, privind reforma în domeniul sănătăţii, republicată în M.Of. nr. 652 din 28 august 2015 / Law no.95 of 14 April 2006, on healthcare reform, republished in Official Gazette no. 652 of 28 August 2015*, available at: http://www.cdep.ro/pls/legis/legis_pck.htp_act_text?idt=72105