POLICY FORUM

RESEARCH ETHICS

International scope of biomedical research ethics review

Many countries consider long-term implications for society

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In the context of biomedical research involving human subjects, the review of research proposals by ethics committees in virtually every country has traditionally focused on informed consent and other protections for individuals participating in research (*1*). However, the substantial societal implications of modern biomedical research and the globalization of scientific inquiry make it important to understand whether research ethics review in each country addresses both individual and societal issues. Knowledge of the practices internationally can promote understanding and can suggest possible innovations for specific countries. Below, we explore three related issues: (i) whether biomedical research ethics review considers the societal and long-term implications of the research, (ii) whether bodies charged with performing research ethics reviews are appropriate to consider these issues, and (iii) the feasibility and likely support for embedding multidisciplinary researchers with scientists to study societal and long-term implications. We address current regulatory policies and offer comments about possible changes.

Scientists conducting research in numerous disciplines, from agronomy to zoology, are often concerned with the societal and long-term implications of their discoveries. Biomedical research, with its distinctive regulatory system for review of protocols for research with human participants, provides additional substantive and procedural challenges for researchers, their institutions and funders, and other stakeholders. The ethical issues are especially daunting for transformative biomedical research, such as xenotransplants, gene therapy, and neural implants, which may have social, psychological, economic, legal, and cultural importance. Even more-established areas of biomedical research, such as pharmaceutical development, can raise meaningful ethical issues related to clinical care, health finance, health equity, and public health.

This work reports the results of a collaboration of scholars with expertise in biomedical research ethics review and law from 22 countries that are geographically, politically, economically, and culturally diverse (see the box) (see supplementary materials for details on the country-level analyses). Various entities may have a role in considering research ethics issues raised by proposed research. This article analyzes the research ethics review bodies created by legislation or regulation with the authority to approve, conditionally approve, or disapprove proposed research on the basis of established criteria. Such entities are most commonly called research ethics committees (RECs), but some countries call them research ethics boards (REBs), ethics review committees (ERCs), or institutional review boards (IRBs). For simplicity, they are all called RECs throughout, except when referring to ethics review in a specific country using a different name. The regulations and policies of the countries discussed here generally pertain regardless of the funding source of the research and reflect national policies.

INDIVIDUAL AND SOCIETAL INTERESTS

The Nuremberg Code (*2*), Declaration of Helsinki (*3*), Belmont Report (*4*), and other foundational documents of research ethics were drafted in response to egregious human rights abuses committed in conducting biomedical research. These abuses often occurred in settings of extreme coercion and duress, without informed consent or the weighing of risks and benefits to those subjected to intolerable experimentation. Because of this history, research ethics principles and policies emphasized the welfare of individuals and declared that the potential scientific benefits from research do not outweigh the interests of individuals in autonomy, bodily integrity, and human dignity.

Despite recognizing the primacy of individual interests, contemporary research ethics reviews often address broader and longer-term consequences of the research. Assuming that biomedical research is conducted safely and complies with best scientific practices, societal and long-term ethical concerns generally are in one of two broad categories. First are threats to humanity, such as possible use of the research to develop biological weapons, genetic interventions that could lead to eugenics, or fundamental changes to our understanding of the notion of "human" through xenotransplants or neural implants (*5*). Second are ethical issues of a sociopolitical nature, including equitable access to the fruits of biomedical research and freedom from their discriminatory use.

Some contemporary societal issues raised by groundbreaking biomedical research include whether it is possible to overcome the hesitancy or refusal by substantial numbers of individuals to receive safe and effective vaccines based on mRNA platforms, whether equitable access will be afforded for various CRISPR-based gene therapies, and whether future organ transplantation policy should rely on widespread use of xenotransplants.

As discussed below, societal and long-term implications of biomedical research may be addressed by various public and private entities. Nevertheless, the starting points for analysis in many countries are the deliberations and pronouncements of RECs. Therefore, this study sought to identify the policies and practices of RECs regarding societal and long-term implications of proposed research.

SUMMARY OF COUNTRY REPORTS

Require, permit, or prohibit

Of the 22 countries surveyed, 21 either require (8) or permit (13) RECs to consider societal implications of proposed research, and only one country, the United States, prohibits the practice (see the box). For countries requiring consideration, other criteria may also apply. For example, in South Korea, IRBs must "include at least one person who has sufficient experience and

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knowledge to evaluate social and ethical validity" (*6*). In Spain, evaluation of psychosocial issues in clinical trials is mandated by royal decree (*7*). In China, four government agencies recently released a joint measure requiring ERCs to examine whether proposed research involves socially sensitive ethical issues (*8*).

For countries permitting consideration, national regulations or policies in three countries explicitly grant permission, whereas permission can be implied in 10 countries from the lack of explicit prohibitions and the existence of broadly worded regulations and policies. There are subtle differences among the countries. For example, the law in Poland includes a very general provision stating that an REC may, but does not have to, investigate the societal implications of proposed research (*9*). In Australia, similar policies include a general statement but, in contrast, explicitly state the need to be mindful of societal implications for research with a particular focus or subject group, such as research involving Indigenous peoples (*10*). Among countries without explicit language, RECs in Israel, the Netherlands, and Qatar commonly consider societal implications, but it is not common practice in France, and in Japan, it is left to the discretion of RECs.

In the United States, federal research regulations prohibit consideration of societal issues. "The IRB should not consider possible long-range effects of applying knowledge gained in the research (e.g., the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility" (*11*). The stated purpose of the prohibition is to avoid having risks of possible long-range effects preclude beneficial research, but the provision could also be viewed as not wanting potential societal benefits to outweigh harms to research participants. Concerns expressed in the above-quoted provision about the effects on public policy would seem to include societal issues.

Of the 22 countries surveyed, 21 either require (3) or permit (18) RECs to consider long-term implications of proposed research. The United States is once again an outlier, explicitly prohibiting IRBs from considering long-term implications. Of the countries that require consideration, Argentina lists long-term implications as a risk that must be considered, and Mexico includes delayed consequences as a risk to consider. In Germany, ERCs apply the standards of good scientific practice, which stipulate that the possible consequences of research must be considered.

Of the 18 countries permitting consideration of long-term implications, three countries state at least one long-term consequence that may be considered. In South Africa, for example, the benefit of proposed research to future hypothetical beneficiaries could be a consideration. Nigeria emphasizes considering the social value of the research, community involvement, and mechanisms ensuring that benefits of the research are shared with the community or individuals being studied. Kenya requires the results of clinical trials to be made accessible to the participant communities.

Among the 15 countries permitting consideration without express provisions, regulations or guidelines may include language authorizing such consideration in specific situations. In Singapore, long-term implications are explicitly permitted if pertaining to the review of consent-taking and documentation, risk evaluation, and access to new inventions.

Can research ethics review bodies consider societal implications?

Do biomedical research ethics regulations or policies require, permit, or prohibit research ethics review bodies from considering societal implications of proposed research, such as the economic, health equity, and public health implications?

Require (8): Canada, China, Mexico, Nigeria, South Africa, Spain, Sweden, United Kingdom

Permit – May consider societal implications (3): Australia, Lebanon, Poland

Permit – There are no explicit requirements or prohibitions (10): Argentina, France, Germany, Israel, Japan, Kenya, Netherlands, Qatar, Singapore, South Korea

Prohibit (1): United States

Role of funders

In addition to REC consideration of societal and long-term implications of proposed research, in half of the countries surveyed, public research funders also consider societal and long-term implications. For example, Genome Canada requires scientific grant applications to address broadly construed ethical, legal, and social issues. In the United States, societal implications and research priorities are often considered in awarding federal grants by the National Institutes of Health (NIH), applying criteria that may vary by institute or type of research; however, the rationales for individual funding decisions are not usually disclosed beyond research applicants.

The Wellcome Trust, based in the United Kingdom, was the only private research funder identified by respondents as strongly encouraging consideration of societal and long-term implications through what it calls an "engaged research approach." In some countries, such as Lebanon, funders do not consider such implications because other entities have already addressed related issues. Nonetheless, respondents from 20 countries believed that societal and long-term implications of proposed research should be considered regardless of funding or regulatory requirements. Respondents from two countries, Poland and South Korea, agreed but stated that societal and long-term implications should only be considered for particular types of research. If societal and long-term implications were considered in ethical assessments of research, respondents from 13 countries stated that RECs would be the appropriate entities to undertake the assessment, often noting that RECs already do this work.

Role of IRBs in the United States

In the United States, regardless of the regulatory prohibition noted above, IRBs may not be the most appropriate body to consider societal and long-term implications of research. Systemic sociopolitical issues, such as equitable access to health care, may be beyond the expertise of many IRB members, who are chosen for their scientific and research ethics expertise. Adding the assessment of broader implications of biomedical research to their mission could impose a substantial burden on IRBs as currently constituted and funded (*12*). Nevertheless, as review is consolidated into large central IRBs for most big health data projects, it may be feasible and appropriate for IRBs to consider the societal implications of the research. Some respondents from other countries in this study also raised concerns about burdening research ethics review and asserted that variations among RECs on broader issues would make it difficult to develop consistent national policies.

Unlike research ethics review bodies in most other countries, IRBs in the United States overwhelmingly are affiliated with local research institutions. Furthermore, federal regulations extend only to federally funded research and research conducted to support a submission for approval by the Food and Drug Administration. Thus, it is arguable that IRBs were designed to address a narrower range of issues than the indepen-

dent, publicly staffed, and disciplinarily diverse RECs in several other countries.

Alternative models

Even if they have broad authority, RECs reviewing typical protocols may not need to consider societal and long-term ethical issues if they determine that such issues are not implicated by the research or were addressed previously. Instead, RECs focus on important issues of a smaller scale, such as individual risks and benefits, equitable selection of participants, and informed consent. For groundbreaking research, the ability of RECs to address societal and long-term issues depends on their legal mandate, workload, time constraints, funding level, multidisciplinary expertise, and political support.

In the United States, only new legislation or regulations can implement mandatory policies regarding societal approaches to innovative biomedical technologies. Nevertheless, some other measures can facilitate consideration of the ethical implications of research and lead to voluntary actions and help frame ethical and policy debates.

One approach to ethics consideration that is generating increased interest around the world is to embed multidisciplinary scholars along with researchers from the earliest stages of the research. Such arrangements can promote greater understanding by ethics personnel of the research processes, goals, and implications. It can also produce actionable evaluations more promptly than awaiting publication or disclosure of scientific findings. In the United States, this approach could be used by institutions funded by the National Center for Advancing Translational Sciences at the NIH. These leading institutions, funded by a single government program, have the resources and expertise to address complex bioethics issues at the level of single institutions or across multi-institution collaborations (*13*).

Respondents from nearly all of the surveyed countries (21) believed that embedding scholars from the social sciences, humanities, law, and other disciplines with biomedical researchers would be a useful and timely way to analyze societal and long-term implications, but responses differed on the likelihood of adopting such an arrangement. In Sweden, collaboration of biomedical researchers with multidisciplinary scholars is common, and similar efforts are underway in Germany. In Canada, research guidelines recognize the importance of including additional perspectives in the research process (*14*).

For many countries in this study, embedding multidisciplinary scholars with scientific researchers would represent a new direction in research ethics, and it is not clear how well it would be received by biomedical researchers. Respondents from most countries (18) predicted that researchers would object to embedding multidisciplinary scholars with them (9) or were unsure how researchers would respond (9). Likely researcher concerns were assumed to include fears that their research or funding might be curtailed, suspicions about the motives or methods of the social scientists and other scholars, or discomfort that their scientific integrity or commitment to ethical research could be questioned.

Another alternative to using RECs or embedded bioethics experts to assess societal and long-term implications of innovative research is the presence of an expert advisory body to prospectively examine thorny ethical issues. Such bodies provide guidance to local RECs as well as national policy-makers. For example, this approach has been used by the Council of Europe and its member countries. In the United Kingdom, the independent Nuffield Council on Bioethics plays this role. In the United States, six federal bioethics commissions or similar entities have been appointed since 1974 to address issues such as research using fetal tissue or stem cells, somatic cell nuclear transfer, and human enhancement, but there has not been any commission since 2017 (*15*). Studies by the National Academies of Science, Engineering, and Medicine or by other respected bodies often make important contributions in studying newly emerging biomedical technologies, but there is no continuing public entity charged with studying these issues. Many countries have recognized that new societal challenges posed by biomedical research require new paradigms of research ethics assessment.

CONCLUSION

Our international collaboration indicates an overwhelming consensus that societal and long-term implications of biomedical research are extraordinarily important and should be considered in ethics assessments. However, much work remains to get a complete picture of current approaches in operation around the world. For example, the specifics of when, how, and by whom these issues are addressed varies among the countries studied. In most countries, it is generally not known how often research ethics bodies consider these issues, the nature of their reviews, the degree of rigor, and whether the reviews have had any effects on the proposed research or society. Greater transparency, including possible publication of review determinations, could illuminate decisions by RECs and other bodies and point the way for policy development.

This study focused on the practices of RECs because in many countries they are the entities specifically directed or permitted by legislation or regulation to address societal and long-term implications of biomedical research. Wide-ranging bioethics review by RECs, however, may not be the appropriate or preferred approach in some countries for considering these issues. In any event, there is tremendous international support for establishing or maintaining some type of expert body to conduct ethical assessments of possible societal and long-term consequences of transformative biomedical research. ■

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