AMERICAN LAW AND THE GOVERNANCE OF RESEARCH ETHICS

Time for International Change*

Professor Capron indicates that the US has taken the lead among nations in adopting a system of ethical review conducted by committees known as institutional review boards ("IRBs"). The "Common Rule" implemented by the Office for Human Research Protections ("OHRP") specifies the requirements for the establishment of IRBs, their operation and the standards for their decisions about research protocols and in overseeing ongoing research. A research institution must comply with these requirements in order to receive a "Federal Wide Assurance" ("FWA") from OHRP. All research institutions that receive support from the US government for human subject research or whose staff collaborates on such research must have obtained an FWA. Professor Capron explains that the present US rules are a response to particular problems and scandals in research and were developed in the context of the bureaucracy underlying US medical science. It is inappropriate for research ethics committees around the world to have to apply for an FWA from a US agency, as many do. Despite its influence on a number of jurisdictions, there is nothing magical about the US regulatory approach and no reason for it to constitute the global norms and procedures for research ethics. Professor Capron argues that however salutary a role the US rules may have played, the time has come for a less US-centric form of global governance of the ethics of research with human subjects. The dominance of the US regulations discourages governments from taking sufficient responsibility to ensure that research conducted within their jurisdictions is ethical. Yet, some means of common governance is needed to avoid a "race to the bottom". All countries should have and enforce basic standards of research ethics and accountability for sponsors and investigators. Governance includes less formal means of directing action or regulating behaviour, not only through law. International arrangements can take four forms: formal or informal at either a governmental or

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non-governmental level. Professor Capron considers a possible arrangement would be for governments to agree on a common framework that would set enforceable standards and then proceed to develop a system akin to the WHO's International Health Regulations with enforceable obligations and defined decision-makers.

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I. Introduction

1 This article seeks to address a central problem concerning the role of law in overseeing the ethics of research with human subjects, namely, the question "whose law?" The article's thesis is that US law has played, and continues to play, a disproportionate role in the governance of biomedical research (especially clinical trials) which has now become a global activity involving collaborations between public and private research sponsors and investigators from developed countries, on the one hand, and physicians, patients and medical institutions in less developed countries, on the other.

2 Saying that the US plays an inappropriate role in the manner in which research ethics is governed worldwide does not imply that the rules promulgated in the US are necessarily misguided or ineffectual; indeed, over the past several decades, it is likely that more problems would have arisen had the rules not existed and played the global role they have. One of the reasons that countries may be cautious about changing the governance paradigm is the absence of other means for ensuring something like a level playing field regarding ethical review. Yet, for reasons that are explored below, change is needed and will probably require combined action by the US government under its existing regulations and by an intergovernmental body such as the World Health Organization ("WHO").

II. The development of US regulations

3 The law that governs the ethics of research with human subjects has been shaped by the recurrent scandals that have marred the history of this vital area of human activity for more than a century. Repeatedly,

human beings – often patients and typically poor and vulnerable – have become unconsenting vehicles for the development of new techniques to prevent and treat diseases and injuries; occasionally, they seem simply to have been the victims of physicians' scientific curiosity.[1] Experiments in the early years of the 20th Century that involved among other things exposing individuals in orphanages and prisons to syphilis and gonorrhea, as well as public protests over contaminated vaccinations, led the German government in 1931 to adopt regulations on medical innovation that required "unambiguous consent" from research subjects. Yet the failure to enforce those guidelines led to the greatest atrocity, the experiments conducted on Nazi concentration camp inmates during the Second World War, from which came the so-called Nuremberg Code, the set of ten principles to govern research with human beings articulated by the US military tribunal in passing sentence on the Nazi physicians and their colleagues in 1947.[2]

4 Although the Nuremberg Code – which was an early example of international human rights law and some of whose provisions became part of the Universal Declaration of Human Rights in 1948 and subsequent covenants and other instruments – was written by judges from the US and heavily influenced by medical testimony regarding alleged research practices in US institutions at that time, the Code had little influence on investigators in the US in the decades after it was handed down. Not only did the infamous Tuskegee Syphilis Study, which had been begun in 1932, continue unabated until it was revealed by a journalist in 1972, but other studies of sexually transmitted diseases were conducted with government support that went beyond observing the course of illness in already-infected persons (as in the Tuskegee study) to infecting mentally incapacitated patients, prison inmates, sex workers and soldiers in Guatemala and prison inmates in Indiana and New York.[3] To cite only some examples from a depressing litany of unethical research, the Atomic Energy Commission sponsored secret radiation experiments using prisoners and orphans for 30 years beginning in the mid-1940s,[4] the Armed Forces and the Central Intelligence Agency conducted studies on psychoactive drugs (seen then

1 See S E Lederer, *Subjected to Science: Human Experimentation in America Before the Second World War* (Baltimore, MD: Johns Hopkins University Press, 1995); W Weyers, *The Abuse of Man: An Illustrated History of Human Experimentation* (New York, NY: Ardor Scribendi, 2003).

2 P J Weindling, *Nazi Medicine and the Nuremberg Trials: From Medical War Crimes to Informed Consent* (London, UK: Palgrave, 2004).

3 T R Friedman & F S Collins, "Intentional Infection of Vulnerable Populations in 1946–1948: Another Tragic History Lesson" Journal of the American Medical Association 2010; 304: 2063–2065 (published online 11 October 2010 at <http://jama.ama-assn.org> (accessed 20 October 2010)).

4 *The Human Radiation Experiments: The Final Report of the Advisory Committee on Human Radiation Experiments* (New York, NY: Oxford University Press, 1996).

as being potentially used by an enemy regime) that resulted in several deaths of subjects who had been deceived or coerced, researchers at a state institution for retarded children intentionally infected them with hepatitis, and investigators injected cultured cancer cells into non-consenting, elderly, debilitated patients at the Jewish Chronic Disease Hospital ("JCDH") in Brooklyn, New York.[5]

5 The rules that govern human subject research today began to emerge in the mid-1960s as the topic received increased attention (such as when the World Medical Association approved the Declaration of Helsinki in 1964) and as information began to emerge more widely into professional circles and even the lay press concerning some of the unethical studies, especially when Henry Beecher, a leading faculty member of the Harvard Medical School, developed a long list of unethical studies that had appeared over the course of a year in a leading medical journal, which he described in a lecture and then published in June 1966.[6] The National Advisory Health Council concluded in 1965 that the policies which had been in place for a number of years for intramural research at the National Institutes of Health ("NIH"), requiring informed consent and prior peer review, should be extended to NIH-funded research carried out at universities and other external research centres. At the time, considerable attention was being paid to the legal proceedings in New York to censure and reprimand the physicians who had conducted the JCDH experiments, partly with NIH funding. On 8 February 1966, Surgeon General William H Stewart announced a policy that research supported by the Public Health Service would have to undergo prior review "by a committee of [the investigator's] institutional peers".

6 With the revelation of the Tuskegee study in 1972 – along with public alarm over certain research using prisoners and a study, conducted in Scandinavia, involving perfusion of the severed heads of aborted human foetuses – the US Congress held hearings on the manner in which human subjects were or were not protected in research conducted by US scientists, especially with federal funding. When it appeared in 1974 that Congress might engage extensive regulations, the Department of Health, Education and Welfare (the predecessor to the present Department of Health and Human Services ("HHS")), in an attempt to avoid legislation, issued a full set of regulations. (This strategy was a partial success for the Department, as the National Research Act merely required consent from research subjects and the establishment of "Institutional Review Boards" at research institutions

5 J Katz, with A M Capron & E S Glass, *Experimentation with Human Beings* (New York, NY: Russell Sage, 1972).

6 H K Beecher, "Ethics and clinical research" New England Journal of Medicine 1966; 274: 1354–1360.

and left the details of any regulation to the Department, in response to the recommendations that would be forthcoming from the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research.) An important feature of the 1966 policy was its reliance on the research institution as the relevant unit to provide ethical review. The 1974 regulations retained the same basic approach although membership in the review committee, in addition to peers in the investigator's discipline and from other scientific fields, was broadened to include at least one member not otherwise affiliated with the institution. The reason for treating the research institution as the relevant unit for conducting ethical review was neither any empirical evidence as to the efficacy of such a policy nor a set of governance principles. Rather, since the job of administering the 1966 policy was initially assigned to NIH's office of research grants (until the Office for Protection from Research Risks was created five years later), the ethics policy was simply handled in the same manner as policies on grant administration. Funds for research are distributed based on the institution where an investigator is employed; each grantee institution was required to give an "assurance" that it would spend the funds in the manner described in the grant application and in accordance with federal regulations. Subsequent revisions in the research ethics rules in response to the 1978 recommendations of the National Commission did not alter the basic governance structure when new regulations were issued in 1981 by the HHS and the Food and Drug Administration ("FDA"). Likewise, when the various federal departments and agencies that sponsor or conduct research with human beings responded to a 1981 report by the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research[7] by issuing the so-called "Common Rule" in 1991, the major effects were to remove small idiosyncrasies in the different sets of rules and to consolidate the issuance of "Federal-Wide Assurances" ("FWAs") in the Office for Human Research Protections.[8]

III. Why a US-centric system is unwise

7 The story of US regulations is set out above not because it is unique but simply to remind us that the present rules are a product of human actions (both good and bad), of politics, law, and bureaucracy, rather than of a rational, scientifically directed process. As suggested at

7 President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, *Protecting Human Subjects: First Biennial Report on the Adequacy and Uniformity of Federal Rules and Policies, and Their Implementation, for the Protection of Human Subjects in Biomedical and Behavioral Research* (Washington, DC: US Government Printing Office, 1981).

8 Office for Human Research Protections ("OHRP"), *Assurances* at <http://www.hhs.gov/ohrp/assurances/assurances_index.html> (accessed 10 October 2010).

the outset, this history does not make the resulting rules wrong but merely parochial and, more to the point, unsustainable as the basis for an international system of research ethics governance. A well-functioning system to oversee human subject research simply cannot depend on the rules and administrative structure of a single nation, but at the same time, some means of common governance is needed to ensure that comparable standards are applied globally to avoid a "race to the bottom".[9] Before sketching what is required in an intergovernmental framework to provide comparable protection for research subjects worldwide (with reference to such a framework in a related aspect of research oversight), we must first look at some of the problems that arise when the US regulations, whose history has just been briefly recounted, function as the *de facto* governance model around the globe.

8 Beginning in the 1960s, the US took the lead among nations in adopting a system of prior ethical review conducted by a committee, called an IRB (Institutional Review Board), of research protocols using human subjects. The Common Rules specifies how IRBs should be formed and operated and the decisional standards they should use in reviewing and approving protocols and overseeing ongoing research. Under the Common Rule, any research institution that receives federal support for human subject research or whose staff collaborates on such research must have obtained an FWA. To do that, it must satisfy the Office for Human Research Protections ("OHRP") that it has established an IRB that complies with the Rule and must promise that the IRB will apply the relevant review standards at least as to federal research, though most research organisations voluntarily promise to apply the same process and standards to all research. Substantially similar rules apply to research whose results will be submitted to the FDA for licensing of drugs and devices, except that the FDA does not require prior certification of ethics review committees through the FWA process.

9 When the basic federal research review framework was developed, the quantity of US-sponsored clinical research conducted overseas was still relatively small. With the exponential growth in the amount of this research – and particularly drug company-sponsored clinical trials from which data will be submitted to the US FDA – the number of research ethics committees around the world has skyrocketed.

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9 Adriana Petryna, *When Experiments Travel: Clinical Trials and the Global Search for Human Subjects* (Princeton and Oxford: Princeton University Press, 2009) at p 189 (in ailing health-care systems of Poland and Brazil, resources-strapped administrators and researchers find the possibility of introducing clinical trials to be attractive).

10 In the past decade, many countries have articulated, through statutes and regulations, a set of expectations for the ways in which research ethics committees must operate. (The OHRP maintains an international list of approximately 1,100 laws, regulations and guidelines that govern human subject research in 96 countries.)[10] No longer is it acceptable for ethical approval to come simply from a single, senior official or physician – perhaps even the researcher himself – as was true in many countries as recently as a decade ago. Instead, the rules specify how committees are formed, their members appointed, their business conducted, and their decisions made and communicated. When such rules are accompanied by strong efforts to build capacity in protocol review – through the provision of appropriate administrative support and education of investigators and committee members – the quality of ethical review can be very high. Of course, in many countries, such standards are not yet fully achieved. For example, despite a great deal of effort by the Ministry of Health in China, only a small portion of hospitals have the ability to do research ethics review, and knowledgeable insiders say that the majority of research conducted still does not undergo advance, independent ethical review.

11 Some countries have modelled their ethics review structure on the system used in the US. The Tri-Council Policy Statement on the ethical conduct of human subject research in Canada, for example, contains many provisions that seem to have been lifted from the Common Rule. But some countries have rules that differ procedurally and substantively. For example, some countries conduct ethical review independently of research institutions, on a regional or national basis, depending upon the amount of human subject research that occurs and the availability of resources to support review; other countries, such as Singapore, have domain specific review boards.

12 In most countries, ethics review employs a similar set of considerations, such as minimising risks, ensuring a favourable balance of benefits to risks, requiring informed consent of subjects and selecting subjects fairly, as elaborated in the Belmont Report, the seminal 1978 report of the National Commission for the Protection of Human Subjects in Biomedical and Behavioral Research. Yet some countries have brought in additional ethical values, such as solidarity, community welfare and dignity.

13 Yet when US researchers carry out international collaborations in another country, then in addition to approval by the IRB at their

10 Office for Human Research Protections, US Department of Health and Human Services, *International Compilation of Human Research Protections, 2010 Edition* at <http://www.hhs.gov/ohrp/international/HSPCompilation.pdf> (accessed 11 October 2010).

home institution, they must also obtain review and approval of the research by a research ethics committee ("REC") at their foreign collaborators' institution that itself has an FWA (or, for drug research, that can satisfy the rules of the US FDA). In issuing what is called an international FWA, the OHRP permits committees outside the US to use the Declaration of Helsinki[11] as their guiding document, rather than the Belmont Report, which has otherwise been regarded in the US as the touchstone document on basic ethical principles for human subject research for the past 30-plus years. Except for that one difference, however, the requirements for international FWAs are really no different than the requirements that apply to a US organisation. Any non-US research ethics committee that will review research funded by the US federal agencies must adhere to the Common Rule, and there are now many hundreds of research ethics committees around the world that have jumped through the necessary hoops to obtain an FWA.

14 There are at least three things wrong with this situation that would seem to make it unsustainable. First is the inherent imbalance, when committees in nations with their own systems of research oversight have to know and, more to the point, have to be compliant with the expectations and rules of another nation. Frankly, this rather smacks of imperialism, especially when one realises that in some countries the committee in question may have been appointed by the Ministry of Health or the Ministry of Science and Education and hence actually be a governmental body.

15 Second, it is inappropriate to insist not only on US standards but US procedural expectations as the only way to operate research ethics review. The norms and standards in the Common Rule reflect a peculiarly American set of views about what is important. It is unlikely that US regulatory officials have sufficient understanding of how local cultural factors and institutional arrangements worldwide affect the appropriateness and adequacy of institutional oversight outside the US. Many international issues were simply omitted from the US rules. For example, the European Group on Ethics, which advises the European Commission, has considered group benefit versus group risk, a trade-off that does not appear in the US regulations.[12] The European Group has also considered the importance of having a system of compensation for research injuries, which likewise is not addressed in the Common Rule, which merely requires disclosure on this point.

11 World Medical Association, 2008.

12 European Group on Ethics in Science and New Technologies to the European Commission, *Ethical Aspects of Clinical Research in Developing Countries* (February 2003) at <http://ec.europa.eu/european_group_ethics/publications/docs/avis17_complet_en.pdf> (accessed 20 October 2010).

16 It is unlikely that the OHRP would withhold an FWA designation simply because a committee considers ethical principles other than those set forth in the Belmont Report or the Declaration of Helsinki, so long as the additional principles do not undermine the ethical framework expected in the US. Indeed, the Common Rule explicitly provides that "[t]his policy does not affect any foreign laws or regulations which may otherwise be applicable and which provide additional protections to human subjects of research",[13] just as the Rule also specifies that to be compliant researchers and institutions must also follow any other pertinent federal, state or local laws or regulations that "provide additional protections for human subjects".[14]

17 But when it comes to the other, more procedural aspects of ethics review, the provisions in the Common Rule are simply not grounded on empirical evidence of comparative efficacy. The US rules have a particular form and substance because they evolved over time in light of specific events and particular US institutional structures, in terms of relations between Congress and the executive departments (including both the political appointees and the career, professional employees), and between federal government and researchers. Why should these US rules set the global norm? To take a few examples:

(a) Why, in order to protect against biased and arbitrary decisions, must a review board have gender balance and include at least one scientist, at least one non-scientist, and at least one member not affiliated with the institution?

(b) Why must the committee that provides initial review of research projects be the same as the committee that provides continuing review?

(c) Why must an ethics review committee review the scientific merits of a protocol, rather than relying on outside review by a separate committee?

18 On their face, there is nothing wrong with such rules; they seem sensible enough. But there is also nothing magical about them, and a well-functioning and effective committee could be structured in different ways.

19 Indeed, the bedrock of the US framework for research ethics review, namely, that research institutions provide an "assurance" of compliance with the Common Rule, is not aimed at ensuring the quality of research; indeed, it is not even aimed primarily at investigators, but at the institutions that employ them. Yet other, non-institution-based

13 45 Code of Federal Regulations §46.101(g) (1991).
14 45 Code of Federal Regulations §46.101(e) and (f) (1991).

means of reviewing the ethical acceptability of research proposals are effectively placed out-of-bounds by the role that the US regulations play in global governance of research with human subjects.

20 The third and perhaps most important concern is that the emphasis on meeting US standards and obtaining approval from a US agency puts the responsibility in the wrong place. It should be clear to countries that it is their job to adopt a suitable set of research ethics rules and to ensure that they are applied with care and consistency to all human subject research conducted in the country, and this is not something that they can count on another country doing for them, putting aside the question of whether they wish to have to submit their committees for approval by another government. Moreover, there is no reason to think that the OHRP is equipped to actually evaluate the capabilities of committees in distant lands. They have no capacity to conduct inspections of how the committees operate and are wholly dependent on the accuracy of the picture presented by the committee on paper when it submits its application for an FWA. (Also, the FDA, which does look at the operation of ethics review when it inspects research sites, actually examines less than 1% of all ethics review committees outside the US.)

21 The situation does not have to be this way because the Common Rule actually gives the federal agency the power to recognise another country's system of protecting research subjects as providing protection "equivalent to" that provided by the Common Rule.[15] If the OHRP were to do this, then it would place responsibility squarely with the country and permit research to be approved by any committee that was recognised by the Government in question as being in compliance with its research ethics regulations.

22 To do this, the US government would need to identify a set of "procedural criteria and a process for determining" that another country's system provides equivalent protection.[16] In April 2001, the National Bioethics Advisory Commission, in a report on ethical and policy issues in international clinical trials, recommended that the Government do exactly this. A few months later, the Office of the Inspector General for the HHS urged the OHRP to address how it could "better assess whether other nations' laws and practices afford equivalent protection".[17] After a brief flurry of bureaucratic activity –

15 45 Code of Federal Regulations §46.101(h) (1991).

16 National Bioethics Advisory Commission, *Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries* (Bethesda, MD: NBAC, 2001).

17 J Rehnquist, *The Globalization of Clinical Trials: A Growing Challenge in Protecting Human Subjects* (Washington, DC: Office of the Inspector General, US Department of Health and Human Services, 2001).

which arose because the bureaucrats thought that Congress might force the OHRP to give substance to the regulatory promise that at least *some* countries' regulations protect research subjects at least as well as the US regulations – the threat of legislation abated and the HSS reverted to that great temporising stratagem of appointing another group to study the issue. In 2003, that working group concluded that the decision that a research institution was operating under rules equivalent to the Common Rule should rest on the finding that the institution had met the requirements of the Common Rule at the institutional level.[18] This is totally at odds with the whole notion that the US should move to a system where committees are judged to adhere to their own national standards and requirements which had been found by the OHRP to offer "equivalent protection". Yet, as stated by Jordan Cohen, the President of the Association of American Medical Colleges, determinations of *equivalence* should not be equated with determinations of *identity* between the foreign rules and those in the US.[19] Rather, a determination of equivalence should be based on a finding that a national system – with its own, nationally appropriate counterpart to the Common Rule – achieves a level of protection of human subjects that is roughly the same as what the US system achieves, not that individual institutions have adopted procedures which satisfy all the specific requirements of the Common Rule.

23 In sum, the present arrangement is problematic in many ways: it is too narrow and parochial, it is too unreliable, and it is unseemly, to say the least, for researchers and their institutions from around the world to have to petition a bureau in Rockville, Maryland, USA for permission to conduct research and in the process to demonstrate that they meet US standards rather than the standards adopted by the legitimate authorities in their own jurisdiction. Moreover, reliance on the Common Rule discourages the development and implementation of strong domestic regulations that would be better adapted to each local situation. More significantly, it dampens the drive toward other more effective and more responsive forms of global governance.

24 Before explaining what is meant by global governance and how it might be achieved, it should be stated that although we may be critical of the failure of the US government to recognise other nation's systems

18 US Department of Health and Human Services, *Report of the Equivalent Protections Working* Group (submitted to Dr Bernard Schwetz, Director, Office for Human Research Protections, 2003).

19 J Cohen, *Comments on the Protection of Human Subjects, proposed criteria for determinations of equivalent protections, letter of May 24, 2005, to Ms Gail Carter, Division of Policy and Assurances, Office for Human Research Protections* (Response to a Notice published in the Federal Register on 25 March 2005) (70 Fed Register 15322) at <www.aamc.org/advocacy/library/research/corres/2005/052405.pdf> (accessed 11 October 2010).

as providing "equivalent protections", it is likely that, historically speaking, we would have been much worse off without the present arrangement, however US-centric it has been. In the absence of true global governance, at least the present system has provided some common, mandatory international standards, the importance of which will be described in a moment.

IV. Global governance of research ethics

25 Replacing the present system of "global governance" of research ethics – which rests on the rules of a single nation – with something that is truly international, does not necessarily involve the Government (that is to say, something that has a formal structure and the power to enforce its will). Governance includes less-formal means of directing action or regulating behaviour, not necessarily through the law. Governments do exercise governance, but not all governance is through a government. Governance connotes steering an organisation or activity by setting goals and general directions. It may include some formal powers such as the authority a board of directors has to control an organisation, but the term is used especially for situations that involve influence, direction and regulation through less-formal and binding means, such as the ability of members of a research ethics committee at a hospital to improve the ethics of clinical trials through their interaction with colleagues and the example they set.

26 As Professor James Rosenau of George Washington University has argued, the development of global governance implicates four conditions: transnational problems, interdependent solutions, lack of existing overarching authority and independence of the actors. It involves the interaction of transnational actors and is aimed at solving problems that affect more than one state or region.[20] The essential point here is that it denotes regulation directed at interdependent actions among a group of free equals. Ideally, these would be independent states that need to form a regular, as opposed to *ad hoc*, relationship, in the absence of an overarching political authority such as a United Nations body.

27 Such international arrangements can take four forms: formal or informal at either a governmental or non-governmental level. A prime example of a formal, governmental governance arrangement is a treaty – for example, the WHO's International Health Regulations ("IHR"), the latest version of which was adopted by the World Health Assembly in

20 J Rosenau, "Toward an Ontology for Global Governance" in *Approaches to Global Governance Theory* (M Hewson & T J Sinclair eds) (Albany, NY: State University of New York, 1999) at pp 287–302.

2005.[21] The IHR is a binding document. The countries sign on and then they have to fulfil the obligations established by the IHR and submit to determinations made by the WHO. Similarly, when countries join the World Trade Organization, they subject themselves to obeying various trade agreements. Some formal international arrangements are non-governmental, such as the rules and procedures established by sports federations that conduct international competitions through agreements that bind the parties, even though the federations do not have governmental powers.

28 The second form of arrangements represent informal governance, where there is no power to enforce compliance. On the governmental side are instances of co-operative action through ongoing institutions, such as those set up amongst central bankers where they have a means of reaching collective, albeit non-binding, decisions. Likewise, there are many examples of informal governance practices in non-governmental realms. For example, the editors of scientific and medical journals have agreed to require authors to disclose conflicts of interest, to report information about institutional review board approval of research involving human subjects, and to have entered research projects into a clinical trial registry prior to their commencement. These arrangements may be informal, but they constitute a form of governance not simply of the parties to the agreement but also of those engaged in the underlying activity, such as carrying out and reporting on research. The governance arrangements control or steer what happens among independent actors so as to achieve a particular goal.

29 If we need a system of global governance for research ethics other than that now administered by the OHRP in Rockville, Maryland, how might it fit within this analytic framework? The conditions for global governance are all present. Research with human beings is a transnational problem in need of interdependent solutions. Clinical trials and other forms of research are increasingly carried out around the world. Often the same or similar trials are being conducted simultaneously in multiple countries. Greater consistency in standards and regulation is highly desirable.

30 At the moment no overarching governance authority exists. The World Medical Association, whose Declaration of Helsinki sets forth a set of ethical standards, has no enforcement authority. Nor does the Council for International Organizations of Medical Sciences, whose 2002 ethical guidelines for biomedical research are widely relied upon by research ethics committees outside the US, particularly in developing

21 World Health Organization, *International Health Regulations* (Geneva: WHO, 2005, Reprinted 2008).

countries, to help them apply the Declaration of Helsinki. Thus far, the United Nations agencies have not exercised their standard-setting authority. The United Nations Educational, Scientific and Cultural Organization's (UNESCO) bioethics declarations are just generalities, and its guidelines for formation and operation of ethics committees are merely advisory. Similarly, the guidance for research ethics committees provided by the TDR (the Special Programme for Research and Training in Tropical Diseases, based at the WHO) is basically procedural and technical, not a document approved by its governing bodies. In short, there is no organisation with overarching authority in the area of global research ethics.

31 The closest we have to global governance are the so-called Good Clinical Practice ("GCP") rules of the International Conference on Harmonization, which have three major disadvantages: first, the guidelines are specific to pharmaceutical research; second, they are a product of a trilateral process involving the drug regulatory authorities of Europe, Japan and the US, not of all countries; and third, the GCP rules are very thin on the ethics side, focusing instead on making the technical aspects of drug registration consistent rather than on addressing many of the most important and difficult issues facing RECs, researchers, and the private and public sponsors of research, from the Wellcome Trust and the Bill and Melinda Gates Foundation to the Medical Research Councils and NIHs.

32 Perhaps the strongest argument for a global system is the need to ensure that all countries have and enforce basic standards of research ethics and accountability for sponsors and investigators. This is of course essential if the rights and welfare of the human beings involved in clinical trials and other research are to be appropriately safeguarded. And it is also necessary if countries are not to be subtly – or even explicitly – pressured to adopt low standards and lax procedures in order not to scare away sponsored research.

33 Why would governments be tempted to place minimal ethical barriers to research when doing so may expose their population to avoidable harm? Putting aside corruption as a motive, even officials who desire to bring benefits to their people may think that there are advantages to being seen as very research-friendly, in terms of attracting the funds that come with research, as well as the training obtained by their researchers from foreign investigators, the facilities and services provided by sponsors, and so forth. What is even more dangerous is that if there are no agreed minimal standards for ethical approval, then each country will be tempted to lower its own standards to compete for clinical trials and other research projects; if sponsors say they are going to take a study to a neighbouring country instead, the pressure to cut back further is there, and a vicious circle takes over.

V. Responding to the need for a new governance structure for research ethics

34 The need and conditions for global governance of research ethics are therefore clear. Any of the structural arrangements identified by the four combinations of formal/informal and governmental/non-governmental properties might be appropriate for some aspect of global governance. What is lacking is a system with the hallmarks of effective governance. At present, participation does not include all relevant stakeholders; capacity for governance, where present, has not been exercised; legitimacy is compromised when those bodies with the greatest relevant expertise lack the means of exercising authority and oversight; and effectiveness cannot be established when no organisation or group has the ability to adopt and implement binding decisions and solve conflicts should they arise among the participants.

35 An opportunity therefore exists for developing global research ethics governance. We can begin with governments agreeing upon a framework that would set non-enforceable standards and then move toward something more like the IHR with enforceable obligations and defined decision-makers. Indeed, the WHO has recently taken several actions in the area of ethics that may point us in the right direction. The first example is the WHO Guiding Principles on Cell, Tissue and Organ Transplantation, which were first adopted in 1991 and then re-endorsed with some additional provisions by the World Health Assembly in May 2010. Among other things, the Guiding Principles establish the minimal characteristics for national systems of organ transplantation – focusing on the promotion of deceased donation but recognising the role of the donation of certain organs (principally kidneys) by living donors, provided that there is no payment for the organs. The Guiding Principles, along with technical assistance from the WHO, have been very influential with countries adopting regulations in this field, as indeed, Singapore has done in the past year. The second example is the WHO's Clinical Trials Registry Platform, a set of required information that must be collected by a clinical trial registry (such as a registry operated by a national government) in order for the registry to be recognised as meeting global standards. Registries have several purposes, including making information about clinical trials more accessible to patients and their physicians, but one major purpose is ethical: to ensure that, by requiring trials to be registered before they begin enrolling subjects, it is possible to monitor the conduct of the trial and to compare the results it produces with those it was intended to produce. There are too many examples of trials that have not gone well from the viewpoint of research sponsors simply disappearing or of endpoints being adjusted to demonstrate a positive result when the original endpoints showed none.

36 Thus, the Member States of the WHO, drawing on examples such as these, should begin discussing how they can establish a set of basic ethical standards and procedures for acceptable review of research with human beings. The articulation of the particular rules and their enforcement would continue to be carried out at the national level, but with the aim of having every country's system at least meet the basic, globally recognised standards and procedures needed to protect human subjects. The WHO is at work on updating the TDR guidelines, but this activity will need before long to move from being a technical one for the WHO Secretariat to a political one for the Member States.

37 Others have addressed the role that law has played in improving the safety and ethicality of human subject research around the world, as well as examples where the law has failed. In arguing for a set of globally recognised common standards that should be met by the laws and regulations of all nations where research takes place, this article should be understood to incorporate by reference other authors' evaluation of the limitations as well as the strengths of the rule of law as it relates to clinical trials and other types of biomedical and behavioural research. The thesis of the present article is that it is essential is that there be common standards that provide equivalent protection to all subjects and that these not arise simply because the long arm of one nation's bureaucracy follows that nation's research-funding or drug-approval-authority. A single nation has neither the practical means nor the cultural competence to do an adequate job of overseeing research around the globe. The appearance that it is doing so is not only unseemly but dangerous because it may lull others, including responsible officials in countries that host international research studies, into believing that their own oversight obligations have been discharged by the nation that established the rules to which the host country's research institutions must adhere when approving clinical research. In place of the system we now have – a system that grew up by chance, fuelled not only by good intentions but by scandals, and brought to prominence by the rapid growth of biomedical research that crosses national boundaries – we need a proper system of global governance of the ethics of research with human beings.