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Graefes Archives FULL Book Review

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The Oxford Textbook of Clinical Research Ethics

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The Oxford Textbook of Clinical Research Ethics is a comprehensive, multi-authored, reference book and textbook that critically reviews research with human beings. Five ethicists at the U.S. National Institutes of Health and one at Indiana University served as editors of the book. These ethicists and other scholars who work in the field of human research contributed the 73 chapters that comprise the book. The goals of the editors were to produce a book that is useful for the training of researchers, and is noted for its comprehensiveness and its systematic analysis that is both wide-ranging and incorporates international perspectives. After a careful, critical reading and analysis I can state that this book fulfills the editors' goals.

The teachings of Hippocrates provide clinicians with the guideline: *primum non nocere*, "first of all, do no harm." While this dictum is still valid, today the clinician is faced with a rapid

sequence of developments in biomedical technology, biology, and medicine; these events place enormous challenges on the practice of medicine and clinical research. In our time public knowledge of the egregious behavior of clinicians, in many countries and over many decades, has resulted in new formulations of guidance in clinical research that has manifested itself in the promulgation of codes, declarations as well as national and local laws that affect both the patient-clinician relationship, the dissemination of medical records and information, and the conduct of experiments on humans and animals.

During the last decades it has become apparent that the growth and the complexity of clinical research has often outpaced the norms, codes, regulations, and laws that were designed to regulate research with humans and provide human protections. The clinician is often obligated to follow several levels of laws and regulations; in each country there are federal and state laws, local statutes in individual cities and towns, regulations with legal status on required behavior associated with the acceptance of federal, state, and corporate grants of equipment and funding to an individual investigator. In addition, individual universities, research institutes, hospitals, clinics, and private corporations may have their own sets of codes and regulations that mandate and prohibit specific research practices. Many professional societies, for example national and local medical associations, scientific societies, advocacy groups, and religious groups may have their norms and codes of behavior that are promoted among their members. Among these multiple levels of norms, codes, regulations, and laws there are both differences as well as common ground related to clinical research ethics. In order to address the present complexities I suggest *The Oxford Textbook of Clinical Research Ethics* as a source for scholarly exposition of the history, the multifaceted arguments for and against many of the ethical issues involved with clinical research, and the known impacts of alternative sets of practices. The book's discussion is approached from many levels; historical, philosophical, social, moral, ethical, medical, as well as the economic and practical aspects of medical practice and clinical research.

The Oxford Textbook of Clinical Research Ethics provides the clinician with a single source that is clear in its exposition, broad in its scope, current in its coverage (legal and regulatory standards of informed consent in research, embryonic and stem cell research, risk-benefit analysis, multinational research, independent review and oversight, and clinical investigator behavior), and is well documented. Many of the codes, regulations, and laws as well

as conferences and symposia related to clinical research ethics that are discussed in the book are cited as URLs and readily available on the internet. I am particularly impressed with the balanced presentation of alternative points of view that are embodied in conflicting arguments. The written text is augmented with charts and tables and a well organized index helps the reader to rapidly locate specific topics. I highly recommend *The Oxford Textbook of Clinical Research Ethics* for clinicians, to medical students, and also suggest it as a textbook and reference book for use in the classroom and for short courses on clinical research ethics.

In the last decade the controversy surrounding medical research has been put into sharp focus in the public mind. Among the many contentious issues are the following: the use of placebos in developing countries, research with children and mentally incapacitated patients, and the recent discovery and condemnation of the plethora of undisclosed financial conflicts of interest from academic researchers. Furthermore, the deaths of Jesse Gelsinger and Ellen Roche while they were participants in clinical research trials, as well as the suspension of clinical research at Duke University and at Johns Hopkins University emphasizes the dangers and the need for improved oversight and compliance with Federal and other applicable regulations that are designed to protect participants involved in clinical research. In addition, the persistent revelations of the suppression of adverse drug events by pharmaceutical corporations and the failure of principal investigators and authors of clinical papers to disclose their financial links to the suppliers of medical devices or pharmaceutical agents (conflicts of interest), as well as the allegations of scientific misconduct (the fabrication of data in research and clinical trials) provides additional evidence of the scope and the severity of the current problems.

Clearly ethical guidelines, statutes, and professional codes are dynamic entities; they vary with time and across state and national boundaries. For example, the rules for stem cell research supported with federal funds in the United States were abrogated with the change of administration in the White House. However, there are common principles that clinicians can adhere to. A highly recommended ancillary reference on medical ethics is the seminal book by Beauchamp and Childress (*Principles of Biomedical Ethics, Fifth Edition*, New York, Oxford University Press, 2001) that clearly discusses four guiding moral principles. These principles are: (1) respect for autonomy; respecting the decision making capabilities of autonomous persons, (2) nonmaleficence; do not cause harm, (3) beneficence; the balancing of risks, benefits, and risks, and (4) justice; how to distribute the risks, benefits, and costs in a fair manner. The

main difficulty is how to implement procedures that insure compliance with the statutes and regulations and codes that are derived from these guiding principles.

As *The Oxford Textbook of Clinical Research Ethics* editor's point out, many of the ethical codes and declarations were the response to prior egregious violations and behavior that became public scandals. For example, Walter Reed's five principles followed Sanarelli's ethical violations (Giuseppe Sanarelli, an Italian bacteriologist working in Uruguay performed experiments on humans and several of them died during the experiments); the Nuremberg Code was a response to Nazi war crimes; the Belmont Report followed from the infamous Tuskegee Syphilis Study; the ethical guidelines promulgated by the Advisory Committee on Human Radiation Experiments was the response to the radiation experiments in the United States, and the more recent revision of the Declaration of Helsinki is the response to the use of placebos in controlled trials that took place in developing countries. Thus, the need exists for a more general framework for research ethics that will serve both the research community and protect humans involved in clinical research.

The Oxford Textbook of Clinical Research Ethics contains comprehensive chapters on these guidelines as well as others that are in effect in various countries around the world. Each guideline is assessed for its strengths, its weaknesses, deficiencies, and ambiguities and uncertainties in its interpretation. The guidelines on the ethics of biomedical research with humans, for example the Nuremberg Code (Nuremberg Military Tribunal decision in *United States v. Brandt et al.*, 1947), the Declaration of Helsinki (World Medical Association, amended 2004), Belmont Report (National Commission for the Protection of Human Subjects in Biomedical and Behavioral Research, 1979), 45 CFR 46 know as the Common Rule (U. S. Department of Health and Human Services and 16 other U.S. Federal Agencies, 1991), Convention on Human Rights and Biomedicine (Council of Europe, revised 2005), all aim to promote ethical behavior in clinical research with humans. The implementation of these guidelines is crucial for the respect, safety, and health of human participants in clinical trials.

The book contains outstanding chapters on a wide selection of egregious cases that resulted in the above mentioned guidelines. Hopefully, a clear understanding of the social, political, economic, philosophical and racial aspects of these past events will help in the formulation, promotion, and the implementation of codes, regulations and statutes that will

prevent the reoccurrence of similar events. Only a few of these cases are described in the following paragraphs.

The experiments conducted by Walther Reed were designed to test if the *Aedes aegypti* mosquito was the vector for the parasite of yellow fever. In a manner consistent with medical experiments at the time 1900, two physicians participated in the study as human subjects. This study is the first documented study in the United States in which there was concern for the welfare of human subjects and there was a formal written consent form.

The chapter on the Nazi “medical experiments” describes some of the medical atrocities that German physicians inflicted on their victims during the Third Reich. Numerous scholarly works are available to document and discuss the Nazification of German medical research and with the availability of recently opened archives this heinous history of German physicians continues to be scrutinized by scholars. The conflation of racial theories, nationalism, anti-Semitism, philosophy, racial hygiene, propaganda as well as economic, social, and political forces all played a role in transformation of Nazi medical policy into its horrific implementation. After the war, the Nuremberg Medical Trial was one of the war crimes trials of major Nazi war criminals that were conducted by the International Military Tribunal that represented the United States, Britain, France and Russia in 1945-1946. Many of those on trial were rehabilitated and returned to their teaching positions in German and Austrian universities. The cold war certainly facilitated the politics of denial. In August 1947, the Medical Trial concluded in Nuremberg and the United States judges promulgated the Nuremberg Code. Further insights into this period of history are found in Robert N. Proctor’s scholarly seminal book: *Racial Hygiene, Medicine under the Nazis* that was published by Harvard University Press, Henry Friedlander’s important book: *The Origins of Nazi Genocide, Euthanasia to the Final Solution*, that was published by the University of North Carolina Press, and Michael Burleigh’s book: *Death and Deliverance, ‘Euthanasia’ in Germany 1900-1945* that was published by Cambridge University Press.

In another region of the world the Imperial Japanese Army and physicians experiments that killed thousands of humans in medical experiments took place between 1933 and the end of World War II. The location for these experiments was mainly in Japanese occupied Manchuria and China, but also in Southeast Asia and on the main Japanese islands. These experiments at Unit 731 were carried out under the aegis of the Japanese Imperial Army and were performed on Manchurian or Chinese criminals, political prisoners, and prisoners of war. The broad aims of

these experiments included: explanation of diseases, development of therapies, and research and development of chemical and biological warfare. Again, as in Germany, after the war several physicians involved in these experiments returned to their medical schools as professors. United States officials, under pressure from the Cold War, agreed to offer immunity from war crimes charges to the main perpetrators in exchange for access to the studies on chemical and biological warfare that was derived from these heinous experiments on human subjects.

Two more recent cases that occurred in the United States emphasize the complexity, the duration of egregious behavior of physicians, and the scope of the ethical problems with human clinical studies. The first tragedy resulted in codes and statutes that govern the use of human volunteers in U.S. biomedical research. The second tragedy demonstrates that even with the existence of ethical codes, institutional review boards, federal, state, local, and university regulations, the lack of compliance to these laws and guidelines by the physician in charge of the clinical research resulted in the death of a human volunteer.

In the United States, The Tuskegee Syphilis Experiment, often called The Tuskegee Study, took place from 1932 until it was stopped in 1972. The U.S. Public Health service, conducted a nontherapeutic study of the effects of untreated syphilis on more than 400 African American men in Macon County, Alabama near the county seat of Tuskegee. The human subjects of the study were men with advanced cases of syphilis and the goals of the study were to learn about the serious complications associated with advanced syphilis. The men in the study were given treatment (in a specious manner to get their cooperation in the duration of the study); not enough treatment to affect a cure, but only enough to render them noninfectious. In the course of the study many of the men died from syphilis; others became blind or insane. The prevention of the men from receiving treatment was always a violation of Alabama's public health statutes that required prompt public reporting and prompt treatment for venereal disease. After World War II the availability of penicillin and the Nuremberg trials and the Nuremberg Code had little or no effect on the Tuskegee Study. Only by public disclosure via the *New York Times* newspaper on July 25, 1972 was the study ended on March 1973. Finally, on May 16, 1997, President Bill Clinton held a public ceremony in the White House in which he publically apologized for the Tuskegee Study in the name of the American people.

In another egregious example, the Gelsinger Case illustrates the untoward consequences (the death of Jesse Gelsinger) due to a lack of compliance by physicians performing human research, with the professional codes, the institutional review boards, the Federal regulations and statutes that were designed to protect human subjects. In September 17, 1999 Jesse Gelsinger died during a gene-transfer experiment conducted at the University of Pennsylvania School of Medicine in Philadelphia. This is the first death that is directly attributed to gene transfer. This tragic event raised many questions: the reporting of adverse events, the adherence to research protocols, the nature of informed consent, and the myriad financial conflicts of interest. Researchers that are funded by the National Institutes of Health (NIH) and engage in any type of recombinant DNA research must comply with specific NIH guidelines. Further oversight is provided by the Recombinant DNA Advisory Committee (RAC), which is a public forum that reviews specific recombinant DNA protocols. In addition, the U.S. Food and Drug Administration (FDA) also regulate clinical gene transfer trials. In spite of all the codes, regulations, statues, institutional review boards the system failed and a patient died. As clearly documented in the book's chapter there were serious deficiencies in the conduct of the clinical study: (1) Gelsinger should not have been allowed to participate in the study since his liver was not functioning at the minimal level required for inclusion of the study on the day he received the gene transfer, (2) the researchers failed to inform the FDA when earlier study participants had "Grade III" liver toxicity, (3) the FDA was not notified in earlier experiments that results of tests on laboratory animals subjected to gene transfer protocols suggested a significant risk for humans; some rhesus monkeys developed liver failure and some died, (4) the researchers changed the experimental protocols multiple times and failed to make the changes they had agreed upon, (5) both James M. Wilson, the principle investigator of the gene transfer study and the University of Pennsylvania had undisclosed financial interests in the gene transfer study, and (6) there were gross deficiencies in the informed consent process as points 2-5 were not clearly disclosed in the patient's consent form. This human tragedy clearly demonstrates the weaknesses of the multiple layers of the regulatory system. If the clinicians choose to flout the regulations, to withhold critical information on the informed consent forms, fail to disclose adverse effects in prior trials and studies, and fail to disclose financial conflicts of interest, then similar tragedies may continue to occur.

The second half of the book covers the following topics: participant selection and special populations (the use of ethnic and minority populations in the past resulted in egregious misconduct in clinical research), research with children, research with captive populations, research with fetuses, embryos, and stem cells. Furthermore, the contributors present critical and comprehensive chapters on the following topics: informed consent, independent review and oversight, conflicts of interest, fraud, fabrication, and falsification, the obligation to disseminate the results. The public is exposed to a plethora of cases in which these problems were exposed via the media.

Because the topic of informed consent is central to the entire field of clinical research and also inextricably bound to human protections I include some highlights from the book's six comprehensive and wide-ranging chapters on informed consent. From 400 B.C. the Hippocratic texts that discussed truth telling and advised physicians to hide as much as possible from their patients, to the 2000 revisions in the Declaration of Helsinki that resulted in strengthened informed consent requirements, the ethical criteria for informed consent has evolved. In the 1800's the role of the physician as healer expanded to include the role of the experimenter and the collector of data. The Yellow Fever research study in 1900 was perhaps the first instance in which written and signed agreements between the participants and the researchers that outlined the risks of the study were instituted.

What are the philosophical justifications of informed consent in research? The concept of respecting the autonomy of persons is of primary consideration; however, there are other considerations, i.e. public support and trust for research mandated that the research is conducted ethically. What are the elements of a valid informed consent? The investigators must elucidate in great detail the risks. While this disclosure is for protection against legal liability, it also provides the patient with the knowledge that enable them to make further inquires, to clarify information, and to make informed decisions on their participation in the study. A very important condition for valid consent is that it be voluntary, i.e. without coercion. The implementation of this condition becomes unclear when the research subjects are paid, belong to prison populations, or are in the military. Offers and not only threats can result in coercion. Finally, the research subject must be competent to give his or her consent. Competence requires the capacities for understanding and communication. Again, how to judge the level of competence when the research subject is in some way impaired or is a child?

The origins of informed consent are not in medical ethics but in the law. On December 29, 1900 the Prussian Minister of Religious, Educational and Medical Affairs issued a directive that may be the first regulation of human experimentation. This directive recognized the need for special protections for uniquely vulnerable populations, i.e. children and those who are incompetent. It established criteria for medical interventions, but excluded those for diagnostic, therapeutic, or prophylactic purposes. Specifically, it absolutely prohibited research on minors and those not fully competent. It required unequivocal consent of the person prior to the experimentation, and a prior full disclosure of the possible adverse consequences. These far-reaching human protections included many of the elements of valid consent in human research that are in place today. On February 28, 1931, The Reich Minister of the Interior issued the “Guidelines on Innovative Therapy and Scientific Experimentation.” The 14 points of the Circular included the following: experimentation shall be prohibited in all cases where consent has not been given, experimentation involving children or young persons under the age of 18 shall be prohibited if it in any way endangers the child or young person, and experimentation involving dying subjects is incompatible with the principles of medical ethics and shall therefore be prohibited. These research rules that were issues in pre-Nazi Germany are perhaps more far-reaching and more adequate than the Nuremberg Code.

The 1900 and the 1931 German guidelines and the subsequent failure to protect many humans that were killed in “medical experiments” demonstrated that the existence of legal protections is insufficient to produce ethical research. It is also necessary that these guidelines be enforced. The subject of informed consent, clearly an integral part of these German guidelines, is today the object of much research and deliberation and is in the forefront of human protections in clinical research. In the United States, during the period of World War II and also in the two decades following the war, much of the research and human experimentation frequently ignored the procurement of voluntary consent; this demonstrates the long term, pervasive nature of this offense to the guidelines for human protections in clinical research.

A basic principle in clinical research with humans is respect for human research participants. It is necessary to protect the confidentiality of individually identifiable health information if we are to respect the dignity and the privacy of those human subjects that participate in clinical research. In the United States, the U.S Privacy Rule was issued under the 1996 Health Insurance Portability and Accountability Act (HIPAA) that provides for individuals

to inspect, copy, and amend their health data, to limit the acquisition and uses of their data, and to demand an accountability of disclosures.

The last two chapters of the book present detailed discussions of the onerous topics of fraud, fabrication, and falsification and on the obligation to publish and to disseminate the results of clinical research. Often the news media disclosed spectacular examples of research misconduct; these occurrences are from many countries, educational institutions, and clinics. There are extent definitions of research misconduct; it involves intentional deception, therefore, errors may constitute negligence, but not misconduct. Research misconduct is defined as the fabrication, falsification, or plagiarism in research. Fabrication is the making up of data or results and the recording or reporting of fabricated material. Falsification is the manipulating of research materials, equipment, or processes, or the changing or omitting data or results such that the research is not accurately represented in the research record. Finally, plagiarism is the appropriation of another person's ideas, processes, results, or words without giving appropriate credit. Note that honest errors or differences in opinion are not misconduct, because they are common in scientific research. Conflicts of interest are also not misconduct. In the United States research misconduct (fabrications, falsification, and plagiarism are all considered to be both unethical and illegal, i.e. in violation of United States government statutes and regulations. Many other serious deviations from accepted research practices may be considered to be unethical and or illegal in the United States. For example, sexual and other harassment is both unethical and illegal, the misuse of funds and financial fraud are both unethical and illegal. Other cases such as undeserved or inappropriate authorship, breaching confidentiality in peer review, and exploitation or poor supervision of students or subordinates are unethical but they are not illegal.

Too often major medical and science journals issue statements that previously published articles are to be recalled following the initial accusation and a subsequent investigation. The book reviews the details of many of the high profile cases of research misconduct and the reader often wonders how could these people persist for many years without being disclosed? The final chapter on authorship and publications points out many of the current problems: redundant (duplicate publication and prior publications, the problems of scientific authorship, and the obligations of coauthors. The concept of contributorship, in which the contribution of each contributor is clearly stated, may be a useful substitute for authorship. Furthermore, hiding the names and affiliations of the real authors is a deceptive and pervasive practice. This occurred in

recent clinical papers published in medical journals in which the pharmaceutical companies provided the manuscripts and academic clinicians provided their names and affiliations to the papers.

The Oxford Textbook of Clinical Research Ethics is a compendium of current ethics, codes, regulations, statutes, policies, and practices that reflect the diversity of clinical research ethics as well as the common ground. This book provides international perspective which is critical since much of the research on human subjects is international; thus, it is not only focused on the United States, but on the ethical debates, codes, and regulations from all over the world. In summary, I strongly urge all clinicians to study this highly recommended book and to use it for teaching and training and as a modern reference book for guidance in clinical research.