NOTE: THIS GUIDANCE REPLACES OHRP'S NOVEMBER 16, 2001, GUIDANCE ENTITLED, "GUIDANCE FOR INVESTIGATORS AND INSTITUTIONAL REVIEW BOARDS REGARDING RESEARCH INVOLVING HUMAN EMBRYONIC STEM CELLS, GERM CELLS, AND CELL-DERIVED TEST ARTICLES." CLICK HERE FOR THE NOVEMBER 16, 2001 GUIDANCE.

Office for Human Research Protections

Department of Health and Human Services

Guidance for Investigators and Institutional Review Boards Regarding Research Involving Human Embryonic Stem Cells, Germ Cells and Stem Cell-Derived Test Articles

Date: March 19, 2002

Scope: This document describes when research activities involving human embryonic stem cells (hESCs), human embryonic germ cells derived from fetal tissue, or hESC- or germ cell-derived test articles are considered human subjects research and what regulatory controls apply to that research.

Target Audience: Investigators who conduct research with these cells and test articles, sponsors of such research, institutions where the research is conducted, and Institutional Review Boards (IRBs) that review human subject research involving these cells or test articles.

APPLICABLE REGULATIONS AND LAWS

- Research involving these cells or test articles that is conducted or supported by the Department of Health and Human Services (HHS) or performed at an institution that has agreed under an OHRP-approved assurance to apply HHS regulations to all of its human subjects research may be subject to HHS human subjects protection regulations (Title 45 CFR Part 46, including Subpart B, 45 CFR 46.206), as described below.

- All clinical research involving drugs, devices, and biological products regulated by FDA, including cells or test articles regulated as drugs, devices, and biological products, is also subject to FDA regulations governing investigational new drugs (INDs) or devices (IDEs) (Title 21 CFR Parts 312 or 812), regardless of the source of support. This clinical research is also subject to FDA's IRB and informed consent regulations (Title 21 CFR Parts 50 and 56).

- In addition, clinical research involving the transplantation of cells or test articles derived from human fetal tissue into human recipients is subject to Public Law 103-43, "Research on Transplantation of Fetal Tissue" (42 U.S.C. § 289g–2(a)).

- Other Federal, State or local laws may also apply to transplantation or other research involving these cells or test articles.

CONDITIONS REGARDING FEDERAL FUNDING OF RESEARCH ON HUMAN EMBRYONIC STEM CELLS

- Research involving the derivation and use of human embryonic germ cells from fetal tissue may be conducted with Federal support.

- Research on existing human embryonic stem cell lines may be conducted with Federal support if the cell lines meet the U.S. President's criteria which he announced on August 9, 2001 (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-005.html).

- Research involving the derivation of new stem cells from human embryos or the use of human embryonic stem cells that are not listed on the NIH Human Embryonic Stem Cell Registry may not be conducted with Federal support.

GUIDANCE

Under HHS regulations at 45 CFR Part 46, human subject means a living individual about whom an investigator (whether professional or student) conducting research obtains (1) data through intervention or interaction with the individual, or (2) identifiable private information.

HHS-conducted or supported research that involves neither interactions nor interventions with living individuals or obtaining identifiable private information is not considered human subjects research. Accordingly, *in vitro* research and research in animals using already derived and established human cell lines, from which the identity of the donor(s) cannot readily be ascertained by the investigator, are not considered human subject research and are not governed by the HHS or FDA human subject protection regulations appearing at 45 CFR Part 46 and 21 CFR Parts 50 and 56. IRB review is not required for such research.

Use of Identifiable Private Information

HHS-conducted or supported research that uses human cell lines where the donor(s) may be identified, including cells that retain links (such as a code) to identifying information is generally considered human subject research that is governed by 45 CFR Part 46 because the donors are human subjects. IRB review and approval is required for such research.

In vitro research or research in animals using a human cell line that retains a link to identifying information ordinarily would not be considered human subjects research if: (1) the investigator and research institution do not have access to identifiable private information related to the cell line; and (2) a written agreement is obtained from the holder of the identifiable private information related to the cell line providing that such information will not be released to the investigator under any circumstances. In this case, the research may be considered to not involve human subjects because the identity of the donor(s) could not be "readily ascertained" by the investigator or associated with the cell line. Under such circumstances, an institution or an IRB could determine that IRB review of the research using the cell line was not needed.

Intervention or Interactions with the Individual

All HHS-conducted or supported clinical research that involves interactions with living individuals, including the transplantation of human cells or test articles, such as differentiated cells derived from human embryos or human fetal tissue, into human recipients is human subjects research subject to HHS regulations at 45 CFR Part 46 because recipients are human subjects. IRB review and approval is required for such research.

Furthermore, all clinical research involving use of cells or test articles regulated by FDA as drugs, devices, and biological products is subject to regulation and oversight by FDA. This clinical research must be conducted in compliance with FDA's regulations governing INDs or IDEs regardless of source of funding. All human studies conducted under INDs and IDEs are subject to FDA's IRB and informed consent regulations.

Public Law 103-43, "Research on Transplantation of Fetal Tissue," also applies to clinical research involving the transplantation of cells or test articles derived from human fetal tissue into human recipients.

In addition, other Federal, State or local laws may also apply to transplantation or other research involving these cells or test articles.

RELATED GUIDANCE

- OHRP guidance on the "Engagement of Institutions in Research" (http://ohrp.osophs.dhhs.gov/humansubjects/assurance/engage.htm)
- OHRP guidance on "Issues to Consider in the Research Use of Stored Data or Tissue" (http://ohrp.osophs.dhhs.gov/humansubjects/guidance/reposit.htm)
- NIH Guidelines for Research Using Human Pluripotent Stem Cells (http://www.nih.gov/news/stemcell/NOT-OD-00-050.html)
- The text of Public Law 103-43 (http://ohrp.osophs.dhhs.gov/humansubjects/guidance/publiclaw103-43.htm)
- The NIH Grants Policy Statement (http://grants.nih.gov/grants/policy/nihgps_2001/)
- FDA letter on its regulation of research involving fetal cells (http://www.fda.gov/cber/ltr/fetal113000.htm)
- FDA information regarding tissue regulations (http://www.fda.gov/cber/tiss.htm)
- For further information or specific advice regarding fulfillment of FDA IND requirements, please contact the Center for Biologics Evaluation and Review (CBER) at or 301-827-5102.

For further information regarding this guidance, please contact OHRP (ohrp@osophs.dhhs.gov or 301-496-7005).