Biobanking for health research in Brazil: present challenges and future directions

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Suggested citation: Marodin G, França P, Rocha JCC, Campos AH. Biobanking for health research in Brazil: Present challenges and future directions. Rev Panam Salud Publica. 2012; 31(6):523–8.

SYNPOSIS

This article outlines and discusses Brazil's new regulations on the use of human biological materials for research, specifically, Resolution CNS 441/11, enacted by the National Health Council of Brazil in May 2011, and the National Guidelines for Biorepositories and Biobanks (Ordinance No. 2201) published by the Ministry of Health in September 2011. The authors examine the differences between sample collections for single studies and large-scale collections for multiple studies (e.g., the National Tumor Bank at the Brazilian National Cancer Institute and the A. C. Camargo Hospital Biobank). Also discussed are the ethical and operational implications, i.e., informed consent process, strategies for sample collection, custodianship, access to samples, and rules for disposal. Insights gained may be useful for developing national biobanking regulations in other countries in Latin America.

Keywords: biological specimen banks; ethics, research; informed consent; health research policy; incidental findings; Brazil.

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In 2005, the National Health Council (CNS) of Brazil approved a resolution to regulate the use of human biological materials in research projects (Resolution CNS 347/05) (1). Prior to this enactment, collection of human biospecimens for research purposes had been governed only by certain chapters of prior resolutions. In addition to providing ethical oversight, Resolution CNS 347/05 consolidated some issues and addressed others that had been raised by prior resolutions (2–4); still, it had limitations (5–9). Then, in 2011, the Ministry of Health published the National Guidelines for Biorepositories and Biobanks (Ordinance No. 2201, dated 14 September 2011) (10) and the CNS also approved Resolution CNS 441/11, an amendment to Resolution CNS 347/05 (11).

This article outlines the main advances introduced by these new regulations and examines the differences between sample collection for a single study versus large-scale collections to support multiple studies, as well as the ethical and operational issues associated with each approach, i.e., the informed consent process, sample collection strategies, custodianship, access to samples, and rules for disposal.

BIOBANK VERSUS BIOREPOSITORY

There is a conceptual divergence in the literature with regard to the infrastructure and practices regarding the collection of human biological material for research, wherein the term "biobank" has been used interchangeably with "biorepository." The Organization for Economic Cooperation and Development (OECD) uses the term "biological resource center" (BRC) to refer to, not only repositories, but also suppliers of health research services (12). The International Agency for Research on Cancer (IARC) uses the term "biological resource center" for collections of human cancer samples (13). In the United States of America, the National Cancer Institute defines the term "biorepository" as an "organization, place, room, or container where biospecimens are stored," and the term "biospecimen resource" as the ". . . formal organization as well as informal collections of biological material stored in a freezer by an individual researcher" (14). Likewise, the term "biobank" has been used in this context by other U.S. and European institutions (15–18).

Matters are further complicated by the fact that there are various types of biobanks: population-based, disease-oriented, hospital- or academic-based, networked, or run by the government, non-profit organizations, or commercial companies, among others (19–21). Biobanks also vary in scale, nature of contents (tissues, macromolecules, bodily fluids, etc.), and participants (adults, children, deceased persons, etc.).

Some definitions overlap, and in defining a biobank, there may be "radically contrasting views over how certain attributes should be identified, formulated, defined, or ranked . . ." (22).

In Brazil, the absence of a concrete definition of "biobank" in Resolution 347/05 pointed to a need for different long-term institutional policies that would address the substantially different technical and ethical issues associated with systematic sample collection for future research versus time-limited collection for single, defined projects. In fact, recently, a new classification has been proposed that distinguishes between human biological material collected for single studies/research-groups and those collected for a "formal biobank" that supports multiple studies and diverse research questions (23).

For the purpose of the present article, the term "biobank" will refer to an institutional facility dedicated to the systematic collection of human biological material to support multiple, future studies; while the term "biorepository" will refer to a collection of samples amassed by researchers executing a single, specific research project. These definitions were adopted by the Ministry of Health Ordinance No. 2201 and Resolution CNS 441/11 (10, 11).

The differences between biobanks and biorepositories have implications for ethical and operational procedures. These differences have become quite evident with the development of the A.C. Camargo Hospital Biobank (ACCHB) in 1997 and the National Tumor Bank of the Brazilian National Cancer Institute (BNT-INCA) in 2004 (24–26), two biobanks that support cancer research, and together, have collected over 80 000 sample aliquots from approximately 20 000 donors. A discussion of the main ethical and operational differences between biobanks and biorepositories follows.

ETHICAL ISSUES

Informed consent

In Brazil, patient consent is required prior to collection and storage of human samples for research (2). Although Resolution 347/05 mandated that consent forms include the possibility of specimens being used for future research, it also required that the donor's re-consent be obtained (1). For biorepositories, this approach was, and still is, feasible; however for biobanks, which aim to collect samples for future analysis, it became clear that this approach was inefficient (13, 27). Therefore, a general consent permitting future use was needed (27, 28). Such a form, apart from granting general consent would also need to clearly state a purpose (e.g., cancer research) and meet other conditions (10, 11):

(a) Proper ethics review approval will be obtained prior to the use of samples.
(b) The collection of samples will not harm the pathological diagnosis or analysis.
(c) Steps will be taken to ensure proper standard collection, storage, and maintenance of samples, as well as recording, storage, and privacy of associated data.
(d) The research subject will be offered the opportunity to receive genetic data generated from the use of his/her material, including that which may pose risks to family members or for nonpreventable diseases, and will be granted free access to genetic counseling, if applicable.
(e) The research subject will be given the choice to determine who will have access to his/her genetic information in the event of death or a disabling condition.
(f) Steps will be taken to ensure anonymity in any form of disclosure of information derived from the use of his/her biological material.
(g) The consent can be withdrawn at any time without further explanation or prejudice to the subject.

Because there has not been any study of the public's perception of biobanking in Brazil or of adopting different modalities of "informed consent" (29, 30), the amended legislation was intentional about both fostering biobank-based research and balancing individual and collective rights. By requiring the consent form to include information on the biobank and its management of sample and data-sharing, the expectation is that it will alleviate concerns and garner the public's willingness to contribute samples and grant a general consent for their use (31, 32). Thus, in the case of biobanks, both of the new regulations give donors the option of granting either (i) a general consent authorizing use of the biological materials in any future research project, or (ii) a limited consent that requires reauthorization for future projects. In the case of biorepositories, since the relationship is stronger between researchers and subjects and the samples are by definition used for only a specific project, a general consent is still not permitted, and the legislation in Resolution CNS 347/05 regarding consent for biorepositories was unchanged in Resolution CNS 441/11.

As for the biobanks, offering two levels of consent (general or re-consent) represents a fundamental change in the informed consent process in Brazil. To date not enough time has transpired to assess the effects of this change. How the cost of re-contacting donors will impact biobanks is still unknown, as is any negative effect on the goal of "knowledge for better health care" (6).

Research results

The return of research results is currently a topic of debate. There are some valid concerns. Some of these are: returning results that have not been clinically validated; problems associated with the role of the researcher, who frequently has no medical-practice background; and the fact that much genomic research ultimately aims at improving health care by advancing

knowledge, and rarely provides results that directly impact a study participant (6, 33).

On the other hand, there are several arguments in favor of returning results; these are based on the principle that participants have the right to receive results associated with the use of their samples (34). In Brazil, the regulatory bodies also acknowledge that there are cases in which unexpected, relevant results need to be communicated to the subject, and proper genetic counseling offered. However, a distinction must also be made between an unexpected relevant result—clinically relevant, analytically validated, actionable, and directly related to the study objectives—and an incidental finding—one with potential health or reproductive importance, found in the course of research, but beyond the study's aim (35, 36). Both fall under the definition of the "Duty to Rescue" principle (37), which both the National Commission of Ethics in Research (CONEP, Brasília, Brasil) and the Ministry of Health uphold. However, a clear definition of what differentiates a *relevant result* from *an incidental finding* is lacking in Brazil's new legislation on biobanking (despite the fact that, in differentiating biobanks from biorepositories, it is acknowledged that the depth of relationship is stronger in the latter, and that scientists who access samples from biobanks are expected to notify the original collector of any result that may be important to an individual research participant) (6, 37).

OPERATIONAL ISSUES

Collection strategies

Resolution CNS 347/05 required that samples and collection protocols be aligned with the objectives of the research project and that the start/end periods of sample procurement be defined. Samples could be stored for up to 5 years, after which renewal had to be petitioned. However, these requirements were not feasible for biobanks, designed to collect a wide range of samples for future projects. Also, samples and services vary according to the biobank's mission, impacting the implementation of protocols, types of equipment and consumables used, the personnel involved, and maintenance costs (5, 13). As a result, the decision to establish a biobank should be institutional, rather than investigator-driven. A biobank may also decide to restrict collection, processing, and storage protocols, and therefore, not meet the requirements of all investigators (5).

Taking these differences into account, both of Brazil's new regulatory documents state that the establishment of a biobank must include the submission and approval of a protocol that states the standard operating procedures (SOPs) to the Institutional Ethics Review Board (CEP) or CONEP. These SOPs should also be disseminated widely to researchers, as recommended by international guidelines and other national legislation (9, 12–14).

The procurement of samples during the course of routine medical care has the advantage of avoiding an unscheduled, ancillary procedure, obtaining only surplus material that is not required for diagnosis (13, 14, 38). Both the ACCHB and BNT-INCA follow this approach. Although this may not accommodate representative-population material (as occurs with the "Projeto ELSA Brasil," a multicentric, longitudinal cohort study established to investigate risk factors for diabetes and heart disease) (39), it elicits the patient's consent to provide samples, and facilitates approval by local and national regulatory bodies. Since it does not pose additional physical risk or inconvenience to the individual, it accelerates the adoption of a one-time, general informed-consent model.

Custodianship

Samples and the associated data stored by the ACCHB and the BNT-INCA are the responsibility of the institution; hence, the institution must ensure the integrity of the samples and follow adequate policies and protocols for their distribution. The decision to centralize sample collection and distribution has decisive advantages (9):

(a) Offers support for a wide range of research projects (with differing objectives) that require access to samples which have been collected, stored, and processed using identical protocols.
(b) Eliminates the issue of how to store, maintain, or destroy samples once the study has been completed or if it is discontinued for any reason.
(c) Establishes guidelines for sample distribution and data sharing (see also section on "Access to Samples"), and can ensure that research results are easily accessible and not limited to academic publications.
(d) Encourages the exchange of information and technology, and incorporates research results into the biobank database, increasing its value for subsequent research projects.

Although Resolution CNS 347/05 had already established that biospecimens are the responsibility of the institution in which they are stored, a distinction had not been made between biobanks and biorepositories, where the researcher's responsibility must be considered. The ACCHB and BNT-INCA designate a biobank manager; whereas in a biorepository, the principal investigator should be responsible for samples and associated data. This distinction was incorporated into both the Ministry of Health Ordinance No. 2201 and Resolution CNS 441/11 (10, 11).

Access to samples

Unlike biorepositories, in which access by third parties depends on collaboration with the principal investigator, samples stored at the ACCHB and BNT-INCA are available to any researcher in the scientific community whose project has been approved by the CEP or CONEP. Additional approval by the CONEP is needed when:

(a) Biological human samples are sent to other countries for experiments that cannot be performed locally.
(b) Samples and/or associated data are stored in other countries (or within the country when the research project is performed in association with foreign institutions).
(c) The research anticipates irreversible dissociation (anonymization) of the research subject and the data or biological samples. Although recent technological advances have challenged the safety of this procedure (40), CONEP has the prerogative of approving anonymization since it recognizes the principle of "right to know" and the need to re-contact subjects in the event of an unexpected relevant result.

Disposal of samples

This issue was not addressed in Resolution CNS 347/05, although there are normative documents issued by National Agency for Sanitary Vigilance (ANVISA, Brasília, Brazil) and the National Environmental Council (CONAMA, Brasília, Brazil). The ACCHB and BNT-INCA currently discard samples due to inadequate quality. Samples may also be retrieved for additional diagnostic purposes or by consent-granted withdrawal.

The possibility of bankruptcy also needs to be considered. It is illegal to sell biological human samples in Brazil, and biobanks like ACCHB and BNT-INCA are usually established with grant support from state, federal, and international funding agencies. However, as with biorepositories, such grants are limited in duration. In this case, both the Ministry of Health Ordinance No. 2201 and the Resolution CNS 441/11 state that, provided that the samples are adequate for research, their transfer to another institution should be considered, and destruction—in a manner not permitting recovery, and taking into consideration cultural heritage and/or religious beliefs—should be the last resort (9).

CONCLUSIONS

Brazil now has two mutually supporting documents on biobanking activities related to human health research. Resolution CNS 441/11 sets the guidelines for ethical analysis of research projects involving human samples or utilization of samples stored by prior studies. The Ministry of Health Ordinance No. 2201 establishes a regulatory framework for biobanks and biorepositories.

Donors providing samples for biobanks now have the option of providing a general consent, in lieu of consent for each new research project. Also, donors can indicate whether or not they wish to be re-contacted should any relevant personal health information be derived from use of their biological samples. This approach moves beyond the previous restriction requiring donor consent for each new project, but still respects the individual's rights and preferences.

On the other hand, some aspects of the new legislation still need improvement (for example, the issues surrounding the return of research results and the distinction between relevant results and incidental findings). As acknowledged by other countries and international guidelines, these regulations may need to be adapted to meet future scientific advances and changing public perception (9, 28, 41); however, they reflect the current stage of biobanking activity in Brazil.

It is hoped that insights gained from the experience in Brazil will be useful to developing national biobanking regulations in other countries of Latin America, and even, guidelines for the Region of the Americas.

Acknowledgments. The authors are grateful for the technical and logistical support provided by Secretaria de Ciência, Tecnologia e Insumos Estratégicos (Brasília, Brasil), a division of the Ministry of Health of Brazil.

This work was presented in part as a poster at the 2011 Annual Meeting of the International Society of Biological and Environmental Repositories on (15–18 May 2011, Washington, D.C, United States).

SINOPSIS

Bancos de materiales biológicos para la investigación en salud en el Brasil: retos actuales y perspectivas futuras

En este artículo se describen y se analizan los nuevos reglamentos del Brasil para el uso de materiales biológicos humanos para la investigación; específicamente, la Resolución CNS 441/11, sancionada por el Consejo Nacional de Salud del Brasil en mayo del 2011, y las Directrices Nacionales para Repositorios Biológicos y Bancos de Materiales Biológicos (Ordenanza N°. 2201), publicadas por el Ministerio de Salud en septiembre del 2011. Los autores examinan las diferencias entre la recolección de muestras para un estudio único y la recolección en gran escala para múltiples estudios (por ejemplo, el Banco Nacional de Tumores del Instituto Nacional del Cáncer del Brasil y el Banco de Materiales Biológicos del Hospital A. C. Camargo). También se analizan las implicaciones éticas y operativas, como el proceso de consentimiento informado, las estrategias de obtención de las muestras, su custodia, el acceso a las muestras y las reglas para desecharlas. Estos conocimientos pueden ser útiles para establecer reglamentos nacionales para los bancos de materiales biológicos en otros países de América Latina.

Palabras clave: bancos de muestras biológicas; ética en investigación; consentimiento informado; política de investigación en salud; hallazgos incidentales; Brasil.

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Manuscript received on 8 July 2011. Revised version accepted for publication on 6 February 2012.