The Need to Understand IRB Deliberations

by Philip J. Candilis, Charles W. Lidz, and Robert M. Arnold

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there has been little systematic examination of how IRBs reach their decisions, despite a robust literature on research ethics, persistent criticism of Institutional Review Board (IRB) review of human subjects research, and new policy initiatives to educate and accredit IRBs. Previous studies on the workings of IRBs have focused largely on their administrative structure, how well they meet certain performance criteria, and the outcome of decision-making. Because recent proposed policy initiatives might result in inappropriate, ineffectual, and harmful modifications to the IRB decision-making process, we need a better sense of how IRB decision-making operates.¹

In this article, we explain why there is a need to understand how IRBs make decisions and propose a model for assessing IRB decision-making. Our approach draws from the model of organizational decision-making developed in the late 1970s by Irving Janis and Leon Mann.

What We Know and Don’t Know about IRBs

Numerous studies have identified problems with IRB review of research protocols and oversight of human subjects research. The most comprehensive look at IRBs to date comes from the Bell report of 1998 that surveyed all 491 IRBs using multiple project assurance numbers from the federal government.² In addition to describing general IRB demographics, the Bell report identified high volumes of review, staggering numbers of person-hours spent on review, a broad range of research methodologies, and uneven IRB education levels. There was no description, however, of how these variables affected the decision-making process. More recently, DeVries and Forsberg surveyed a stratified sample of 89 IRBs to show persistence in the findings of the Bell report.³

Most data about the processes of IRB decision-making come from general descriptions of the various individuals who make up IRBs or small groups of IRBs.³ Other data arise from analysis of consent forms or applications to IRBs.³ Investigators at Boston University, for example, examined IRB documents and found flaws in the study designs and statistical methodologies that IRB members approved.⁶ Another study of IRBs found that IRB-approved informed consent documents varied widely in readability, and that IRBs differed in the kind of informed consent they required (from telephone contact to waiver of informed consent).⁷

Different IRB decisions about the same protocol have been an issue for researchers and reviewers in the U.S. for some time, with similar results across time and
region. Studies identifying variation in IRB review of the same protocol indicate that there is often disagreement across IRBs as to whether a protocol should be approved, as well as variable understandings of research risks and benefits among IRB members and across IRBs.

Readability concerns, of course, have also been widespread, from Tarnowski's use of Fry and Flesch analyses to show college-level reading requirements for consent forms to research that suggests IRB review may make little difference to the readability of consent forms.

There is also a more general concern that gaps remain between accepted ethical norms for human subjects research and actual practices of IRBs and researchers. Several commentators have identified barriers to meeting general standards of ethical research review, including inadequate adverse event reporting and IRB postapproval review, problematic clinical study agreements, rudimentary informed consent processes, inadequate IRB documentation and education, and overreliance on paper compliance with ethics standards and regulatory requirements. However, there has been no systematic study of IRB meetings to describe day-to-day gaps between accepted ethical standards of review and actual IRB decisions.

Recent Pressures on IRBs

Several government bodies have identified pressures on IRBs that may affect the decision-making process. The U.S. General Accounting Office determined that heavy workloads and a lack of resources undermined IRB review of protocols, and the Inspector General of the U.S. Department of Health and Human Services identified trends in commercialization of IRBs, increased IRB-shopping by researchers seeking speedy approval, and an increase of private review boards not subject to standard scrutiny as pressures that may negatively affect the IRB system.

Failure of an IRB to require disclosure to research subjects of researcher and institutional financial conflicts of interests was a partial basis for a civil court ruling against the Hutchinson Cancer Center in the death of an experimental subject.

Public and media responses to serious adverse events in research have been at least as critical as those of academics and federal regulators. There has been considerable clamor for changes in IRB functioning.

The death in 1999 of teenager Jesse Gelsinger in a recombinant DNA experiment at the University of Pennsylvania generated congressional hearings and significant lawsuits, the first against reviewing ethicists.

And following the death in 2001 of Ellen Roche, a healthy volunteer in a Johns Hopkins University study, the Maryland legislature passed a law granting greater access to IRB minutes for the purpose of making the IRB decision-making process more "transparent." In April 2002, the U.S. Senate held hearings on the proposed National Human Subjects Protection Act, which included provisions for increased public scrutiny of IRB decisions, including specific protocols and research methods.

Reform initiatives to change the overburdened IRB system also include voluntary accreditation of IRBs and education programs for researchers and IRB members. In the accreditation process, institutions assess the nature of their research enterprise and the accrediting agency monitors their progress toward compliance with a series of oversight policies and outcomes.

Yet, while accreditation and other oversight initiatives offer a new tier of communication between IRBs and the research they review, the oversight does not extend to the actual decision-making process.

With no understanding of such practices, or the level to which such practices affect the quality of IRB outcomes, accreditation guidelines can offer no standards to ensure good practice at the most critical level of group dynamics. This is problematic given that proposed federal legislation includes accreditation requirements for all IRBs. Moreover, there already is concern that the Privacy Rule of the Health Insurance Portability and Accountability Act (HIPAA) has resulted in changes to IRBs that are uninformed by prior study.

The Decision-Making Process

In order to understand the problems of IRB review and to identify the appropriateness of proposed reform initiatives, we need to know how IRBs function, particularly what decision-making process they use and whether different processes lead to different outcomes. Research is needed to determine whether overburdened IRBs focus too heavily on informed consent documents and institutional agreements, whether education and documentation requirements actually influence discussions, how much attention is actually given to adverse events, and why there are variations in assessment of research risk. Answers to these critical conceptual questions may help IRB members obtain a better understanding of the norms that should drive research review: ideals of fairness in distribution of risk, minimization of harm, balancing of risks and benefits, and transparency in the informed consent process.

Several approaches are useful in assessing IRB decision-making. In-depth naturalistic studies focus on describing the actual decision-making processes—on the part of the individual reviewers, the committee members at their regular meetings, and the IRB as an organization—including the staff who process applications. This approach involves
both observation and interview methods because it is important to document both the actual decision-making process and the ways in which participants think about the applications they review. Large-scale surveys and analyses of outcome measures, like those conducted by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research,\textsuperscript{31} the National Bioethics Advisory Commission,\textsuperscript{32} and others,\textsuperscript{33} are likely to be more useful at a later stage.

Ethnographic approaches that observe, record, and then analyze data from research review meetings are an important starting point for assessing IRB decision-making. Naturalistic observers can identify patterns during discussion of individual protocols, characterize interactions between members, and describe the concepts, terms, and regulations used to support decisions. The inductive discussions that arise from these field observations may describe specific patterns and decision-making practices that IRBs have yet to recognize.

In-depth or structured interviews of IRB members in close proximity to their meetings would be an important adjunct to this classic approach. Specific questions designed to elicit information about IRB members’ thoughts that they express in their behaviors or statements at a meeting can provide a better sense of their motivations and reasoning. Influences of departmental or institutional politics, group dynamics of lay and scientific members, and other social influences may otherwise be undetected. Structured interviews of IRB staff members are a critical component of this approach because of staff influence in screening research applications, identifying procedural lapses, and flagging general regulatory concerns for the IRB.

An alternative approach that may be fruitful would be to develop (or adapt) a model that assesses both IRB discussions and related IRB staff activities and routine procedures. IRBs use different forms and procedures that are likely to result in variation in decision-making tasks. For example, reviewer-reporting forms may require IRB members to consider a wide range of actions regarding the protocol and the informed consent process. An empirical question for a new model would be how such forms determine the aspects of decision-making that are most thoroughly covered, since different structural and procedural properties of the decision-making process are likely to influence the outcome of protocol review and discussion.\textsuperscript{34}

A New Approach to Assessing IRB Decision-Making

Our research group has begun investigating how IRBs make decisions about research protocols. We code and describe the use of ethical and research language by IRB members at an IRB meeting. By using the decision about a particular protocol as the analyzable unit, we apply a social-cognitive framework of decision-making directly to the research review process. Drawn from the Janis and Mann model of decision-making, the framework and the questions it generates may be able to assess the comprehensiveness of IRB work. Although there are no ideal models of the deliberative process of IRBs in the literature, more general theories of group decision-making processes can provide a framework within which to think about IRB decision-making.\textsuperscript{35}

Developed at a time when social-cognitive theorists believed that decision-makers weighed probabilities and outcomes in a careful, rational manner, Janis and Mann postulated a reluctant, conflicted decision-maker. They described a more realistic model of decision-making, replete with dysfunctional “coping patterns” and high quality criteria that seemed to confer decisional advantages. Their model recognizes that individuals approach decisions with a variety of presumptions and biases. Consistent with its use in analyzing large-scale political decisions (including the Bay of Pigs invasion), the Janis and Mann model has been tested in emergency decision-making and used to develop instruments measuring the quality of decision-making.\textsuperscript{36} It has also been applied to career decision-making,\textsuperscript{37} to assessing how adolescents and their parents understand management of their diabetes, and to describing the coping and decision-making of breast cancer patients.\textsuperscript{38} Moreover, the model continues to be an important standard for assessing the rationality of organizational decision-making 25 years after its introduction.

This conceptual and prescriptive model lends itself well to the IRB group process. It first suggests the “best” process for making decisions, and then assesses deviation from the ideal. The Janis and Mann model provides anchor points against which to compare actual decision-making practices. The ideal is still that of classic rationality but applied to imperfect group decision-making. It is important, however, not to expect IRBs to live up to the highest standards for deliberation and decision-making advocated in this model. If IRBs reviewed every research protocol with the same thoroughness that Janis and Mann originally suggested, research would be delayed. After all, member and staff time are limited resources. The kind of empirical research we believe is necessary should, at least in its initial phases, describe IRB decision-making, not evaluate it.

The breadth of this model offers a first step in describing the process of IRB decision-making. It can identify the major features of IRB decision-making and the context in which they are considered. It then allows comparison to the ideal: comparison of the protocol elements IRBs most
frequently discuss, of procedures they most frequently use, and of variations that arise from different protocols. The Janis and Mann approach assesses actual organizational decision-making across seven discernible elements, each of which is useful in helping to understand IRB deliberations.

To what degree does the group consider alternative courses of action? What are the options available to the IRB when evaluating a research protocol? Aside from the decision to approve or disapprove the protocol, what alternatives, if any, does the IRB consider regarding the proposed research design, the informed consent procedures, the protections for research subjects, and the use of vulnerable populations? How, if at all, does routine processing of protocols allow for consideration and management of alternatives that the IRB might not consider during formal meetings (i.e., alternatives not mentioned in forms or used in recent institutional memory)? What case features affect which options are considered?

Does the group consider the objectives and the values involved? What objectives do IRB members mention or observe when they review protocols: protection of research subjects; advancement of science; compliance with federal regulations; protection of the institution or the community; the autonomy of subjects? Do different types of protocols raise different values and objectives?

Does the group consider the costs and the risks, as well as the positive consequences, of each alternative? What sorts of risks and benefits do IRBs consider when assessing a protocol? Do they weigh different types of risks (e.g., risk to research subjects, risk/costs to the public at large from the loss of information, risks to the research institution, and risk to the IRB) the same way? How do IRBs consider potential costs, including both financial and temporal costs, in their decision-making?

Does the group search for new information relevant to the alternatives? What sources of information do staff or members of the IRB use in assessing protocols? To what degree do they use sources of information not present in the protocol? How much new information do they request from the researchers or from other sources, including other members of the committee? To what issues and concerns do they direct the information collected? How do different IRBs organize the search for information? What roles do reviewers, staff, and the committee as a whole play in this process of gathering new information?

Does the group use any new information or expert judgment? Do IRB members adapt their views to expertise from other members and to responses to their questions from researchers or special representatives?

Does the group reexamine the consequences of alternatives after gathering information, before making a final choice? Do all IRB members review the protocol or do they just accept the primary reviewer's assessment of it? Do members (especially primary reviewers) consider new information presented during deliberations, or is there a tendency to accept the initial review? How does the division of labor between the staff and IRB members affect the reexamination process across IRBs?

Conclusion

The lack of research on IRB decision-making weakens current efforts to improve research oversight.

Research that has been largely limited to studies of the nature and consistency of IRB procedures cannot address current controversies surrounding research regulation in general and IRBs in particular. Given recent criticisms and reform initiatives to change IRB review through education, accreditation, and regulation, a concerted effort to examine IRB decision-making processes appears appropriate. In the absence of concrete data on how IRBs make decisions, policy and regulatory changes to the IRB system may harm rather than improve the research review system. They could result in harm to human subjects under its protection.

We believe the Janis and Mann approach to assessing organizational decision-making should be applied to research on IRBs. This model offers specific questions relevant to IRB deliberations: balancing of risks and benefits, considering alternatives, and using informational resources and expert judgment. These are the kinds of questions likely to frame the strengths and weaknesses of research review, primarily by describing core decision-making processes. We emphasize again that it is more appropriate to view the elements of the ideal Janis and Mann model as areas of investigation rather than standards to be met. The model allows quantification of the elements that IRBs most frequently discuss and of potential variations based on differences among protocols, reviewers, or sites. Its breadth provides a better opportunity to assess the process of IRB decision-making. IRBs themselves will have to be willing collaborators in conducting such a thorough investigation of their decision-making processes. Applying the Janis and Mann approach can be a critical first step toward obtaining empirical evidence that verifies or refutes the criticisms about IRB procedures and practices.
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References

20. Numerous organizations have now proposed programs for IRB accreditation, including the Department of Health and Human Services, the Institute of Medicine, the National Conference on Quality Assurance, Public Responsibility in Medicine and Research, and the Association for Accreditation of Human Research Protection Programs.
23. See ref. 3, Bell et al. 1998.
Part II: HIPAA and Disclosure Risk Issues

This is the second in a series of three articles whose focus is to assist Institutional Review Boards (IRBs) in providing guidance to investigators and research administrators who need to comply with data sharing requirements. This article begins with a discussion of how data are prepared for sharing. We then proceed to the data sharing provisions of the Privacy Rule of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Next, we turn to the topic of deidentification and show why the mere removal of names and addresses may be insufficient to deidentify data—and would, therefore, preclude data sharing under HIPAA and the National Institutes of Health (NIH) confidentiality provisions. An example of a reidentification technique is provided. The final section briefly looks at some of the elements of a risk evaluation.

Preparing Data for Sharing

When colleagues share data informally among themselves, little needs to be done since the initial researcher is on hand to explain the data, and prudent sharing with trusted colleagues avoids breach of confidentiality. However, within a few months an investigator can easily forget how the data were gathered, how each variable was defined, and so on. Hence, some documentation of the data is always appropriate.

The role of documentation increases when researchers make data available for public use. Most funders that encourage sharing and archives that receive data for public use specify how they want the data prepared. For example, the Inter-university Consortium for Political and Social Research (ICPSR) provides extensive instructions for persons who plan to deposit data in its repository. These excellent instructions include details on how to plan for sharing at the research stage, how to ensure confidentiality, and how to document the data.

As its website indicates, ICPSR prefers that investigators take initial responsibility for removal of all identifiers and other kinds of information that could possibly lead to deductive identification (reidentification) of subjects. However, members of ICPSR’s expert staff work with investigators to help resolve confidentiality issues. Hence, with respect to ICPSR and many other public archives, selecting methods to ensure confidentiality does not rest solely on the researcher or the IRB. Briefly, the main steps of preparation for sharing, in most cases, are as follows.

- **Documentation of Data.** Data documentation consists of describing the data so that secondary users can understand and use the data correctly. Secondary users may encounter many problems when trying to decipher a quantitative data set. Thus, the purpose of documentation is to make data as user-friendly as possible for the secondary user. However, some information supplied in documentation may increase the risk of disclosure of identifying data. The most common problem is revealing the identity of geographic areas with small populations. From such information it may be easy to pinpoint, for example, which participant is the 15-year-old with a PhD, the city mayor, or the 105-year-old man, and from that inference to learn other kinds of sensitive information about the person from the data.

- **Removing Direct Identifiers.** Direct identifiers include names, addresses, employers’ names or addresses, relatives’ names or addresses, dates, telephone and fax numbers, email addresses, Social Security numbers, medical record numbers, account numbers, photos, and so on. Removing these identifiers is an obvious step toward rendering data anonymous.

- **Performing Disclosure Review and Adjusting Data.** Once identifiers have been removed, the remaining data must be checked for possible risk of reidentification through matching with other records that contain identifiers. Typically, checking data for risk of reidentification requires the services of an individual who has knowledge of statistical methods to avoid disclosure.

(such as a statistician, biostatistician, demographer, sociologist, epidemiologist, or health services researcher) and is not normally within the scope of an IRB’s expertise. Rather, the consultation of such an expert by the researcher and the IRB is usually required. Several government agencies employ the services of a permanent or an ad hoc Disclosure Review Board. Research institutions like ICPSR tend to rely on individuals or research teams to fulfill this role. Where necessary, the researcher and the statistical expert(s) select and employ disclosure avoidance techniques to prevent reidentification of the data.

The HIPAA Privacy Rule and Data Sharing

The HIPAA Privacy Rule is designed to protect certain health data from unauthorized uses and disclosures. It applies to “covered entities”—that is, health plans, health care clearinghouses, and health care providers (e.g., hospitals, nursing facilities, and practitioners such as physicians and therapists) who use electronic transactions. For purposes of research, the Privacy Rule permits a holder of identifiable (protected) health information to release that information with or without the individual’s authorization. If protected health information is to be released without authorization, certain conditions must be met. For example, the data holder must receive documentation that an IRB or a Privacy Board has found that the proposed research involves no more than a minimal risk to patient privacy based on several criteria. These criteria include assurances that identifiable information will not be improperly disclosed to third parties not approved in a waiver of authorization. In granting a waiver of authorization, the IRB or Privacy Board must decide on the adequacy of the researcher’s assurance that he or she will not reuse the data for unauthorized purposes and will not disclose protected health information. The IRB and the researcher need to know how data can be deidentified should the researcher want to share data obtained under the Privacy Rule.

The Privacy Rule does not restrict the disclosure or sharing of information that has been properly deidentified. There are several ways to deidentify data that meet the requirements of the Privacy Rule. One way is for the covered entity to ensure that the data are stripped of 18 “identifiers” listed in the Privacy Rule. These identifiers range from name, address, and Social Security number to electronic device and biometric identifiers. When deidentifying data this way, the Privacy Rule requires the

covered entity to be satisfied that what remains in the body of data cannot be used to identify anyone. This involves determining whether data elements, alone or in combination, might lead to identification of a specific person. Knowledge and expertise to assess disclosure risk may not be available to all covered entities. How can an IRB or Privacy Board be sure that what remains in the body of data cannot be used to identify anyone? Because there is no formula for making this determination, each data set offers its own challenges. Thus, the IRB or Privacy Board must develop judgment in these matters as it gains experience with trying to evaluate the disclosure risks connected with various data sets. These entities will need to recognize when it is beyond their ability to make determinations about disclosure risk and obtain the assistance of others with expertise in detecting disclosure risk.

Another way a covered entity can deidentify data is to have a qualified expert determine what modifications are needed to prepare data for anonymous release. Just who can do this (whether specific individuals or statistical organizations) is not specified in the Privacy Rule. Rather, the Privacy Rule describes the knowledge that must be employed—i.e., generally accepted statistical and scientific principles for assessing disclosure risk and implementing disclosure avoidance methods.

Finally, protected data may be provided through the mechanism of a Limited Data Set. In this case, the emphasis is not on deidentification, but on control of the circulation of the data. Such releases may contain geographic detail or variables central to the analysis and known to be identifying by themselves or in combination (such as zip code, dates, and street address) but not personal identifiers of an individual.

Implications for Informed Consent

Under the HIPAA Privacy Rule, individuals are not required to authorize the release of protected data that are deidentified. Moreover, federal human research regulations (the Common Rule) do not regard deidentified data as human subjects data. However, information useful for research is nearly always of a detailed nature, and these very details that make analysis so fruitful also make disclosure risk high. Therefore, as a rule, information sharing will probably involve potentially identifiable data. This is even more evident when researchers expect to share data such as videotapes of family interactions or of dynamics within a certain group. In either case, informed consent is essential. Participants should
Table 1: Reidentification Example

<table>
<thead>
<tr>
<th>File</th>
<th>File content</th>
</tr>
</thead>
<tbody>
<tr>
<td>File with direct identifier (original research file)</td>
<td>Name ABCDEFGHIJKL</td>
</tr>
<tr>
<td>File with direct identifier removed (shared research file)</td>
<td>ABCDEFGHIJKL</td>
</tr>
</tbody>
</table>

Table 2: Matching of Hypothetical Research File with External File Using Items Held in Common

<table>
<thead>
<tr>
<th>File</th>
<th>File content</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shared research file (created in Table1)</td>
<td>ABCDEFGHIJKL</td>
</tr>
<tr>
<td>Material available from</td>
<td>ABC...WXYZ Name</td>
</tr>
<tr>
<td>Kentucky Marriage File</td>
<td></td>
</tr>
</tbody>
</table>

Table 3: Key to Variables Listed in Tables 1 and 2

<table>
<thead>
<tr>
<th>Alphabetic designation</th>
<th>Variable</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Age, male</td>
</tr>
<tr>
<td>B</td>
<td>Age, female</td>
</tr>
<tr>
<td>C</td>
<td>Date of marriage</td>
</tr>
<tr>
<td>D</td>
<td>State of birth</td>
</tr>
<tr>
<td>E</td>
<td>Race</td>
</tr>
<tr>
<td>F</td>
<td>Race of spouse</td>
</tr>
<tr>
<td>G</td>
<td>HIV status of subject</td>
</tr>
<tr>
<td>H, etc.</td>
<td>HIV status of spouse</td>
</tr>
</tbody>
</table>

If the researcher fails to plan ahead and does not include adequate detail about sharing identifiable data when informed consent is obtained, either study participants need to be recontacted or the file needs to be deidentified. Both of these procedures are likely to result in a loss of data quality and usefulness.

What are the implications of sharing identifiable data within one's institution? The answer to this question depends on such factors as the sensitivity and degree of identifiability of the data and the degree of supervision of the recipient by the original Principal Investigator (PI). When the data are sensitive and identified, some kind of data use agreement may be needed to specify the conditions under which the data may be used (see Part III for details).

Ordinary Methods of Removing Identifiers Are Sometimes Insufficient

It is often assumed that the removal of so-called "direct" identifiers such as name and street address is sufficient to render a data set "anonymous." As the latter term implies, there would no longer be "names" associated with the data. It has been demonstrated repeatedly, however, that some research files contain more than enough information to lead an intruder back to name or address if he/she also has access to files containing direct identifiers whose information "overlaps" with that of the anonymized file. An example of how this process works is presented in the next section, but here we would like to stress that, given such vulnerabilities, we need to consider two factors: motive and opportunity.

- **Motive.** Data are a commodity. Thus, for certain items there may already be an active, often completely legitimate market for such a commodity. Certainly, large public list searches are readily available. Employers and insurance companies can save millions of dollars by knowing the health or genetic status of prospective employees or insurables. Reidentified data could show HIV+ status, cancer diagnoses, bankruptcy, criminal behavior, or mental illness.

- **Opportunity.** Record linkage technology continues to advance. The reidentification of data that 10 years ago would have taken an unreasonable amount of time and resources can now be accomplished quickly and cheaply. Thus, the probability of reidentification can no longer be considered low because it would require too much work or money. Indeed, some data that were considered to be completely deidentified a decade ago can...
now can be at least partially reidentified.

Given motive and opportunity on one hand, and ethical, legal, and scientific imperatives on the other, it is clear that today's researcher needs to become aware of, if not relatively proficient in, the assessment of disclosure risk and methods to limit disclosure.

An Example of a Reidentification Technique

How can anonymous data be reidentified, and how does one prevent reidentification of one's data? A simple example will illustrate why reidentification of sensitive data is of concern.

Let's say we have a file, which we will label the "original research file," and that we need to create a "deidentified" data set for sharing with other researchers or for release to the general public. Reidentification requires that one have independent knowledge of some details about persons in the research file and that this knowledge be associated with a name, address, or other information that will lead to a name or address. There are many sources of such details. One is a data base, available on the Internet, that contains records for 1.1 million marriages in the state of Kentucky from 1973 to 2001 (the Kentucky Marriage File). These records include name, age, race, residence, and number of prior marriages for the bride and groom, as well as the date and county of the marriage and the marriage certificate number.

Suppose one has a data set from research conducted with residents of Kentucky. The names have been removed, but the data include gender, age, age of spouse, state of birth, and date of marriage, as well as sensitive data about them, e.g., their health status and their race. Tables 1 and 2 show how reidentification of respondents might be done after the names have been removed.

In Table 1, we removed the names and created a file for sharing (shared research file). In Table 2, we show the two files, the shared research file and the Kentucky Marriage File, and their variables. Note that both files hold certain variables (bolded in Table 2) in common. Under the given circumstances, it may be concluded that an individual who has these characteristics in common is the same person in both data sets, and the name associated with these characteristics in the Kentucky Marriage File can be appended to the shared research file. What's more, not only is a name associated with the information held in common, but the rest of the information in that file is now known to be associated with that person. In case the reader is wondering just how possible such a scenario might be, consider that when the people in the Kentucky data base are classified by age and date of marriage, fully half of these couples are unique. For those couples, the combination forms an identifier that matches to one, and only one, pair of names. We are well accustomed to the idea that a name or address serves to identify a research participant; we also need to be aware that certain combinations of data can serve an enterprising intruder almost as well.

This is a simplified example of how the data in one file may be used, in conjunction with similar data in another file, to reidentify a research participant. Of course, actual situations are rarely this simple, and a variety of factors must be considered in evaluating the feasibility of a match between two files: for example, age differences between files; item comparability; specificity of variables; and, perhaps most importantly, the sheer number of overlapping variables.

Evaluating Disclosure Risk of Microdata

Recall that microdata files are computerized files that consist of individual records, each containing values of variables for a single person, household, business establishment, or other unit. There are two distinct types of disclosure risk of microdata: 1) the data may be linkable to external data containing the identity of some respondents and unique cases subject to reidentification; and 2) the data may include some highly visible records (e.g., a 12-year-old with a college degree) that are readily recognizable to locally knowledgeable people.

Guarding against these two problems is a critical step in data sharing.

To discover whether there are linkable external data that might be used to identify some respondents, one needs to review what other data, if any, have been released on those respondents, or what information is generally available to the public. The most obvious form of other data that have been released are those that came from the PI. Other forms of released data include those released by other investigators who have worked with the population, professional license data, hospital discharge data or local government data on births, deaths, and marriages. It is impossible to check everything, but researchers should ask themselves: "How can I reidentify these data?" For example, if the research data are restricted to some sort of administrative unit...
(like state, county, school district, or hospital service area), data published for that area should be screened for variables also found in the research data. The variables in the research data likely to be found in external files are called key variables. These usually include demographic information like age and sex, but may also include more specific information such as profession, educational degree, “is a registered voter,” etc. In our hypothetical example in the preceding section, the key variables used to “link” the two files were age of wife, age of husband, and date of marriage.

The inclusion of variables that describe some aspect of an area (contextual variables) can increase the risk of disclosure. Contextual variables are generally not part of the original data collection but are added to the research data set. For example, a PI conducts a survey and is interested in the relationship of medical care to poverty. The address of each respondent is known and mapped to the census tract, and the census tract is mapped to a poverty rate. To deidentify the file, the PI deletes the respondents’ names and addresses but includes two variables that pertain to place of residence, i.e., three-digit zip code and poverty rate. The PI should do his/her best to ensure that this information cannot result in the reidentification of the geographic area which in turn might lead to the reidentification of unusual individuals in the file. Generally, the contextual data should not be so specific as to permit a match back to its source, which has a more detailed geography. In the case of the poverty rate, some sort of rounding usually can resolve the problem so that the data cannot be tracked back to a specific geographic area.

After constructing a list of key variables, the central question is how to determine if these variables can be used for record linkage. A useful ballpark estimate to assess disclosure risk is based on the combination of key variables, i.e., the size of the population must be more than three times the product of the cross-classified key variables. For instance, suppose a study (of any size) involves physicians and the PI wants to include five key variables (age, sex, marital status, specialty, and practice size) in the research data file. First, the PI hypothesizes that the age range for practicing physicians is between 29 and 68 years of age—this equals 40 categories. The next step involves recording two variables: the specialization is collapsed to 10 categories, and the practice size is categorized to four (single, small, medium, and large). Computing the cross-classified key variables (age by sex by marital status by specialty by size) is 40 x 2 x 2 x 10 x 4 = 6,400 cells. Therefore, in order for the average cell size to be three, the population should have at a minimum 6,400 x 3, or 19,200 physicians.

Let’s compare two states—Nebraska and Texas. Nebraska has approximately 3,500 physicians—far fewer than the minimum of 19,200. Consequently, a microdata file that includes these five key variables with that degree of specificity would more than likely uniquely categorize many Nebraska physicians, and the data would be at risk of reidentification.

On the other hand, reidentification would be much harder in Texas, which has 50,000 physicians. With an average cell size of approximately eight in the cross classification of the key variables, most of the physicians in a Texas study cannot be distinguished from other physicians that share those same characteristics. For Texas, most—though not all—of the data are protected from reidentification by force of numbers. However, the final determination of disclosure risk would need to take into account that some records may contain odd combinations of characteristics. This ballpark estimate provides a preliminary determination of whether population sizes are sufficient to protect data from reidentification.

Researchers can locate highly visible and recognizable records by visually scanning the content of small data sets, or, for larger data sets, by cross-tabulating some or all of the key variables to discover unusual categories or combinations of categories of data. These cross-tabulations should then be compared to external sources. For example, Texas recently commercialized its public licensing data for physicians (cost is $165,000), which contains detailed information including age, gender, medical school, year of graduation, type of practice, and medical specialty. The cross-tabulations of the PI’s data will reveal unique combinations; the license data can determine whether they are artifacts of sampling. For example, if the license data shows that there are only one or two practicing female oncologists over the age of 55, then the 55-year-old female oncologist in the PI’s data set is a disclosure risk.

Some examples of highly visible records would be a billionaire in Nebraska or a practicing 60-year-old black female dentist with twin grandsons living with her. Other combinations are less noticeable but may be nonetheless distinguishable in external records. Some examples are the 13-year-old mother in a metropolitan area, the family with an income of $500,000 or more in a small county, or a 20-year-old widow.

Most of the techniques used to deidentify data can be
learned by quantitatively oriented researchers. Experience shows that persons with quantitative skills can develop these abilities with some exposure to problems and practice. However, an expert should be consulted when data are sensitive, and especially when geographical information is contained in the data and it is unclear when data can be released without risk of reidentification. Part III of this series will describe two basic methods of protecting the confidentiality of data, as well as the situations that call for the skills of an expert.

The evaluation of disclosure risk is generally beyond the purview of an IRB. Yet it is critical that IRB members be aware of such risks. IRBs need to be assured that appropriate steps have been taken to deidentify tabular or electronic data. In Part III we suggest a threepronged approach for achieving this goal and discuss data sharing agreements and the IRB’s role in meeting the challenges posed by data sharing.

Disclaimer

The order of the authorship is alphabetical. The views expressed are those of the authors and not necessarily those of the United States Census Bureau or the National Center for Health Statistics.

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References

3. For example, the Bureau of Labor Statistics, Bureau of the Census, Bureau of Transportation Statistics, National Center for Education Statistics, and National Center for Health Statistics have Disclose Review Boards.
5. It is ultimately the covered entity’s decision whether to allow a researcher to use or disclose such information under a waiver of authorization. The waiver of authorization does not compel a covered entity to use or disclose protected health information.
6. The National Institutes of Health has issued a number of guidance documents to assist researchers with the HIPAA Privacy Rule. See http://privacyruleandresearch.nih.gov/.
7. See ref. 4, 45 CFR 164.514(b).
8. See ref. 4, 45 CFR 164.514(b)(1)(i) and (ii).
9. See ref. 4, 45 CFR 164.514(e).
11. For an example of the kinds of public list searches one can buy, see http://www.accurint.com/pricelz.html.
13. There are websites that provide lists of publicly available data, e.g., http://www.searchsystems.net/index.php.
15. “Each data record includes a . . . unique ID, license number, name, mailing address, practice address, birth year, birthplace, medical school, graduation year, license issuance date, license expiration date, registration status code & date, county name, gender code, and ethnicity code. Physician databases also include the degree, primary and secondary specialty, method of licensure, state/country of reciprocity, practice type code, practice setting code, and practice time code fields. . . . The complete database is produced at the beginning of every month.” http://www.tmrb.state.rr.us/consumers/products/electronicdb.php.
"You May Have Already Won....": An Examination of the Use of Lottery Payments in Research

Payment of human subjects to participate in research remains an unresolved ethical issue facing Institutional Review Boards (IRBs). Though ethical concerns over this practice have existed for many years, there are few regulatory guidelines to shape institutional and individual IRB policy.

As an added complication to the issue of compensation for research participation, occasionally IRBs receive a request to allow the use of a lottery or raffle (of money or goods) as a form of subject compensation, or as a method of encouraging participation in research. Subject participation in the lottery may occur upon enrollment in the study, or may be contingent upon compliance with the protocol and completion of the study.

In view of the lack of regulatory guidance, it should come as no surprise that there seems to be little agreement on conditions under which lotteries can be conducted. A recent informal survey conducted through the Social Psychology List Serve revealed that of the 25 responding institutions that use IRBs, 10 had few if any restrictions on lottery payments. Of these, two institutions allowed research participants to receive different odds of winning based on the extent of their participation in the study. Although the other IRBs placed restrictions on lottery payments (including avoiding the word lottery, prohibitions on advertising, and limiting payouts), no institution in this informal survey prohibited lotteries categorically.

Our IRB at the University of Nebraska Medical Center (UNMC) has occasionally been asked to determine the acceptability of lottery payments in proposed research. In one such project (which we will refer to as the book lottery), the protocol described a study to assess pediatric residents' level of knowledge about a rare but serious disease. With the cooperation of the program directors at accredited pediatric residency programs in the United States, a large number of residents would receive a letter inviting them to participate in the research and complete a short online questionnaire. It was estimated that the questionnaire would take less than 10 minutes to complete. As soon as the online questionnaire was completed, the responses would automatically be anonymized.

To "entice" pediatric residents to participate in the survey, the investigator proposed a lottery, whereby all subjects completing the questionnaire would have an equal chance of winning $1,250 worth of professional books or computer equipment. As justification for the lottery and the sum of money offered, the investigator stated "this research is highly unlikely to attract sufficient subjects unless we can offer some form of compensation to the subjects to offset the minimal inconvenience of completing an online survey." The investigator was unwilling to divide the money among all the potential participants because such an approach would "render the compensation laughable and offering no compensation will, as you know, produce too few responses."

In another study (which we will refer to as the ticket lottery), the investigators wished to conduct a survey of a health initiative on a college campus. Undergraduates would be asked to complete an anonymous online survey. The investigators had a very limited budget that would allow compensation of only 50 cents per subject. To encourage completion of the questionnaire, they proposed enrolling participants in a lottery to win two tickets to a college hockey game. The cost of these tickets was the same as the total compensation budget for the project or roughly 50 cents per subject. They argued that the cost of mailing 50 cents to each subject exceeded the value of the compensation, and that, without some compensation, participation would be so low as to endanger the validity of the study.

In both cases, because the UNMC IRB had concerns relating to fairness and the potential for undue influence, it was unwilling to approve the use of a lottery as compensation for research participation. Neither investigator

resubmitted his respective protocol from which the lottery form of compensation had been removed. In this article, we explore our IRB's analysis of the ethical implications of lottery-based compensation for human subject research and show how this analysis led to the conclusion to prohibit the use of lottery payments.

**Justice Argument: Only One Person Gets Paid**

Discussions of the principle of justice in research usually refer to either the equitable selection of subjects or equal access to participation. Both of these notions guard against the possibility of discrimination against participants based on nonrelevant features like gender, age, or socioeconomic status. Unless there is a justifiable reason for doing so, limiting research participation based on these features violates the doctrine of treating equals equally, sometimes called the "formal principle of justice." 2

In addition to having equal access to the research, participants in the study must be treated fairly. Note that to be treated "fairly" does not necessitate that subjects must be treated in exactly the same way. However, the way subjects are treated cannot be arbitrarily different. That is, one subject cannot receive compensation while others do not.

This is, in fact, what happens with lottery forms of compensation in research: one person receives a prize that others do not receive. Insofar as some participants receive goods that others do not, some would argue that this differential system of reward violates the principle of justice. The principle of justice not only requires a fair distribution of burdens and benefits to the subject; it also requires a fair distribution of goods of value.

However, justice does not require that all subjects receive the exact same compensation in a research study. For example, if participants are being compensated for travel time, and subject A travels farther than subject B, it is acceptable for the compensation to reflect this difference. Alternatively, if a subject fails to complete a study, it is acceptable to prorate the compensation to the point where s/he withdrew from participation. In these cases, the difference in the participant’s situation accounts for the differences in compensation. Without such differences, compensation should remain equal among participants.

Some argue that the compensation in studies offering a lottery is not the prize itself, but the chance to participate in the lottery. Therefore, as long as the procedure for participating in the lottery is fair, then whether the outcome is "fair" is irrelevant. As John Rawls points out, this is the situation in gambling, where as long as a series of bets were placed fairly, the distribution of cash subsequent to these bets is fair, regardless of the fact that one person is likely to end up with much more than another. 3

We contend that this analogy does not apply to using a lottery as a means to compensate subjects in research. In the gambling scenario, the purpose of the enterprise is a redistribution of wealth and therefore an equitable distribution of goods is undesirable. On the other hand, we and others 4 hold that when compensating human subjects for participating in research, the purpose is for each subject to be reimbursed for the time expended on the study. Therefore, it is not just the procedure that must be fair in this case, but the outcome as well. 5 Thus, the relevant analogy is not gambling but, say, the division of a cake, where each individual wants the largest piece possible. 6 A fair outcome is for everyone to have a piece of the same size, and procedural justice requires the development of a procedure to lead to this outcome. In dividing the cake, a relatively complex procedure (such as the first person cutting and offering the next person either the piece, or the knife for the next cut) might be required. With monetary compensation, the procedure is much easier: we simply use a calculator. 7

Finally, in order for a lottery to be fair as a means of compensating human subjects, one must believe that subjects participate for a chance to win, as that is the fairly-divided good. If, instead, subjects are participating in the belief that they will win, or because they do not understand the probability of winning (as will be discussed in detail below), the lottery payment either fails the test of justice (by paying only some subjects) or it undermines subject autonomy by inadvertently deceiving subjects.

**Informed Consent and the Perception of Lottery Payments**

In addition to concerns about equity of compensation across participants, there is a very real concern that lottery payments undermine the process of informed consent. In order for informed consent to occur, participants must correctly understand the value of a certain percentage chance of a given reward. There is considerable evidence to suggest that this is not the case.

First, consider that people routinely overestimate the
occurrence of highly memorable events. This effect, known as the availability bias, leads people to overestimate the occurrence of such events as airline crashes and nuclear accidents. Therefore, because lottery wins are considerably more memorable than lottery losses, subjects are likely to overestimate the probability of winning. This possibility is exacerbated because subjects rarely know the number of participants in a payment lottery and thus lack the necessary information to compute the odds of winning the prize. If phrased in terms that are useful to subjects (not an easy task), specifics about the number of participants and their worst bounded odds for winning might address this problem, but in practice, no one offers this information.

Kahneman and Tversky have examined a similar effect. They point out that people (in a variety of contexts) tend to overvalue opportunities to “buy” chances in lottery-type events. For instance, subjects might be asked to bid on a 1% chance to win $100. The rational value of such a chance is $1. Interestingly, although people tend to undervalue higher probability opportunities, they overvalue low probabilities (0-5%) of positive events. For instance, in the example above, people offer to pay more than the rational value (i.e., $1) of the ticket. Thus, research participants will likely overvalue the opportunity to win a lottery ticket as compensation.

One might argue that such an effect is too small to affect behavior outside the laboratory. However, we note that just such an effect can account for both state lottery purchases (where a chance typically worth 50 cents is purchased for $1.00) and lottery promotions (e.g., “You may have already won $1,000,000”). The appeal of lottery promotions to advertisers is that a one-in-a-million chance of winning $1,000,000 (a value of $1) will motivate consumer behavior more than a certain chance at $1. This difference in perception allows advertisers maximum behavioral impact with minimal investment and neatly demonstrates that subjects are likely to respond to the size of the hypothetical reward rather than the true value of a chance at that reward.

We note here that there is an emerging literature on the effects of lotteries on participation. Although these studies give some insight into the effects of payment on survey return rate, none of the studies directly compare the rational value of a lottery ticket to the same amount of cash compensation.

Alternatively, one might contend that the distortions introduced by the lottery are already inherent to many research situations. After all, any benefits that come from participation in a clinical trial are allocated probabilistically. Consider a common path to benefit: first, a participant must be randomized to the active drug. Then, the participant must be one of the fortunate subjects who benefit from the drug. If participants are unable to consent to lotteries because they may overestimate benefit, how can they consent to participate in research at all? Such an argument has merit, but we would point out that the probabilistic nature of clinical studies is unavoidable. Lotteries are not. Increasing subjects’ ability to comprehend the risks, benefits, and compensation of study participation is an ongoing task, and banning lotteries is just one small step toward achieving this goal.

Subject Autonomy: How Much Is Too Much?

The effect of lottery payments is likely to be exacerbated in cases in which the prize is large, and therefore particularly salient, and the chance of winning is small. This introduces another possible threat to subject autonomy. To the extent that the absolute value of the hypothetical award captures a subject’s attention, that reward can serve as an undue inducement to participate in the research.

Undue inducement can be a problem in any sort of study. Research participation should be based on a potential subject’s evaluation of the risks and benefits inherent to the research. Such benefits may include relief from disease, diminished symptoms, or obtaining diagnostic information. For research that does not provide a direct medical benefit, risks are generally weighed against an altruistic desire to benefit society.

It has been suggested that any payment to subjects can induce them to participate when they would not ordinarily have done so based solely on the risks and benefits of the study. To a greater or lesser extent, subjects may consider payment for their services an additional benefit of participation. In this case, risk is balanced against a health or societal benefit and against financial reward. The scale is shifted by the addition of payment. The extent of this shift increases when payments are large. Hence, subjects no longer act solely for the benefit of their health, or for altruism, but for financial reasons.

Because of this, our IRB typically limits financial inducement to subjects to $10 per hour of participation. We also encourage investigators to explain subject compensation in terms of an hourly rate, rather than listing the total compensation (e.g., “$10 for each of 25 visits”
rather than "$250”).

Undue inducement becomes particularly likely when lottery payments are used. By their very nature, lottery payments make a large compensation figure particularly noticeable. In the book lottery that we described in the introduction, the lottery was for a chance at $1,250 in books. If subjects are indeed participating because they perceive the payment as winning $1,250, instead of a chance to win $1,250 in books, then the investment of 10 minutes in a survey might be particularly attractive. However, a payment of $1,250 would vastly exceed our allowed compensation.16 This makes the book lottery case even more problematic than the ticket lottery. That is, although the ticket lottery and the book lottery suffer from the same underlying problem, the book lottery, because of the size of the potential payout and the low chance of winning, is particularly problematic.

What if There Are No Costs?

The previous arguments—that it is wrong to deceive subjects and wrong to unduly induce them to participate—are sufficient to defeat the notion of a lottery. Yet, some investigators offer a different argument in favor of lottery payments. The investigator of the book lottery made the argument that undue inducement is only a problem if participants are influenced to overlook certain costs or risks of participation that might otherwise preclude their participation.17 Since the book lottery had no attendant costs, he argued, the inducement was not a problem. We call this the “no harm, no foul” argument. Because some investigators hold this position, we think it worthwhile to discuss it.

Although all research participation requires the weighing of costs and benefits, such a calculation is more significant in some situations than others. Studies involving some treatments for serious illnesses, for example, may carry the risk of death. Yet subjects still enter these studies when they judge that the possibility of benefit (tumor shrinkage or symptom relief, perhaps) outweighs those costs.

Costs are not just limited to therapeutic protocols. In survey research investigating the adequacy of date rape counseling services, for example, costs of participation include the real chance of psychological harm subjects may experience by bringing memories of their trauma to the forefront. Yet the benefit to society from having data about their experiences may lead subjects to agree to participate despite these costs.

What about the “no harm, no foul” argument? We believe every study carries a cost: if nothing else, the time it takes to participate in the study. Moreover, we have argued elsewhere18 that risk analysis has a subjective component that only the participant can evaluate. Thus, we are concerned whenever factors extrinsic to the study influence a participant's ability to weigh risks and benefits. Even those rare instances in which we feel comfortable stipulating that the cost is negligible, the concept of participant autonomy is not a function of the potential cost of participation. That is, even if the only “cost” of participation is ten minutes of their time, subjects should be allowed to determine whether to participate based on complete information and free of any undue influence. Therefore, anything that undermines subjects’ ability to accurately weigh costs and benefits is unacceptable.

Some might argue that society accepts the practice of influencing the behavior of people through financial inducement. For example, a university might offer a starving philosophy professor a large raise to move to that institution. Yet we would argue that research participation is not governed by the same rules that govern commerce. If it were, then there would be no inherent problem in advertising research participation using celebrity endorsements, biased and subjective benefits, or appeals to emotion (e.g., don't you owe it to humanity to test this drug?). Research participation is a special activity and participants must be offered a level of fairness above and beyond (or just beyond) that accorded in commerce.

Conclusion

We have three concerns with studies that offer lotteries as the form of compensation. First, the principle of justice is violated because of the unequal distribution of something of value—namely, that only one person wins the lottery. This justice consideration applies to lotteries for large sums as well as for those with small prizes. Second, given that most people overvalue their likelihood to win a lottery, the offering of a large payment serves to undermine the process of informed consent. Because this overvaluing is greatest when chances to win are small, lotteries with large prizes and small probabilities of winning (as in the case of our book lottery) are particularly problematic. Finally, no study is entirely free of costs, and those studies with small costs ought to have correspondingly small compensation. Payment of large prizes to a very small number of participants violates this balance of subject participation.
and compensation, creating serious concerns about undue inducements to participate. For these reasons, our IRB rejects the use of payments via lottery for research participation.

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5. Note that we say “fair” here and not “equal,” as other factors may affect the actual amount of compensation (e.g., travel time and distance, etc.). Our argument contrasts pure procedural justice with perfect procedural justice. For a discussion of this distinction, please see ref. 3, Rawls 1991, p. 74-75.
7. We recognize that if the investigators in our two examples followed this procedure, the low level of compensation may have failed to attract sufficient participation in the study. While we are sympathetic to this problem, it is a separate consideration from the ethical justification of the lottery itself.
12. As an additional note, one might recall that Daniel Kahneman won the Nobel Prize in Economics for his work in this area, suggesting that economists, at least, consider these effects large enough to influence behavior in a significant manner.
15. See ref. 4, Gordon et al. 2002.
16. Note that we are not asserting that subjects are being paid $1,500 for 10 minutes work, but only that to the extent they perceive the situation that way, the amount could unduly influence subjects’ choices to participate.
17. In this case, we use the word “costs” to include all expenditures, including money, time and effort, as well as all potential harms arising from participation in the research.
Revisiting the Stored Tissue Issue

Concerns about the potential misuse of stored tissue have come to dominate debates about the moral limits of scientific pursuits. The result has been a highly adversarial environment in which researchers and other professionals in the research community find their work increasingly subject to public scrutiny.

In *The Stored Tissue Issue: Biomedical Research, Ethics, and Law in the Era of Genomic Medicine*, Robert Weir and Robert Olick examine a range of professional and lay perspectives on research involving stored human tissue. Their goal is to offer a comprehensive analysis of ethical, legal, and regulatory issues that is both "reasonably balanced" and mindful of the ethical complexities involved (p. vii). As such, the authors purposefully avoid many of the most incendiary elements that have shaped current political debates around the use of stored tissue.

In Part I the authors describe a range of potential research applications involving stored human tissues and examine sources of ongoing controversy. The historical precedents they review include well-known cases such as the *Moore* decision and the Icelandic initiative coordinated by DeCODE Genetics, as well as less familiar cases involving the use of human biological materials such as the NHANES study conducted by the U.S. Centers for Disease Control and Prevention. Readers will appreciate the rich descriptions and corresponding analyses of ethical and scientific challenges the authors provide.

Focusing mainly on the U.S., Part II describes current law and regulatory policy relating to human tissue research. Beginning with a discussion of specific federal regulatory requirements and moving to an analysis of the larger legal frameworks that govern research practices, the authors examine issues of particular interest to those involved in the oversight of research involving human subjects. While discussion of international law and policy is limited primarily to policies in Canada and Western Europe, it offers an opportunity to compare these regulations.

The final section of the book, Part III, examines lessons to be learned from recent ethical, professional, and legal debates about stored tissue research. The authors provide extensive discussion of current informed consent practices and recommend alternative strategies for addressing public worries about the use of human tissue in research. This is perhaps the most contentious section of the book. Readers familiar with the recommendations offered by the National Bioethics Advisory Commission (NBAC), for example, will be struck by the extent to which Weir and Olick's proposal reflects a far more expansive view of what respect for patient autonomy entails in the context of this research. Departing from more conventional perspectives, the authors maintain their approach will promote "greater collaboration between investigators in human tissue studies and the persons from whom those tissues come" (p. 324).

The strength of this book is its thoroughness. Although persons new to these issues might be overwhelmed by the sheer volume of information presented, those seeking a comprehensive overview of ethical and legal issues in stored tissue research will find much to explore. Because each chapter concludes with a series of cases and vignettes related to the preceding discussion, readers also have an opportunity to continue thinking through these issues in concrete terms. This aspect will make the book especially useful for teachers.

There are, however, a number of important issues not considered by Weir and Olick. For example, throughout the text the authors attempt to capture concerns expressed by research subjects by appealing to abstract ethical principles like beneficence, respect for autonomy, non-maleficence, and justice. They argue that the concerns of identifiable communities (e.g., Ashkenazi Jews, Native Americans, breast cancer support groups) "can frequently be understood, correctly, as expressions" of such principles (p. 272). A point they overlook, however, is that many identifiable groups, especially indigenous peoples, do not call for increased collaboration or procedural critiques. Rather, they challenge the nature and scope of scientific research itself, the unequal distribution of benefits, and the basic proposition that biomedical research, when conducted properly, is a boon for humanity. The widespread belief that "[a]ll of us are beneficiaries of modern biomedical research" (p. viii) operates as a normative assumption that has far-reaching implications for research involving stored tissue. However, even if we accept that biomedical research is an unequivocal social good, questions about the distribution of that benefit, both nationally and transnationally, will remain matters of considerable dispute.

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Taking a Closer Look at Research with Children

Informed consent as a protection for research participants is central to modern research ethics. Ramsey called informed consent "the canon of loyalty" and "a statement of fidelity" between a subject and the person who performs medical investigational procedures that enables them to become "joint adventurers in a common cause." Given their inability to consent, children cannot become "joint venturers" in this sense. Ramsey and others debated the inclusion of children in research, particularly when there was no prospect of medical benefit. Federal regulations in the U.S. allowing pediatric research under restricted conditions brought only a certain amount of clarity and did not resolve questions of their moral grounding, interpretation, and application. Yet until very recently, questions surrounding the ethics of pediatric research received relatively little scholarly or policy attention.

Such inattention has been problematic. Historically, pharmaceutical firms avoided the small and ethically complex pediatric market. As a result, only one-third of drugs used to treat children have been studied adequately in pediatric populations and have appropriate use information on the product label. For all the rest, information regarding safety and efficacy for use in children is either insufficient or absent. Similar ignorance remains for many surgical interventions that have not been evaluated in comparative trials with adequate statistical power. In areas other than drug or surgery research, applying pediatric ethics guidelines is also not straightforward. Health and social scientists often shy away from the challenges of certain research, particularly when it means addressing value-laden social problems concerning sexuality, drugs, racism, stigma, and so forth.

Clearly, such lack of attention is unacceptable. Pediatric patients can suffer from unpredictable adverse events, lack of drug efficacy, or even the reluctance of some physicians to use a medication outside the terms of its regulatory approval. Recent federal initiatives to increase pediatric research have shown some results, with demonstration of improved safety for children taking certain drugs. However, a general lack of investigators' experience in conducting pediatric research along with an absence of appropriate ethical guidance on the design and implementation of such trials leaves pediatric research participants at a disadvantage. When health and social science researchers shy away from value-laden research, this too creates ethical dilemmas, as vulnerable children and adolescents may be systematically and unfairly excluded from the potential benefits of participating in research. It further creates gaps in our understanding of the factors influencing disparities in the health and social status of vulnerable groups.

Most jurisdictions have recognized that research with children is appropriate. Some supporters go so far as to call it morally mandatory, lest children remain "therapeutic orphans," denied access to benefits health research has brought to adults. Regulations or guidelines have been established permitting pediatric research with restrictions on allowable risks and the necessity for parent or guardian authorization. Yet they provide no universally applicable moral compass for allowable risk or children's participation in decision-making (compare, for example, differences in 45 CFR 46, Canada's Tri-Council Policy Statement, and the Council for International Organizations of Medical Sciences Guidelines), complicating the process of deliberation in particular cases. Nor do they assist in developing the sensitivity required for research involving sick or dying children, or those with complex family situations. As a consequence, they provide insufficient guidance for Institutional Review Boards (IRBs) and researchers, causing inconsistent development, review, and approval of research protocols and studies.

In this new volume, Eric Kodish brings together a distinguished and experienced group of scholars and other experts to promote "more thoughtful attention to the complex ethical problems that arise when research involves children" (p. 4). The book is organized around chapters that begin with a case presentation, followed by discussion and a series of questions to promote further dialogue and debate. The 18 cases selected demonstrate a remarkable range of clinical scenarios and ethical difficulties involving participants from the maternal/fetal dyad to neonate, young child, and adolescent. Grouping the chapters into three categories (healthy children, at-risk children, and children with serious illness) recognizes that children, those who care for them, and those who study them frequently face different issues depending on the child's health status. Topics covered include evaluation and minimization of risk, parental permission to participate, involvement of older children in decisions, payment of children or their parents for participation, difficulties with longitudinal research, surgical innovation and nonvalidated treatment, environmental and behavioral research, disease and risk screening, justice and international research, studies involving community, and ethical issues raised by certain features of research.

study design.

Most chapters are exceptionally good. It is not possible to do justice to all of the contributions within a short review. However, the chapters selected as the opening and closing deserve mention. Both the Kodish chapter and that of Miller and Weijer make it clear from the beginning that evaluating research for potential harm and benefit is a required first step in the ethical evaluation of research to determine whether the research itself is appropriate. Issues of consent, which are important in their own right, deal for the most part with how to proceed in the ethically appropriate manner, e.g., what, when, and how to disclose, and to whom. Consent cannot make up for an inappropriate exposure to risk. Miller and Weijer’s chapter lays out very clearly a structure for evaluating research benefits and harms. Bluebond-Langner, DeCicco, and Belasco close the book with a discussion on how to involve children with life-shortening illnesses in research. They successfully weave their case presentation throughout the chapter, forming the kind of “thick” description rarely seen in discussions of research ethics. They conclude that policy involving children with life-limiting illness must be based on an individually negotiated framework that takes into account the societal realities of family life and the needs of individual families and children, which may at times conflict with regulatory requirements.

While there has been an increasing interest in research ethics within the bioethics and health care communities, there remains a great need for pediatric materials such as contained in this book. Some readers, especially non-Americans, might find the constant parsing of the U.S. regulatory language (45 CFR 46) in some of the chapters a distraction from substantive questions of whether a research protocol disadvantages participants. However, IRB members, investigators, students, and, in some cases, prospective participants or their parents will benefit greatly from materials in this book and discussions based upon them.

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2. Ramsey P. The enforcement of morals:

7. See ref. 4, Roberts et al. 2003.
8. See ref. 5, Leadbetter and Glass (in press).
UPDAtED GUIDELINES

INSTRUCTIONS FOR AUTHORS

IRB: Ethics & Human Research is a peer-reviewed journal that publishes scholarly articles and columns offering insight on issues of critical importance to research with human subjects, including findings and analyses of empirical studies. Manuscripts are typically 3,500 words, though we will review longer and shorter pieces. Word count includes text, tables, figures, references, appendices, etc. Please keep tables to a minimum. References should be to the most pertinent and up-to-date sources. Manuscripts may be placed in one of the following columns: “Insight” emphasizes theoretical and conceptual concerns; “In the Field” identifies and assesses institutional, national, and international policy developments; “Case Study” focuses on specific research studies, ethical dilemmas, and IRB policies and deliberations; “The Participant” offers personal reflections about the human research enterprise. Final decision for placement of all manuscripts resides with the editor.

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