

**TOPIC:****Human Stem Cell Research: 2009 NIH Guidelines****INTRODUCTION:**

On July 6, 2009, the National Institutes of Health (“NIH”) issued final “Guidelines for Human Stem Cell Research” (“Guidelines”) [\[1\]](#). The Guidelines implement President Obama’s March 9, 2009 Executive Order 13505, “Removing Barriers to Responsible Scientific Research Involving Human Stem Cells [\[2\]](#)” as it relates to NIH-funded research. Executive Order 13505 permits the Secretary of Health and Human Services, through the Director of NIH, to “support and conduct responsible, scientifically worthy human stem cell research, including human embryonic stem cell research, to the extent permitted by law.” It revoked prior restrictions put in place by former President George W. Bush, who limited federal funding for research involving human embryonic stem cells (“hESCs”) to certain existing hESC lines.

The Guidelines took effect on July 7, 2009. On July 30, 2009, President Obama instructed other federal agencies and departments that support and conduct stem cell research to adopt NIH’s Guidelines “to the fullest extent practicable in light of legal authorities and obligations [\[3\]](#).” He also gave such agencies and departments 90 days to submit to the Office of Management and Budget any proposed changes to existing guidance, policies, and procedures pertaining to stem cell research. In light of that directive, although this Note addresses NIH-funded research, other federal agencies can be expected to implement similar standards and processes for hESC research the agencies fund.

**DISCUSSION:****Underlying Principles**

The Guidelines are based on two core principles: (1) hESC research offers the possibility of better comprehending “human health and illness” and identifying “new ways to prevent and/or treat illness”; and (2) voluntary informed consent should be obtained from individuals who donate embryos for research purposes.

**Basic Outline**

The Guidelines answer several key questions regarding NIH-funded hESC research. Such questions include:

- (1) From what sources may hESCs involved in NIH-funded research be derived?
- (2) What types of hESC research are ineligible for NIH funding?
- (3) How will NIH determine whether hESCs are eligible for use in NIH-funded research? What process will institutions need to follow to show that particular hESC lines satisfy the new NIH criteria?

(4) What is NIH's funding policy for research using hESCs derived from embryos donated before the Guidelines took effect, which may not always satisfy the new eligibility criteria?

(5) What is NIH's funding policy for research involving hESCs derived from embryos donated outside the United States, where hESC requirements may not mirror those adopted by NIH?

### **Basic Eligibility Criteria for NIH Funding**

Subject to specified conditions, the Guidelines generally permit NIH funding of research that involves the use of NIH-registered hESCs [\[4\]](#) and "certain uses of induced pluripotent stem cells." The various conditions imposed by NIH are discussed below.

The Guidelines identify several categories of stem cell research that are ineligible for NIH funding, even if the stem cells to be used would otherwise satisfy the Guidelines. For instance, the Guidelines make clear that NIH will not support research involving hESCs or human induced pluripotent stem cells that are "introduced into non-human primate blastocysts." Nor will NIH fund research that involves the "breeding of animals where the introduction of hESCs . . . or human induced pluripotent stem cells may contribute to the germ line." In addition, NIH rejected calls from organizations such as the Association of American Universities ("AAU") to expand the sources from which eligible hESCs may be derived [\[5\]](#). Specifically, the Guidelines provide that NIH funding will not be available for research involving hESCs derived from sources such as therapeutic cloning (also referred to as somatic cell nuclear transfer ("SCNT")), parthenogenesis, or embryos created for research. In the preamble to the Guidelines, NIH explains that it declined to allow funding for research using hESC lines or pluripotent cells derived from these types of additional sources because such research raises "complex ethical and scientific issues" on which there is no public consensus.

The Guidelines further note that annual appropriations legislation prohibits "NIH funding of the derivation of stem cells from human embryos." Known as the Dickey-Wicker Amendment, the appropriations rider to which the Guidelines refer bans the use of federal funds for the creation of human embryos for research purposes or for research in which human embryos are "destroyed, discarded, or knowingly subjected to risk of injury or death greater than that allowed" for federally-funded research on fetuses in utero [\[6\]](#). Although there is some support among members of Congress to eliminate the limitations imposed by the Dickey-Wicker Amendment, such limitations remain in place to date.

### **Eligibility Processes and Conditions**

#### Stem cells derived from embryos donated in the United States on or after July 7, 2009

The Guidelines describe two processes by which an institution can establish NIH funding eligibility for research that involves hESCs derived from embryos donated on or after July 7, 2009, the date on which the Guidelines took effect. The institution may either:

(1) Propose to use hESCs from the newly-created NIH Human Embryonic Stem Cell Registry ("Registry") [\[7\]](#), which lists hESC lines that are approved for use in NIH-funded research and is updated as hESCs are reviewed and found eligible ("Option 1"); or

(2) Assure NIH that the hESCs proposed for use satisfy certain specified conditions, and submit supporting information ("Option 2"). NIH will make a determination as to eligibility and eligible lines will be added to the Registry.

If the institution determines to proceed under Option 2, it must assure NIH that the hESCs were derived from human embryos in accordance with seven criteria and provide certain supporting documentation such as consent forms and written policies for review by NIH. The seven criteria:

(1) Purpose of embryos' creation: The embryos were created through in vitro fertilization for reproductive purposes and "were no longer needed for this purpose."

(2) Consent for use in research: The donor(s) sought treatment for reproductive purposes and provided “voluntary written consent for the human embryos to be used for research purposes.”

(3) Options discussed: The donor(s) received information regarding all options available with respect to the leftover embryos in the health care facility where treatment was sought.

(4) No compensation offered: There was no offer of payment (cash or in kind) for the donated embryos.

(5) Quality of care unaffected: The health care facility had policies/procedures providing that quality of care would not be affected by an individual’s decision to consent or refuse to consent to the donation of embryos for research.

(6) Separation between decision to create embryo and decision to donate: “There was a clear separation between the prospective donor(s)’s decision to create human embryos for reproductive purposes and the prospective donor(s)’s decision to donate human embryos for research purposes.” In particular, three conditions must be met:

(a) Any decision to create human embryos for reproductive purposes “should have been made free from the influence of researchers proposing to derive or utilize hESCs in research.” The attending physician who was responsible for reproductive care should not be the same person as the researcher deriving/using hESCs, “unless separation was not practicable.”

(b) Consent for donation was obtained at the time donation took place. An earlier indication of an individual’s desire or willingness to donate is not sufficient.

(c) The donor(s) was advised of his or her right to “withdraw consent for the donation of the embryo until the embryos were actually used to derive embryonic stem cells or until information which could link the identity of the donor(s) with the embryo was no longer retained, if applicable.”

(7) Elements of informed consent: The donor(s) was informed:

(a) “[T]hat the embryos would be used to derive hESCs for research”;

(b) What would happen to the embryos in the course of such derivation;

(c) That hESCs derived from the embryos could be retained for many years;

(d) That the donation is not subject to any “restriction or direction regarding the individual(s) who may receive medical benefit from the use of the hESCs, such as who may be the recipients of cell transplants”;

(e) That the research “was not intended to provide direct medical benefit to the donor”;

(f) That the results of the research “may have commercial potential, and that the donor(s) would not receive financial or any other benefits from any such commercial development”; and

(g) “[W]hether information that could identify the donor(s) would be available to researchers.”

NIH will conduct a review of submitted information, and the NIH Director will make a final determination as to whether a hESC line is approved for use in NIH-funded research. Approved lines will be added to the NIH Registry.

### Stem cells derived from embryos donated in the United States before July 7, 2009

Stem cell lines derived from embryos donated in the United States before July 7, 2009 also must satisfy the new eligibility requirements. The stem cell lines previously approved for NIH-funded research by the Bush administration are not exempt from the new requirements – that is, they are not “grandfathered.”

An institution can use the two processes described above to establish NIH funding eligibility for research that involves hESCs derived from embryos donated in the United States before July 7, 2009. In addition, the Guidelines also create a third process, whereby hESC lines created prior to issuance of NIH’s Guidelines that do not satisfy the specific informed-consent and other procedural requirements of Option 2 may nonetheless be considered and, where appropriate, approved by NIH for NIH funding. Institutions may submit, to a Working Group of the Advisory Committee to the NIH Director, materials such as consent forms and written policies. The submitted materials must show that the hESCs were derived from human embryos that (a) were created for reproductive purposes using in vitro fertilization, (b) were no longer needed for reproductive purposes, and (c) were donated for research purposes with the voluntary written consent of the donor.

In evaluating hESCs’ eligibility for use in NIH-funded research, the Working Group will consider the principles espoused in Option 2. It will also consider whether, as part of oral or written informed consent communications, donor(s) were (1) “informed of other available options pertaining to the use of the embryos”; (2) “offered any inducements for the donation of the embryos”; and (3) “informed about what would happen to the embryos after the donation for research.” In appropriate cases, it may also consider federal regulatory principles applicable to human subjects research (45 C.F.R. Part 46, Subpart A or the “Common Rule”); however, basic research on deidentified hESCs typically does not trigger applicability of the Common Rule. The Working Group recommends to the Advisory Committee whether hESCs should be found eligible. The Advisory Committee in turn makes its own recommendations to the Director of NIH, who renders final eligibility determinations.

### Stem cells derived from embryos donated outside the United States

The Guidelines permit use of hESCs derived from embryos donated outside the United States either before, on, or after the effective date of the Guidelines. Institutions that seek NIH funding for research involving hESCs derived from embryos donated outside the United States generally must adhere to the processes and criteria described above for embryos donated before, on, or after July 7, 2009. NIH recognizes, however, that foreign governments “may not or cannot change their national donation requirements to precisely comply with the NIH Guidelines” and views “ethically derived foreign hESCs” as “an important scientific asset” for the United States. Accordingly, the Guidelines provide an alternate approval mechanism for foreign hESCs. Under that mechanism, institutions planning to use foreign hESCs in NIH-funded research may submit an assurance (and supporting documentation) that “the alternative procedural standards of the foreign country where the embryo was donated provide protections at least equivalent” to those set forth in Option 2. The Working Group will review the submission and make a recommendation to the Advisory Committee regarding whether the foreign country’s procedures are equivalent to those of NIH. The Director of NIH renders final decisions on foreign procedural equivalence.

### **Assurance Prior to Use of NIH Funds**

The Guidelines advise that, prior to expending NIH funds, a funding recipient will be required to assure NIH that hESCs involved in the funded project appear on the NIH Registry. Such assurances should be provided “when endorsing applications and progress reports submitted to NIH for projects using hESCs.” In addition, NIH clarified in a July 15, 2009 Notice that use of grant funds for hESC research will not be approved, and no new uses of hESCs may be initiated in ongoing funded studies, until the hESC line(s) to be used is approved through the new NIH process and listed in the Registry [\[8\]](#). For hESC lines that an institution proposes for addition to the Registry, the institution is required to submit an assurance providing that the donation of the embryo from which the cell line was derived met the eligibility requirements of the Guidelines.

## Practical Considerations

Eligibility submissions: Institutions and investigators proposing to conduct federally-funded hESC research may wish to submit, as soon as feasible, proposals for NIH approval and registration of hESC lines. In conjunction with the submission, institutions are required to provide an assurance that the proposed line meets the criteria in the NIH Guidelines. Over time, as NIH populates the Registry, uncertainty about whether particular lines may be used in NIH-funded projects will disappear. Before that happens, institutions should consider what steps should be taken to ensure the accuracy of the required assurance.

Segregation of non-fundable hESC research from federally-funded research: In response to President Bush's restrictions on federally-funded hESC research, many institutions put in place procedural and physical barriers to keep separate their hESC research from their federally-funded research activities. The purpose of this separation was to avoid situations in which it might be said that funding received from a federal research sponsor had been used to support non-fundable hESC research. In light of President Obama's Executive Order revoking Bush administration policy and NIH's Guidelines regarding permissible uses of hESCs in NIH-funded research, institutions may wish to evaluate whether they need to retain such special separations. An institution that correctly applies the basic federal rules governing allocation of costs among sponsored projects will in general, by so doing, ensure that no federal funds are used to support non-fundable hESC projects. While the Bush administration hESC policy was in effect, however, there was a heightened risk existed that even an inadvertent failure to follow basic federal cost allocation rules might embroil an institution in allegations that it had allowed federal funds to be used to support non-fundable hESC research, in violation of the Bush administration policy. Under the Obama administration policy, it seems far less likely that an institution that makes a cost allocation error of this kind would be exposed to severe sanctions or criticism by federal officials. It may be time, therefore, for institutions to reconsider which if any categories of hESC research should remain segregated from federally-funded research, and how stringent the segregation measures still need to be. For example, an institution might choose to retain segregation measures to separate hESC derivation research (for which federal funding remains prohibited by the Dickey-Wicker Amendment) from federally-funded research, and remove or reduce measures designed to segregate federally-funded research from other less controversial categories of non-fundable hESC research.

State law: Some states have adopted laws that govern hESC research. Because state law provisions are in some cases more restrictive or are different than the NIH Guidelines, institutions should consult both federal and state requirements in connection with research that involves the use of hESCs.

National Academy of Sciences Guidelines: In addition, National Academy of Sciences ("NAS") Guidelines for Human Embryonic Stem Cell Research will likely continue to be viewed as a "best practices" source for institutions engaged in hESC research. As recommended by the NAS Guidelines, many institutions have established bodies such as Embryonic Stem Cell Research Oversight Committees ("ESCROs") to oversee their hESC research.

## FOOTNOTES:

**FN1.** Available at <http://stemcells.nih.gov/policy/2009guidelines.htm>.

**FN2.** Available at [http://www.whitehouse.gov/the\\_press\\_office/Removing-Barriers-to-Responsible-Scientific-Research-Involving-Human-Stem-cells/](http://www.whitehouse.gov/the_press_office/Removing-Barriers-to-Responsible-Scientific-Research-Involving-Human-Stem-cells/).

**FN3.** See Memorandum from President Obama to the Heads of Executive Departments and Agencies Regarding Guidelines for Human Stem Cells Research (July 30, 2009), available at

[http://www.whitehouse.gov/the\\_press\\_office/Memorandum-from-the-President-for-the-Heads-of-Executive-Departments-and-Agencies-Regarding-Guidelines-for-Human-Stem-Cell-Research/](http://www.whitehouse.gov/the_press_office/Memorandum-from-the-President-for-the-Heads-of-Executive-Departments-and-Agencies-Regarding-Guidelines-for-Human-Stem-Cell-Research/).

**FN4.** The Guidelines define hESCs as “cells that are derived from the inner cell mass of blastocyst stage human embryos, are capable of dividing without differentiating for a prolonged period in culture, and are known to develop into cells and tissues of the three primary germ layers.”

**FN5.** See, e.g., May 26, 2009 [AAU Response to Draft NIH Guidelines for Human Stem Cell Research](#).

**FN6.** Omnibus Appropriations Act, 2009, Pub. L. No. 121-008, § 509, 123 Stat. 524 (2009).

**FN7.** Available at [http://grants.nih.gov/stem\\_cells/registry/current.htm](http://grants.nih.gov/stem_cells/registry/current.htm).

**FN8.** Available at <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-09-123.html>.

## AUTHORS:

Alexander Dreier, Partner, Hogan & Hartson LLP, Washington, DC is a partner in the Washington, D.C. office of Hogan & Hartson L.L.P. and a member of the firm's Education and Health Groups. His practice is focused on advising higher education clients on federal regulatory issues, especially those related to academic research, student privacy, civil rights, and student affairs. Prior to joining Hogan & Hartson, Mr. Dreier was assistant to the provost and adjunct professor of law at the University of Oklahoma. He is an active member of NACUA and a frequent speaker on legal developments of interest to higher education clients. He received his B.A., magna cum laude, from Harvard University; an M.A. from Oxford University, where he was a Rhodes Scholar; and his J.D. from Yale Law School.

Robert Kenney, Partner, Hogan & Hartson LLP, Washington, DC is the Director of Hogan & Hartson's Government Contracts and Grants Group. His practice involves the representation of universities and other institutions engaged in federally-sponsored research. He has represented numerous research institutions in investigations and other matters involving allegations of false claims, fraud and misconduct, and frequently advises institutions on research compliance issues. He is a graduate of Harvard College and Harvard Law School.

Jennifer Stillerman, Associate, Hogan & Hartson LLP, Washington, DC

## RESOURCES:

### Statutes:

- [Dickey-Wicker Amendment, Omnibus Appropriations Act, 2009, Pub. L. No. 111-008, § 509, 123 Stat. 524 \(2009\)](#)

### Executive Orders and Directives:

- [Executive Order 13505](#)

- [Memorandum from President Obama to the Heads of Executive Departments and Agencies Regarding Guidelines for Human Stem Cell Research](#)

### **Government Guidance:**

- [NIH Stem Cell Information Website](#)
- [NIH Guidelines on Human Stem Cell Research](#)
- [NIH Human Embryonic Stem Cell Registry](#)
- [NIH Human Embryonic Stem Cell Registry, Submitted hESC Lines Pending Review](#)
- [NIH Notice No. NOT-OD-09-123, Status of Applications and Awards under the New NIH Guidelines for Human Stem Cell Research](#)
- [Office for Human Research Protections, Guidance for Investigators and Institutional Review Boards Regarding Research Involving Human Embryonic Stem Cells, Germ Cells and Stem Cell-Derived Test Articles](#)

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