Institutional Review Board Approaches to the Incidental Findings Problem

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With rapidly expanding technological capacity, research has outpaced the existing infrastructure of ethical and regulatory guidance. In the area of incidental findings (IFs), this is particularly true.

The regulations under which most Institutional Review Boards (IRBs) operate were established over 25 years ago and have not been substantially altered in the intervening years.[1] The technology available today that creates the opportunity for IFs was not conceived of, or considered, in the crafting of those regulations. Therefore, little guidance can be derived directly from these regulations. Rather, aspects of existing ethical guidance and regulations can be adapted to assist IRBs and researchers in dealing with issues surrounding IFs.

IRBs are obliged to ensure that researchers have plans in place to protect the rights and welfare of human research subjects. This requirement is embodied in the ethical principles outlined in the *Belmont Report*.[2] This document is the cornerstone of most IRB decisions and directives to researchers because it outlines the basic ethical principles governing the acceptable conduct of human subjects research. These principles are widely applied and discussed in the literature and practice of IRBs: they are respect for persons, beneficence, and justice.

An often overlooked aspect of the *Belmont Report*, however, is the distinction it draws between therapy and research. This distinction is especially pertinent to the discussion of IFs and IRBs. In research, there is no guarantee of benefit to the subject, whereas in treatment encounters, the patient has an expectation of benefit. Researchers are specifically cautioned by IRBs to draw this distinction carefully for their subjects who are not patients in order to avoid the therapeutic misconception. The therapeutic misconception suggests that individual direct benefit will be derived from participation in a research study. These lines are further blurred when a patient is offered an opportunity to participate (i.e., to be a subject) in a research study. In genetic and imaging research, either scenario could exist — patients as subjects or healthy volunteers as subjects. The IRB's consideration of IFs may be influenced by the type of subject involved and

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by the nature of the researcher's interaction with the subjects.

Compelled by the principle of respect for persons, suggesting that individuals have rights to true and continuing informed consent, IRBs are faced with a quandary concerning what to do with information about IFs. The questions of what to tell subjects, when to tell them, who should convey the information, in what form the information should be communicated or retained in a record, and under what circumstances the information should be withheld are unaddressed in existing IRB ethical guidelines and regulations. Consequently, IRBs are left to grapple with these questions unaided.

Another challenge emanates from the *Belmont* principles of beneficence. IRBs and researchers are expected to assess the relationship between risks and benefits of participation in research and assure that risks have been minimized to the extent possible, that benefits have been maximized, and that the research will yield sufficient knowledge to justify the exposure to risk.

In research involving children, the regulations are more stringent in that there is an expectation of direct individual benefit accruing to the child in research involving greater than minimal risk.[3] Questions of what to tell parents about IFs, what to tell children, and when the possibility of IFs should be factored into IRB consideration of risk and benefit are all difficult for an IRB to navigate.

IRBs must determine whether IFs pose a risk or present a potential benefit to the subject. In considering risk, an IRB generally considers immediate harm — the probability and magnitude of the risk. The IRB typically considers risk as a result of procedures performed in the course of the research participation, rather than risks or benefits derived from the results of those procedures.

Benefits can be perceived as immediate or long term. An attempt to subjectively calculate risks and benefits is one of the significant challenges for an IRB. There may be considerable discussion in the IRB about whether it is beneficial or harmful to disclose IFs to research subjects. In some instances, the IF may reveal a condition that poses an immediate danger to the subject as in an imaging study that reveals a heretofore undiagnosed tumor. In other instances, such as in some genetic studies, a finding may be anomalous but be of uncertain risk or lacking potential for intervention. The question for the IRB is who decides whether the IF should be disclosed to the research subject and what information should be conveyed?

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> The regulations require a consideration of risks but not long-range effects:
> In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.[4]

Some might argue that the admonition not to consider long-range effects of applying knowledge gained in research to the risk/benefit evaluation suggests that IRBs should not play a role in arbitrating disclosure of IFs. Others might argue that the authors of the regulations were trying to control the impact of political considerations on research, by not controlling the handling of findings pertaining to individuals.

The third ethical principle outlined in the *Belmont Report* is justice, in the sense of distributive justice. This principle suggests that the benefits and burdens of research should be distributed in the population in fair and equitable ways. Consideration of the equal treatment of subjects with respect to what information is imparted may be a factor in IRB consideration. Does the researcher tell some subjects about IFs and not others? Is a uniform standard acceptable, or should individual cases be considered?

The ethical principles outlined in the *Belmont Report* intertwine and cannot be considered in isolation from

one another, and in IRB practice, cannot be separated from the regulations that support the principles.

The compelling principle of respect for persons, from which the mandate for informed consent emanates, requires disclosure of all material information to study subjects. In particular, the regulations require that new information developed during the course of the research be shared with the subjects so the subject may consider whether to continue participation or withdraw from the study. The new-information mandate specifically states that the consent process and form must include the following: "A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject."[5] This requirement suggests that IRBs should consider what the probability of an IF is in a particular study, and should create a plan for identifying the IF and communicating significant findings to the subjects. Yet it is unclear whether the responsibility to determine "significance" rests with the researcher or with the IRB. It implies that the information would be considered important to the subject or to the subject's consideration whether to continue in a study. In many cases, the IF may not be discovered until after participation in a study has ended. In imaging studies, particularly those involving healthy normal volunteers, an image may be obtained and not analyzed for some time.

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IRBs must also consider how the IF will be analyzed and by whom. Images require expert interpretation and clinical analysis to determine their importance. Then the concern arises about who performs the analysis, and under what circumstances the IF is disclosed. In genetic studies, trained genetic counselors, who have the skills necessary to impart delicate news to subjects, would be required to fulfill the mandate of respect for persons.

Another area of the regulations which suggests that IRBs have a role in managing IFs is the area of "unanticipated problems."[6] An important distinction exists between adverse events — harms caused by research procedures, medications, or research interventions — and IFs. Incidental findings are not caused by the research intervention, but are identified during the course of research involvement, either in the immediate, or during data analysis. Recent regulatory guidance from the Office for Protection from Research Risks (OHRP) provides the following definition of "unanticipated problems":

> The phrase unanticipated problems involving risks to subjects or others is found but not defined in the HHS regulations at 45 CFR part 46. OHRP considers *unanticipated problems*, in general, to include any incident, experience, or outcome that meets **all** of the following criteria:
> (1) unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied; (2) related or possibly related to participation in the research (in this guidance document, *possibly related* means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and (3) suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.[7]

If IRBs and researchers do not anticipate IFs and plan for their management, then one could interpret them in accord with the unanticipated-problem regulation and be required by federal agency agreements to report these IFs to the institutional official, regulatory, and funding agencies.[8] In fact, that reporting requirement is separate and apart from considerations about whether to inform subjects of the IF.

Also providing some assistance to IRBs and researchers is the regulatory requirement for a process of informed consent. The provision indicates that IRBs have broad discretion to require information in the process of informed consent and in the consent form, in addition to that information required by regulation, to ensure that subjects are fully informed.[9]

The limits of ethical and regulatory guidance leave IRBs and researchers with several unaddressed areas. IRBs should develop guidance in the areas of research where an IF may occur. IRBs should give consideration to addressing several issues when developing that framework.

IRBs will struggle with questions concerning what is "unanticipated." If the general population has known incidence of tumor, is it also expected then that the same relative percentage of the study population would be similarly afflicted, so that researchers may argue that the tumor is not "unexpected" and the researcher should have no special obligation?

If an IF is of unknown importance, as opposed to a clearly diagnosable and treatable condition, do the informing and reporting obligations change?

What are the expectations of study subjects with respect to information gleaned during research procedures? If researchers go to great lengths to tell subjects what they will not disclose, are subjects going to be, or feel, deceived?

Mere disclosure of findings may be considered insufficient. Implications of findings and action plans may be expected by IRBs or subjects. Cost factors and duration of obligation to the subject follow from disclosure. Candor in the consent process — i.e., avoiding use of seemingly prohibited language, such as exculpatory language that appears to waive rights — is essential in research where IFs may be identified.

Time parameters should be considered. Some samples and images are retained for long periods of time. If an IF is discovered some time distant from subject participation, is it acceptable and feasible to go back to the subject? Who does that detective work, who pays for it, and what are the limitations on effort to find past subjects? Is there harm in a surprise contact from a researcher some months or years after participation?

Are there group or community interests involved, as in genetic studies which often have implications for persons not tested or in studies? How are those aspects to be factored into researcher or IRB consideration?

Researchers working in genetics/genomics and imaging areas should consider IFs and work collaboratively with IRBs to develop mechanisms for determining when and how they should effectively communicate findings with subjects. IRBs must be willing to exercise all flexibility allowed in regulation and guidance to foster strong collaborative relationships with researchers working in novel areas that are unaddressed by existing regulations.

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References

1. Expectations that all drugs entering the U.S. marketplace be tested in humans were established in the mid-1960s. The federal regulations requiring that all federally funded research be reviewed by Institutional Review Boards (IRBs) followed slowly in 1974. The current set of regulations was established in 1983, with only minor revisions in content since that time. For a historical timeline of the evolution of the regulations, see "Historical Resources: Timeline of Laws Related to the Protection of Human Subjects," compiled by Joel Sparks, June 2002, *available at* <http://history.nih.gov/01docs/historical/2020b.htm> (last visited February 19, 2008).
2. *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research* was a product of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research and was presented on April 18, 1979. Still widely quoted and applied, it is considered to be the cornerstone document for modern human subjects' protections. It can be found at <http://ohsr.od.nih.gov/guidelines/belmont.html> (last visited February 19, 2008).
3. The federal regulations in Subpart D of 45 C.F.R. 46 state the requirements for direct benefit to children participating in research. The regulations outline specific requirements for IRB determinations and documentation, specific requirements for parental permission, minor assent, and waivers of consent. Regulations can be found at <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm> (last visited February 19, 2008).
4. 45 C.F.R. § 46.111 (a) (2), *available at* <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#46.111> (last visited February 19, 2008).
5. 45 C.F.R. § 46.116 (b) (5), *available at* <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#46.111> (last visited February 19, 2008).
6. 45 C.F.R. § 46.103 (b) (5), *available at* <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#46.103> (last visited February 19, 2008).
7. As recently as January 2007, the Office for Human Research Protection (OHRP) has issued guidance and interpretation of the regulations pertaining to unanticipated problems. Entitled *Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events*, this document distinguishes the requirements for adverse event reporting from other problems requiring reporting in a research context. It can be found at <http://www.hhs.gov/ohrp/policy/AdvEvntGuid.htm> (last visited February 19, 2008). (Emphasis added.)
8. See *supra* note 6.
9. See *supra* note 5. The IRB may require that information, in addition to that specifically mentioned in § 46.116, be given to the subjects when, in the IRB's judgment, the information would meaningfully add to the protection of the rights and welfare of subjects.