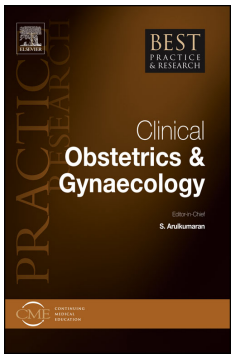
Accepted Manuscript



Ethical Issues in Research

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PII: S1521-6934(17)30005-6

DOI: 10.1016/j.bpobgyn.2016.12.006

Reference: YBEOG 1684

To appear in: *Best Practice & Research Clinical Obstetrics & Gynaecology*

Received Date: 3 December 2016

Accepted Date: 9 December 2016

Please cite this article as: Artal R, Rubenfeld S, Ethical Issues in Research, *Best Practice & Research Clinical Obstetrics & Gynaecology* (2017), doi: 10.1016/j.bpobgyn.2016.12.006.

ETHICAL ISSUES IN RESEARCH

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Abstract

Biomedical research is currently guided by ethical standards that have evolved over many centuries. Historical and political events, social and legal considerations and continuous medical and technological advances have led to the prevailing research ethics and practice.

Currently, patients and research subjects have complete autonomy while under medical care or when volunteering as research subjects. Enrolling volunteers in human subjects research includes a detailed and meaningful informed consent process that follows cardinal principles of ethics: autonomy, beneficence, non-maleficence and justice. These principles were adopted gradually after World War II, primarily in response to the unethical behavior of German physicians and scientists during the Third Reich.

This review emphasizes the importance of historical milestones and the essential role that ethics has in contemporary medical research. Research protocols should achieve maximum benefits for the society, have clinical and scientific value, be subject to independent review, respect human dignity and follow the principles of informed consent and most importantly, subjects should have complete autonomy.

However, current principles and regulations cannot cover every conceivable situation, particularly in view of new advances in science and technology.

New and evolving medical technology, genetic research, therapeutic interventions and innovations, challenge society to maintain the highest moral and ethical principles.

Keywords: Research ethics principles, eugenics, Nazi medicine, informed consent, women subjects in research, the fetus as a patient

Introduction and historical perspectives

Medical ethics and ethical principles have been practiced and debated for centuries in the Hippocratic tradition but ethical human research standards, protection principles, laws, regulations and guidelines were gradually introduced and slowly adopted, or updated only in the last few decades, primarily as a result of historical events and atrocities committed in the name of research. In recent years, the focus of contemporary medical research ethics has shifted to the protection of the individual patient or volunteer when enrolling as a research subject. Patients are now better informed and aware of their rights and options, especially their right of refusal. The informed consent process has evolved with an emphasis on the subject's autonomy and choice and the adoption of protective procedures for patients who are less than fully autonomous, including the unborn fetus.

Eugenics had a significant influence on the direction of medical research.
In the 1880s Francis Galton in England coined the term "eugenics" a so-called "scientific" concept with the aim of purportedly improving racial quality through abortions, sterilization of races deemed "less desirable", and also introduced forms of population control. He promoted procreation and medical care for the superior races and discouraged procreation and medical care for the inferior races. Eugenics was quickly adopted by many prominent academic and research institutions around the Western world. Eugenics, ultimately provided a rationale for initiating and pursuing some of the most unethical human research projects ever undertaken, such as compulsory sterilization, forced abortions, involuntary euthanasia and mass murder (1). In Germany physicians and bioscientists promoted eugenic ideas for three decades before the rise of Hitler, who incorporated them into his public health policy of "applied biology".
American eugenicists, arguably the world's leaders in eugenics, provided moral, legal and philanthropic support to the German eugenics movement. The unethical behavior by many scientists who adopted eugenics was driven by moral and racial attitudes promoting state over individual rights, biologic determinism, and concern over medical expenses for patients with chronic diseases and disabilities.
Eugenics medical and scientific research was by and large poorly defined and unregulated.
In the U.S., prior to 1906 there were no regulations regarding the ethics of human subjects in research, no regulatory agencies, no Food and Drug Administration (FDA), no Common Rule, and no Institutional Review Boards (IRB). In 1906 the Pure Food and Act was passed, and included the first research regulations in the U.S. with a focus on manufacturing (2). Other countries permitted human research while ignoring the basic principles of ethics: **autonomy, beneficence, non-maleficence** ("first, do no harm") **and justice.** In addition to these principles, the benefits derived from the research intervention should significantly exceed their risks.

The concept and the process of informed consent for medical/surgical interventions or research (willing and un-coerced acceptance of medical procedures after disclosure of risks, benefits and alternatives) was either not recognized, or simply disregarded. Among the most publicized unethical research studies in the U.S. was the Tuskegee Syphilis Study that was initiated by the US Public Health Service in 1932. Despite the availability of effective treatment, the researchers withheld it from 400 poor African American men diagnosed with syphilis. The "research study" resulted in severe complications and many deaths. As disreputable as this research was, it pales in comparison to the unprecedented scale of unethical experiments conducted by Nazi physicians and scientists during the Third Reich. Physicians and their allied scientists during the Nazi regime totally ignored the most basic principles of ethics and were unprecedented in its scale.

Ethics, Nazi Human Experiments and historical background

"Ethics became nazified, as justifying a researcher's duty to undertake coercive research… It was not that Nazi research conducted on human subjects had no ethics, but rather that ethical formulations were shaped by distinctive Nazi priorities" (3).

Soon after the Nazis government came into power in 1934 they passed the Law for the Prevention of Genetically Diseased Offspring or the Sterilization Law. The Nazis found support for their involuntary sterilization law in the United States and other Western countries. The first involuntary sterilization law in the world was passed in Indiana in 1907. 28 American states had involuntary sterilization laws at the time of the 1928 Buck v. Bell, Supreme Court decision that declared involuntary sterilization was constitutional and did not require informed consent (4). At least 12 countries had approved involuntary sterilization laws before Nazi Germany.

A substantial portion of Nazi medical research focused on racial selection with research projects in genetics, virology and hormonal applications, with the ultimate goal of achieving racial superiority. The sick, the disabled, healthy Jews and Roma subjects were the first experimental research victims of the opportunistic researchers at the Kaiser Wilhelm Institute in Germany (the equivalent of the U.S. National Institutes of Health) supported by the German Research Fund (DFG). The researchers at the Kaiser Wilhelm Institute pursued eugenic research in anthropology, psychiatry and "racial improvement" research including involuntary sterilization methodology (such as surgical castration and irradiation) frequently lethal. One of the objectives was to maintain a sterile work force. Research subjects also included pregnant subjects and their fetuses (3,5).

Anthropologists and racial researchers developed policies and algorithms for the implementation of "racial cleansing" including euthanasia. The "researchers" hypothesized that there was a link between psychiatric conditions, "inferior races" and brain abnormalities. An opportunistic "research" program was attached to the nationwide "euthanasia" program to harvest and study brain tissue obtained from adults and children victims (6).

After the outbreak of World War II the Nazis undertook lethal military experiments, to test human tolerance to extreme physiological or adverse conditions including torture, for the benefit of the Nazi military and their agenda (3). Needless to mention that informed consents were never considered. (Table1). Aside from the "scientists" many medical students witnessed and participated in these experiments and chose to use the criminally obtained data for their M.D. theses, which led to indoctrination in Nazi medicine values very early in their careers. Many of these students became indoctrinated in the Nazi medicine values very early into their careers. Published records documented 30 research projects and experiments performed on concentration camp prisoners, most of them Jewish victims, during World War II (7). The experiments are listed in Table 1

Table 1. Nazi Medicine Research experiments

- **Genetics**
- **Infection disease**
- **Hypothermia and Freezing**
- **High Altitude (Decompression)**
- **Sterilization**
- **Twins exposure to pathogens**
- **Irradiation**
- **Pharmacological experiments**
- **Nutrition and Starvation**
- **Traumatic Injuries and other**

Years later, medical ethicists and scientists questioned the scientific validity of the data obtained in such an unethical manner from these many lethal “experiments” and concluded that they should not to be used or published (7).

At the conclusion of the Nazi Doctors’ Trial in 1947 the justices issued **The Nuremberg Code** the first international code of human subjects research ethics with a primary concern for voluntary consent (8). For the purpose of the trials procedures, the judges developed principles to be used in human experimentation. Among the Code’s ten principles: human subjects are necessary, voluntary consent and withdrawal, minimal research risks, the research to be terminated if research subjects could or get injured or harmed, the research should benefit society, research must be based on pre-clinical animal studies and most important the research subjects have the right to end participation in the study.

Ironically, it has been argued that the Nuremberg Code was based upon the German Guidelines for Human Experimentation or the Berlin Code, previously drafted in 1931, but suppressed and never implemented. (9)

Soon after the Nazi Doctors‘ Trial in 1948, the **Universal Declaration of Human Rights** was adopted by the General Assembly of the United Nations (10). In 1964 the World Medical Association issued the **Helsinki declaration** on Ethical Principles for Medical Research involving Human Subjects that have been updated and clarified nine times since then. (11)

The U.S. Congress established a milestone in human subjects research in 1974 with the **National Research Act**. In 1979 the Department of Health, Education, and Welfare issued the **Belmont Report**, which emphasized 3 ethical principles (12):

-1) **Respect for persons**, the ability to control his/her own actions and requirements to obtain informed consent.
-2) **Beneficence,** minimizing harms and risks and maximizing benefits from study participation.
-3) **Justice,** equitable distribution of benefits and risks/harms and equitable subject selection (to avoid social inequalities and disparities in subjects’ selection).

The National Research Act and the Belmont Report stimulated and directed the creation of informed consent principles and policies that remain in use today.

In 2002 the Council for International Organizations of Medical Sciences affirmed and adopted the **International Ethical Guidelines for Biomedical Research**, which include (13):

1) Ethical justification of the research, 2). Scientific validity. 3) Review and approval by ethics committee. 4) Informed consent.
5) Inducements to participate. 6) Risks and Benefits. 7) Research in low resource populations
8) Choice of control groups in clinical trials. 9) Research including vulnerable subjects.
10) Confidentiality. 11) Compensation for injury as a result of research. 12) Ethical obligation to provide health services as needed.

These guidelines are periodically updated and also modified to conform to local regulatory ethical rules. The guidelines also define the roles of sponsors, investigators, monitors and research associates.

In 2012, 65 years after the issuance of the Nuremberg Code for research on human subjects, the German Medical Assembly issued the “Nuremberg Declaration” acknowledging the initiation by, and participation of, the scientific and medical community in Germany and Austria in the most unethical and inhumane “research experiments” on concentration camps prisoners (14).

Notwithstanding this belated admission after many years of unregulated and unethical research (table 2}, the International Ethical Guideline for Biomedical Research of 2002 were gradually adopted and affirmed by the scientific community

Table 2. Research Ethics; Time Line, Milestones and examples of Unethical Human Experimentation.

1796- Edward Jenner in the UK conducted smallpox vaccines experiments on his son and neighborhood children without their knowledge or understanding of risks

1932-1972 Tuskegee Syphilis Study. Researchers withheld treatment from subjects.

1939-45 Research by German and Austrian scientists on concentration camps prisoners, and Japanese scientists on Chinese prisoners of war.

1946-47 Researchers at the University of Rochester injected uranium-234 into human subjects to study human body tolerance.

1947 **Nuremberg Code for Research on human subjects adopted**

1940-80 U.S. government sponsored research on the effects of radiation on uninformed or consented human subjects (cancer patients, pregnant women, military personnel)

1950-1963 U.S. mind control research, including administration of LSD to unwitting subjects

1960- Patients, without informed consent, at the Jewish Chronic Hospital in Brooklyn were Injected with live cancer cells by Chester Southam to investigate how human bodies "fight invasion of cancer cells"

1956-1980 S. Krugman and J. Giles hepatitis experiments on mentally disabled children. (Experiments approved by New York Department oh Health)

1964 **World Medical Association, Helsinki Declaration on ethical principles for Research on human subjects**

1960-85 Policies on Humane Care and Use of Laboratory Animals

1974 **Congress passes the National Research Act-** federal agencies authorized to develop human research regulations

1979 **The National Commission releases the Belmont Report, principles of ethical research on human subjects**

1981 **The U.S Department of Health, Education, and Welfare (now Department of Health and Human Services) conducts major revisions of the federal human research regulations on human subjects research**

1989 The NIH requires that all graduate students on training grants receive education in responsible conduct of research

1990 The U.S. launches the Human Genome Project

1991 All U.S. government agencies, except Environmental Protection Agency, accept one basic regulatory framework for human research, known as "the Common Rule"

1993 Fertility researchers successfully clone human embryos

1994 The Clinton Administration declassifies information on radiation experiments and issues an apology

1998 Scientists perfect methods for growing human embryonic stem cells. Some countries ban the research, others promote it

1999 **Present:** The NIH and the OHRP (Office for Human Research Protections) provide leadership and directions in the protection, rights, welfare and wellbeing of human subjects involved in research conducted or supported by the U.S. government.

The directives require all individuals conducting or overseeing human research to have training in research ethics.

2002 **International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences and World Health Organization)**

Women Subjects and the Fetus in Research

For many years women were not recruited into research studies primarily because of the fear of unrecognized pregnancy and potential harm to the fetus and the preference was to use all-male subjects to simplify data-analysis (17). Because of multiple and complex ethical issues in obstetrical and gynecological practice, these concerns are being addressed. The concept of the fetus as a patient has evolved in recent years, thereby new ethical issues have emerged and are being addressed; currently directive versus non-directive counseling include fetal benefits (18).

Contemporary Principles of Ethics in Biomedical Research

Ethical principles are currently guided by justice (a concept of fairness administered lawfully) There are four basic ethical principles currently followed in medical practice and medical research:

1. Respect for patient autonomy; the recognition of the individual's right to make informed decisions based on personal beliefs, convictions and values.
2. Beneficence
3. Non maleficence
4. Justice

The informed consent doctrine and practice dictates (19):

- Research scientists and physicians should provide full disclosure and adequate information to the patient/subject about the medical/surgical intervention, its benefits and risks, and available options and alternatives.
- The information given to the patient/subject should be clear and easy to understand, such that the patient can make an informed decision in line with their values and beliefs.
- The research scientists/physicians must ensure that the decision to accept or reject an intervention is a free and voluntary choice of the patient

In 2010 the National Institute of Justice in the United States published and recommended human research subjects rights (20):

1. Voluntary participation and informed consent.
2. Respect for persons: treated as autonomous agents
3. The right to end participation in research at any time
4. Right to safeguard integrity
5. Benefits should outweigh cost
6. Protection from physical, mental and emotional harm

7. Access to information regarding research

One other important ethical concept and concern in medical research is "**therapeutic misconception**", which occurs when research subjects misinterpret the research study protocol and believe that the study intervention may directly benefit them (common perception in Phase 1 cancer trials), the same perception may occur in randomized studies using placebo. Thus, the importance of full disclosure, informed consent, voluntary participation and available alternatives is essential. (21)

The guidelines are applicable to most or all types of human research including:

1. Drugs and Devices
2. Research Injury
3. Privacy/Data Protection
4. Human Biological Materials
5. Genetic
6. Embryos, Stem Cells, and Cloning

It is important to emphasize that contemporary guidelines cannot address all conceivable clinical or research situations, especially as new technologies, create unforeseen and novel controversies. For such innovations, the majority of decisions will involve straightforward application of ethical rules in research (22). A summary of these ethical rules should include among other the following codes for: honesty, objectivity, integrity, carefulness, openness, respect for intellectual property, confidentiality, responsible publication, responsible mentoring, respect for colleagues, social responsibility, non-discrimination, competence, legality, respect and care for research animals, human subjects protection. And when conducting human subjects research, minimize harms and risks and maximize benefits; respect human dignity, privacy and autonomy (23).

Could Genomic Medicine Revive Eugenics?

Gene-editing techniques such as CRISPR/Cas9system are able to precisely and permanently modify endogenous gene expression through targeted genome editing and with tremendous potential for curing inherited diseases, and several forms of cancer. These technologies could be used in conjunction with in vitro fertilization. However, concerns have been raised that related research could be exploited for non-therapeutic aims and that the evolving ethical issues have significant legal, social and political aspects. (24)

Potentially genomics could generate discrimination similar to that unleashed by the eugenics movement. There is already a concern that specific genetic information could be used to deny access to health insurance, employment, education and that medical information and confidentiality could be violated (25). The same technique may be used to create "designer babies", supermen contemplated by eugenicists in the 1930's. A group of geneticists at Shanghai Tech University in China is currently seeking permission to genetically modify discarded human embryos and the same group has reported using a gene-editing technique to modify embryos who developed into live monkeys.(26)

Despite the safeguards for confidentiality in the U.S. Health Insurance Portability and Accountability Act (HIPPA) some regulations may encourage discrimination. New genomic technologies raise ethical questions such as: should these innovations be used by the government to screen the population at large or limit its use by the medical community only under accepted ethical and confidentiality rules ? With limited exceptions, the "Common Rule "(27) mandates

that researchers in the US obtain informed consent for federally funded research involving a living individual, including pregnant women, children, neonates and fetuses and prisoners. However, the informed consent process, and most likely clinical medicine as well, will have to periodically take into account the rapidly evolving genomic technology and its novel ethical and confidentiality considerations.(28,29)

Scientific Misconduct

One other ethical concern is scientific misconduct, rarely mentioned in the literature. Examples could be found in the literature on how of scientists who fabricate, plagiarize, falsify or misrepresent research data, also in many cases because of biases. In one systematic review and meta-analysis it was determined that 1.97% of scientists admitted to have fabricated, falsified or modified data or results at least once, 33.7% admitted questionable research practices, and up to 72% admit for other questionable research practices. (30), while another survey determined that 29% of the respondents were involved in misconduct but never discovered. (31).

The basic requirements for ethical research should address the following (32):

1. Scientific Validity,
2. Social Value,
3. Minimum human risk,
4. Benefits should outweigh risk,
5. Informed Consent,
6. Protection of Confidentiality and Privacy,
7. Equitable subject selection; scientific or moral justification for including or excluding subjects from research
8. Protection from harm or exploitation of vulnerable subjects: children, prisoners, mentally disabled subjects.
9. Data integrity and safety monitoring
10. Independent review (IRB- Institutional Review Board oversight)

CONCLUDING REMARKS

Ethical principles have been debated for centuries; historically they reflected philosophical and religious thoughts, advances in science, historical events, political orientation, morality, and many other considerations. Biomedical research ethical standards were established only after World War II, primarily but not exclusively as a result of experimental atrocities committed by Nazi physicians and scientists.

The Nuremberg Code (8) was the first international code of ethics that established criteria for ethical conduct in human subjects research that led to the practice of informed consent in clinical medicine and research.

Scientific integrity and compliance with codes of ethics are at the core of contemporary medical practice and research; the main emphasis is on minimal risks and protection of the human subjects participating in research and emphasizes their voluntary participation.

Currently, ethical requirements, rules and policies are clearly spelled out in laws and policies adopted by national and international organizations and overseen by independent Institutional Review Boards or Research Ethics Committees.

Practice Points

- Informed consent for research subjects should include the following principles: patient autonomy, beneficence, non-maleficence and justice
- Women and pregnant women, for their benefit should be included in research projects
- The fetus is considered a patient and research counseling should include fetal benefits
- Ethical principles should be developed in tandem with new medical technology
- The history of human subjects research should be included in the curriculum of all medical schools

Research Agenda

Establish guidelines to develop ethical principles for human genomic research and its clinical applications, and for novel technologies.

Conflicts of Interest

Raul Artal, M.D.: Consultant/Advisory Boards: NovoNordisk, Alexion
Sheldon Rubenfeld, M.D.: None

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Highlights

- Brief historical review of the background and evolution of ethical principles in research
- Review of the significance of the Nuremberg Trials in relation to ethics in research
- Description of contemporary ethical principles and guidelines for the conduct of research.
- Review of ethical challenges in relation to new evolving technologies and diseases.