POLICY

Triggers for Research Ethics Consultation

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Research ethics consultation services are designed to help scientists address ethical and societal issues that may not be considered in the context of existing regulatory frameworks, such as institutional review boards. Here, we identify some types of biomedical research for which the research process can benefit from consultation with ethicists.

Researchers and policy-makers have raised questions about the scope of research ethics consultation services (RECS) since their emergence in the last decade (*1*). RECS can foster partnerships between scientists and ethicists (*2*) or serve as a forum for researchers to address ethical and societal issues that go beyond existing regulatory frameworks (*1*). RECS can serve as an adjunct to institutional review boards (IRBs) and other institutional oversight bodies, essentially expanding the reach of regulatory oversight (*3*). As RECS proliferate, especially through the Clinical and Translational Science Awards funded by the U.S. National Institutes of Health (NIH) (*4*), it is important to clarify the theoretical and practical roles of the consultation service.

In this Commentary, we suggest specific situations in which RECS can complement an IRB for one of two reasons. First, there are areas of research that, by federal regulations, lie outside the scope of an IRB. Two examples are nonhuman subjects research and issues of broad social risk. Second, there are areas that federal regulations and guidelines do not currently address, including issues for which there is not yet authoritative consensus. In the absence of such requirements or guidance, many IRBs remain silent on these issues. Although IRBs arguably should maintain their focus on regulatory issues, this vision leaves a gap that needs to be filled, especially with respect to ethical issues for which there is no consensus (*5*–*8*).

We propose that certain types of research activities and ethical issues should be triggers for consideration of research ethics consultation. These triggers emanate from 6 years of RECS experience at Stanford University, as well as from conversations with consultants at other institutions. The rationale behind articulating these triggers is to alert researchers to ethical issues about which they otherwise may not be aware. Furthermore, some of these triggers represent areas in which either there is no consensus or consensus was reached too recently to be reflected in any regulatory guidance. Finally, there are ethical issues that arise in research that are, and will always remain, outside the scope of IRBs or other oversight bodies (*9*). If researchers are cognizant of these ethical issues early in the research process, they can be more adequately addressed (possibly with the help of RECS) at any point in the study, from planning to publication of the research (*5*, *10*, *11*).

Because IRBs are mandated regulatory bodies and RECS are purely advisory, RECS can never replace IRBs or other mandated regulatory bodies (for example, embryonic stem cell research oversight; animal welfare, health, and safety; or conflict of interest committees) and do not provide a mechanism for researchers to avoid regulatory review. Furthermore, not all institutions have RECS or similar expertise. Nevertheless, the wide variability among IRBs in scope and decisions (*12*), and a lack of consensus about many ethical issues, provide opportunities for researchers to consider, debate, and seek advice on these issues proactively and in ways that go beyond responding to regulatory requirements. We believe that RECS can provide more time for active engagement of ethical issues, which can be difficult to accomplish in the context of an IRB meeting that may feel threatening to investigators, occurs well after investigators have invested significant effort in designing a study, and has limited deliberation time.

TRIGGER POINTS

Innovative treatment. It can be difficult to distinguish when an innovative therapy should be performed under an IRB-approved research protocol. Research is defined as a "systematic investigation designed to develop or contribute to generalizable knowledge" (*13*). In contrast, clinical treatment has the primary goal of benefiting the individual patient (*14*). It is unclear what, if anything, an IRB is supposed to do in these situations. Many professional societies recommend IRB review for innovative treatments as a safety precaution.

For example, in 2011, the American Society of Transplant Surgeons published recommendations stating that, given the investigational nature of the field, (i) all composite tissue allotransplantation programs

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Fig. 1. New frontiers. Clinical trials for cutting-edge therapeutics can dramatically enhance scientific knowledge but can raise cutting-edge ethical issues as well. "Progress flies into our lives" (*33*), and RECS may help researchers tame the trial design process.

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should be subject to institutional regulations for human subjects research and (ii) patients should be enrolled in IRB-approved protocols (*15*). Despite these recommendations, other institutional mechanisms may be more appropriate to evaluate the plans of a surgeon who seeks to perform, for example, hand transplantations on a small number of patients, including whether the surgery is for the direct benefit of the patients. Indeed, the border between research and clinical practice is still contested territory. Perhaps reflecting this controversy, several institutions have specific and comprehensive policies and oversight procedures regarding innovative treatment that do not include involvement of an IRB. RECS can be helpful in providing guidance to the institution and in making sure that the nonvalidated nature of the treatment is included in the informed consent if the procedure is deemed not to be part of a research protocol.

Tissue/DNA banking. The U.S. Office for Human Research Protections (OHRP) IRB guidelines describe considerations specific to genetic research (*16*). However, conventional mechanisms for protecting research participants, such as informed consent and deidentifying data, may not adequately protect participants in genetic research. In a recent survey, a majority of Public Responsibility in Medicine and Research members involved in human subjects protection indicated feeling that genetic studies require special guidance for writing consent forms, planning for sharing research data, developing a data repository or biobank, and using large-scale data repositories (*17*). Many respondents also indicated that considerable discussion was necessary between investigators and their IRBs regarding procedures for protecting participants' personal information or samples, returning genetic research results to participants, and reconsenting research participants for a new study or change in purpose.

No consensus exists among human subjects protection professionals regarding how best to handle these issues (*17*). The existing guidance and regulations set an important baseline for IRBs, but this does not necessarily mean that the research will not be exposed to criticism or opprobrium. RECS can serve as a guide for investigators during the development process to help researchers with study design issues, such as sampling, that take social context into consideration. Or, as another example, although studies of deidentified tissue samples are not considered to be human subjects research according to federal regulations, RECS can help researchers understand the implications of not obtaining consent for their studies.

Incidental findings and returning research results. An incidental finding is a research result that may have clinical significance but is not within the scope of the study's purpose (*18*). Investigators should decide how they plan to deal with incidental findings before the research begins. The OHRP IRB guidelines suggest that the IRB ensure that investigators have adequately dealt with the possibility of incidental findings (*12*), but the guidance leaves open how best to address the issue. In contrast, there is a great deal of literature and an emerging consensus on how to deal with incidental findings. RECS can help researchers implement these recommendations.

During the pilot period of Stanford University's Benchside Ethics Consultation Service, incidental findings and returning research results accounted for nearly 50% of all requested research ethics consultations (*4*). These situations are triggers because researchers do not yet know how to interpret the growing body of literature on the topic. RECS consultants can assist investigators in anticipating possible incidental findings, developing the best method to handle these findings, and, for researchers who have no experience in doing so, designing language for informed consent forms that makes this method clear.

Stem cell clinical trials. Frontier research (Fig. 1) refers to clinical trials that are at the cutting edge of research, where there is the greatest likelihood for dramatic increases in basic science knowledge. Because these trials involve interventions that differ from any existing treatment, there is insufficient evidence to make claims about the probability of success in progressing from a phase I through a phase III clinical trial (*19*).

Controversy over the frontier nature of stem cell–related clinical trials necessitates ways to help researchers identify and anticipate ethical and legal issues. Consultation could include helping researchers become aware of myriad requirements, such as those of the California Department of Public Health or recommendations of the International Society for Stem Cell Research (ISSCR) (*20*). In states other than California, a RECS consultant can help researchers identify areas of their protocols that are relevant to recommendations by ISSCR or other nonfederal bodies. In addition to these safeguards, RECS consultants can play an important role in risk-benefit analyses and constructing language in the consent form so that participants are not confused about the goals of the intervention, as there is a high risk of therapeutic misconception in phase I clinical trials (*21*).

The meaning of "minimal risk" in pediatric research. The U.S. Department of Health and Human Services' Code of Federal Regulations institutes four categories of pediatric research, differentiating each one by the prospective level of risk and benefit to the research subjects. In the first category, research with children as the subjects may be approved if there is not more than a minimal risk to the child. U.S. regulations state that minimal risk means "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" (*9*). A consensus has not been reached between, or even within, IRBs about how to interpret the subjective concept of risks "encountered in daily life" (*22*). An "absolute" interpretation considers the risks of daily life to be those encountered by a typical, healthy child. A "relative" interpretation would contextualize risks to those encountered by a child with a particular disease (*23*). RECS can provide advice on whether a subjective or objective approach is appropriate for individual studies.

Early-phase first-in-class trials in pediatric research. There are pediatric diseases and conditions that can only be addressed directly in children, without any previous knowledge obtained by studies with adults. If a first-in-class trial is being conducted in a pediatric population, there are questions of minimizing risk, balancing the risk-benefit ratio, and interpreting the meaning of the prospect of direct benefit. Although addressed by IRBs, these issues are fraught with ethical conundrums, and RECS can help investigators provide an IRB with the types of information it will need to know in order to evaluate these risks. As with the interpretation of minimal risk, there is no consensus on how to interpret the "prospect of direct benefit." RECS can advise investigators and discuss with IRBs the interpretation of this language in ethically challenging cases.

Community engagement. The U.S. Food and Drug Administration (FDA) and De-

partment of Health and Human Services (HHS) initiated community consultation as a practice in 1996, when these agencies enacted policies that limit the informed consent requirements for enrolling critically ill patients in emergency treatments (*24*). These protocols seem to conflate consultation with consent and draw parallels among individuals, families, and communities. Of particular concern is that emergency research often takes place in traditionally underrepresented communities.

Despite the mandate and recognition of the importance of community consultation for research in underprivileged or vulnerable communities, there is little guidance about what constitutes an effective community engagement process. Moreover, various models of community engagement exist. Consultation with RECS personnel could be useful in developing best practices and methods of community consultation (*25*).

In population genetics research, research findings can have implications that extend beyond the research participants to larger populations (*26*). RECS can help investigators, in the research design process especially, to protect the interests of identifiable and vulnerable groups, such as racial or ethnic minorities, which may increase the likelihood of their participation in future research.

Research on indigenous peoples and selected ethnic groups. The U.S. Code of Federal Regulations (CFR) for the protection of human subjects establishes measures to safeguard vulnerable populations, including pregnant women, children, and prisoners. IRBs review protocols for research involving vulnerable populations to ensure that the selection of human subjects is equitable and that informed consent is adequate (*9*). However, research that involves broad classes of populations, such as racial minorities and indigenous peoples (*8*), does not receive special scrutiny despite the subjects' vulnerability.

Over the past decade, several organizations have developed guidelines for research with indigenous populations, including (but not limited to) the American Medical Association; the World Health Organization (WHO); the United Nations Educational, Scientific, and Cultural Organization; and the Canadian Institutes of Health Research (CIHR). For example, CIHR published a set of guidelines in 2007 for health research involving aboriginal people (http://www.cihr-irsc.gc.ca/e/29134.html). These guidelines provide researchers with a checklist of principles they should understand when conducting research with indigenous communities and address issues such as reconsent for subsequent uses of samples and protection of indigenous rights in cultural knowledge.

Study design issues relevant to race and ethnicity—sampling, analysis, interpretation, and reporting—have ethical and social implications and are particularly prevalent in genetics research (*27*). Such issues include how to engage with and talk about ethnic communities and the terminology that should be used when writing about them. These suggestions fall outside the purview of the IRB. RECS consultants can assist researchers in developing ethical studies for, and in working closely with, vulnerable populations to prevent censure of biomedical researchers from the community.

Research in developing nations. Research in developing nations presents a number of unique ethical issues, such as when a placebo versus an active control trial is appropriate and issues of ancillary care. Cultural standards for these issues will vary, and RECS can be helpful in assessing how best to navigate issues such as benefit sharing, social harms, transparency, and self-determination, which can be essential to an ethical assessment of the research. Emanuel *et al*., the Council for International Organizations of Medical Sciences, and WHO have offered guidance with which investigators and IRBs may not be familiar (*28*, *29*). Moreover, although protocols for research in foreign countries are subject to IRB approval, IRBs are unlikely to consider the broader social implications of the research (*9*). RECS can provide researcher guidance on how to address the ethical issues inherent to research in developing nations.

Dual use. Dual use refers to biological research with a legitimate scientific purpose that may be misused to pose a biological threat to public health or national security (for example, studies of Ebola virus or anthrax). The U.S. National Science Advisory Board for Biosecurity (NSABB) was chartered to provide advice, guidance, and leadership with respect to biosecurity oversight of dual-use research. The objectives of the committee include taking into account concerns for national security and the needs of the research community to progress in public health research (*30*). RECS can help make researchers aware of the NSABB's guidance, much of which focuses on issues raised in late stages of the research process. However, even research at early stages of technology development can have dual-use implications that may not be addressed by existing guidance.

Broad social acceptability issues. According to the CFR, 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" (*9*). This directive specifically precludes IRBs from assessing the broad social implications of research. Considering downstream social and policy implications of research is arguably outside of the expertise of most IRBs, and including these considerations makes the already time-consuming IRB review process less efficient. As regulatory bodies, IRBs must be careful about the power they wield, and speculating about possible implications of research could have a chilling effect on research while simultaneously distracting an IRB from the important oversight issues that do fall under its purview (*31*).

The temptation for some IRBs to consider these issues stems from the recognition that broad social implications (many of which can be anticipated) are relevant to the ethical conduct of research. RECS are appropriate bodies for addressing these more general issues in a nonregulatory, nonbinding fashion.

These triggers provide examples of situations that lie at the cutting edge of ethical analysis, that lie outside the scope of existing regulation, and for which more than one reasonable approach exists. Because it is advisory and optional, rather than regulatory and mandated, ethics consultation encourages early consideration of issues in a safe environment for researchers. An often-forgotten component for the protection of research subjects is the presence of an "intelligent, informed, conscientious, compassionate, responsible investigator" (*32*). However, biomedical scientists often do not have training in the ethics of clinical research, particularly in those areas that extend beyond the focus of IRBs. RECS may help investigators to fill this knowledge gap and provide complementary regulatory oversight (*5*, *10*, *11*). Ultimately, however, studies are needed to determine whether RECS improve the ethical conduct of research.

REFERENCES AND NOTES

1. M. K. Cho, S. L. Tobin, H. T. Greely, J. McCormick, A. Boyce, D. Magnus, Strangers at the benchside: Research ethics consultation. *Am. J. Bioeth.* **8**, 4–13 (2008).
2. I. de Melo-Martín, L. I. Palmer, J. J. Fins, Viewpoint: Developing a research ethics consultation service to foster responsive and responsible clinical research. *Acad. Med.* **82**, 900–904 (2007).
3. N. Fost, paper presented at the American Society of Bioethics and Humanities Annual Meeting, Cleveland OH, 23 to 26 October 2008.
4. M. K. Cho, S. L. Tobin, H. T. Greely, J. McCormick, A. Boyce, D. Magnus, Research ethics consultation: The Stanford experience. *IRB: Ethics & Human Research* **30**, 1–6 (2008).
5. L. M. Beskow, C. Grady, A. S. Iltis, J. Z. Sadler, B. S. Wilfond, Points to consider: The research ethics consultation service and the IRB. *IRB: Ethics & Human Research* **31**, 1–9 (2009).
6. J. M. Ladd, M. D. Lappé, J. B. McCormick, A. M. Boyce, M. K. Cho, The "how" and "whys" of research: Life scientists' views of accountability. *J. Med. Ethics* **35**, 762–767 (2009).
7. J. B. McCormick, A. M. Boyce, M. K. Cho, Biomedical scientists' perceptions of ethical and social implications: Is there a role for research ethics consultation? *PLoS ONE* **4**, e4659 (2009).
8. B. Jacobs, J. Roffenbender, J. Collmann, K. Cherry, L. L. Bitsói, K. Bassett, C. H. Evans Jr., Bridging the divide between genomic science and indigenous peoples. *J. Law Med. Ethics* **38**, 684–696 (2010).
9. A. Fleischman, C. Levine, L. Eckenwiler, C. Grady, D. E. Hammerschmidt, J. Sugarman, Dealing with the long-term social implications of research. *Am. J. Bioeth.* **11**, 5–9 (2011).
10. L. F. Ross, A. Loup, R. M. Nelson, J. R. Botkin, R. Kost, G. R. Smith Jr., S. Gehlert, Human subjects protections in community-engaged research: A research ethics framework. *J. Empir. Res. Hum. Res. Ethics* **5**, 5–17 (2010).
11. L. F. Ross, A. Loup, R. M. Nelson, J. R. Botkin, R. Kost, G. R. Smith Jr., S. Gehlert, The challenges of collaboration for academic and community partners in a research partnership: Points to consider. *J. Empir. Res. Hum. Res. Ethics* **5**, 19–31 (2010).
12. L. Abbott, C. Grady, A systematic review of the empirical literature evaluating IRBs: What we know and what we still need to learn. *J. Empir. Res. Hum. Res. Ethics* **6**, 3–19 (2011).
13. Code of Federal Regulations, Department of Health and Human Services, Protection of Human Subjects: 45 CFR 46 (2009), http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html.
14. R. Zlotnik-Shaul, M. F. McKneally, Ethical considerations for innovations and clinical trials. *Semin. Thorac. Cardiovasc. Surg.* **15**, 380–385 (2003).
15. L. Cendales, D. Granger, M. Henry, J. Jones, A. Langnas, D. Levi, J. Magee, R. Merion, K. Olthoff, T. Pruett, J. Roberts, M. Abecassis; ASTS VCA Ad Hoc Committee and Executive Committee, Implementation of vascularized composite allografts in the United States: Recommendations from the ASTS VCA Ad Hoc Committee and the Executive Committee. *Am. J. Transplant.* **11**, 13–17 (2011).
16. OHRP, in *Institutional Review Board Guidebook* (1993), http://www.hhs.gov/ohrp/archive/irb/irb_guidebook.htm.
17. A. A. Lemke, S. B. Trinidad, K. L. Edwards, H. Starks, G. L. Wiesner; GRRIP Consortium, Attitudes toward genetic research review: Results from a national survey of professionals involved in human subjects protection. *J. Empir. Res. Hum. Res. Ethics* **5**, 83–91 (2010).
18. S. M. Wolf, F. P. Lawrenz, C. A. Nelson, J. P. Kahn, M. K. Cho, E. W. Clayton, J. G. Fletcher, M. K. Georgieff, D. Hammerschmidt, K. Hudson, J. Illes, V. Kapur, M. A. Keane, B. A. Koenig, B. S. Leroy, E. G. McFarland, J. Paradise, L. S. Parker, S. F. Terry, B. Van Ness, B. S. Wilfond, Managing incidental findings in human subjects research: Analysis and recommendations. *J. Law Med. Ethics* **36**, 219–248, 211 (2008).
19. D. Magnus, Translating stem cell research: Challenges at the research frontier. *J. Law Med. Ethics* **38**, 267–276 (2010).
20. California Department of Public Health, *Guidelines for Human Stem Cell Research* (2009), http://www.cdph.ca.gov/programs/HSCR/Pages/HSCRPublicHealthGuideline.aspx.
21. G. E. Henderson, L. R. Churchill, A. M. Davis, M. M. Easter, C. Grady, S. Joffe, N. Kass, N. M. King, C. W. Lidz, F. G. Miller, D. K. Nelson, J. Peppercorn, B. B. Rothschild, P. Sankar, B. S. Wilfond, C. R. Zimmer, Clinical trials and medical care: Defining the therapeutic misconception. *PLoS Med.* **4**, e324 (2007).
22. L. M. Kopelman, Children as research subjects: Moral disputes, regulatory guidance, and recent court decisions. *Mt. Sinai J. Med.* **73**, 596–604 (2006).
23. C. B. Fisher, S. Z. Kornetsky, E. D. Prentice, Determining risk in pediatric research with no prospect of direct benefit: Time for a national consensus on the interpretation of federal regulations. *Am. J. Bioeth.* **7**, 5–10 (2007).
24. K. F. Holloway, Accidental communities: Race, emergency medicine, and the problem of polyheme. *Am. J. Bioeth.* **6**, 7–17 (2006).
25. L. F. Ross, A. Loup, R. M. Nelson, J. R. Botkin, R. Kost, G. R. Smith Jr., S. Gehlert, Nine key functions for a human subjects protection program for community-engaged research: Points to consider. *J. Empir. Res. Hum. Res. Ethics* **5**, 33–47 (2010).
26. H. T. Greely, Informed consent and other ethical issues in human population genetics. *Annu. Rev. Genet.* **35**, 785–800 (2001).
27. P. Sankar, M. K. Cho, Genetics. Toward a new vocabulary of human genetic variation. *Science* **298**, 1337–1338 (2002).
28. E. J. Emanuel, D. Wendler, J. Killen, C. Grady, What makes clinical research in developing countries ethical? The benchmarks of ethical research. *J. Infect. Dis.* **189**, 930–937 (2004).
29. "International ethical guidelines for biomedical research involving human subjects" (Council for International Organizations of Medical Sciences and the World Health Organization, Geneva, 2002).
30. National Science Advisory Board for Biosecurity (Health and Human Services, Washington, DC, 2010).
31. M. Havard, D. Magnus, Beyond the IRB: Local service versus global oversight. *Am. J. Bioeth.* **11**, 1–2 (2011).
32. H. K. Beecher, Ethics and clinical research. *N. Engl. J. Med.* **274**, 1354–1360 (1966).
33. From the song "Frontiers," recorded by the rock band Journey; lyrics by Lee "Scratch" Perry.

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