

Existing International Ethical Guidelines for Human Subjects Research: Some Open Questions

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International guidelines regarding ethics, and in particular the ethics of clinical research, are problematic on two broad levels. First, by asserting their universality, "international" guidelines obscure real and legitimate cross-cultural differences in ethical expectations. International guidelines seek to make homogeneous something which is not necessarily so. Second, existing guidelines are ambiguous about their objectives and purposes. On the one hand, guidelines are structured as a set of goals, largely aspirational in language and content. But on the other hand, such guidelines also suggest a normative function, providing a set of standards by which to judge and, if appropriate, sanction investigators' conduct.

These criticisms are not intended to argue that international guidelines are useless. Nor are they intended to question the good faith under which such guidelines are developed. Rather, we wish to suggest that the role of present international guidelines is somewhat more limited than is ordinarily appreciated. In particular, the assumption of a normative function by international guidelines is ethically and practically problematic. International guidelines and *their application* may unavoidably and wrongly marginalize alternative visions of what is ethically correct, and they may therefore proscribe or be used to proscribe necessary investigations in certain locales that are conducted by local investigators in good faith and with local community approval.

International guidelines are not suited to perform a normative function nor has the international machinery been sufficiently developed to accomplish this objective in the case of clinical research. This deficiency is highlighted

by the failure of international guidelines to provide a workable mechanism for dispute resolution. Indeed, conceived of as standards, they largely neglect the very possibility of disputes. This difficulty is only magnified when alternative ethical visions must be reconciled with the broad, predominantly Western orientation of existing international guidelines.

The merits of international ethical standards for clinical research must be evaluated against the specific goals which such standards are expected to achieve. Here, we seek to clarify what in fact these goals are and how successful the guidelines are at achieving them. We will not provide a substantive evaluation of the relative merits of alternative ethical rules nor enter the debate about ethical universalism versus pluralism.¹ However, drawing on the debate surrounding international human rights, we will show how international ethical standards for clinical research do indeed serve a useful aspirational function. We will then evaluate situations in which we believe existing guidelines are limited. We will identify some of the harmful consequences of the misapplication of guidelines as normative standards. Finally, in a preliminary way, we will suggest an alternative approach to the development of guidelines, one that may facilitate the resolution of existing dilemmas. In essence, we will argue that more attention is required to what we characterize as the next step in the debate over international standards for ethical norms, namely, the development of mechanisms to apply the largely aspirational principles of any international guidelines which may be consensually developed to the sometimes conflicting demands of trans-cultural, multi-

national clinical research.

Three international standards

In 1947, after the Second World War and the revelations of human experimentation in Nazi concentration camps, the allied nations promulgated the Nuremberg Code.³ The Nuremberg Code articulated ten basic principles that must be observed in research with human subjects. The first principle is that the "voluntary consent of the human subject is absolutely essential." In elaborating upon this, the Nuremberg Code states that the subject should be free of coercion and "should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision [regarding giving consent]." Other principles in the Nuremberg Code describe the necessity that the proposed research be meaningful and essential, be based on prior animal experiments, and "avoid all unnecessary physical and mental suffering and injury." Scientists are required to end experiments that are "likely to result in injury, disability, or death to the experimental subject."

The Nuremberg Code is thin on specifics regarding these principles, however. The utility of the general principles it outlines is thus limited by the absence of explication of how they might be *applied*. For example, according to the Code, the level of risk involved in an experiment should be in proportion to the "humanitarian importance of the problem." Yet no mechanism for evaluating the level of permissible risk is provided. Also, the Code provides no guidance regarding what constitutes "unnecessary injury." And the Code proscribes investigations in which there is *a priori* reason to believe that death or disability might occur—unless the researcher also serves as a subject. Yet this is like permitting someone to murder if he is willing to commit suicide.

The Declaration of Helsinki, adopted in 1964 and modified in 1975, 1983, and 1989, sought in part to develop more specific guidelines regarding the application of ethical principles to clinical research and sought as well to correct one of the primary deficiencies in the Nuremberg Code: its lack of consideration of the participation in research of less than fully autonomous subjects, those with "legal incompetence."⁴

With respect to specific guidelines, the Declaration states that experimental protocols should be reviewed by "independent committees" (introduced in the 1975 version). The Declaration also states that "every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society."

The Declaration elaborates upon consent, describing the content of the information to be given to the subject, specifying that the consent preferably be in writing, and specifying that an alternate physician be designated to obtain consent from subjects in a "dependent relationship" to the investigator. Strangely, the Declaration permits physician-investigators to request of the independent review committee that informed consent be waived if they deem such a waiver to be "essential." The Helsinki Declaration includes a novel sanction for those violating the Declaration not found in the Nuremberg Code (where sanctions are not discussed at all): research not conducted in accordance with the Declaration "should not be accepted for publication" (introduced in the 1975 revision).

The Nuremberg Code and the Helsinki Declaration share a Western orientation, focusing on the primacy of the individual and, moreover, provide little guidance as to the applicability of their principles in non-Western settings.⁴ A first tentative effort to broaden the applicability of these standards appeared in guidelines promulgated jointly in 1982 by the Council for International Organizations of Medical Sciences (CIOMS) and the World Health Organization.⁵ There was a recognition that Nuremberg and Helsinki were too restrictive to be applied in all research settings. In particular, the stated purpose of the CIOMS guidelines was to amend the principles of the Declaration of Helsinki "to suggest how [these principles] may be applied in the special circumstances of many technologically developing countries." These guidelines betray an appropriate concern that cross-cultural differences in ethical concepts and standards might be cynically perceived by Western investigators as research "opportunities." However, there is also a tension in these guidelines between the belief that "the ethical implications of research involving human subjects are identical in principle wherever the work is undertaken" on the one hand, and the desire for a locally specific application of ethical principles on the other.

The CIOMS Guidelines have a number of novel provisions, most directed to the problem of research in developing countries sponsored by outside agencies, a situation in which the Guidelines recognize that the proposed research might subserve external rather than local interests. The Guidelines recognize the primacy of local concerns when evaluating the objectives of research protocols. Moving beyond the Declaration of Helsinki, they provide specific recommendations with respect to medical care for research subjects and state for the first time in an international standard that those injured in the conduct of research should be compensated.

The Guidelines recognize that obtaining free and informed individual consent is not always possible. While implicitly maintaining this ideal, they state that "[T]he

involvement of human subjects in biomedical research must be contingent, *whenever feasible*, upon freely elicited informed consent and upon liberty to withhold or withdraw collaboration at any stage without fear or prejudice.⁶ And they recognize that not all subjects are so situated as to provide what in the West is considered informed consent:

Ideally, each potential research subject should possess the intellectual capacity and insight to provide valid informed consent, and enjoy the independence to exercise absolute freedom of choice over the extent of the collaboration without fear of discrimination. However, many investigations, and particularly those intended to subserve the interests of underprivileged communities and vulnerable minorities, including children and the mentally ill, would be debarred if these preconditions were accepted as mandatory criteria for recruitment.⁷

In part because of this, a system of proxy consent is proposed:

Where individual members of a community do not have the necessary awareness of the implication of participation in an experiment to give adequately informed consent directly to the investigators, it is desirable that the decision whether or not to participate should be elicited through the intermediary of a trusted community leader.⁸

There will, of course, be considerable variation by culture as to who is acknowledged to be a "community leader."⁹

Commendably, the CIOMS Guidelines also explicitly acknowledge that, even when present, informed consent alone is inadequate to protect subjects from abuse; the performance of an independent review is therefore recommended. Such review "[should accommodate] with advantage...respected lay opinion in a manner that provides effective representation of community as well as medical interests."¹⁰ Thus, in general, the Guidelines deal with the problem of inability to obtain informed consent from all populations by displacing the locus of consent and also by replacing it, to some extent, by ethical review of the research by a disinterested local committee.

Finally, it is worth noting that the CIOMS Guidelines also explicitly recognize that international guidelines have limits in that they acknowledge at least two areas where there is so much cultural and legal variability that no uniform principles could be enunciated: research directed to termination of pregnancy and research involving prisoners. That the Guidelines do not suggest any resolution to conflicting ethical norms in these areas is indicative of the fact that international standards, while well suited to perform an aspirational function, are generally incapable of

eliminating international ethical disagreement and dialogue altogether.

The aspirational function of existing international guidelines

Nuremberg, Helsinki, and CIOMS, like the International Declaration of Human Rights adopted by the United Nations 1948,¹¹ have emerged during a time of a revolution in the field of international law. The assertion of jurisdiction by the International Military Tribunal at the Nuremberg Trials was in part predicated upon the notion of a natural, universal law to which all individuals could be held accountable, notwithstanding the specific laws of the jurisdiction under which their criminal behavior occurred. Such a notion formed a necessary basis for the trial of the heinous crimes committed by Nazi physicians and others. The Nuremberg Code, which emerged from the trials, attempted to set forth a legal framework that would justify clinical experimentation on humans provided that it was "within reasonable, well-defined bounds." The goal of this code was to acknowledge the importance and necessity of clinical experimentation while providing a universal standard for condemning the conduct of Nazi physicians.¹² In this respect, the Nuremberg Code, like the Universal Declaration of Human Rights, attempts to set forth basic principles which may serve as a benchmark for specific standards and legislation to be developed by each nation.

Under such a conception of law, no longer could the treatment of a nation's citizens be viewed as a purely domestic matter. Historically, with limited exceptions, international law applied solely to the manner in which nations interacted with each other. Individuals were deemed to have rights which stemmed from their governments and were enforceable to the extent allowed by their governments.¹³ Since the Second World War, however, this position has lost virtually all its proponents. Though there are nations which differ on how human rights should be applied, no nation in the world has formally repudiated the Declaration or the idea of the importance of human rights.¹⁴

The existing international guidelines for clinical research mirror this development and provide a predicate for international supervision of conduct within nations. The Nuremberg Code states, for example, that "all [protagonists of the practice of human experimentation] agree...that certain basic principles must be observed in order to satisfy moral, ethical, and legal concepts." The Helsinki Declaration also invokes a very broad mandate, setting forth "recommendations as a guide to every doctor in biomedical research involving human subjects."

The Helsinki Declaration, however, is more explicit in its aspirational function: "It is stressed that the standards as drafted are only a guide to physicians all over the world.

Doctors are not relieved from criminal, civil, and ethical responsibilities under the laws of their own countries." The Declaration suggests that it simply sets a floor for what will constitute acceptable conduct rather than defining precise obligations. However, by specifically including host nation "ethical responsibilities" among those obligations that remain binding on a physician, the Declaration specifically leaves open the possibility that conduct not contemplated by the Declaration or potentially proscribed by it—might still be ethically practiced by a physician. In other words, the Declaration eschews a role as an enforceable code, implying that without action by each specific nation the Declaration will not be enforceable.

Beyond breaking down the wall of exclusive domestic jurisdiction, international ethical guidelines for clinical research, again similar to international human rights treaties, have made it commonplace to speak of standards to which individuals and nations will be held to account. Although the precise definition of these universal standards remains problematic,¹⁵ the notion that the adoption and implementation of such standards is a legitimate topic for international efforts has gained wide-spread acceptance.¹⁶ International human rights law provides a close parallel in the evolving nature of human rights norms. For example, since the adoption of the Universal Declaration of Human Rights, a wide variety of covenants have entered into force relating to topics as diverse as civil and political rights, women's rights and economic and labor rights.¹⁷

At the same time, however, human rights scholars have acknowledged that assertions about universality of human rights are problematic. For example, although there may be broad international agreement, at least in principle, to respect these rights, there is little consensus as to a utopian framework of rights.¹⁸ Rather, different nations have set about implementing protections of human rights in a wide variety of ways with varying degrees of good faith. Even in the case of the right to be free from physical abuse, governments have invoked—without any support in international law—national security concerns to defend noncompliance with this norm.¹⁹ Thus, neither human rights norms, nor, as we argue, existing international ethical standards, have decisively resolved the timeless philosophical debates about how a utopian society should be governed and its citizens treated. Instead, and beneficially, a debate has begun in both areas which transcends national borders or simple equations between national power and the ability to dictate rules for others. In short, the effort to arrive at consensual norms through international discussion has begun while parallel effort continues within each society to express international norms in locally meaningful ways.

International ethical guidelines are *not*, however, despite any invocation to such effect, designed to be a code

capable of regulating conduct in specific situations. Without further elaboration and implementation on a local level, the broad aspirational notions expressed remain no more than that—a valuable but incomplete system. Moreover, there is a significant social cost and theoretical unsoundness in the way existing guidelines are applied. Through inappropriate assertions that existing ethical standards provide operational guidelines for ethical conduct, socially valuable and ethically permissible research may be foreclosed.

Problematic cases in the AIDS pandemic

It is in attempting to address disparate local ethical expectations that one becomes acutely aware of the limits to international ethical guidelines and the real societal cost associated with them. In many cases, the existing international ethical codes for clinical research simply do not provide guidance to trans-cultural ethical quandaries. Quite often, a researcher would be forced to choose between two supposedly "universal" ethical principles in a research protocol in a developing society. For example, consider a necessary and important hypothetical protocol involving women in an orthodox Muslim society. Under the principle of informed consent, the researcher must ask each woman's permission. If a woman responds that she will do whatever her husband says, what should the researcher do? Should the research be abandoned? What if the outcome would significantly enhance the well-being of women in this society? The universal principles of autonomy and justice may conflict.²⁰

The influence of specific cultural, clinical, and economic settings on the ethical design of research has been especially manifest in the confrontation of the AIDS pandemic. This pandemic has called into question a universalistic conceptualization of clinical research ethics based on a Western model because, here, the same dangerous disease occurs throughout the world in disparate socio-cultural settings, everywhere raising ethical problems but not invariably yielding the same solutions.²¹ Difficulties have sometimes arisen in satisfying conflicting ethical expectations, and certain research protocols that are unacceptable in the West may be seen as acceptable in non-Western countries.

For example, Michele Barry, a physician at Yale University, described a situation wherein the ethical expectations of the investigators' and subjects' cultures clashed in a Tanzanian research project. In this seroprevalence study, maternal and infant blood was to be sampled upon birth. Her home Institutional Review Board, as part of its approval, had required that subjects be informed of their test results. Tanzanian authorities, however, had a conflicting set of requirements: Worried that the results could cause psychological trauma to the women, and cognizant of the

fact that no meaningful therapy was available for HIV-positive individuals in Tanzania in any case, they insisted that the Western researchers not tell their subjects that blood was being taken or what the outcomes of the tests were. This study, which both the host nation and the investigator felt was valuable, was abandoned because of this conflict.²³ In other situations, disagreement between local ethics committees and those of the international body funding the research have led to accession by the local investigators to some changes in the research protocol—changes which were largely meaningless given local cultural and economic constraints and which were resented by the local participants.²³

Problems have arisen as well in what have heretofore been regarded as relatively settled matters within Western research ethics, such as placebo usage. For example, a Brazilian investigator has recently proposed to compare the drug dideoxycytidine with placebo in order to assess the efficacy of this drug in prolonging survival in HIV-infected patients; an additional goal of the trial is to determine if an investment by the Brazilian government in this drug would be worthwhile. The study raises two major problems when seen from the perspective of orthodox Western research ethics: Is it ethical to conduct a placebo controlled trial when efficacious therapy for HIV infection (i.e., AZT) exists? And, is it ethical to design a clinical study to answer an economic question?²⁴ From the Brazilian perspective, the answer to both of these questions is affirmative. The trial was ultimately not conducted.

A model for the negotiated settlement of trans-national ethical disagreement

As the foregoing examples illustrate, international ethical guidelines may be applied to do something which by their own terms they are not designed to do, namely to define permissible conduct for investigators in a wide variety of cultural and fact-specific situations.²⁵ Within any given nation or state, there exists a debate over ethical standards as they apply to a variety of difficult factual situations, e.g., euthanasia, abortion, transplantation, and so forth. What is novel, in the international context, is that there is both conflict and the absence of an effective arbiter. For example, in the United States, ultimately a local ethical debate will be resolved by the courts or by congress. A recent decision by a doctor to assist one of his patients in ending her life raised many difficult ethical issues. The physician however, was brought before a grand jury. The decision by the grand jury not to indict the physician indicated something about acceptable ethical as well as legal norms.²⁶ There is no comparable mechanism in the international ethical arena.

More appropriately, the international standards articulating certain ideas and norms could be interpreted and

applied to individual countries—despite the fact that the standards are addressed to individual physicians. Disparate interpretations, such as they might exist, would not be configured as problematic so long as there were no contact between believers in the different interpretations. But the conduct of trans-cultural clinical research, particularly in the context of the AIDS pandemic, has brought to light the theoretical limits of ethical guidelines—both in structure and in application—in such a manner. It has become apparent that what existing standards of ethics are not is a mechanism for the resolution of conflicting ethical expectations under circumstances where the universality of the principles articulated within them is not recognized, or under circumstances where the principles articulated within the standards conflict with each other.

To address such situations, we propose a different type of international ethical guidelines, a type with a different objective. Such international guidelines, instead of emphasizing the *content* of research ethics, would emphasize the *process* in which any disagreement over content might be settled. Such “procedural” guidelines would help to settle, through negotiation, possible conflicts between disparate ethical ideals. Ideally, such a negotiation would take place between true representatives of those who wish to conduct the research and those who would be the subjects.²⁷

We would recommend a two step process through which 1) international guidelines are subject to ratification within each nation and 2) a new type of international ethical code is developed which outlines dispute resolution principles for conflicting ethical expectations. Implicit in this recommendation is support for an ongoing international dialogue that privileges all perspectives on the ethics of clinical research (not just Western perspectives).²⁸ The quintessential dilemmas then become 1) to discover local ethical expectations, 2) to assess the good faith and legitimacy of the representatives, and 3) to ensure adequate expertise on the part of the subject representatives. In this way, international guidelines might achieve an increasing level of legitimacy and improve the chances that any codes that were developed would be ratified and implemented on the national level.

Ratification The adoption of the Universal Declaration of Human Rights and the subsequent adoption by the United Nations of a number of human rights covenants designed to implement the broad principles of the Declaration provides an instructive model for the process of nation-by-nation adoption of ethical guidelines for clinical research. Although the Universal Declaration operates as a starting point for the debate over human rights, since 1948 the adoption and implementation of the various human rights covenants have given meaning to the broad *aspirational* values embodied in the Declaration.

The legal focus of many human rights covenants has

been ratification. Human rights advocates argue that such covenants would find their best use if adopted at a national level and made a part of domestic law, perhaps through enabling legislation.²⁹ Indeed, at present, international codes have rarely been invoked as legal precedent at the national level in the United States. There is ongoing debate over the status of such international rules in domestic law.³⁰ For example, the United States has consistently endorsed the notion of international human rights, but has not ratified a number of human rights covenants and has not enacted enabling legislation to accompany the one covenant the nation has actually ratified, the United Nations treaty banning genocide. Human rights advocates have argued that the cause of international human rights would be strengthened if the United States were to ratify and enable human rights covenants.³¹

We would recommend that ethical guidelines for clinical research be subject to a ratification procedure in each nation. In some nations, the government itself may adopt the guidelines as rules of ethical conduct; alternately, and probably less optimally, professional entities or associations within each nation might adopt some or all of the guidelines as standards for members of the professions. Guidelines may be adopted with reservations. In other words, a nation may adopt all but selected provisions of a given ethical code.

Dispute resolution To the extent that nations come to agreement on what is ethical conduct, we believe this represents a significant advance in and of itself. This process will require a fundamental shift in the way international ethical standards are regarded. International ethical standards would not simply be presumed and asserted, but would be posited and explored. However, there are theoretical and practical limitations to this process of consensus building. Researchers and their home institutions and subjects and their representatives will require principled responses to potential conflicts in ethical interpretation and implementation. Specifically, how might the international community both monitor human subjects research and overcome the theoretical limitations in existing ethical codes? How might one deal with the problem that international ethical guidelines, including the existing ones, may become inapplicable, if not irrelevant, when confronted with the cultural and economic variation that is manifest at locales around the world? With an eye towards respecting the local ideals of both subject and investigator, we propose the following general standards:³²

1. The host country for the research, or, more specifically, the representatives of research subjects, should have a presumptive claim to ethical guidance. In the event of a conflict, the host country's ethical standards, if they are more restrictive, should always prevail. In other words, if there are two interpretations of what would be ethical—one favoring the research and the other barring the re-

search—if the interpretation barring the research is favored by the host community, the research must be viewed as unethical.

2. A researcher retains an allegiance to his base institution, his local community. To the extent a base institution views the research as unethical, the researcher should not go forward irrespective of what the host nation says, unless the ethical dispute can be negotiated.

3. To the extent that any nation or institution adopts ethical guidelines, including any internationally promulgated guidelines, it should be bound by those guidelines irrespective of to whom they are being applied within the nation. There should not be favoritism in application of agreed-upon standards.

4. When research that is considered desirable by either party is proscribed by existing international standards or by either party's own standards, formal negotiations between the parties to understand the source of disagreement and to arrive at a consensus, if possible, should take place. The proposed research should not simply be abandoned. Relevant international standards might here serve as aspirational guides. If a consensus is reached, the research should be viewed as necessarily ethical, its deviation from any international standards notwithstanding. The negotiations, or course, must be fair.³³

Ideally, such guidelines would encourage a negotiated settlement of ethical differences, so that both parties, researchers and subjects, might be comfortable with the proposed research, ethically and clinically. But as a necessary predicate to the application of these guidelines—and for the negotiations to be fair—we emphasize that the legitimacy and good faith of local representatives is fundamental to the process. We are not advocating the view that the assertion by a host nation regarding these matters is perforce acceptable. Otherwise, for example, it is easy to envisage the selective abuse of minorities within host nations or bad faith actions by research subject representatives. This type of evaluation is analogous to the inquiry common in human rights investigations. Monitors of international bodies are not ordinarily satisfied by a mere formal adoption of applicable human rights covenants by a given nation.³⁴ Moreover, the potential for coercion of impoverished host nations by initiating countries will need to be addressed.

In the same way, our proposal does not mean that Western investigators can be released from their own commitments to ethical behavior. We are not sanctioning a lower standard of conduct for Westerners simply because they are in a nation which allows them to “get away” with research that would not be ethical in their own cultures. Researchers are not excused from their own ethical norms because they are operating within the framework of another system. This principle is critical for ensuring that other ethical systems are not manipulated by outsiders to

accomplish research which would otherwise not be possible within their own culture. What this proposal underscores is the need for respect for differing ethical systems and a recognition that differing socio-economic settings will give rise to alternative procedures.

Universal principles pose an aspirational value. Without further action on the part of a given nation, they are nothing more than that—principles. We suggest that the system of international clinical research ethics, lacking such dispute resolution mechanisms as courts, legislatures, and executives, poses a unique challenge. We recognize the value and importance of existing guidelines. But we wish to advance the debate towards formal adoption of the codes and towards creating systems for dispute resolution. Not only do we believe that this will facilitate socially useful research in a fair way, but we believe that ultimately it will lead to a more expansive and just vision of human subjects research.

References

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5. Council for International Organizations of Medical Sciences, *Proposed International Guidelines for Biomedical Research Involving Human Subjects*, (CIOMS: Geneva, 1982), hereafter *CIOMS Guidelines*.
6. *CIOMS Guidelines*, p. 7, emphasis ours.
7. *CIOMS Guidelines*, p. 8.
8. *CIOMS Guidelines*, p. 26-27.
9. Community leader consent may be the only alternative—however unsatisfactory by Western standards—to individual consent in many cases where beneficial research is essential. This alternative may not necessarily be ethically incorrect for the society of which the research subject is a member. Western investigators should also appreciate that what appears to them to be coercion may, from the perspective of local inhabitants, represent cooperation and identification with the groups to which the individual belongs. This observation, however, does not relieve Western investigators of the responsibility to avoid coercion arising from their *own* actions.
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15. For example, it is unclear that existing international standards reflect a truly wide-based consensus regarding clinical research, developed, as they were, to reflect largely Western ethical ideals, and unrecognizant, as they are, of real situations in the developing world. Indeed, even when seen from within a Western perspective, existing codes for clinical research ethics often draw heavily from analytic philosophy, ignoring other equally important Western approaches, such as existentialism, communitarianism, and so forth. For some discussion of possible approaches to potentially disparate research ethics, see: N.A. Christakis, "Ethics are Local," *op. cit.*
16. See, for example, H. Steiner, "The Youth of Rights (Review of Henkin: The Age of Rights)," *Harvard Law Review* 104 (1991): 917.
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