

Protecting the Privacy of Family Members in Survey and Pedigree Research

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A FUNDAMENTAL PRINCIPLE OF CONTEMPORARY RESEARCH ethics is that research should not place individuals at risk of harm without explicit informed consent.¹ In large measure, the development of ethical standards and regulations has focused on research subjects either as autonomous individuals capable of weighing decisions about participation, or as incompetent persons for whom proxy permission and other safeguards must be satisfied to justify their inclusion in research. Ethical obligations to protect the privacy and confidentiality within the professional-patient relationship and within the investigator-subject relationship are relatively well established. However, absent from much of the discussion in research ethics is a consideration of rights and responsibilities that arise through family and social relationships. Since each of us live within a complex web of biological and social ties, decisions by and information about one person have implications for others. Obligations to protect privacy and confidentiality within family or social relationships are less well established. Further, the obligations of investigators to protect the privacy and welfare of family members and social contacts of research subjects have not been determined.

A recent controversy at Virginia Commonwealth University (VCU) highlights this complex set of ethical issues in biomedical research with families. This case exemplifies a common model of research in which individuals (the primary subjects) are contacted by an investigator and asked to provide personal health and family history information. Through contact with the primary subject alone, potentially sensitive information about family members (or other social contacts) can be acquired by investigators. Informed consent typically is obtained from the primary subject but personal data often are retained on family members or social contacts of the primary subject without their consent.

The VCU case involved an adult woman who was being recruited to participate in a twin study.^{2,3} Her father read a mailed survey instrument that included questions about the health of her parents and other family members. The questionnaire reportedly asked, among many other items, whether the subject's father suffered from depression and whether he had abnormal genitalia. The father was concerned that providing this information constituted a threat to personal and family privacy and that informed consent should have been

The recent controversy at Virginia Commonwealth University involving research ethics raises important and complex issues in survey and pedigree research. The primary questions are whether family members of survey respondents themselves become subjects of the project and if they are subjects whether informed consent must be obtained for investigators to retain private information on these individuals. This article provides an analysis of the ethical issues and regulatory standards involved in this debate for consideration by investigators and institutional review boards. The analysis suggests that strong protections for the rights and welfare of subjects and their family members can be incorporated into survey and pedigree research protocols without hindering projects with extensive consent requirements.

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sought from family members. The father contacted the National Institutes of Health's Office for Protection from Research Risks (OPRR; now the Office for Human Research Protections), which ruled that the VCU institutional review board (IRB) should have considered whether family members were human subjects of this research by virtue of their relationship to the respondent and the nature of the family information obtained from the respondent. After review of the IRB procedures, the OPRR and the Food and Drug Administration suspended human subject research at VCU stating that the IRB had inadequately documented its monitoring of research protocols.³ The VCU case forces consideration of the broader question of whether family members of the primary subject become research subjects themselves (secondary subjects) and if informed consent is necessary from secondary subjects to retain their information. Clearly these are not new circumstances, but they raise a set of ethical issues that have not been adequately addressed to date.

The IRB review of research protocols in this regard involves 2 levels of analysis. First, determine whether family members should be deemed human subjects of the research. Second, if family members are deemed human subjects, when

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must informed consent be sought for the retention of private information? This discussion will focus on family members as potential secondary subjects; however, the issues are identical in research protocols that seek information from one individual regarding any others about whom private information might be known, such as coworkers, patients, significant others, students, etc. Ultimately, it is individual IRBs that are responsible for interpreting federal guidelines in the context of each research proposal. The following analysis is offered for consideration by investigators and IRBs in their development and review of protocols.

Human Subjects

Federal departments or agencies that conduct or support research with human subjects adhere to a set of federal regulations termed the *Common Federal Rule*.⁴ The following is the definition of human subjects in the Common Rule:

Human subject means a living individual about whom an investigator (whether professional or student) conducting research obtains (1) data through intervention or interaction with the individual, or (2) identifiable private information. . . . Private information must be individually identifiable (ie, the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects.⁵

Individuals who are not human subjects under this definition are not protected under regulations embodied in the Common Rule. This definition highlights an important compromise that has been struck in contemporary ethical standards for research. In brief, the standards do not recognize a right of individuals to control all personal information. Not all individuals about whom information is obtained are considered human subjects and, as discussed below, not all information obtained in research requires consent of the individual. The standards focus on protecting individuals from harm during research, and ensuring that consent is obtained if modest risks are posed, rather than ensuring that individuals are afforded absolute privacy and control over all personal information. A breach in privacy is not considered a harm per se, rather it is the risk of harm that may result from a breach that is the relevant consideration. Therefore, the standards represent an attempt to balance risk conferred by potential breaches in privacy with the social benefits of health research.

The first challenge for investigators and IRBs is to decide under what circumstances family members should be considered human subjects using this definition. (It should be noted that family members who are deceased are not human subjects. Therefore, information about deceased individuals can be retained without the consent of surviving family members.) Two terms in the regulations require further analysis in this context. First, an interpretation of “individually identifiable” is important since only individuals whose identity can be readily ascertained by the investigator are considered human subjects. Second, an interpretation of what constitutes private information will be important since the

acquisition of public information (assuming information is either public or private) does not make the individual a research subject for the purposes of the Common Rule. In summary, family members qualify as human subjects if they are readily identifiable and if the information obtained in the research is private information.

Readily Identifiable Individuals

If unique individual identifiers are being obtained on family members from the primary subject, then family members are readily identifiable. In contrast, family members would not be readily identifiable in at least 2 circumstances. First, if the primary subject is anonymous and if no unique identifiers are obtained for family members. Second, the family data are rendered anonymous by unlinking them from an identifiable source. If the investigators primarily are seeking epidemiologic information, then rendering the primary subject or family data anonymous may be feasible without limiting the productivity of the research. However, if family data are being obtained to identify “interesting families” for subsequent detailed evaluation, then anonymous primary subjects are of limited value.

It should be noted that if the primary subjects are anonymous, then the project may be exempt from IRB review entirely. Under the Common Rule, exemptions from IRB review include research projects in which the subjects cannot be identified and disclosure of the subject data would not place the subject at risk for legal action or social discrimination.⁶

If the primary subject is not anonymous or if the family data are linked to an identifiable primary subject, then the identifiability of family members becomes the key issue. The question is whether family members can be readily identified from simply knowing the identity of the primary subject and the family relationship involved. In most circumstances, a family relationship alone is a poor lead for identifying relatives. Surnames are often widely shared in the population, names of women typically change through marriage, and family members often are geographically dispersed. For example, knowledge by investigators that a subject has 2 brothers and 2 living parents would provide virtually no information on the identities of these family members, even if investigators had detailed medical histories on these individuals. Unless the investigators were provided specific identifiers such as names, addresses, a unique job description, or Social Security numbers, family members would be virtually impossible to identify with any degree of certainty. (In some sense, we might say that John Brown’s mother is a unique identifier, but absent the additional knowledge that John Brown’s mother is a specific Lisa Brown, Lisa is likely to be safe from stigma or discrimination from information provided by John about his mother.)

The VCU case was somewhat atypical in that the primary subject was an adult single woman living with her parents. The research project in question did not ask the primary subjects for unique identifiers for family members. Neverthe-

less, the father was considered identifiable by the OPRR and by the father himself, presumably because he shared the same last name, address, and phone number of the primary subject. However, if she had been married (using her husband's family name) and/or living out of the home, her father would not have been readily identifiable without additional personal identifiers. Indeed, unless the survey instrument in this case established that the daughter was living with her parents, it is highly questionable whether the identity of the father could have been ascertainable by the investigators.

In general, family members of adult individuals are not readily identifiable to third parties based on family relationship alone. This is particularly true for second- and third-degree relatives of the primary subject. It is important to emphasize that the regulations clearly state that individuals must be readily identifiable to the investigator, so that it is not relevant that specific family members are readily identifiable to other family members based on family relationship alone, or to individuals who have a social relationship with the family. However, identifiability to the investigator is a concern in the unusual circumstance in which the investigator shares a social relationship with the family under investigation. In addition, surveys addressing rare diseases conducted by investigators who are familiar with many or all individual cases within the target region may lead to family member identification through creation of a unique pattern of data elements. For example, a combination of age, race, and rare diagnosis might identify a family member to an investigator who provides clinical care to regional patients with the disease in question. Finally, subjects who are well-known public figures may pose similar problems with respect to the identifiability of family members. Investigators and IRBs should be alert to these unusual circumstances in the development of survey research protocols.

In summary, family members of primary subjects are readily identifiable when the primary subjects provide investigators with names or other unique identifiers of family members. Family members of primary subjects are not identifiable if the primary subject is anonymous or if research data are not linked to the identity of the source. The problematic situation is when the primary subject provides health or personal information on family members who are identified by their relationship alone to the primary subject. In general, it is reasonable for IRBs to consider family members as not "readily identifiable" in this circumstance. Even when the IRB considers some first-degree relatives to be readily identifiable, it may be appropriate to consider second- and third-degree relatives as not identifiable, depending on the nature of the data.

Private Information

The regulations require that information on an identifiable individual obtained in research be private for the individual to be considered a research subject. The Common Rule does not provide a relevant definition of private information. Le Bris

and Knoppers⁷ observe that ". . . although privacy is a commonly used and frequently invoked concept, it is multifaceted, fluid, and evolving." One consistent aspect of informational privacy is the idea that people want substantial personal control over information they consider private.⁸ One purpose of control is to limit access to the information by others who might use it to adversely affect our interests. In contrast, personal information to which others have easy access must be considered public information. For example, casual social contacts, such as many friends, neighbors, coworkers, members of the same church, know a basic set of information about an individual. This includes their approximate age, body build, marital status, family structure, race, cultural background, and occupation. These are elements of personal information that we usually cannot conceal as we engage in normal social interactions. In contrast, personal information that is generated or shared in intimate relationships between individuals typically would be considered private. A relationship with a physician, a counselor, an attorney, an employer, or a teacher involves personal information over which most individuals want and can exert control. Of course, it is the standard of confidentiality in each of these social interactions that enables this control. Therefore, private information is personal information over which individuals typically want and can exert control.

In its statement to members regarding the VCU case, the American Society of Human Genetics raised questions about whether information on relatives obtained from primary subjects should be considered private.⁹ The American Society of Human Genetics statement suggests that health information is not strictly private if it is known by family members, and that second-hand information can be considered hearsay in some circumstances. *Hearsay* is defined in Webster's dictionary as "unverified information acquired from another; rumor."¹⁰ These potential objections to the private nature of health information are not convincing. There are different spheres of privacy and a decision to share information with close friends and relatives does not imply a willingness to share information more broadly. While standards of confidentiality in family relationships are ambiguous, the sharing of health information between a father and daughter should not make it fair game for investigators at the medical center. Second, although second-hand information may not be considered sufficiently reliable in some legal, clinical, and research contexts, presumably it is sought by investigators from primary subjects only if it has sufficient validity to be useful for the research. It would be disingenuous for investigators to claim that they should be able to obtain information on family members without consent because the information lacks validity. In any case, many secondary subjects would be equally concerned about research that systematically acquired misinformation on family members. In summary, most information about the health status of relatives of the primary subject should be considered private information.

Waiver of Consent

A primary concern of many investigators following the OPRR's interpretation of the VCU case is that they will be required to obtain informed consent from numerous family members for the retention of their information. This potential obligation is viewed as time-consuming and expensive and a hindrance to valuable research if family members cannot be located or refuse to participate. As noted, the first threshold for the IRB is to determine whether family members are human subjects. If family members are subjects, then a determination must be made whether informed consent can be waived. There are 4 requirements for the waiver of consent listed in the regulations. All of the following criteria must be satisfied: (1) the research involves no more than minimal risk to the subjects; (2) the waiver or alteration will not adversely affect the rights and welfare of the subjects; (3) the research could not practically be carried out without the waiver or alteration; and (4) whenever appropriate, the subjects will be provided with additional pertinent information after participation. Of particular concern for this discussion are points 1 and 3.

Minimal Risk

With respect to the concept of minimal risk, the regulations stipulate:

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.¹¹

If the investigators are seeking a waiver of informed consent for secondary subjects, the IRB must consider whether the risks posed to secondary subjects in research exceed the threshold of minimal risk. Many IRBs may consider virtually all survey research to be of minimal risk. However, advances in genetic research in particular have raised broad concerns about stigma and discrimination, primarily in the arenas of insurance and employment.¹² These risks arise from the creation or transfer of genetic information per se and not from physical interventions. Concerns are most prominent in situations in which healthy individuals are found to have an increased risk of future illness based on the results of a genetic test. In these situations, the generation of new health information through a research project places the individual at risk if there is a breach in privacy or confidentiality. Individuals who are currently affected with genetic or nongenetic health conditions also are at risk for stigma and discrimination. However, a research project that merely records existing health information only poses a risk if the project leads to disclosure of sensitive information to those who did not know it already and who are in a position to harm the subject. Therefore, research projects that generate new health information are much more likely to confer risk than projects that simply document existing health information. In the context of survey research, health information on secondary subjects

obtained from the primary subject is by definition existing information. Therefore the question for the IRB is whether the documentation of existing health or personal information through a research project poses greater than minimal risk to secondary subjects.

Judgments concerning minimal risk require an assessment of both the likelihood of harm and the magnitude of harm involved. Likelihood in this context is the probability that a breach of privacy will occur combined with the probability that the breach will lead to adverse events. The research protocol must outline the measures to be taken to protect the integrity of the research data.¹³ Such measures may include unlinking the data from individual identifiers, securing the data physically and electronically, and developing protocols for access to individually identifiable data. The investigators and the IRB should make every effort to ensure that the risk of a breach of privacy is extremely small.

The magnitude of the harm resulting from a breach in privacy for secondary subjects will depend on the nature of the information and on the relationship of the subject to the person who inappropriately receives private information. Fortunately, access to research data on secondary subjects by insurers or employers is highly unlikely. In family-based research, inappropriate disclosure of private information within the family itself is a breach more likely to produce adverse consequences from the perspective of the subject. Privacy within the family or within one's intimate social sphere is often much more important than protecting information from disclosures to unknown third parties.¹⁴ Therefore, investigators and IRBs must be particularly alert to protocol features that might allow histories obtained from one family member to be shared with other family members.

An IRB must make a determination about minimal risk based on the security of the data and on the general sensitivity of the information being obtained in the research protocol. Fortunately, in contemporary society, common diagnoses such as cancer, diabetes, and arthritis are in general no longer considered highly sensitive conditions. In contrast, conditions with a behavioral or psychiatric component, such as alcoholism or schizophrenia, remain stigmatizing. Other personal traits, or aspects of personal history that are not strictly health-related, also may be stigmatizing, including sexual orientation, reproductive history such as abortions, and criminal records. This interpretation of the relative sensitivity of different types of information is consistent with federal policy regarding issuance of certificates of confidentiality.¹⁵ It may be appropriate for an IRB to consider protocols to be greater than minimal risk for secondary subjects when the family history pursued includes such highly sensitive information. In contrast, IRBs may consider protocols to be of less than minimal risk when the family history includes only information about existing health conditions of low or moderate sensitivity, such as heart disease, cancer, or diabetes, and when strong data security measures are in place.

Table. Recommendations for Investigators and Institutional Review Boards Regarding Privacy of Family Members in Research

- I. Are the family members human subjects?**
- A. Are family members readily identifiable by the investigators?
- Yes, if unique identifiers are associated with individual data of primary subjects and their family members.
 - No, if the primary subject and family members are anonymous.
 - No, if data on family members are unlinked from the unique individual identifiers of the primary subject.
 - No, in most circumstances, if family members are linked by family relationship alone to an identifiable primary subject.
- B. Does the information obtained from the primary subject about family members constitute private information?
- Yes, if the information consists of health status, health history, reproductive history, behavior history, etc.
 - No, if the information consists only of the family relationship and commonly available personal data such as age, race, or occupation.
- Responding yes for items IA and for IB means the individual is a human subject. Responding no for either item IA or IB means the individual is not a human subject.*
- II. If family members are human subjects, can informed consent be waived?**
- A. Does the research involve more than minimal risk?
- Yes, if the information obtained is highly sensitive such as psychiatric history, sexual orientation, criminal history, etc.
 - Yes, if strong data security measures have not been prepared and the information is considered sensitive or highly sensitive.
 - No, if the information obtained on family members is not highly sensitive and strong data security measures are detailed in the proposal.
- B. Does the waiver adversely affect the rights and welfare of the subjects?
- C. Can the research be practically carried out without the waiver?
- D. When appropriate, can the secondary subjects be provided pertinent information after the completion of the research?
- Responding no for items IIA, IIB, and IIC and yes for section IID means that informed consent can be waived for secondary subjects.*

Practicality of Research Without a Waiver

The third criterion for waiver of consent states that the research could not practically be carried out without the waiver. The practicability of obtaining consent from secondary subjects may be an important point for discussion by the IRB. In some studies involving the analysis of data obtained in the past, it may not be feasible to track down large numbers of subjects years hence. In the context under discussion, however, the primary issue is whether it is feasible to obtain consent when data are being acquired prospectively on families. As noted, obtaining consent from widely dispersed family members may be labor-intensive and thus time-consuming and expensive. For projects that have not anticipated this requirement, these additional burdens may be prohibitive. However, this does not mean the research cannot be practically carried out without the waiver, only perhaps that the current project is insufficiently funded or organized to obtain the necessary consent. Insufficient organization or funding of a research project is not a valid justification for forgoing appropriate human subject protections. The key question for the IRB is whether an important avenue of research would be essentially blocked without the ability to waive consent. In the aftermath of the VCU case and its interpretation, investigators must anticipate the demands of their IRB in this regard and apply for sufficient funding to obtain consent from secondary subjects when necessary.

In parallel, funding organizations should expect investigators to detail measures and costs for human subject protections and to adequately fund these aspects of research projects.

Conclusions and Recommendations

The TABLE lists recommendations that investigators and IRBs should consider in the conduct of research in which primary subjects are asked for information on family members or social contacts.

It should be noted that this conceptual analysis hinges on an interpretation of current regulations and ethical standards, neither of which were written with consideration for these issues. More importantly, there are no data available from research participants and their family members or social contacts to guide the development of policy in this arena. This may be a valuable and productive area for research.

There can be no question that the issues raised by the VCU case are legitimate and complex. The interests of secondary subjects warrant careful attention and protection by investigators, IRBs, and funding agencies. The burden and expense of these protections are not justifications for forgoing these efforts. However, this analysis suggests that it is justifiable to proceed with research without the explicit consent of family members for many research protocols that meet the criteria outlined above.

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