

THE ROLE OF THE FEDERAL GOVERNMENT IN OVERSEEING MEDICAL RESEARCH

GIL VAN BOKKELEN*

I. INTRODUCTION	299
II. FEDERAL FUNDING OF MEDICAL RESEARCH.....	300
A. <i>Selecting the Medical Research To Fund</i>	301
B. <i>Funding Acceptable Medical Research</i>	302
III. EMERGING AVENUES OF RESEARCH RAISE DIFFICULT QUESTIONS	304
A. <i>Determining What Is Acceptable</i>	304
B. <i>Determining Who Decides What Is Acceptable</i>	305
1. The Federal Government: Establishing the Laws of the Land	305
2. The Federal Government: Establishing Legal Parameters	306
3. The Federal Government: Establishing the Federal Budget.....	306
C. <i>Determining What To Do When an Ambiguity Exists</i> .	307
IV. CONCLUSION.....	308

I. INTRODUCTION

The United States enjoys a unique position among the world community in a number of respects. Although it is not the largest or most populated country in the world, the United States is considered one of the wealthiest.¹ Our significant national wealth affords us with some interesting opportunities. In particular, it allows us to devote a portion of those resources toward causes that we as a nation feel are worthy and significant. For example, such causes include charitable aid programs, in the name of promoting global economic development and world peace. The United States leads in this category as well, donating an annual \$27.5 billion in unrestricted charitable foreign aid to promote international economic development through the Office of Development Assistance of the United Nations.² Private

*Co-founder, Chairman, and CEO, Athersys, Inc.; Ph.D., Genetics, Stanford University Medical School. The views expressed in this article are the author's and not necessarily those of Athersys.

¹Aneki.com, Largest Countries in the World, <http://www.aneke.com/largest.html> (last visited May 24, 2007); Aneki.com, Most Populated Countries in the World, <http://www.aneke.com/populated.html> (last visited May 24, 2007); Aneki.com, Richest Countries in the World, <http://www.aneke.com/richest.html> (last visited May 24, 2007).

²Global Issues: Sustainable Development, The U.S. and Foreign Aid Assistance, <http://www.globalissues.org/TradeRelated/Debt/USAId.asp> (last visited Feb. 17, 2007).

philanthropy from the United States is even greater, with an estimated \$71 billion being given in 2004 from private individuals, foundations, churches, and other organizations.³ In total, nearly one percent of our national income is given away to individuals, groups, and countries in need around the world.⁴

Another one of the ways in which we have chosen to spend (or invest – depending on one’s perspective) a portion of our national wealth is in the area of research. Such research covers a broad range of areas, including medical research, technology development, space-related research, material sciences, and a host of other activities. The funding provided to conduct this research comes from both public and private sources. We invest heavily as a nation in government sponsored research across a range of areas. One area in particular rises above the rest in terms of committed resources – medical research. Note that this funding is provided almost entirely to not-for-profit entities, such as colleges, universities, and research institutions, and is distinct from the funding provided by the private sector.

II. FEDERAL FUNDING OF MEDICAL RESEARCH

The National Institutes of Health (NIH) is the primary governmental agency charged with conducting and supporting medical research. According to the official NIH website, the explicit objective of the agency is to “lead the way toward medical discoveries that improve people’s health and save lives.”⁵ Although the NIH can trace its roots back to 1887, our national effort and commitment to invest tax dollars in medically related research took a dramatic turn in the early 1970’s when then-President Richard Nixon declared “war on cancer” in his State of the Union address in January 1971.⁶ With the approval and oversight of Congress, the National Cancer Act was passed in December 1971, and federal funding toward diagnosing and treating cancer and other diseases began to dramatically increase.⁷ As recent statistics demonstrate, this long-term investment in conjunction with other events (such as a decline in the rate of smoking) is apparently starting to yield dividends in the form of a reduced rate of deaths due to cancer, cardiovascular disease, and other significant causes of morbidity and mortality.⁸

³The Chronicle of Philanthropy, *Americans Send \$70 Billion to Poor Countries* (Apr. 20, 2006), <http://www.philanthropy.com/free/update/2006/04/2006042001.htm>.

⁴Carol C. Adelman, *The Privatization of Foreign Aid: Reassessing National Largesse*, FOREIGN AFFAIRS Nov./Dec. 2003, available at <http://www.foreignaffairs.org/20031101facomment82602/carol-c-adelman/the-privatization-of-foreign-aid-reassessing-national-largesse.html>.

⁵U.S. Department of Health and Human Services, National Institutes of Health, <http://www.nih.gov> (last visited Feb. 17, 2007).

⁶President Richard Nixon, State of the Union Address (Jan. 25, 1971).

⁷*See generally*, National Cancer Act of 1971, Pub. Law No. 92-218, 85 Stat. 778. “An Act [t]o amend the Public Health Service Act so as to strengthen the National Cancer Institute of Health in order to more effectively to carry out the national effort against cancer.” *Id.*

⁸Coalition for Health Funding, *Examples of How the Public Health Continuum Works to Keep Americans Healthy*, available at <http://www.aamc.org/advocacy/healthfunding/healthcontinuum.htm> (last visited May 24, 2007).

The explicit objective of the dramatic increase in NIH funding is to improve the health and well being of the citizens of the United States – clearly a laudable objective (at least for those of us that value our health and well being). Unfortunately, it is not immediately obvious or self-evident as to how best to accomplish that goal. While most may agree that it is worthwhile to invest significant taxpayer resources to help identify and develop new ways to diagnose and treat diseases, there are many ways we could allocate the available resources, which while substantial are also finite. The number of ways in which the currently available dollars could be used far exceeds the currently available supply of resources.

A. Selecting the Medical Research To Fund

The longstanding solution to this resource allocation conundrum relies on a competitive grant system that is governed by a system of “peer review.”⁹ In short, guidelines (requests) for research proposals are established and released by the NIH.¹⁰ Investigators from across the country produce detailed proposals that they submit to grant application review committees composed of highly qualified scientists from the NIH and research institutions across the United States.¹¹ These committees then review and score the grant proposals, ultimately awarding funding to those proposals that are deemed to be of the highest quality.¹²

To critics, this system is really a form of “self-policing” in which the most likely recipients (leading scientists from a variety of disciplines and institutions across the United States) are also responsible for evaluating and grading the research proposals of their colleagues – hence the term “peer review.” If not properly managed, this self-policing mechanism can ultimately result in unintended conflicts of interest that may be difficult to detect and manage. It can also result in other challenges that need to be carefully managed, such as determining where to draw the line with respect to establishing what constitutes ethical or appropriate research that should be funded with taxpayer dollars.

The ongoing debate over the appropriateness of certain types of research raises some interesting and thorny questions regarding the appropriate role of the federal government in the field of medical research. On one side of the debate, there are those that feel that elected members of the federal government are not qualified to determine the potential merits or significance of various lines of scientific or medical research and, therefore, should have no direct say in establishing the limits of such research activities. In essence, this view is based on the premise that neither the president nor members of Congress are scientifically qualified to evaluate or judge the implications of highly technical research that are viewed as having tremendous medical potential, such as working with embryonic stem cells. Because they cannot fully understand the technical or medical implications of the research, they are not

⁹For an overview of the peer-review process, see The National Institutes of Health’s Center for Scientific Review, The Peer Review Process, *available at* <http://cms.csr.nih.gov/AboutCSR/Overviewofpeerreviewprocess.htm> (last visited May 24, 2007).

¹⁰*Id.*

¹¹*Id.*

¹²*Id.*

qualified to limit the research, and the system of peer review is an appropriate means of handling such issues, or so the argument goes. However, not everyone agrees with this view, and that begs the question – just who should decide what the limits of ethically acceptable medical research are or should be? Or, the distinct but highly related question, who should decide the ethical limits of taxpayer funded research?

B. Funding Acceptable Medical Research

Unfortunately, there have been occasions throughout history where individuals that were engaged in varying forms of so-called “medical research” committed unethical acts. Extreme acts, such as those forms of experimentation which are intended or unavoidably result in harm to an individual (whether temporary or permanent), or acts that are performed without informed consent are typically easy to identify as reprehensible and morally repugnant. Accordingly, it is relatively easy to define such activities as unacceptable. But clearly, there are forms of research that fall into what many people view as a “gray area.”

For example, there may be healthy disagreement regarding the appropriateness of using various animal models in the effort to develop safer and more effective medicines for people, especially if such research may result in the injury, illness, or death of an animal. What may be acceptable to one group (e.g., it is acceptable to conduct experimentation on mice, rats, or larger animals that more closely reflect human biology in order to develop safer and more effective ways to diagnose or treat human disease), may be totally unacceptable to others (e.g., animal rights groups that are opposed to any form of experimentation on animals or individuals that feel that experimentation on mice and rats is okay, but not on larger animals such as dogs or monkeys). Obviously, there is a gray area here as well – as evidenced by the recent case of the surgeon at the Cleveland Clinic who performed an experimental procedure on a dog for the purpose of “sales training” utilizing a particular medical device that resulted in the animal’s death.¹³ Obviously, the physician felt the act was justifiable, at least at the time.

Another example would be experimentation on children that are too young to provide informed consent. If the proposed act does not intend harm to the child and provides a potential benefit to the child, then most would view such research as ethically acceptable. But what if the research provides no immediate or clearly defined benefit to the child, but likely creates potential harm to the child, although it may provide a potential future benefit to others? Most would agree that such acts should be strictly prohibited because the needs of the child come first. If one accepts the premise that there are potential forms of medical research that are inherently or should be considered unethical or inappropriate, then the obvious corresponding question becomes who should decide what forms of medical research are acceptable and which research should be explicitly prohibited? In the case of animal related research, the federal government has in effect, decided, by establishing federal statutes that require that special review committees be established at every research institution to evaluate and render an opinion as to whether proposed forms of animal

¹³Sarah Treffinger, *Dog Killed at Clinic in Demo of Device; Firm's Salespeople Watch Procedure*, PLAIN DEALER (Cleveland, OH), Jan. 12, 2007, at A1.

research are ethically acceptable or not.¹⁴ These special review committees are called the Institutional Animal Care and Use Committees (IACUC).¹⁵

Internationally, human clinical research activities have been guided by the Declaration of Helsinki, the Nuremberg Code, and conferences and treatises that examine the issues of patient rights. In the case of human clinical research occurring within the United States, guidelines established by the United States Department of Health and Human Services (HHS) and the United States Food and Drug Administration (FDA) largely govern research activities.¹⁶ For example, such guidelines stipulate that before commencement proposed clinical studies require a review by an appropriately constituted Institutional Review Board (IRB).¹⁷ In addition, there are other regulations that apply to research that is sponsored in whole

¹⁴See generally 9 C.F.R. § 1.1 (2006); 9 C.F.R. § 2.1-2.133 (2006); 9 C.F.R. § 3.1-3.142 (2006).

¹⁵*Id.*

¹⁶The Food and Drug Act of 1938, 21 U.S.C. § 355 (2006), and the National Research Act of 1974, 42 U.S.C. § 289 (2006), empower the Secretary of the Department of Health and Human Services to issue regulations affecting human-subject research.

The Secretary shall promulgate regulations for exempting from the operation of the foregoing subsections of this section [which require prior approval of an application before a person introduces a drug into interstate commerce] drugs intended solely for investigational use by experts qualified by scientific training and experience to investigate the safety and effectiveness of drugs. Such regulations may, within the discretion of the Secretary, among other conditions relating to the protection of the public health, provide for conditioning such exemption upon [for example] (A) the submission to the Secretary, before any clinical testing of a new drug is undertaken, of reports, by the manufacturer or the sponsor of the investigation of such drug, of preclinical tests (including tests on animals) of such drug adequate to justify the proposed clinical testing. . . .

21 U.S.C. § 355 (2006).

The Secretary shall by regulation require that each entity which applies for a grant, contract, or cooperative agreement under this Act for any project or program which involves the conduct of biomedical or behavioral research involving human subjects submit in or with its application for such grant, contract, or cooperative agreement assurances satisfactory to the Secretary that it has established (in accordance with regulations which the Secretary shall prescribe) a board (to be known as an "Institutional Review Board") to review biomedical and behavioral research involving human subjects conducted at or supported by such entity in order to protect the rights of the human subjects of such research.

42 U.S.C. § 289(a).

¹⁷45 C.F.R. § 46.103(b) (2006).

Departments and agencies will conduct or support research covered by this policy only if the institution has an assurance approved as provided in this section, and only if the institution has certified to the department or agency head that the research has been reviewed and approved by an IRB provided for in the assurance, and will be subject to continuing review by the IRB.

Id.; see also 21 C.F.R. § 56.103 (2006). "[A]ny clinical investigation which must meet the requirements for prior submission . . . to the Food and Drug Administration shall not be initiated unless that investigation has been reviewed and approved by, and remains subject to continuing review by, an IRB meeting the requirements of this part." *Id.*

or in part by HHS, such as those regulations that ensure that studies will comply with the HHS protection of human subjects regulations.¹⁸ So, from a precedential standpoint, it is clear that the federal government is directly responsible for issuing what constitutes ethically acceptable research behavior, as well as issuing guidelines for establishment of institutional mechanisms, such as IACUC and IRB, that govern research involving animals or human subjects.

III. EMERGING AVENUES OF RESEARCH RAISE DIFFICULT QUESTIONS

While substantial guidelines are already in place to protect the well being of human clinical research participants, there are emerging avenues of research that the existing rules and guidelines did not contemplate when they were established. Relevant examples of this kind of research include embryonic stem cell research and human cloning. As a result, it may not be so easy to immediately characterize such activities as ethically (or even legally) acceptable or to establish clear mechanisms that allow individual research projects to be conducted in a manner that is unambiguously deemed to be ethically appropriate and legal. Some of the fundamental questions that we as a society face with respect to thorny issues, such as embryo research, cloning research, and other areas of active debate, involve questions that are not easily answerable.¹⁹

A. *Determining What Is Acceptable*

Can we definitively establish what is acceptable, such as with respect to the harvesting or use of embryo tissue or human cloning? Clearly, there are research activities that are ethically unacceptable, such as those that involve intentional harm or that do not involve informed consent. Historical examples include activities in Nazi Germany that ultimately led to the Nuremberg Code,²⁰ and the Tuskegee syphilis experiments conducted by the United States public health service, and other activities that led to subsequent regulations governing clinical research established by Congress. If we accept that such activities have occurred in the past and may *potentially* occur in the future due to the lack of appropriate oversight and limitation, then we as a society are morally compelled to define as best we can what constitutes acceptable and unacceptable behavior, even if it has to be done on a case-by-case basis.

¹⁸45 C.F.R. § 46.101(a) (2006). “[T]his policy [i.e., the HHS policy for the Protection of human research subjects] applies to all research involving human subjects conducted, supported or otherwise subject to regulation by any federal department or agency which takes appropriate administrative action to make the policy applicable to such research.” *Id.*

¹⁹For one perspective on this debate, see Dr. Robert P. George, Family Research Council, At the Podium, *The Ethics of Embryonic Stem Cell Research and Human Cloning*, Issue No. 87, available at <http://www.frc.org/get.cfm?i=PD02D5> (last visited May 20, 2007).

²⁰For a summary of the origin of the Nuremberg Code, as well as the Helsinki Declaration and current regulations, see UNLV’S Office for the Protection of Research Subjects, History of Research Ethics, available at <http://research.univ.edu/OPRS/history-ethics.htm> (last visited May 20, 2007).

B. Determining Who Decides What is Acceptable

Who decides what is acceptable? Should it be the federal government, state government, or should it not be legislated at all? And, how do they decide? Should it be decided by federal statute, agency, or by an institutional mechanism such as an IRB? No matter what the answer to this question, the federal government has a major role and responsibility in determining and setting the limits of medical research. Specifically, there are at least three fundamental reasons why the federal government *must* participate in setting these limits.

1. The Federal Government: Establishing the Laws of the Land

The explicit role and responsibility of the federal government is to establish the laws of the land, especially those that govern or may impact basic human rights. Research that involves human subjects has implications in the area of human rights. However, the issue of embryonic stem cell research or human cloning research is not a human rights issue in the minds of many – but to others it is. Take for example the case of parents and doctors who need (or simply choose) to utilize *in vitro* fertilization to conceive a child. From the moment the fertilized embryos are successfully established, the parents and doctors are faced with a series of ethical choices. How many fertilized eggs are implanted? What if there are “extra” fertilized embryos – how are they handled? For some, these decisions are difficult and have no clear “right” or “wrong” answer. Clearly, the embryos are treated with respect and safeguarded by clinicians, nurses, and biological parents as the potential lives they were meant to be.

For some, fertilized eggs do not constitute a “life” and, therefore, may be freely used for research purposes if consent is provided by the parent(s), such as their use to create embryonic stem cells. However, given that the creation of the embryonic stem cells unavoidably results in the destruction of the fertilized egg/embryo, many people find this concept disturbing because it creates irrevocable harm to a *potential* individual, yet provides that individual with no benefit whatsoever. The counter to this is that it may provide a benefit to others, but as discussed earlier in the context of research on children, if an act provides no benefit to a child but does (or will) create potential harm to the child, it is probably not going to be endorsed as ethically appropriate, even if it provides a *potential* future benefit to others.

Related questions include the following: if a fertilized egg is capable of survival in a mother and has the true biological potential to grow to become a viable person, does it have any rights prior to birth? Do those rights depend on the stage of development? If so, when do the rights become vested or manifest: only upon implantation in the womb; only upon reaching a certain stage of maturity; or only after birth? Clearly, these are difficult questions that touch on the very nature of what it means to be “human.”²¹

One interesting consideration that is rarely discussed or considered in these debates is that presumably an embryonic stem cell that has the true biological ability to form the normal healthy tissue of an adult can only come from a fertilized egg that has the potential to form an actual individual. If the fertilized egg does not have the

²¹See National Institutes of Health: Stem Cell Information, Research Ethics and Stem Cells, <http://stemcells.nih.gov/info/ethics.asp> (last visited Feb. 17, 2007) (listing a variety of references on the ethics of stem cell research).

potential to form a viable, healthy individual, its medical utility is probably limited at best. Therefore, by definition, the creation of a medically useful embryonic stem cell line requires the sacrifice of a *potential* individual, which occurs by the destruction of a fertilized egg that has the true biological potential to form a viable person. But, if this is one *potential* life to save many others, and the egg has no hope of survival pre-implantation, is that ethically problematic? Do these and the other considerations described above make this a human rights issue? Again, some would say yes, others no, but it makes sense that the federal government would give this issue some consideration.

2. The Federal Government: Establishing Legal Parameters

As it has in the case of establishing parameters that govern research activities related to the use of animals, the federal government is legally empowered, by statute and precedent, and even compelled to establish legal parameters with regard to determining what constitutes acceptable or unacceptable research activities that involve human subjects. At a minimum, this case involves the embryo donors, if not the embryo itself. The federal government may do this through direct legislative action or indirectly through established agencies, such as the HHS or the FDA, or through an institutionalized decision making framework, such as an IRB. Such an institution would then have the explicit authority to decide on a case-by-case basis what is permissible, while operating in accordance with the legal principles and guidelines that are defined in the Code of Federal Regulations (CFR).

Note that the ultimate power to define legislative parameters, which approach to use, or what constitutes acceptable versus unacceptable activities rests primarily with the legislative and executive branches. At the agency level, the leadership appointments are made by the president and approved by Congress.²² At the legislative level, Congress passes the legislation that establishes the laws of the land, and the president may or may not sign the legislation into law.²³ However, if the president vetoes proposed legislation, then Congress may override the veto with a two-thirds majority, in effect superseding the president.²⁴ Even if Congress and the president pass a new law, the judicial branch ultimately has a say as to how the law may be interpreted or whether the law is valid and enforceable.²⁵

3. The Federal Government: Establishing the Federal Budget

Third, the federal government is responsible for establishing the federal budget and, therefore, the president and Congress are legally, morally, and politically accountable for how funds obtained from the United States taxpayers are spent. The

²²U.S. CONST. art. II, § 2, cl. 2. “[The president] shall nominate, and by and with the Advice and Consent of the Senate, shall appoint . . . other public Ministers and Consuls, . . . and all other Officers of the United States, whose appointments are not herein otherwise provided for, and which shall be established by Law.” *Id.*

²³U.S. CONST. art. I, § 7, cl. 2. “Every Bill which shall have passed the House of Representatives and the Senate, shall, before it become (sic) a Law, be presented to the President of the United States; If he approve he shall sign it, but if not he shall return it, with his Objections to that House in which it shall have originated. . . .” *Id.*

²⁴*Id.*

²⁵*Marbury v. Madison*, 5 U.S. 137 (1803) (establishing the doctrine of judicial review).

annual budget for the NIH is more than \$28.6 billion.²⁶ More than eighty percent of this funding is awarded in the form of peer-reviewed grants to over 212,000 researchers at more than 2800 universities, medical schools, and research institutions across the United States and in other countries around the world.²⁷ Over ten percent of the total funding is invested in research conducted directly at the NIH research campus in Bethesda, Maryland.²⁸

No matter how you slice it, that is a lot of money. And that funding comes from a single source – the taxpayer. Not only do we provide the funding every year, through our federal tax payments, but we also elect the people that are directly responsible for determining how our tax dollars get spent – the members of Congress and the president. The United States was founded on the very notion of “no taxation without representation” – in other words we the citizens agree to pay federal taxes, but only if we get a say through our elected representatives, as to how our money gets spent.²⁹ If we want or do not want our tax dollars to be spent on certain activities, then we have the opportunity, if not the moral obligation, to let our elected representatives know about it. So, it seems clear that there are multiple reasons why the federal government can and does have a role, whether direct or indirect, in establishing the limits of certain research related activities.

C. Determining What To Do When an Ambiguity Exists

What do we (as a society) do when the moral or ethical “acceptability” of something is in question and intensely debated? Do we prohibit the activity until it is unequivocally determined to be acceptable? Or, do we allow it to continue until moral unacceptability has been unequivocally established, and then prohibit it? These questions concern what we should do when there is no clear and immediate answer regarding the ethical appropriateness of a particular activity. In such cases where ethical acceptability is in question, do we allow the activity to continue until it is unequivocally deemed morally unacceptable, or do we prohibit it until and unless

²⁶See U.S. Department of Health and Human Services, National Institutes of Health, About NIH, <http://www.nih.gov/about/> (last visited Feb. 17, 2007). See also U.S. Department of Health and Human Services, National Institutes of Health, Director’s Page, <http://www.nih.gov/about/director/index.htm> (last visited Feb. 17, 2007) (explaining that the NIH budget for the 2006 fiscal year was \$28.6 billion, including both intramural and extramural research). *Id.*

²⁷See U.S. Department of Health and Human Services, National Institutes of Health, Biographical Sketch of Dr. Elias A. Zerhouni, <http://www.nih.gov/about/director/directorbio.htm> (last visited Feb. 18, 2007).

²⁸*Id.*

²⁹THE DECLARATION OF INDEPENDENCE (U.S. 1776).

The history of the present King of Great Britain is a history of repeated injuries and usurpations, all having in direct object the establishment of an absolute Tyranny over these states. To prove this, let Fact be submitted to a candid world. . . . *For imposing Taxes on us without Consent.* . . . We, therefore, the Representatives of the united (sic) States of America, . . . publish and declare That these united Colonies are, and of Right ouhgt to be Free and Independent States, that they are Absolved from all Allegiance to the British Crown. . . .
Id. (emphasis added).

we deem it to be acceptable? Once again, there may be no obvious right or wrong answer here, but it seems likely that one's viewpoint may be influenced by the nature of the activity in question, as well as many other factors. For example, is the need or desirability of embryonic stem cell related research impacted at all by the success or failure of parallel research efforts using adult or other non-embryonic stem cells?

IV. CONCLUSION

Unfortunately, there are no easy answers to these questions. But there are two quotes that come to mind when I consider the issue. The first is from the United States Declaration of Independence and serves to remind me that our government was created expressly to secure and protect the most basic of human rights, even if those rights are not fully or perfectly defined: “[w]e hold these truths to be self-evident, that all Men are created equal, that they are endowed by their Creator with certain unalienable Rights, that among these are Life, Liberty and the Pursuit of Happiness. That to secure these Rights, Governments are instituted among Men.”³⁰ The second quote is from Pope John Paul II. Although it does not directly bear on the role of government in preserving and protecting human rights, it does provide an interesting perspective on how society and by extension the government of that society should be measured: “[a] society will be judged on the basis of how it treats its weakest members; and among the most vulnerable are surely the unborn and the dying.”³¹

³⁰THE DECLARATION OF INDEPENDENCE para. 2 (U.S. 1776).

³¹Pope John Paul II, Address of the Holy Father to the New Ambassador of New Zealand to the Holy See (May 25, 2000), *available at* http://www.vatican.va/holy_father/john_paul_ii/speeches/2000/apr-jun/documents/hf_jp-ii_spe_20000525_ambassador-new-zealand_en.html.