Moral Science: Ensuring Human Subjects Research Is Ethical

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Learning Objectives:

1. Describe the recommendations on human subjects research made by the Presidential Commission for the Study of Bioethical Issues.
2. Examine the number and range of human subjects research projects funded by the federal government.
3. Analyze some of the ethical reasons given to support the Commission's recommendations.
4. Identify how the Commission's recommendations compare with other Common Rule reform efforts.
5. Provide appropriate care and counsel for patients and their families.

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In November 2010, President Obama asked the Presidential Commission for the Study of Bioethical Issues to oversee a thorough review of current regulations and international standards for human subjects research that is federally funded, no matter where it is conducted. The request arose in response to revelations concerned unethical practices in research into sexually transmitted diseases conducted in Guatemala in the late 1940s. As part of its work, the Commission was asked to conduct a fact-finding investigation into this research conducted by the U.S. Public Health Service.

The Commission concluded that current regulations generally do protect people from avoidable harm and unethical treatment. However, some government agencies are currently unable to identify basic information about all of their human subjects research. This limitation makes it impossible to determine whether all federally funded research provides optimal protection against avoidable harms or unethical treatment. Given these limitations and other criticisms of the current system, the Commission made fourteen recommendations to improve the current federal system.

Introduction

Research is an important means of advancing knowledge, and also contributes to growth and prosperity in many areas of society. For reasons such as this, society encourages and supports research of many different types. At the same time, the pursuit of progress does not justify all means of conducting research. What Benjamin Franklin called "wolfish humanity" can lead to what Hans Jonas called "too ruthless a pursuit of scientific progress."[1] This leads to a "sacred trust and responsibility … to ensure that human research subjects are protected from harm and unethical treatment."[1] Society must regularly revisit whether its research is being conducted ethically. Sometimes it takes fresh revelations about research subjects being abused to stimulate reflection on research ethics. Such has been the case with the disclosure of unethical research in Guatemala during the 1940s.

In May 2010, Professor Susan Reverby disclosed details of "reprehensible" medical experiments in Guatemala by U.S. researchers conducted between 1946 and 1948.[2] The research involved prisoners, soldiers, psychiatric patients, and prostitutes, some of which were deliberately infected with sexually transmitted diseases. Informed consent was not used. The studies were never published. The research was funded by the National Institutes of Health (NIH), which current director Francis Collins called "a dark chapter in the history of medicine."[3] The research was widely denounced and soon led to an apology from President Obama to the Guatemalan president and the hundreds of people used in the research.

The Commission reviewed the available records and found that the records revealed "unconscionable ways in which the researchers sometimes used people as a mere means to advance what [was] sometimes called 'pure science.'"[4] The second part of its assignment was to determine whether current research ethics, rules, and regulations are adequate to ensure that participants are protected from harmful or unethical treatment in federally funded research. This article will focus on the findings of this part of the Commission's work, published in the report, *Moral Science*.[1]

The Commission defined "moral science" as ethically sound science that is conducted in accordance with widely accepted and enduring ethical principles that are rooted in moral philosophy; theological traditions; and codes, regulations, and rules. Adherence to these rules leads to public confidence in researchers and support for their research. Without this, sufficient participants may not be available and critical research jeopardized. "More than these measurable effects, society risks irretrievably losing sight of what is inherently owed to fellow human beings and those who deserve special protection by virtue of their willingness to participate in experiments designed to benefit others and advance scientific and social progress."[1] Ethics is required because the danger exists, as highlighted by the Guatemalan experiments, that the quest for scientific knowledge can blind researchers to the humanity of the people they enroll in research studies.

Beyond Procedural Approaches

Research ethics has developed significantly since the 1940s. Various codes and regulations place importance on ethical concerns that are now well-known: informed consent, minimization of risk, fair subject selection, independent ethical review, confirmation of scientific validity, transparency about potential conflicts of interest, and, most importantly, respect for potential and enrolled subjects.[5]

Rules, regulations, and principles provide an important basis for respecting research subjects and protecting them from harm. However, these do not, in and of themselves, ensure that subjects are respected or protected from harm during research. To move beyond procedures and principles, the Commission pointed to the importance of "the virtuous researcher."[1] The ethical theories of utilitarianism and deontology are regularly referenced in research ethics. Virtue theory is also important because of its emphasis on cultivating moral character in individuals. "For research, this focus on virtuous character translates into a focus on the internal ethical motivation of individual investigators, not only the rules and regulations that externally motivate investigators toward compliance."[1] Such internalized moral motivations may arise from the researcher's personal moral development, but in addition they need to be addressed in research education. How this would be done raises challenges, but research training needs to include developing a personal commitment to being ethical in one's research and to the social responsibility entailed with research.

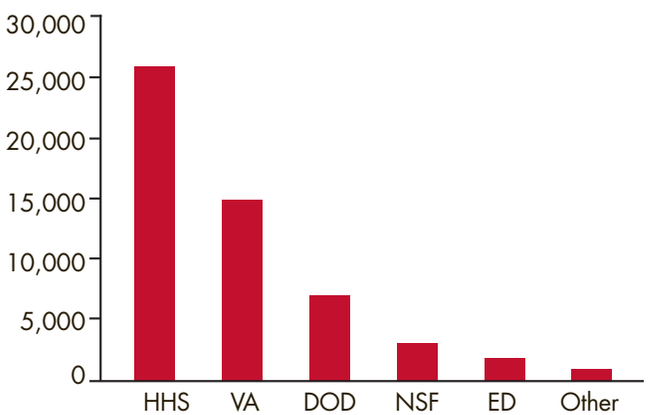
Human Subjects Research Landscape Project

To complete its work, the Commission analyzed federally funded research in the Human Subjects Research Landscape Project. Information was requested from all Common Rule departments and agencies. Research projects were analyzed even if details could not be reported for national security concerns or because they were classified. The project had only about 6 months to collect data, so the analysis was somewhat brief. In addition, some agencies were limited in their ability to identify basic information being sought.

Overall, federally funded research is occurring around the world and at enormous expense. In 2010, more than 55,000 projects were supported, about three-quarters of which were in medical and health-related fields. Those fields were the ones for which data were most readily available and complete. However, projects were funded in a wide variety of non-health fields including, education, engineering, and justice. Human subjects projects are distributed across many different federal departments and agencies (*see Figure 1*).

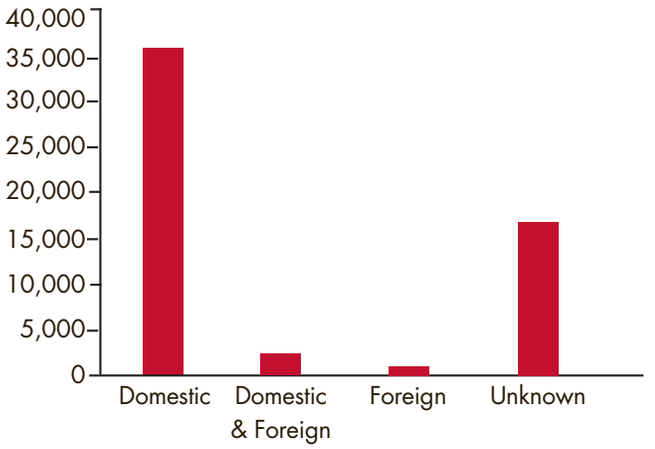
The project found much variability in the data available on human subjects research. Some agencies undertook a project-

Figure 1: Distribution of Human Subjects Projects by Agency in 2010[1]



HHS (Department of Health and Human Services), VA (Department of Veterans Affairs), DOD (Department of Defense), NSF (National Science Foundation), ED (Department of Education), Other (12 other agencies)

Figure 2: Distribution of Human Subjects Projects by Research Location in 2010[1]



by-project examination for the Commission, but others did not. In terms of where research was being conducted, details varied. Some agencies can only fund research in the United States, while others list projects only as domestic or foreign. Some were unclear about where research was occurring. In spite of the incompleteness of information, federally funded research was occurring in at least 117 countries in 2010. Of those which reported where the research was conducted, 65.1% were entirely domestic while 4.6% had some international component (*see Figure 2*).

Funded research can be conducted within government agencies (intramural research) or by external bodies such as academic centers (extramural research). The proportion of intramural to extramural research varies widely between agencies and departments. In 2010, based on numbers of projects, extramural research made up 54% of all human subjects research. These projects were conducted at 3,100 institutions 200 of which were outside the United States. The total amount of funding provided to these institutions was $16.7 billion.

The Common Rule regulations are enforced by different authorities within the different agencies. The Office for Human Research Protections (OHRP) evaluates compliance and complaints about Department of Health and Human Services (HHS) research only. Reviews of OHRP enforcement actions show that the vast majority address procedural violations related to Institutional Review Board (IRB) initial review and informed consent documents. However, some substantive violations have occurred. For example, 8% of violations arose because of failure to obtain informed consent.[6]

Based on this review, the Commission concluded that given the large volume of research supported by HHS, improvements in the current system are both possible and desirable. More thorough collection of data on projects will allow better monitoring. In addition, interviews with researchers and other stakeholders, as well as site visits, should be conducted to identify the practical ethical challenges arising during research projects.

International Research Ethics

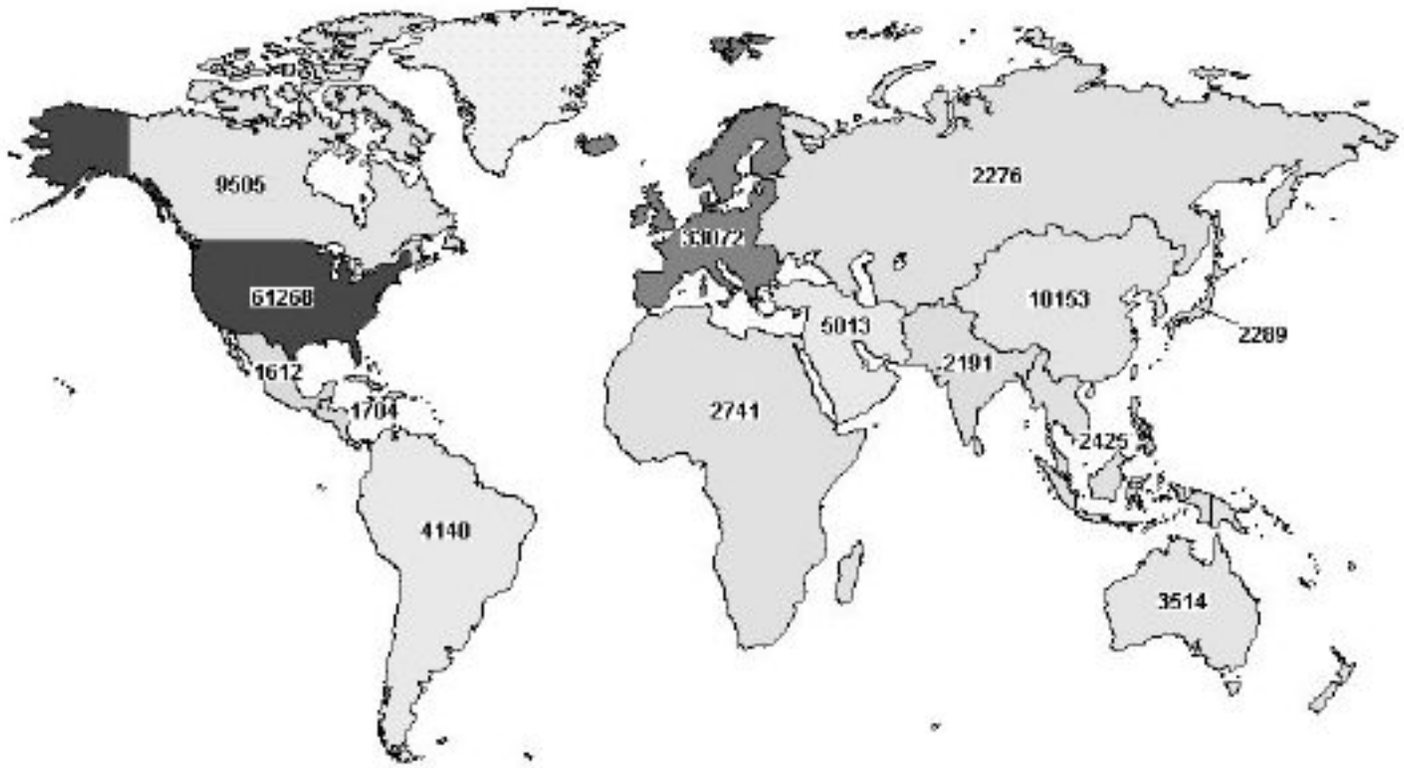
Human subjects research now occurs around the world (*see Figure 3*). The Commission was asked specifically to review federally funded research conducted overseas. To do this, it convened the International Research Panel composed of experts in bioethics and biomedical research from Argentina, Belgium, Brazil, China, Egypt, Guatemala, India, Russia, Uganda, and the United States. The panel focused on biomedical research and reported that much progress had been made in the last 50 years to protect human subjects.[7]

The panel identified much variability in the rules, standards, and practices both within the United States and in different countries. It noted the importance of continued dialogue between the United States and equivalent bodies around the world, particularly on the application of rules where other countries provide "equivalent protections" to U.S. regulations. Improvements could be made by enhanced public accountability of researchers, improved transparency, stronger monitoring, and clearer responsibility for violations. The panel highlighted a wide disparity between the United States and other nations in addressing research-related injuries. Most other developed countries require sponsors, investigators, or others to provide treatment for research-related injuries or to reimburse subjects for the costs of such treatment. The panel recommended that such compensation also be required in the United States.

Connection with Other Reform Proposals

The rules and regulations for federally funded research have remained largely unchanged since 1991. Some agencies previously had developed policies that still underlie current regulations. Yet research involving human subjects has continued to evolve. A wide variety of non-academic bodies now conducts oversees research. The diversity of methods has expanded. In addition to medical and biological research, federally funded research is now conducted using social science methods, databases, or the Internet. Human subjects research is often multicentered and sometimes international. Research has become a global enterprise, raising new and challenging issues of international collaboration and global justice (*see Figure 3*).

Figure 3: Map of All Studies in ClinicalTrials.gov[8]



While not asked to assess other reform proposals, an Advance Notice of Proposed Rulemaking (ANPRM) was issued by the Office of the Secretary of HHS and the White House Office of Science and Technology Policy (OSTP) while the Commission was conducting its work.[9] The ANPRM sought comments reforming the Common Rule to improve protections for human research subjects. The Commission thus considered how it could contribute to this reform and comment on the proposals made in the ANPRM.

Commission Recommendations

The Commission issued 14 recommendations, classified according to eight general themes (*see Table 1*). It concluded that current policies and regulations are sufficient to prevent anything like the ethical violations found in the Guatemalan research from the 1940s. However, current practice has weaknesses that could be corrected. The recommendations are intended to enhance and strengthen the current system and contribute to current reform efforts.

1. Improving accountability

The Commission found that greater accountability by federal agencies for the research they fund was needed and readily attainable. Much variability exists in the ways agencies and departments make information available. The Department of Energy and the NIH have publicly available databases of human subjects research. Others lack such databases, and in some case do not have a systematic way to link information about human subjects research and its funding. Other agencies have numerous internal databases that cannot easily communicate between one another.

Public access to information on research projects will not ensure greater protection of subjects or reduced risk of harm. However, it can enable further scrutiny and accountability. Intellectual property concerns must be taken into account, but science is a communal activity. Society has the right to know how public funds are being used in research. Making research more transparent may help improve its quality through raising questions about why projects are being conducted in certain sites or with certain groups of people. Such information may reduce unnecessary duplication. It can also make it harder to hide unwanted results, unnecessary risks, or adverse effects. Public feedback also may help scientists understand public values and preferences, and provide valuable input from those not directly engaged in research projects.

The availability of national and international clinical trial

Table 1. Recommendations of the Commission's Report, *Moral Science*[1]

Theme	Recommendation	Summary	Follow-up
Improving accountability	1. Improve accountability through public access	All federally funded human subjects research should make publicly available a minimum data set on each project. A central web-based portal should link to each agency or departmental system.	OHRP or applicable department or agency
	2. Improve accountability through expanded research	Systematic approaches to assess the effectiveness of research ethics procedures and human subjects protections should be expanded and supported.	OHRP or applicable department or agency
Helping those harmed by research participation	3. Treating and compensating for research-related injury	OSTP or HHS should expeditiously study the area of research-related injuries to determine if a national compensation or treatment system is needed. If so, a pilot study should be funded to evaluate possible program mechanisms.	OSTP/HHS
	4. Treating and compensating for research-related injury follow-up	Previous advisory bodies have made similar recommendations, without a clear response from the federal government. The federal government should publicly issue reasons for changing or maintaining the status quo.	OSTP/HHS
Creating a culture of responsibility	5. Make the ethical underpinnings of regulations more explicit	The core ethical standards fundamental to regulations should be made more explicit and clearly articulated.	HHS/OSTP
	6. Amend the Common Rule to address investigator responsibilities	The Common Rule should be amended to make the obligations of individual researchers more explicit. This would bring it into line with FDA regulations and international standards.	HHS/OSTP
	7. Expand ethics discourse and education	All those involved in human subjects research should adopt more effective ways of integrating a lively understanding of personal responsibility into professional research. Bioethics should be taught rigorously at undergraduate, graduate, professional, and investigator levels.	
Respecting equivalent protections	8. Respect equivalent protections	The federal government should adopt or revise the recommendation of the 2003 HHS Equivalent Protections Working Group. A process of determining equivalent protections should be implemented.	OHRP

HHS = Department of Health and Human Services; OHRP = Office for Human Research Protections; OSTP = Office of Science and Technology Policy

registries assists in this area. The Declaration of Helsinki now requires registration for clinical trials, as does federal law for clinical trials of most drugs and devices.[1] Although public accountability exists for "applicable" clinical trials, it does not apply to other types of biomedical research including first-in-human studies and other early-phase trials. Social, behavioral, and economic research involving human subjects is not required to make such disclosures. The NSF and the Department of Education are among the top five agencies funding human subjects research, yet information

Table 1. Recommendations of the Commission's Report, *Moral Science*[1] (cont.)

Theme	Recommendation	Summary	Follow-up
Promoting community engagement	9. Promote community engagement	The UNAIDS/AVAC guidelines should be examined to develop a standardized framework for community engagement practices that promote ethical research. The effectiveness of this framework should be evaluated so that it can be strengthened.	OHRP
Justifying site selection	10. Ensure capacity to protect human subjects	Research funders should determine that research sites have the capacity — or can build the capacity during the research — to protect all human subjects.	
	11. Evaluate responsiveness to local needs as a condition for ethical site selection	Justifications and procedures for ethical site selection should be developed and evaluated, taking into account the needs of the broader community around the study site.	OHRP or applicable department or agency
Ensuring ethical study design	12. Ensure ethical study design for control trials	A placebo or other control intervention that is not the best proven can be justified provided all the following criteria are met: the best proven intervention is not known to be the best for a particular study population; the scientific rationale and ethical justification have been reviewed to ensure the control is of limited duration, subjects are carefully monitored, rescue measures are in place, and withdrawal criteria are established.	
Promoting current reform	13. Promote current federal reform efforts	The level and intensity of review should be calibrated with the level of risk in the research. Certain lower-risk research should not require review, and the research categories eligible for expedited review should be updated regularly. Multisite studies should not undergo unnecessary, duplicative IRB review. However, institutions should remain responsible to protect subjects enrolled at their sites. Standardized consent form templates should be available. Human subjects regulations should be harmonized. One system for reporting adverse events should be adopted.	OSTP/OHRP
Following up	14. Respond to recommendations	The appropriate government agency should respond to each recommendation giving reasons for changing or accepting the status quo.	OSTP or applicable department or agency

HHS = Department of Health and Human Services; OHRP = Office for Human Research Protections; OSTP = Office of Science and Technology Policy

on the projects funded by them is not available publically as it is for clinical trials.

To improve public access to information, the Commission recommended that all agencies and departments should make a minimum dataset available on all their research projects. This should be available through a web-based portal. At the same time, the development of a unified reporting system should be investigated to determine if this might be a more cost-effective approach to improving public accountability.

A second way that greater public access to data about research studies would help is to permit more empirical research on research ethics. A coordinated set of data on human subjects research would allow independent evaluation of human subjects protection mechanisms. Current procedures in research ethics are somewhat controversial, in part because data on their effectiveness is lacking.[10] Better tools to evaluate these procedures are needed. For this reason, the Commission recommended that research into the effectiveness of research subject protection mechanisms be promoted and funded. Systematic assessment of human subjects research regulations and standards should be supported and expanded.

2. Helping those harmed by research participation

The Commission held that those who sponsor or conduct human subjects research have an ethical obligation to protect those who volunteer to act as research subjects. This duty encompasses both primary and secondary senses of protection. In the primary sense, researchers should protect subjects from exposure to undue risk. Not all risks in research can be avoided or foreseen, but ethical research seeks to reduce those risks. This can be done by ensuring sufficient knowledge is obtained prior to involving human subjects, and by ensuring that researchers are competent in the research methods of the study.

Those who sponsor or conduct human subjects research have an ethical obligation to protect those who volunteer as research subjects.

The secondary sense of protection is less well established in the United States, but is accepted elsewhere and ethically justified by many. The secondary sense of protection would hold that researchers should limit or reverse the harm subjects experience as a result of participating in research by providing appropriate medical care. This has been recommended by several past commissions, including the Presidential Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research (1982), the National Bioethics Advisory Council (NBAC, 2001), and the Institute of Medicine (2002).[1] In recent years, almost all other developed countries and many international research ethics organizations have placed such an obligation on researchers or their sponsors. The latter include the CIOMS International Ethical Guidelines for Biomedical Research Involving Human Subjects[11] and the International Conference on Harmonisation's Guideline for Good Clinical Practice.[12] The Commission recommended that the United States establish such a system to compensate subjects for the medical care required from harm experienced during biomedical research.

The primary argument in favor of such a system involves justice and fairness. Those who become research subjects take on the risk of injury, while society benefits from their acceptance of these risks. In fairness, those who benefit should help those who are harmed. Those who are harmed should not have to bear the additional burden of the costs of that harm. Those who benefit can help relieve that burden by paying for the resulting costs of medical care. It should not matter whether the harm was avoidable or foreseeable.

The main argument against providing compensation has been one of justice. This argument is that as long as subjects understand the risks and benefits of participation, and freely consent to be involved, they relinquish any claims to compensation for harm experienced during the research. The Commission claimed that this argument rests on a fallacious conflation of avoidable and unavoidable risks. Society does not permit subjects to take on any and all risks in research. IRB review is carried out to identify and minimize avoidable risks. However, some risks remain unavoidable and subjects who are informed may accept such risks. The cost of medical treatment for harms experienced during the research is a risk that can be avoided.

Many researchers are also clinicians who have professional obligations to protect and promote the good of patients. Such clinician-researchers have a professional obligation not to engage in research unless there is a mechanism to care for those harmed by that research. Providing such a compensatory system could have pragmatic benefits. People may be more inclined to participate in research if they know they will not have to pay for resulting harms. Given the difficulties with recruiting adequate numbers of participants, this could be a significant benefit. Such a system would also allow further harmonization of research policies and standards. It would allow greater harmonization with international guidelines and the voluntary practice of an increasing proportion of privately funded research in the United States.

When compensation as an ethical obligation is accepted, many practical questions arise about how this would be administered. Decisions would have to be taken about the types of injuries covered, the scale of compensation, who

bears the cost, and whether one or several administrative systems would be established. Various systems already exist that could serve as models, like the National Vaccine Injury Compensation Program. Some agencies and departments already provide compensation for research-related injuries, and some insurance programs cover such injuries. Most industry-sponsored research projects carry insurance to cover the costs of research-related injuries, which is regarded as good business practice. The Commission recommended that a careful study be conducted before changes are made to the current situation.

The Commission made a distinction between compensation for injuries resulting from unavoidable risks in research and reparation for unethical research. When unethical research comes to light, its sponsors bear responsibility to acknowledge the wrong and make some expression of reparation. This could include compensation for resulting harms, but other means were suggested such as public apologies or establishing a charity to prevent future repetition of similar wrongs.

3. Creating a culture of responsibility

According to the Commission, "The most fundamental obligation of research involving human subjects is to protect the rights and welfare of individuals who offer themselves for the good of both science and society and, in some cases, for the hope of personal benefit."[1] As persons, they should not be treated as mere means to the ends of others, even those who are suffering or the common good.

Subjects often put themselves into unequal relationships when they rely on the expertise and wisdom of others. Such arrangements set up competing interests, such as when the design of the study must be balanced against the best interests of subjects. Conflicts of interest may arise, which can be financial or nonfinancial. All these point to the importance of the researcher's personal integrity and character. Henry Beecher's seminal 1966 article on research ethics placed greater importance on the researcher's virtuous character and compassion than an external regulatory framework.[13] However, oversight of research ethics has come to emphasize regulations and enforcement.

The Commission calls for the development of "a dual system of external regulatory checks and internal embodiment of appropriate professional norms, such as respect for persons."[1] External regulation can (and some would claim already has) become so burdensome that it can weaken individuals' resolve to develop the personal virtues that ensure ethical research and respect for subjects. The Common Rule is primarily procedural, and it would help if it more explicitly articulated the ethical principles underlying its procedures.

Viewing ethics as part of professional practice helps balance external regulation and personal commitment to ethical values. Professional ethics reminds researchers of the personal responsibilities that go with a privileged position in public service. "Professional standards correlate with ethical duties toward subjects and with the privileges of office and cannot be waived or ignored for expediency, convenience, perceived interests of the many at the expense of the few, or the allegedly superior demands of science."[1]

Professional codes can assist in this area, but professional training needs to go beyond instruction in regulations and procedures. Creative, flexible, and innovative educational programs should be developed to engage researchers with rigorous ethical analysis and a personal sense of ethical responsibility to subjects and society. The Commission recommended that such bioethics training be incorporated into all levels of education, not just left until students are enrolled in professional schools.

4. Respecting equivalent protections

Clinical research is increasingly a global enterprise. Both privately and publicly funded projects are conducted around the world (*see Figure 3*). Most federally funded research must comply with either the Common Rule or FDA regulations, regardless of where it is conducted. Foreign collaborators must agree to comply with the Common Rule. U.S. researchers may accept foreign standards so long as they provide "protections that are at least equivalent" to those in the Common Rule. However, U.S. departments and agencies rarely, if ever, accept foreign procedures as equivalent. The process by which foreign regulations would be deemed equivalent is unclear and controversial. Yet in some cases, other countries have human subjects research regulations that are more extensive than the Common Rule.

The Commission recommends that a procedure for determining equivalent protection be developed and implemented. This would show respect to foreign collaborators and their regulatory mechanisms, and would reduce the burden on U.S. IRBs that currently review research approved under foreign regulations. This recommendation was also made in 2001 by the NBAC and the U.S. Office of Inspector General, and in 2003 by a HHS working group.[14] To date, no country has had its protections formally recognized as equivalent by OHRP. Meanwhile, FDA does accept data from foreign studies conducted according to international standards. Greater clarity and consistency is needed in this area.

5. Promoting community engagement

Community engagement is a term that can mean many different things, including: participatory research where

researchers engage the community as equal partners, using communities as a unit of study or randomization, setting research priorities in consultation with communities, giving community "consent," or using community advisory boards. Underlying such approaches is the value of providing members of the community the opportunity to weigh the risks and benefits of research, identify implications not anticipated by the researchers, and evaluate the protective mechanisms.

Community perspectives on human subjects research have become increasingly important in response to concerns about international research projects. The International Research Panel convened by the Commission pointed to this as an important way to increase accountability for researchers and allow communities a greater sense of partnership in research projects. While the 2002 CIOMS guidelines and the 2008 Declaration of Helsinki do not address community engagement, more recent international guidelines do, particularly those focused on international HIV prevention studies.[15] Countries like Canada and Australia have already incorporated community engagement into their guidelines for research involving minorities within their own countries.[16]

While community engagement is increasingly valued, little evidence is available on the effectiveness of various strategies. UNAIDS and AVAC published guidelines in 2011 on a variety of strategies to promote community engagement.[17] The Commission cited this as an important contribution to research ethics, although focused specifically on HIV prevention trials. For this reason, the suitability of its approach needs to be evaluated for human subjects research more generally. However, these recommendations are grounded in several ethical principles and values that apply to all research: respect, mutual understanding, integrity, transparency, accountability, and community stake-holder autonomy.

At the same time, the Commission and the panel recognized that community engagement does not mean accepting all proposals made by a community. The panel stated that "researchers cannot — and should not — accept uncritically everything that a community recommends or requests."[7] Accommodating community norms should not lead to the violation of widely held ethical principles in human subjects research. For example, several sets of international research ethics guidelines accept that certain communities may have good reasons to use methods other than written documents for informed consent. On the other hand, these same guidelines do not accept replacing individual consent to participate in research with a collective community consent or that of a community leader just because some communities may propose such approaches.

6. Justifying site selection

Site selection for research is important for two ethical reasons. First, only sites that allow for the protection and ethical treatment of subjects should be used. Second, research subjects should be chosen for reasons directly related to the research topic, not because they are easily available, vulnerable, in a dependent relationship with researchers, or other reasons unrelated to the research topic. In addition, the group studied should be able to benefit from the results of the research. The latter is a problem if the subjects who bear the risks or burdens of the research would be unable to afford the interventions subsequently developed. The STD research in Guatemala is the most recent example of research where vulnerable populations were exploited to develop knowledge that would benefit others.

Appropriate site selection can promote good science and provide new information and interventions that are valuable for local communities. International research is rapidly expanding into low- and middle-income countries. Sometimes this is for good reasons, but in some cases the reasons are ethically questionable. Sites can be selected because subjects are vulnerable or have not been exposed to many pharmaceuticals, because regulations are less burdensome, or because protective mechanisms are not developed. For these reasons, "The Commission strongly affirms that the same ethical principles that apply to domestic research should also be applicable on the international front."[1] These principles are that people should not be treated as mere means to others' ends, that people should be treated fairly and with respect, and that risks should be reasonable and balanced with proportionate benefits. These principles do not vary depending on where the research is conducted.

In selecting sites in low-income countries, both ethical and research infrastructure should be in place, or capacity-building should be part of the project. At the same time, limited resources should not be diverted by research away from other local needs. Several factors must be balanced against one another, highlighting the importance of involving local communities, professionals, and IRBs. The Commission stated that much further deliberation is needed on the ethical responsibilities of researchers for the health needs of the broader community from which human subjects volunteer. Such considerations went beyond the remit of this report.

7. Ensuring ethical study design

The ethical concern here is whether scientific advancement is being put ahead of human subjects protection. This issue has been highlighted in recent years around the use of placebo arms when effective treatments are known to exist. The controversy has centered on placebos that were used in trials of the antiretroviral drug AZT, but other cases have occurred also. For placebo trials, the Commission supported the "middle ground" approach proposed several years ago.[18]

This position starts by affirming that ethical research must begin with sound, rigorous science. A clinical trial is justified when there is uncertainty about the effectiveness of treatments. If a study is scientifically flawed, there is no justification for exposing subjects to any risk. Therefore, if it is well established that drug A is better than drug B, giving some subjects drug A and others drug B would not be justified ethically. However, the "middle ground" approach takes some other factors into consideration.

Genetic differences between people may mean that an effective drug in one community may be of unknown effectiveness in another community. A trial of the relative effectiveness of two drugs may be justified then, even if the trial occurs in a low-income country. Also, the control arm may provide the standard of care available in a region, even if that is not the best proven intervention. Concerns have been raised that this leads to a double standard, where subjects in the control arm in a high-income country might get a more effective intervention than those in a similar trial in a low-income country. The Commission holds that different control interventions in different countries can be justified provided certain rigorous conditions are met.

Ethical research must begin with sound, rigorous science. A clinical trial is justified if there is uncertainty about the effectiveness of treatments.

The first is that the control intervention should be based on the local standard of care that should be available at the study site. This does not mean that if no health care is available, placebos are justified. Instead, it requires a careful evaluation of what could or should be available given local conditions. The Commission recognized that this issue continues to generate debate, but if the best proven therapy is insisted on, much important research will not occur because it will be declared unethical.[19]

The second factor is that "it is highly desirable that the meaning and significance of studies be contained within the study itself."[1] An equivalence study might show that a new drug is as effective as an old one, but then another study would be needed to show if either is more effective than placebo. This is less than ideal, while a placebo study would itself show if the new drug is effective. This could justify a study design using a placebo arm.

Third, if the best-proven therapy is not used in the control arm, the risk of harm to subjects must be minimized as much as possible. The types of harm to which the subjects are exposed should not be serious or severely uncomfortable. For example, asking depressed patients not to take established medication as part of a placebo-controlled study could put them at risk of suicide. The proportionality of the additional risks should be carefully scrutinized by IRBs before approving such studies.

8. Promoting current reform

The Commission generally supports the objectives and goals of the ANPRM published in July 2011 by HHS and OSTP.[9] The Commission held that many of its recommendations could be acted on during the current reform effort. This is particularly the case for improving human subjects protection and reducing the burden, delay, and ambiguity for researchers. Many low-risk and minimal-risk studies continue to be reviewed by full sittings of IRBs, leading to concerns that some research is being over-regulated.

The Commission addressed the importance of balancing intellectual freedom against regulation in an earlier report.[20] This argued at length that the level of regulatory review needs to be calibrated against the level of risk to human subjects. The degree of oversight needs to match what is necessary to ensure justice, fairness, respect, security, and safety. Reform that eliminates review of certain lower-risk research is supported, as well as a commitment to ongoing evaluation of the types of research that may undergo expedited review.

At the same time, review of research that involves more than minimal risk should be thorough and complete. This will be facilitated by reducing reviewers' workload by removing lower risk protocols. The Commission agreed with the ANPRM's introduction of exempt research that would be registered to allow it to be tracked.

Regarding multisite studies currently reviewed by many IRBs, the Commission supports efforts to reduce duplication of effort. Multiple reviews can unnecessarily delay important research, be costly, lead to scientifically problematic changes, and delay potential benefits reaching patients. Multiple reviewing is also of questionable benefit in enhancing subject protection. The Commission accepts the ANPRM proposal that a single IRB of record may be sufficient for multisite

studies, but should not be obligatory.

The Commission agreed with the ANPRM's concerns about how informed consent is currently operationalized. Some informed consent forms read like sales documents rather than presentations of the most important information people need to decide about participation. Reform must bring renewed attention to the ethical principles underlying the informed consent process and identifying approaches that achieve such consent. Empirical data are needed to guide such decisions. Flexible guidelines and procedures for informed consent are needed, especially for social and behavioral science research.

Finally, all federal guidelines should be consistent. The harmonization and clarification of existing rules is a higher priority than the creation of new rules.[7] Standardization is also needed in adverse event reporting. A web-based portal is currently used by some federal agencies and should be rolled out across all departments and agencies supporting human subjects research.

Conclusion

The Commission provided a concise set of recommendations, with clear justifications for those where ethical debate continues. Its review of current human subjects research provides some statistical detail about the amount and type of research. However, it provided little information on how well current ethical guidelines are being implemented or whether they are protecting subjects. Such an investigation was not feasible in the short time period given to the Commission. Given the challenges identified in collecting basic data on studies, it is unlikely that the detailed information needed to examine such factors is readily available.

Many of the Commission's recommendations were not new or innovative. The report was strongly critical of this. It pointed out where the same recommendation had been made in previous research ethics reports going back several years. In many, no response to the recommendations came from any arm of the federal government. Such silence raises questions about the commitment to ethical reform. To avoid a similar silence, the Commission calls on specific bodies to respond one way or another to all its recommendations. One certainly hopes it will not take revelations of another ethical disaster to bring about necessary and appropriate reform to ensure current human subjects research is moral science.

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