POLICY FORUM: MEDICINE

IRB Review and Consent in Human Tissue Research

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Human tissues are collected by physicians during routine diagnostic and therapeutic medical care. These valuable research resources may be retained for many years; some pathology archives are more than 100 years old. Concerns have been raised because these tissues can be accessed and used without patient knowledge and consent (*1*). Proposals for limiting the retention and use of tissues and requiring informed consent for their use in research have spawned heated debate (*2*). These issues are currently being examined by the National Bioethics Advisory Commission (*3*).

Most large hospitals, universities, and medical schools in the United States have a Multiple Project Assurance (MPA) with the Office for Protection from Research Risks of the National Institutes of Health (NIH). The MPA binds the institution to establish an institutional review board (IRB) and comply with federal rules regulating human subjects research (the so-called Common Rule) (*4*). The IRB protects human subjects by minimizing risks, ensuring that the benefits of research outweigh the risks, and verifying the adequacy of the informed consent process. Generally, review by the full IRB is required for research on human subjects. Proposed research that poses no more than "minimal risk" (*5*) to subjects may be approved by expedited review, in which only the chair of the IRB or a designee reads and approves a protocol.

Under the Common Rule, the use of tissues in research is generally considered to be human subjects research if the investigator can identify individual subjects. Subject consent may be waived by an IRB for research that poses no more than minimal risk to subjects and does not adversely affect their rights or welfare, when the research could not practicably be carried out without the waiver. Thus, for particularly sensitive research, investigators must obtain consent or anonymize samples by removing all identifiers or links to specific subjects (*6*).

Use of archived tissues may be exempt from the rules requiring IRB approval and informed consent if the investigator cannot identify the individual from whom the tissue was collected either directly or by use of linking codes. Nonetheless, some MPA institutions have stipulated that all research performed under their auspices will be approved by the IRB (*7*).

We examined the degree to which published studies involving human tissues document IRB approval and informed consent (*8*). We chose nine journals (*9*) and reviewed all original articles, research reports, and technical correspondence published in a 3-month period. We identified 105 papers that involved human tissues other than cell lines and that had first or communicating authors at U.S. institutions. All but four studies in our sample were done at MPA institutions (*10*). Full details of the statistical analyses performed are available as supplementary material at *Science* Online (www.sciencemag.org/feature/data/987193.shl).

IRB approval was documented in 30% of the articles, and informed consent was mentioned in 23% (Table 1). There were no significant differences in reporting of IRB approval by journal nor by whether the journal's policy requires the mention of compliance with institutional guidelines on human subjects research (*11*). However, papers appearing in a journal requiring mention of informed consent were more likely to state that consent was secured than those appearing in journals having no such policy. Consent was more likely to be mentioned if IRB approval was mentioned.

We surveyed the authors by telephone (*12*). Of the 95 we were able to contact, 5 refused to participate, 85 were interviewed by telephone, and 5 completed our questionnaire by e-mail or fax. Questions and responses are summarized in Table 2.

Multivariate statistical analyses showed that consent was more likely to be secured for genetic studies and less likely to be secured for studies using tissues collected only for clinical purposes. Other factors were not related to variability in obtaining consent.

Of 64 articles that did not mention IRB approval, 19 had actually not been approved. We interpret this to mean that the studies were not submitted for approval, not that the studies were rejected. Exploratory statistical analysis suggests that approved studies were more likely to involve securing consent from subjects, to acknowledge external funding, and to involve genetics. In fact, all of the familial linkage studies in our sample were IRB-approved. Non-approved studies were more likely to be published in a pathology journal and to report clinical test development or validation. In turn, pathology journals were more likely to publish method papers than were other journals. Development and validation of clinical tests may not be considered research. Nonetheless, authors of 16 of 27 methods papers had secured IRB approval, and we could discern no systematic differences between those having approval and those not.

Multivariate logistic regression identified several factors related to IRB approval. First, external funding of research was associated with an increased likeli-

TABLE 1. ARTICLES ANALYZED*

Abstracted information	N
Journal type:	
Pathology	46
Genetics	55
General science	4
Use of tissue was:	
Retrospective	18
Prospective	53
Both	5
Unclear	29
Sample collected for:	
Clinical purpose	40
Research purpose	40
Both	13
Unclear	12
Type of study:	
Methods development†	31
Somatic genetics	10
Germline genetics	54
Linkage	25
Case report	6
Other‡	18
Discussion of ethics issues:	
Only IRB approval	17
Only informed consent	10
IRB and consent	14
Neither IRB nor consent	64
Funding acknowledged:	
None	32
Federal	60
Foundation	47
Foreign source	12
Other§	33

*Some studies were of more than one type; most had multiple sources of funding. †Included studies comparing old and new diagnostic methods and those describing the development and validation of a new clinical assay. ‡Included studies of protein expression, cellular or disease processes, and infectious disease. §Included university and departmental research funds and corporate support.

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hood of IRB approval. Of 32 studies failing to acknowledge any source of funding for the research, 15 (47%) were not IRB-approved. Eleven of these 15 involved clinical test development.

Second, investigators with access to clinical samples were less likely to obtain IRB approval. Of 41 studies involving tissues collected for clinical purposes, 17 (41%) had not been reviewed by an IRB.

Third, investigators using samples without consent or IRB approval were more likely to use them in identifiable form than were investigators who had IRB approval. Of 13 studies performed without consent or IRB approval, only 3 (23%) used non-identified samples. In the 15 comparable IRB-approved studies having no subject consent, 10 (67%) used nonidentified samples. This could be due to specific IRB requirements or to greater investigator sensitivity to confidentiality issues and the need for IRB approval.

TABLE 2. SURVEY QUESTIONS AND RESPONSES*

Survey question	N
Was the study:	
Retrospective	29
Prospective	37
Both	24
Tissues collected for a:	
Clinical purpose	41
Research purpose	41
Both	8
Tissues were collected from:	
Patients or subjects	77
Physicians	25
Other researchers	8
Pathology (discarded tissue)	11
Surgery or surgeon	8
Tissue bank	4
Identify subjects?	
No	13
Yes, directly	58
Yes, by using a linking code	19
IRB-approved?	
No	19
Exempt (by IRB)	1
Expedited review	14
Full IRB approval	53
No response	3
Did subjects consent?	
Yes	62
No	28

*Multiple tissue sources were sometimes used.

Only 1 of the 19 unapproved studies may be exempt under the Common Rule (but might still require IRB approval under the investigator's institutional MPA) (*13*), because researchers used anonymous samples provided by a tissue bank. The other 18 studies used samples retaining subject identifying information or linking codes.

Most investigators reported that their studies received full IRB review (Table 2) (*14*). Research on germline genetic mutation in disease or familial linkages was more likely than other types of studies to have been reviewed by the full IRB, according to the authors. This suggests that IRBs (and perhaps investigators) perceive genetics studies as posing more than minimal risk to subjects.

Our findings support the following conclusions and recommendations. First, some human tissue research is being performed without IRB approval. However, we believe that investigators who did not obtain IRB approval are not trying to avoid oversight but rather do not understand the requirements. There need to be stronger efforts to educate the research community about ethical and practical concerns regarding the use of identifiable tissues, as well as requirements for and the desirability of IRB review. Even if investigators think their studies are exempt, they should submit protocols to their IRB. This process may even improve the quality of their research.

Second, investigators should adopt, and IRBs should require, procedures to anonymize samples to the extent practicable consistent with the research goals. One author reported having express IRB exemption for all studies done under procedures for stripping identifiers from samples. Such procedures can minimize risks to subjects and related ethical concerns, expedite review, and facilitate research.

Third, pathologists or others having custody and control of patient specimens should require investigators who wish access to document IRB approval, as do (or should) medical records departments.

Fourth, insofar as IRBs do not have the resources to monitor compliance (*15*), we propose three points of intervention: (i) institutions should evaluate all grant applications (not just federal) for IRB approval; (ii) schools or departments should establish procedures for internal review of protocols, thereby ensuring that standards are created, communicated, and satisfied; and (iii) journals should set criteria for publication, communicate those to prospective authors, and uphold those standards in peer and editorial review. Paradoxically, all 19 non-approved studies in our sample were published in journals with editorial policies requiring that authors discuss their compliance with human subjects research regulations. Journals should act as gatekeepers and refuse to publish studies for which institutional oversight requirements have not been satisfied (*16*). IRB approval is not just an ethical nicety. Compliance with human subjects regulations ensures a level of social control over and integrity of the scientific enterprise (*17*).

References and Notes

1. E. T. Jeungst, in *The Ethics of Research Involving Human Subjects: Facing the 21st Century*, H. Y. Vanderpool, Ed. (University Publishing Group, Frederick, MD, 1996), pp. 401–429.
2. Compare G. J. Annas *et al.*, "The Genetic Privacy Act and Commentary" (Boston Univ. School of Public Health, Boston, MA, 1995) and E. W. Clayton *et al.*, *JAMA* **274**, 1786 (1995) with American Society of Human Genetics, *Am. J. Hum. Genet.* **59**, 471 (1996); W. W. Grody, *Diag. Mol. Pathol.* **5**, 74 (1996); and American College of Medical Genetics Storage of Genetics Materials Committee, *Am. J. Hum. Genet.* **57**, 1499 (1995). See E. Marshall, *Science*, **271**, 440 (1996); J. Stephenson, *JAMA* **275**, 503 (1996).
3. *The Use of Human Biological Materials in Research: Ethical Issues and Policy Guidance*, Draft for Public Comment (National Bioethics Advisory Commission, Washington, DC, 3 December 1998) (available at bioethics.gov/pubs/hbm_pub_comment/index.html).
4. 45 Code of Federal Regulations (CFR) § 46.101-409 (1998).
5. "*Minimal risk* means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests." 45 CFR § 46.102(i) (1998).
6. J. F. Merz, *IRB: Rev. Hum. Subj. Res.* **18**, 7 (Winter 1996); P. R. Reilly, M. F. Boshar, S. H. Holtzman, *Nature Genet.* **15**, 16 (1997); J. F. Merz, P. Sankar, S. E. Taube, V. Livolsi, *J. Inv. Med.* **45**, 252 (1997).
7. J. F. Merz, *Ann. Epidemiol.* **8**, 479 (1998).
8. It has been well established in general medicine and specialty journals that authors fail to document IRB approval and consent, even when editorial policies require manuscripts to address these issues [D. T. Kim and W. H. Spivey, *Ann. Emerg. Med.* **23**, 70 (1994); M. G. M. Olde Rikkert, H. A. M. J. ten Have, W. H. L. Willibrord, *Br. Med. J.* **313**, 1117 (1996); C. M. Olson and K. A. Jobe, *Resuscitation* **31**, 255 (1996); R. J. Amdur and C. Biddle, *JAMA* **277**, 909 (1997); I. Matot, R. Pizov, C. L. Sprung, *Crit. Care Med.* **26**, 1596 (1998); J. H. T. Karlawish, G. W. Hougham, C. B. Stocking, G. A. Sachs, *J. Am. Geriatr. Soc.*, in press].
9. The pathology journals reviewed were the *American Journal of Pathology* and the *American Journal of Clinical Pathology*; the genetics journals were the *American Journal of Human Genetics*, *Nature Genetics*, *Molecular Diagnosis*, *Human Molecular Genetics*, and the *Journal of Medical Genetics*; and the general science journals were *Nature* and *Science*.
10. See http://helix.nih.gov:8001/ohsr/mpaflist.php3
11. The journals' instructions for authors indicated that three have no policy, five require a statement of IRB approval or conformance with institutional guidelines, and four require a statement of informed consent.
12. This study was approved by the University of Pennsylvania Committee on Studies Involving Human Beings, and oral consent was secured from participants after a description of the study and assurance of absolute confidentiality.
13. Our statistical analysis results are robust to the removal of this potentially exempt study. By these criteria, we found two other studies in our sample that could qualify for exemption, but both investigators had secured IRB approval for their research.
14. We did not ask for copies of IRB letters or approval numbers, nor did we try to speak to IRBs directly.
15. *Institutional Review Boards: A System in Jeopardy?* (Inspector General, Department of Health and Human Services, Washington, DC, 1998); J. Moreno *et al.*, *JAMA* **280**, 1951 (1998).
16. World Medical Association, *JAMA* **277**, 925 (1997).
17. *Integrity and Misconduct in Research: Report of the Commission on Research Integrity* (Department of Health and Human Services, Washington, DC, 1995).

18. We thank N. Martins, A. Kahan, and the many authors who participated in this study and M. Merz, S. Alpert, A. Kahan, V. Livolsi, A. Caplan, and J. Wilson for comments. Funded in part by the NIH, DOE, and VA Consortium on Informed Consent Research and the Greenwall Foundation.