INFORMED CONSENT *and* FEDERAL FUNDING *for* STEM CELL RESEARCH

by ROBERT STREIFFER

A review of the consent forms signed by those who donated embryos for the NIH-approved embryonic stem cell lines reveals several problems, providing ethical as well as scientific reasons to overturn the Bush administration's restrictions on federal funding for stem cell research.

President Bush's compromise policy on human embryonic stem cell research, announced on August 9, 2001, provides federal funding for the research. However, it restricts the funding to research on cell lines derived before the announcement from embryos left over from infertility treatment and donated with informed consent. This policy would, said Bush, allow "us to explore the promise and potential of stem cell research without crossing a fundamental moral line, by providing taxpayer funding that would sanction or encourage further destruction of human embryos that have at least the potential for life." The National Institutes of Health now has a registry of twenty-one lines that are eligible for funding and available for distribution.

Despite the indisputable utility of the NIH lines, several scientific obstacles stand in the way of exploring the full potential of human embryonic stem cell research—often known as hESC research—so long as federal funding is restricted to lines derived prior to August 9, 2001. Because there are only twenty-one of these lines, they represent a narrow range of genetic diversity. Also, they were grown on mouse cells, which contaminate other cells with animal products capable of eliciting an immune response from humans,[1] and they were grown in poorly defined media conditions using dated protocols that make the cells difficult to thaw and grow in culture.[2] Substantial progress has been made on these problems with hESC lines established after Bush's

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announcement, but because of his policy, these lines may not be used in federally funded research.[3] Such progress has made Bush's policy increasingly unsatisfactory for exploring the tremendous potential of hESC research and has fueled widespread criticism from the scientific community and from such high-level government officials as Elias Zerhouni, director of the NIH, and Story Landis, director of the NIH's National Institute of Neurological Disorders and the person responsible for implementing Bush's policy.[4]

What has not been appreciated, however, is that an examination of the consent forms under which the NIH lines were derived reveals a parallel ethical argument for expanding federal funding. In the course of establishing the registry, the NIH collected samples of the consent forms used with the donors of the embryos from which the NIH lines were derived. I obtained copies of these forms from the NIH through a Freedom of Information Act request. A review of the consent forms reveals several problems that have not been acknowledged by the NIH or the National Academy of Sciences, despite their oversight and guidance in this area. Some forms make explicit commitments to donors that preclude redistribution of the cells or that limit acceptable research. Some fail to inform donors about the nature of stem cell research, the option to refuse donation without jeopardizing medical care, or the possibility that donors' biological materials might be transplanted into embryonic or fetal animals to create animal-human chimeras. These problems provide ethical reasons not to perform several kinds of important research with the NIH lines. But given the importance of this research, they also provide ethical reasons for allowing research with new lines to receive federal funding.

The Importance of Informed Consent

The importance of informed consent, specifically in the context of embryo donation, has long been recognized:

- The NIH Human Embryo Research Panel concluded in 1994 that embryos could be used for research only if the donors had provided informed consent for such use. The panel found that the consent process must provide specific information about the nature and purpose of the research, as well as any facts that a reasonable individual would consider relevant to the donation decision.[5]

- In a 1997 statement, the American Society of Reproductive Medicine also concluded that informed consent for embryo donation was required. Informed consent requires disclosure of information about "the purpose, nature, and risks and benefits of the research." One such risk "is that [donors] may later regret not having saved the embryos for their infertility treatment or for donation to other couples." The statement also stressed the importance of telling potential donors that failure to donate would not adversely affect their medical care.[6]

- The National Bioethics Advisory Commission discussed consent in their report on human embryonic stem cell research in September 1999 and found that "Potential donors of embryos for ES cell research must be able to make voluntary and informed choices about whether and how to dispose of their embryos."[7] Potential donors should be told both that refusing to donate would not affect their medical care and that their embryos would be destroyed in the derivation process.[8]

- Under President Clinton, the NIH promulgated draft guidelines for federal funding of human embryonic stem cell research in December 1999, and final guidelines in August 2000.[9] The guidelines restricted federal funding to lines derived from embryos donated with informed consent, specifying, among other things, that donors should have been informed that their embryos would not survive the derivation process.

Research involving the transplant of human cells into an animal during early stages of development raises the very troubling possibility that the materials of some donors would be used in ways that they would quite reasonably find morally objectionable.

To be sure, the reports from HERP, ASRM, and NBAC were only advisory, and the procurement processes for some of the embryos from which the NIH lines were derived were completed before some of these documents were available. The requirement that cells derived from embryos donated to research be used only with informed consent, however, is based largely on a concern about autonomy, and the importance of autonomy—and its implications for research participation—have been internationally recognized in both ethi-

cal discussions and legal regulations for decades.[10]

Review of the Consent Forms

The NIH registry lists twenty-one lines from six different providers as being available for distribution. Two of the providers are academic institutions: the University of California, San Francisco and the Technion-Israel Institute of Technology. Another provider, the Wisconsin Alumni Research Foundation, is a nonprofit foundation affiliated with the University of Wisconsin, Madison. The other three providers are biotechnology companies: BresaGen (now merged with Novocell), Cellartis AB, and ES Cell International.

In December 2006, I submitted a Freedom of Information Act Request asking for photocopies of the sample consent forms for the available human embryonic stem cell lines on the NIH registry. The NIH returned eleven forms from the six providers.[11] The dates on the forms ranged from October 1997 to May 2001, except for the form for ES Cell International, which was undated. The analysis here is of the English versions and assumes that donors had access to all the forms for the relevant provider.

The problems with the consent forms can be divided into two categories: they omit information that is important for informed consent, and they set restrictions that obstruct key areas of research. Both kinds of problems are important. The requirement for informed consent is violated both when embryos donated for research are used in ways not adequately explained to the donors and when they are used in ways that contradict the donors' likely understanding of the consent form.

In terms of omissions, BresaGen's form is the most problematic. The form is not really a consent form for participation in human embryonic stem cell research; it is a consent form for the embryo donors' infertility treatment. Although the form goes into detail about the infertility treatment, it has only one sentence relating to the donation of embryos for research: "if fertilization occurs with too many sperm or if embryos form but are not developing or living, scientific study of these may be undertaken." Even though couples were donating embryos that the clinicians judged unsuitable for implantation, the question of whether the donation was made with informed consent still arises, as it does for any donation of human biological materials to research. Moreover, the science behind judgments about whether an embryo has "died" or irreversibly ceased development is not well established (even to this day), yet the form fails to mention that there is a risk of destroying salvageable embryos.[12] The form also fails to inform subjects about the nature of hESC research, about the voluntary nature of their donation, and about their option to refuse donation for research purposes without affecting medical care. These last two omissions mean that subjects could have been misled into thinking that consenting to in vitro fertilization required consenting to the donation. This probably does not count as informed consent for research at all, and it is surprising that the NIH concluded that these lines satisfied Bush's requirement that patients must have given informed consent for the donation of the embryo.

The methods used to establish the NIH lines destroy the embryo in the process of removing the inner cell mass (the clump of cells from which the stem cells are derived). That donors should be told this seems obvious, but only the form for the UCSF lines clearly does. None of the forms mention any psychological risk of donation—such as regret if a donor changes his or her mind after the embryo is destroyed—and only the forms for UCSF and WARF mention a risk of loss of privacy if the confidentiality of the subjects' records is breached. The form for the Technion-Israel lines has a section for risks, but following the section title it only says "irrelevant."

None of the forms tell donors that cells derived from their embryos might be transplanted into animals to create animal-human chimeras—organisms whose cells come from both animal and human embryos. Creating animal-human chimeras by transplanting human embryonic stem cells, or more specialized cells derived from them, into animals at various embryonic, fetal, and postnatal stages provides investigators with an indispensable tool for exploring the potential of the stem cells or their derivatives to functionally integrate into a living organism, which is a key issue in regenerative medicine. However, animal-human chimeras are the subject of much ethical controversy right now.[13]

While there is no direct, systematic data on whether donors would morally object to cross-species uses of their biological materials, the general tenor of the public discussion about what has been dubbed "the other stem cell debate" in the *New York Times Magazine* makes the failure to inform donors about chimeric research problematic.[14] Extensive social science research on public attitudes in the United States toward another kind of species-mixing, transgenic food, finds that a substantial proportion of the public (23 to 58 percent) reports objections to transgenic crops. An even greater percentage of Americans (around 20 percent more in most studies) reports objections to species-mixing involving animals, and the intensity of the disapproval is greater as well.[15] These attitudes cannot be dismissed as unreasonable: they are not based on a simple misunderstanding of the science involved or on unfounded food safety concerns, nor do they reflect a general fear of science and technology; instead they reflect deep and important values that go beyond narrow scientific considerations.[16] The widespread existence of such attitudes makes it likely that some donors would not want their own biological materials to be incorporated into nonhuman animals, and even more likely that some donors

would be upset at not having at least been given an informed choice as to whether to participate. Also worth noting is that the 1994 Human Embryo Research Panel had significant concerns about the "extensive mixing" that would result from introducing human embryonic stem cells into early-stage developing animals. They concluded with a very broad recommendation: "The Panel unanimously opposes, on ethical and scientific grounds, the creation of heterologous, or human-nonhuman chimeras, with or without transfer [into a uterus]."[17] The use of the NIH lines in chimeric research, especially in research involving the transplant of the human cells into an animal during embryonic or early fetal stages of development, therefore raises the very troubling possibility that the materials of some donors would be used in ways that they would quite reasonably find morally objectionable.

In addition to these omissions, several consent forms also include restrictions on the scope of the research that would rule out using those lines in important kinds of research. On this score, the Cellartis consent form is the most problematic. It states that the project in which the embryo donors were participating was limited to developing a technique for longer-term cultivation of embryonic cells, and that after the study was completed all the cells would be destroyed. That statement is incompatible with distributing cells from those lines to laboratories across the world, many of which then establish their own cell lines that can be propagated indefinitely. It is disconcerting that the NIH, instructed to fund research only on lines obtained with informed consent from the embryo donors, would find it appropriate to fund research incompatible with the very terms of the informed consent document.

The Technion-Israel Institute of Technology form states that donors are free to stop participating in the research at any time, a statement donors might reasonably understand to mean that they can withdraw their materials from the study at any time. However, the Institute's material transfer agreement—the agreement between the Institute and recipients of their cells—effectively prevents the Institute from complying with such a request. The agreement reserves for the Institute the right to ask researchers for the return or destruction of the cells only after the researchers have finished their research program, which could be long after the donors desire to stop participating.

The consent form used for the WARF lines states that research using cells derived from the study will not involve the intermixing of human embryonic cells with a nonhuman embryo. If this proviso is to be respected, WARF's lines cannot be used in important research such as that carried out by Ronald Goldstein at the Bar-Ilan University involving transplants of undifferentiated hESCs into chick embryos. Such research attempts to discover an "accessible . . . experimental system for the study of in vivo development of human ES cells."[18]

Work such as that carried out by Fred Gage at the Salk Institute for Biological Studies would also be ethically problematic with WARF's lines. Gage's work involves transplanting human embryonic stem cells into mouse embryos to demonstrate that they can produce functional neurons inside living mice, thus permitting "the study of human neural development in a live environment, paving the way for the generation of new models of human neurodegenerative and psychiatric diseases [and having] the potential to speed up the screening process for therapeutic drugs."[19] Daylon James at the Rockefeller University has also introduced undifferentiated hESCs into mouse embryos to gain a more thorough understanding of the cells' developmental and integrative potential than can be acquired through tissue culture or teratoma assays.[20] James had to derive two new cell lines so he could do this experiment without running afoul of the material transfer agreements for the NIH lines, which all include language prohibiting the introduction of the cells, while undifferentiated, into an embryo. (Goldstein's publication does not identify the source of the cell lines in his research; Gage's group used a non-NIH line.)

Donors' understanding of the word "embryo" is unlikely to include a sharp distinction between embryonic stages and fetal stages of development. (Indeed, it is common to use "fetus" and "embryo" interchangeably, referring to the conceptus from conception to birth.) This uncertainty as to where donors would draw the line between embryo and fetus makes it unclear whether respecting the donors' likely understanding of the consent form is compatible with using WARF's lines in research such as that carried out by James Thomson at the University of Wisconsin, Madison, and Esmail Zanjani at the University of Nevada, Reno. Their research involved the transplantation of hESCs and hESC-derived hemato-

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poietic stem cells (stem cells found in the blood and bone marrow) into fetal sheep.[21] Hematopoietic stem cells can regenerate all types of blood cells and are used in treating leukemia and other blood disorders. However, hematopoietic stem cells are difficult to propagate and expand, and work such as that by Thomson and Zanjani is an important step in assessing whether hESCs, which are more easily grown, can provide a renewable source of transplantable hematopoietic stem cells.

Donors are also unlikely to make a sharp distinction between undifferentiated hESCs and more specialized cells derived from those hESCs. Respecting the donors' likely understanding of the consent form, then, has implications even for projects using those cell lines for the transplantation of specialized derivatives into fetal or embryonic animals. One such project currently under way is work by Su-Chun Zhang at the University of Wisconsin, Madison, that involves transplanting hESC-derived neural cells into chick embryos to test whether the transplanted cells can form appropriate connections to the developing chick's spinal column.[22] Knowledge about such integrative capacity is important for researchers working on amyotrophic lateral sclerosis (also known as Lou Gehrig's disease).

So the consent forms for the NIH lines have several omissions and restrictions. The requirement for informed consent means that there are ethical reasons for limiting the use of the NIH lines to research that respects the restrictions imposed by the consent forms and that falls within areas about which donors were adequately informed.[23] Because the importance of informed consent is not derived solely from concerns about physical, economic, or psychosocial risks, the problems with the forms are not obviated by the fact that the NIH lines are anonymized before they are distributed. Such distribution reduces the risk of certain kinds of harm, but donors nonetheless retain an important, autonomy-based interest in how cells derived from their embryos are used. This interest is even more important when donated materials may be used in ways that donors might reasonably find morally objectionable, as is the case with chimeric research. Moreover, failing to abide by the ethical reasons to limit the use of the NIH lines threatens to undermine the public's trust that researchers will honor both the letter and spirit of the agreements between researchers and subjects. Such trust is crucial to the long-term success of the scientific research enterprise.

The National Academy of Sciences' 2005 Guidelines and 2007 Amendments

The existence of significant problems with the consent forms might come as a surprise to people who have been following reports on hESC research by the National Academy of Sciences and the Institute of Medicine. In 2004, the NAS and the IOM, concerned about the lack of detailed guidance or regulations on hESC research, formed the Committee on Guidelines for Human Embryonic Stem Cell Research to develop a set of consensus guidelines. The product of the committee's work, "Guidelines for Human Embryonic Stem Cell Research," include detailed recommendations about informed consent for embryo donation.[24]

Although the NAS guidelines were largely welcomed by the scientific community as guidance for future procurement efforts, an unanticipated difficulty became apparent shortly after their publication. The guidelines include a nonwaivable requirement for documentation of consent for research not just from embryo donors, but also from all donors of sperm or eggs used in the generation of the embryos. James Battey, the former head of the NIH task force on hESCs, noted that some of the NIH lines might have been derived from embryos generated with donor sperm or eggs, but that the donors might have consented only to the use of the resulting embryos in IVF treatment, not to their use in research.[25] If the guidelines were to be applied not just prospectively, but also retrospectively, institutions following them would likely have to forgo the use of the only hESC lines eligible for federal funding.

As initially published, the guidelines did not explicitly address whether the recommendations should be applied retrospectively or prospectively, and the issue was unresolved until 2007. Then, the Human Embryonic Stem Cell Research Advisory Committee, successor to the committee that wrote the guidelines, published a set of amendments and clarifications that included an explicit decision to "grandfather" the NIH lines. The new committee concluded that institutional review boards and embryonic stem cell research oversight, or ESCRO, committees should treat a line's presence on the NIH registry as satisfying the guidelines' nonwaivable requirement that the provenance of all hESC lines be adequately documented.[26] With the NIH lines now explicitly allowed under the amended NAS guidelines, the worry that institutions could not commit themselves to following the NAS guidelines without forgoing use of the NIH lines was eliminated.

The consent problems have not gone away, however. The committee premised its argument for grandfathering on the claim that "The protocols under which the NIH-approved cell lines were derived were consistent with ethical norms then in place, were substantially similar to those now adopted in these Guidelines, and were adequately documented."[27] Each part of this claim is false.

As already mentioned, informed consent and its implications for disclosure of important information about research have been recognized as an important ethical and legal norm for decades.[28] As HERP noted in 1994, "These concerns [about consent to embryo donation] parallel concerns addressed by well-estab-

Table 1. Comparison of the National Academy of Sciences' 2005 recommendations with the consent forms used for human embryonic stem cell lines eligible for federal funding

Information that NAS recommends be shared	BresaGen	Cellartis	ES Cell Int'l	Technion	UCSF	WARF
1. Patients have no obligation to donate embryos for hESC research	No	Yes	Yes	Yes	Yes	Yes
2. Patients have various options for the care and disposition of their embryos, including freezing for later use, donation to others for reproductive use, research use, or discard without research use	No	No	No	No	Yes	No
3. Embryo donors have a right to withdraw until derivation	No	Yes	Yes	Yes	Yes	Yes
4. The blastocysts will be used to derive hESCs for research that may include research on human transplantation	No	Ambiguous	Yes	No	Yes	Ambiguous
5. The donation is made without any restriction or direction regarding who may be the recipient of transplants of the cells derived, except in the case of autologous donation	No	No	No	No	Yes	No
6. Donors' identities will/will not be readily ascertainable to those who derive or work with the resulting hESC lines	No	No	Yes	No	Yes	No
7. If the identities of the donors are retained (even if coded), then donors may decide whether they wish to be contacted in the future to receive information obtained through studies of the cell lines*	Depends	Depends	Yes	Depends	Yes	Depends
8. Participants in research projects will follow applicable and appropriate best practices for donation, procurement, culture, and storage of cells and tissues to ensure, in particular, the traceability of stem cells	No	No	Yes	No	Yes	No
9. Derived hESCs and/or cell lines might be kept for many years	No	Ambiguous	Yes	Yes	Yes	Yes
10. The hESCs and/or cell lines might be used in research involving genetic manipulation of the cells or the mixing of human and nonhuman cells in animal models	No	No	No	No	No	No
11. The results of study of the hESCs may have commercial potential, and the donor will not receive financial or any other benefits from any future commercial development	No	No	Yes	No	Yes	Yes
12. The research is not intended to provide direct medical benefit to the donor(s) except in the case of autologous donation	No	Yes	Yes	Yes	Yes	Yes
13. Embryos will be destroyed in the process of deriving hESCs	No	No	Ambiguous	No	Yes	Ambiguous
14. Neither consenting nor refusing to donate embryos for research will affect the quality of any future care provided to potential donors	No	Yes	No	Yes	Yes	Yes
15. Risks to the donors are specified**	Depends	Depends	Depends	Depends	Depends	Depends
16. Donors have the option to participate in some forms of hESC research but not others	No	No	No	No	No	No

- "Yes" indicates that the consent form satisfies the recommendation.
- "No" indicates that it does not.
- "Ambiguous" indicates that the consent form has language that is relevant to the recommendation, but whether it satisfies the recommendation is not clear.
- "Depends" indicates that whether the recommendation is satisfied depends on facts about the research that cannot be discerned from the consent form alone.

* Whether the cells retain identifiers was not apparent from some of the consent forms.

** None of the forms mentions psychological risks of donating, and only one mentions risks resulting from a loss of privacy, but whether there are in fact such risks cannot be discerned from the consent form alone.

lished ethical guidelines for all human research."[29] So these were ethical norms then in place, and yet the review of the consent forms identified numerous ways in which the forms were inconsistent with those norms.

Moreover, comparing the consent forms with the guidelines' recommendations shows that many of the forms were *not* substantially similar to what is recommended by the guidelines (Table 1). For example, the BresaGen consent form fails to comply with at least fourteen of the sixteen NAS recommendations. None of the forms satisfy the NAS's recommendation that donors be informed that their human biological materials might be used to create animal-human chimeras. The consent forms for three of the six providers fail to comply with the NAS's recommendation that consent forms mention that the study of hESCs might have commercial potential but that donors will not receive any financial benefits. Three of the forms clearly fail to satisfy the recommendation that the consent forms mention that embryos will be destroyed in the derivation process. And none of the consent forms comply with the NAS's recommendation that donors be given the option of participating in some forms of hESC research but not others.

Finally, to say that the protocols were adequately documented is to say, at the very least, that the documentation is sufficient to confirm that the protocols satisfied the "basic ethical and legal principles of procurement."[30] But given the problems with the consent forms already mentioned, it follows that the protocols did not satisfy those principles. Hence, they were not adequately documented.

Also worrisome is the fact that the amendments to the guidelines appear to have been adopted without any review of the actual consent forms. The amendments concede that "The precise details of the consent process for the NIH approved cell lines may not have included each element called for in the National Academy's Guidelines," when even a cursory review of the forms would have required much stronger language—such as that *none* of the forms included every element, and that some of them failed to include most elements.

That the argument for grandfathering in the NIH lines is unsound does not by any stretch mean that the NAS guidelines should be applied en masse to the NIH lines. The result would be that institutions adopting the guidelines would be unable to use the NIH lines for any purpose, which would clearly be unwarranted: apart from the Cellartis and BresaGen forms (identified above as the most problematic), the consent forms are adequate to cover a wide range of research uses. What the Advisory Committee needs to do is shift from a blunt approach that simply asks whether the NIH lines were obtained with informed consent to a more nuanced approach that instead asks which research uses are those for which informed consent has been obtained.

Informed Consent and Federal Funding

Those involved in the hESC research enterprise—providers, distributors, intellectual property holders, researchers, IRBs, and ESCRO committees—should be attentive to these consent problems in their deliberations about which kinds of research to pursue or allow, and should not presume that the consent processes have been adequately reviewed either by the NIH or by the NAS. If the providers of the NIH lines have additional documentation of the consent process pertinent to the issues raised here, they should make it publicly available to aid the other groups in their decision-making. Taking steps to ensure that the uses of cell lines are restricted to those for which adequate informed consent was obtained is important both to show respect for the donors and to maintain the public's trust in the scientific research enterprise.

Some providers have given these consent issues attention: WARF's material transfer agreement prohibits introducing undifferentiated hESCs from WARF's lines into an embryo, in accordance with the consent form used for WARF's cell lines, and it was recently revised to require compliance with the NAS guidelines. Although this is a good start, it fails to do justice to the likely understanding of the donors of embryos from which WARF's lines were derived: once the cells being used have started to become more specialized cells, the prohibition on introducing them into an embryo no longer applies. Furthermore, the restriction does not apply if the animal into which the cells are introduced is not an embryo on WARF's understanding of the term, which may differ from the donors' understanding. And finally, compliance with both the material transfer agreement and the guidelines is consistent with introducing undifferentiated hESCs into nonhuman primates after the embryonic stage of development and with introducing derivatives into any prenatal animal whatsoever. Some donors may reasonably find such uses morally objectionable.

Although not perfect, the NAS guidelines offer a robust set of elements that should be included in most consent forms for those who donate embryos for hESC research. Consent forms that accord with recommendations from the guidelines would be a significant improvement over the consent forms that were used with the NIH lines. If federal funding were available for research with new lines derived with improved consent, then researchers using federal funding would not have to restrict their research in important ways to avoid using cell lines with problematic or limited consent. That would certainly be ethically preferable to the current situation.

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8. Ibid.

9. 64 *Federal Register* 67576 (1999); 65 *Federal Register* 51976 (2000), respectively. Cited in D. Duffy, Congressional Research Service, "Background and Legal Issues Related to Stem Cell Research," *Almanac of Policy Issues*, June 12, 2002, at http://www.policyalmanac.org/health/archive/crs_stem_cell.shtml.

10. R. Levine, *Ethics and Regulation of Clinical Research* (London, U.K.: Yale University Press, 1986), at 95-153.

11. For ES Cell International, BresaGen, and WARF, there was one form each. The forms for UCSF included two copies of a research subject consent form that were identical except for different dates of institutional review board approval, an embryo and gamete donation consent form, and an "Experimental Subject's Bill of Rights." From Cellartis and the Technion-Israel Institute of Technology, there was an English form for each and a form in Swedish and Hebrew, respectively.

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22. ALS Association, "Update on Stem Cell Research and Potential Treatments for ALS," August 6, 2004, at http://www.alsa.org/news/article.cfm?id=455.

23. Going back to the original donors and asking them to sign improved consent forms would also eliminate these problems but would pose severe logistical difficulties and would itself constitute a serious invasion of the embryo donors' privacy.

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27. Ibid.

28. Levine, *Ethics and Regulation of Clinical Research*, at 95-153.

29. National Institutes of Health, *Report of the Human Embryo Research Panel*, at xiii.

30. Committee on Guidelines for Human Embryonic Stem Cell Research, *Guidelines for Human Embryonic Stem Cell Research,* at 105.