IRBs and the Ethical Conduct of Human Research

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Both the FDA regulations[1] and the Common Rule[2] require institutional review board (IRB) review of much human research. Each stipulates overlapping though not identical requirements for IRB approval.[3] For IRBs to approve research, the Common Rule requires that risks to participants be minimized and that risks be reasonable relative to the expected benefits of the study, that participant selection will be equitable, that informed consent will be sought and documented when required by the regulations, that plans are made to protect subject safety, that privacy and confidentiality of data will be maintained, and that additional safeguards will be employed when some or all participants may be vulnerable.[4]

Numerous shortcomings of the oversight system have been identified.[5] One criticism is that IRBs do not give sufficient attention to major ethical issues in human research and attend too heavily to procedural compliance and documentation. One possible way to address this problem is for IRBs to incorporate explicitly into the review process consideration of ethical principles governing human research, the requirements that flow from the principles, and the ways in which the requirements for the ethical conduct of research are interrelated.

The ethical principles that gave rise to the regulations governing human research in the U.S. are outlined in the *Belmont Report:* respect for persons, beneficence, and justice.[6] The *Belmont Report* outlines some of the specific requirements for the ethical conduct of research that these principles engender, such as the obligation to obtain informed consent, to ensure that a study's benefits exceed its risks, and to select subjects fairly. Ezekiel Emanuel, David Wendler, and Christine Grady examined not only the *Belmont Report* but other documents pertinent to the ethical conduct of research, such as the Declaration of Helsinki[7] and the International Ethical Guidelines for Biomedical Research Involving Human Subjects[8] in order to identify requirements for the ethical conduct of research.[9] They identified seven requirements that can inform the work of IRBs:

— a study must have social or scientific value;
— a study must be scientifically valid;
— investigators must have a plan to ensure that subjects will be selected fairly;
— a study must have a favorable risk-benefit ratio;
— a study must be reviewed independently;
—informed consent must be obtained; and
— respect must be shown for potential and enrolled subjects.[10]

Additional ethical principles and guidelines can and should inform the work of IRBs in Roman Catholic health care organizations, such as those outlined in the *Ethical and Religious Directives for Catholic Health Care Services* (ERDs).[11] For example, the IRB may consider whether the *Ethical and Religious Directives* provide any guidance concerning research practices in general or how the ERDs relate to a particular study.

IRBs seeking to consider more explicitly ethical issues in their review of proposed research may use Emanuel et al's framework of seven requirements and the ERDs to guide their review and ensure that research conducted within the institution is consistent with the general ethical requirements for research and with the organization's mission as a Catholic institution. IRBs can ask how proposed practices align with all the various requirements, as discussed in examples below. Explicit attention to the ethical requirements that should guide human research can promote thoughtful reflection and allow IRBs to consider research practices in a broader context. Research practices often have more than one consequence and may have implications for various obligations. As a result, the ethical requirements should not be considered in isolation, yet this can happen easily when we think of research practices as connected only to specific requirements and we fail to consider the ways in which one practice may affect multiple principles. There is an obligation to honor all the requirements governing

human research, and attempts to fulfill one requirement might compromise fulfillment of another requirement. At times, efforts must be made to "juggle" obligations and find the approach that best respects all the relevant requirements. In reviewing protocols in light of specific ethical requirements, IRBs can avoid narrow reviews that treat the ethical conduct of research in a piecemeal fashion.

Consider the following examples. Some IRBs, when a potential participant is not proficient in English, routinely disallow investigators from using the provision at 45 CFR 46.117.b.2 that would allow them to give a short consent form written in a potential participant's native language and use an interpreter to translate verbally most of the information in a standard consent form. The short-form-consent-process typically is used when an investigator anticipates very small enrollment of persons who speak a language other than English. IRBs that disallow this practice altogether may believe that use of the standard informed consent document is essential to ensuring that a participant made an informed choice and to fulfilling the obligation to obtain informed consent. It may be useful to review such proposals in light of the possibility that the obligation to obtain informed consent may be fulfilled in more than one way and that other ethical requirements may be short-changed if short-form-written-consent with verbal translation is prohibited in all or almost all cases. Other requirements that may be adversely affected include fair subject selection (because some are denied the opportunity to participate in research and some bear a greater participation burden) and social or scientific value (because results may not be generalizable to some populations).

The Common Rule requires that subjects not be coerced or unduly influenced to participate in research.[12] Both are aspects of fulfilling the principle of respect for persons, which requires the free and voluntary informed consent of most participants. The definitions of coercion and undue influence found in the *Belmont Report* often inform discussion of these obligations:

Coercion occurs when an overt threat of harm is intentionally presented by one person to another in order to obtain compliance. Undue influence, by contrast, occurs through an offer of an excessive, unwarranted, inappropriate or improper reward or other overture in order to obtain compliance.[13]

Coercion can be avoided by ensuring that persons are not threatened with loss of otherwise-available services and benefits if they choose not to participate in a study or withdraw from a study early. Undue influence has been explained in terms of irresistible offers[14] or offers that lead potential subjects to be unable or unwilling to judge risks and benefits of participation.[15] In practice, the obligation to avoid undue influence often is interpreted as requiring that subjects not be paid[16] or that payments be modest.[17] Unfortunately, decisions about how much money is too much typically are based on IRB members' instincts or reactions rather than data. Few studies have examined the role of payments in research participation decisions.[18] We know very little about how different people respond to different offers, at what point offers become irresistible or when offers render people unable or unwilling to judge a study's risks.

When decisions about whether payments to subjects are appropriate and, if so, what level of payment is appropriate, are made primarily with the aim of avoiding undue influence so as to obtain free and voluntary informed consent, other important ethical obligations may be compromised. Decisions about payments should be informed not only by the requirement to obtain free and voluntary informed consent but, for example, by the obligation to ensure that a study is scientifically valid as well as scientifically or socially valuable, and that there is fair subject selection. It is possible that by keeping payments low, investigators will be unable to recruit or retain a sufficient number of subjects to make the study scientifically valid. Or, it may be that there will be a disproportionate number of people enrolled from lower socioeconomic groups, raising questions about generalizability (social and scientific value) and fair subject selection. There are multiple obligations that can be considered in evaluating a payment plan, and IRBs can avoid conducting ethically narrow reviews by asking about the implications of proposed payment structures for all of these ethical requirements rather than focusing only on the one that seems pertinent (informed consent).

Completion bonuses sometimes are controversial because some people believe that research participants might feel that they must remain in a study from which they would prefer to withdraw. Thus, there has been an emphasis on prorating payments during the course of studies that extend beyond one or two visits to avoid unduly influencing

subjects to continue their participation, i.e., to ensure that subjects feel free to leave knowing that they will be compensated for the time they did spend in a study.[19] Because informed consent reflects an ongoing willingness to participate and not an isolated event that occurs at the time of enrollment, this view reflects a concern with fulfilling the requirement of free and voluntary informed consent by avoiding undue influence. Even if payments are prorated, there may be justification for prorating them unequally during the study and for offering a completion bonus. The permissibility of completion bonuses should be evaluated not only through the lens of avoiding undue influence but in light of other requirements for the ethical conduct of research. A completion bonus may serve not only as a means of recognizing the value of contributions made by subjects who remain in a study for its entire duration, but as a means of retaining subjects throughout a study, which is essential to ensuring the validity and value of a study. This may be especially important for studies that seek long-term follow-up (see, e.g., Festinger et al 2005). Long-term follow-up of subjects can yield important information that increases the overall benefits of a study and that, in some cases, is important for judging the interventions tested or for ensuring subject safety. Studies that are not valid because, for example, they did not enroll and retain a sufficient number of subjects, lack social and scientific value and are ethically problematic. In such studies, subjects are exposed to risks and burdens without compensating social and scientific benefit. The possibility of a failure to retain subjects and the implications this has for the ethical conduct of research should be considered as part of evaluating payment plans. The focus should not be solely on avoiding undue influence as if that were the only ethical requirement relevant to evaluation of payment plans.

IRBs can conscientiously incorporate consideration of all the requirements for the ethical conduct of research into their reviews, asking how particular practices relate to the various ethical principles. In doing so, they can avoid conducting research reviews that focus too narrowly on the way a practice affects a single ethical principle and attend to the full set of obligations for the ethical conduct of research. This is important because sometimes practices that seem to promote ethical behavior because they are compatible with one principle may undermine other obligations. IRBs can go beyond their regulatory functions and promote the ethical conduct of human research by explicitly incorporating consideration of ethical principles in their reviews. ■

NOTES

1. 21 CFR 50 and 21 CFR 56
2. 45 CFR 46
3. U.S. Food and Drug Administration. 2000. Comparison of FDA and HHS Human Subject Protection Regulations. Available online at: http://www.fda.gov/oc/gcP/comParison.html (last accessed September 25, 2008).
4. 45 CFR 46.111
5. Emanuel E.J., A. Wood, A. Fleischman, A. Bowen, K.A. Getz, C. Grady, C. Levine, D.E. Hammerschmidt, R. Faden, L. Eckenwiler, C. T. Muse, J. Sugarman. 2004. Oversight of human participants' research: Identifying problems to evaluate reform proposals. *Annals of Internal Medicine* 141: 282-291; Institute of Medicine. 2002. *Responsible Research: A Systems Approach to Protecting Research Participants.* Washington, DC: IOM; National Bioethics Advisory Commission. 2001. *Ethical and Policy Issues in Research Involving Human Participants.* Washington, DC: U.S. Government Printing Office.
6. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. 1979. *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research.* Washington, DC: U.S. Government Printing Office.
7. World Medical Association. Declaration of Helsinki. Available online at: http://www.wma.net/e/policy/b3.htm (last accessed September 25, 2008).
8. Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO). 2002. International Ethical Guidelines for Biomedical Research Involving Human Subjects. Available online: http://www.cioms.ch/frame_guidelines_nov_2002.htm (last accessed September 25, 2008).
9. Emanuel E, D. Wendler, and C. Grady. 2000. What makes clinical research ethical? JAMA 283(2): 2701-2711.
10. Emanuel et al supra note 6 at p. 2703.
11. United States Conference of Catholic Bishops. 2001. *Ethical and Religious Directives for Catholic Health Care Services,* Fourth Edition. Available online at: http://www.usccb.org/bishops/directives.shtml (last accessed September 9, 2008).
12. 45 CFR 36.116
13. National Commission *supra* note 6 at C.
14. Faden, R. and T.L. Beauchamp. 1986. *A History and Theory of Informed Consent.* New York: Oxford University Press, at p. 356.
15. Ackerman, T.F. 1989. An ethical framework for the practice of paying research subjects. *IRB: A Review of Human Subjects Research* 11: 1-4; Grady, C. Payment of clinical research subjects. 2005. *The Journal of Clinical Investigation* 115(7): 1682-1687; Emanuel, E. 2005. Undue inducement: nonsense on stilts? *American Journal of Bioethics* 5(5): 9-13; Levine, R. 1986. *Ethics and regulation of clinical research, 2nd ed.* Baltimore, MD: Urban and Schwarzenberg; Macklin\, R. 1981. On paying money to research subjects. *IRB: A Review of Human Subjects Research* 3: 1-6; McGee, G. 1997. Subject to payment? *JAMA* 278(3): 199-200; Wilkinson, M., and A. Moore.1997. Inducement in research. *Bioethics* 11(5): 373-389. See

also Dickert, N., E. Emanuel and C. Grady. 2002. Paying research subjects: An analysis of current policies. *Annals of Internal Medicine* 136(5): 368-373; Tishler, C.L., and S. Bartholomae. 2002. The recruitment of normal healthy volunteers: A review of the literature on the use of financial incentives. *Journal of Clinical Pharmacology* 42: 365-375.

16. McNeil, P. 1997. Paying people to participate in research: Why not? A response to Wilkinson and Moore. *Bioethics* 11(5): 390-39; Reame, N. K. 2001. Treating research subjects as unskilled wage earners: A risky business. *American Journal of Bioethics* 1(2): 53-54.
17. Grady, C. 2001. Money for research participation: Does it jeopardize informed consent? *American Journal of Bioethics* 1(2): 40-44; Dickert, N., and C. Grady. 1999. What's the price of a research subject? Approaches to payment for research participation. *New England Journal of Medicine* 341(3): 198-202.
18. See, for example, Bigorra, J. and J.E. Baños. 1990. 'Weight of financial reward in the decision by medical students and experienced healthy volunteers to participate in clinical trials. *European Journal of Clinical Pharmacology* 38(5): 443-446; Halpern S.D., J. H. T. Karlawish, D. Cawsarett, J. A. Berlin and D. A. Asch. 2004. 'Empirical Assessment of Whether Moderate Payments Are Undue or Unjust Inducements for Participation in Clinical Trials,' *Archives of Internal Medicine* 164: 801-803; Bentley, J.P. and P.G. Thacker. 2004. 'The influence of risk and monetary payment on the research participation decision making process,' *Journal of Medical Ethics* 30: 293-298; Festinger, D. S., Marlowe, D. B., Croft, J. S., Dugosh, K., Mastro, N., Lee, P., DeMatteo, D. S., & Patapis, N. S. (2005). Do research payments precipitate drug use or coerce participation? *Drug and Alcohol Dependence.* 78, 275-281; Croft, J.R., D. S. Festinger, K. L. Dugosh, D. B. Marlow, and B. J. Rosenwasser. 2007. 'Does Size Matter? A Look at Institutional Review Board Members in the Netherlands,' *IRB* 29(4): 15-19. Casarett et al 2002; D. Casarett, J. Karlawish, and D. A. Asch. 2002. 'Paying Hypertension Research Subjects,' *Journal of General Internal Medicine* 17(8): 651-653; Kirkpatrick, M.A.F. 1991. 'Factors that Motivate Healthy Adults to Participate in Phase I Drug Trials,' *Drug Information Journal* 25: 109-113.
19. See FDA. 1998. 'Payment to Research Subjects,' http://www.fda.gov/oc/ohrt/IRBS/toc4.html#payment (last accessed September 9, 2008).