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Custodianship as an Ethical Framework for Biospecimen-Based Research

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Abstract

Human biological specimens (biospecimens) are increasingly important for research that aims to advance human health. Yet, despite significant proliferation in specimen-based research and discoveries during the past decade, research remains challenged by the inequitable access to high quality biospecimens that are collected under rigorous ethical standards. This is primarily caused by the complex level of control and ownership exerted by the myriad of stakeholders involved in the biospecimen research process. This article discusses the ethical model of custodianship as a framework for biospecimen-based research to promote fair research access and resolve issues of control and potential conflicts between biobanks**, investigators, human research participants (human subjects), and sponsors. Custodianship is the caretaking obligation for biospecimens from initial collection to final dissemination of research findings. It endorses key practices and operating principles for responsible oversight of biospecimens collected for research. Embracing the custodial model would ensure transparency in research, fairness to human research participants, and shared accountability among all stakeholders involved in biospecimen-based research.

Introduction

Biospecimens are important for advancing knowledge and improving human health through new targeted diagnostic, preventive, and therapeutic research (1,2). The promise of personalized medicine is fueling an increasing demand for high-quality, well-annotated biospecimens. Although there are more than 300 million biospecimens stored in the United

** In this paper, the term “biobank” is used to refer to a collection of human specimens and associated data that are intended for research purposes and all relevant processes and policies

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States (3), their continued availability to the scientific community depends on the fair and timely access to existing collections and the willingness of human research participants to contribute new biological materials to research.

In recent years, the scientific community has struggled with a number of ethical and legal conflicts related to the collection and use of biospecimens in research. The issues ranged from protracted legal battles over who owns stored biological materials as tangible property (4–6) to charges of improper informed consent and subsequent inappropriate research use of contributed biospecimens (7). The central issue in many of these conflicts is the failure to appropriately account for and manage potential differences between stakeholders involved in the biospecimen research process. Each stakeholder may seek to influence the complex series of decisions regarding biospecimen collection and use in ways that prioritize their own interests. Without clear practices and policies, the fragile synergistic relationship between stakeholders could be jeopardized, decreasing human research participation and biospecimen availability and, ultimately, delaying drug development and tissue-based biomarker discovery and validation. One method to restore trust is to develop and implement fair and transparent practices that are based on ethical, rather than strictly legal, principles to govern the collection and use of biospecimens in research (2,8,9).

Herein, we discuss and advocate an ethical model of custodianship, which underlies the caretaking responsibility of the biobanking community for contributed biospecimens while promoting fair research access and recognizing the altruism of human research participants. Custodianship clarifies control of biospecimens and minimizes conflicts between concerned stakeholders. This ethical concept of custodianship is broader than a legal framework of ownership, which views biospecimens as property with exclusive rights and control vested solely with the owner (10). Custodianship calls on individuals and organizations engaged in biospecimen-based research to recognize their ethical obligations and serve the best interests of biomedical research.

Ethical Principles for Biobanking

Several ethical principles in addition to policy mandates should be observed in the conduct of biospecimen research activities. Key ethical principles include respecting the autonomy of human research participants and protecting them from breaches of privacy and confidentiality through sound practices. Policy issues comprise adhering to relevant Federal and State regulations surrounding the collection, storage, dissemination, and use of biospecimens in research (11). Biobanks and investigators should consider existing policies and best practices according to the mission of the biobank and the objectives of the research project to determine the most appropriate management model.

Principles that govern access to biospecimens and their associated data set(s) are an important component of the biobank management, particularly if a broad use of the collection is anticipated. In general, access policies should be based on transparency, scientific merit, ethical considerations, and the scientific value of the biospecimen (11–13). In biobanks where access decisions are complex and numerous, an independent advisory board with multidisciplinary expertise should be implemented to assess the scientific merit of access requests, recommend access decisions, and limit potential conflicts.

Management of discontinuation of participation in research by human research participants should also be accounted for by the biobank. The right to discontinue participation in research is both a regulatory and ethical requirement (8,14,15). As discontinuation of participation is historically rare, granting such request to human research participants will promote a sense of autonomy among them and increase their trust in research. Modern electronic document management systems can facilitate tracking and processing requests for

discontinuation of participation in research without draining research efforts. Upon any discontinuation request, the collection of identifiable biospecimens and data and their research use should cease immediately. Remaining identifiable biospecimens and data should be withdrawn from the biobank but anonymous or coded samples and/or data that have been transferred to investigators cannot be withdrawn.

Disclosure and appropriate management of financial conflicts of interest (FCOI) is another important principle that can promote objectivity in research by ensuring that such conflicts will not bias the design, conduct, or reporting of research (16). Accordingly, FCOI should be disclosed in the informed consent document, an associated supplementary material, or through the biobank's website. Such disclosure would include any known or reasonably foreseeable benefit to the biobank, investigators, or institutions, as well as the way benefits would be allocated. As financial benefits are not always foreseeable when the research is conducted, institutional tracking, reporting, and management of FCOI that materialize later is crucial and offers the best approach to maintaining objectivity and transparency in research.

Access of human research participants to aggregate research findings should be viewed as a way of demonstrating respect for their important contribution to research. Historically, human research participants have not been advised on research outcomes and have had to rely on their own ability to gather news reports or research publications in order to track findings, a practice that may be out of reach for many lay people. Today, however, a variety of methods are available to disseminate aggregate research findings, and new approaches are emerging with time. Each method, whether it's a periodic newsletter, an internet site, or others, requires time, expertise, and funding to prepare and sustain and this should be considered in the planning of the biobank.

Lastly, contingency plans addressing potential administrative changes including termination of the research project, loss of grant support, or transfer of the project director should be well defined by the biobank. The long term financial sustainability of the resource needs to be considered early in the project, particularly if the biobank houses specimens with important research value. If financial sustainability cannot be attained, the biobank may transfer its collection to another suitable resource using the same decision-making criteria for the transfer of biospecimens to researchers and consistent with the informed consent terms for the initial collection.

Models of Biospecimen Oversight

Several ethical models have been proposed to address the greater challenges of research involving biospecimens (2,17,18). The tissue trustee (also known as the honest broker (19), the trusted intermediary) model is based on the designation of a tissue trustee whose role is to protect human research participants (17). The trustee is interposed between human research participants and their health care providers (i.e., biospecimen sources) and researchers, and manages access to biospecimens and associated data to protect research participants' privacy and preserve confidentiality. The trustee's role can be filled by a biospecimen resource, an entity within an academic institution not involved in the research, a subcontracted third party, or an informatics system.

A variation of the tissue trustee model designates a trained medical archivist, who is part of the medical center infrastructure, as a third party responsible for the management of a research biobank and the function of a data protection officer (18). This model rests on the assumption that the lead investigator obtains institutional approval to conduct a research project and to create a biobank for long-term storage and future analyses of biospecimens. Two alphanumeric codes are established and assigned to distinct parts of the study to ensure

that the investigator's use of banked samples is limited to research without being able to link samples and data to human research participants.

These and other models provide practical approaches for the protection of privacy and confidentiality, the addition of follow-up information on participants without compromising confidentiality, and, in the case of the two-code model, the use of a trained medical archivist. The models also prompt biospecimen holders and decision makers to act as ethical stewards of biospecimens, demonstrating respect and consideration for human research participants (8,9). The models, however, do not provide established biobanks with an all-encompassing concept for the variety of significant obligations for governing such resources, which range from managing access requests to transfer or disposition of samples upon the end of a project.

The Custodianship Model

The custodianship model assumes that the caretaking responsibility for biospecimens starts at the planning of a research project, prior to the initial collection, and continues through research use to final dissemination of findings (11,12). Under this model, biobanks would undertake the role of the trusted intermediary and demonstrate accountability by ensuring that biospecimens are collected and used according to the wish of the human research participant as expressed in the informed consent document. Custodianship does not entail the right to ownership but acknowledges that a biospecimen is provided to research as a "gift" to be used only with consent to advance science for the benefit of society. Custodianship does not regard a biospecimen as commodity for profit-making, a practice that not only circumvents the informed consent terms, but breaches the trust between stakeholders and threatens participation in future research.

The custodian of biospecimens should be recognized in the project documents and preferably be someone other than the research investigator or sponsor(s) of the biobank to eliminate any existing or potential FCOI and ensure that biospecimens are collected, stored, and accessed with consistent oversight and ethical standards. In projects where the roles of the primary holder of biospecimens and investigator cannot be separated, investigators should adopt the same duties of custodianship and abide by the ethical standards practiced by established biobanks. Assigning custodial responsibility to human research participants may not be ideal since most research projects typically use biospecimens from multiple contributors. This may lead to confusion or disagreement among human research participants as well as biases of certain interests that could impede the progress of research.

Custodianship calls for advanced and judicious planning by structuring the biobank's governance plan, the blueprint of policies and best practices guiding key operational decisions. The governance plan should be established prior to the inception of specimen and data collection with guidance from stakeholders and/or an independent advisory board, when feasible, and consideration for the diverse and evolving scientific questions and changes in research directions. The plan should identify who is the custodian of biospecimens and outline methods employed by the resource for samples and data oversight to ensure the long term quality of samples and the integrity of their associated data. The plan should define principles for protecting the privacy of human research participants and the confidentiality of their associated data, access to biospecimens and data, management of discontinuation of participation in research, and potential administrative changes during the term of the project. Consideration should be given to disclosure and management of FCOI to avoid the bias of research agendas or study outcomes, and management of intellectual property to preserve open access to biospecimens and to promote downstream commercialization of inventions while fostering future research. Methods for timely and

efficient dissemination of aggregate research findings for the benefit of human research participants and the public should also be addressed. A summary of the governance plan represented by a simple graphic could be included with the informed consent document to help human research participants appreciate the resource's level of basic oversight.

In considering what custodial principles are applicable to a research projects, biobanks and investigators with small biospecimen collections should align their custodial obligations with the objective of the project. While established biobanks are expected to abide by all the principles defined herein, investigators with a small collection should adopt relevant best practices, including privacy and confidentiality protections, well-documented protocols for the collection, storage, and use of biospecimens and data, disclosure and management of FCOI, and others. Alternatively, investigators with a small collection stored for future research should consider joining a regulated biobank to ensure that consistent ethical principles, in addition to baseline quality standards, are applied to the collection.

Implementing the Custodianship Model

The economics of biobanking is a field that is still in its infancy. Cost models for biobanking are complicated by the so-called "hidden costs", such as staff who contribute to the biobank but are paid by the host institution or other institution or sources, the difficulty in estimating the true value of a biospecimen and its accompanying data, and other factors. For established biobanks, the capital costs of instituting a custodianship model are likely to be low since they would most probably already have the needed elements for implementation. Upgrades to informatics, however, may be required to meet custodial duties such as tracking of consent, managing discontinuation of participation in research, and ensuring the long term integrity of biospecimens and data. More staff time may also be required for activities such as long-term planning and communications. For small investigator-driven collections, and depending on the nature of research, cost saving measures and efficiency could be realized through joining a regulated biobank to meet the goals of the custodianship model. In all cases, implementation costs should be estimated in advance during the planning of the project.

Determining the metrics for monitoring success of the custodianship model is rather difficult since many of the proposed benefits are intangible and can not be quantitatively measured. The emphasis on long-term planning and careful monitoring of biospecimen and data integrity will result in an optimal collection that is suitable for modern research. The prospective development of contingency plans should help the biobank to maintain sustainability and should reduce disputes related to the transfer and/or disposition of samples. The focus on transparency and communication to all stakeholders should lead to improved relations with human research participants and better understanding of the importance of biobanks to medical research. Finally, the institution of fair access policies should result in timely and efficient research use of biospecimens without undue burden to investigators.

Concluding Remarks

Biospecimen-based research is distinct from other research activities because of the longevity of biospecimens, the unique ethical and social issues raised by such research, and the emotional and personal factors associated with biospecimen donation (11). These properties may justify the espousal of ethical principles beyond those established for medical research in general. Custodianship endorses the adoption of clear principles for the continual caretaking of biospecimens during the life of the project and following its termination to promote a biomedical research endeavor that is based on transparency,

fairness, and accountability, to maximize human participation in future research, and to extend the benefits of biospecimen research to all humans.

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