

**The dilemma of clinical research. Historical and philosophical considerations of physicians' ambitions and patients' fear**

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Hundreds of years ago, the tradition of experimenting on individual patients was carried out sporadically. There was very little distinction between experimentation and therapy as most therapies were experimental. Systematic evidence of the effectiveness of various treatment interventions was lacking. Experimental therapies were then tried to benefit ailing patients. Unfortunately at times such therapies led to worsening medical status. Most researchers were medical practitioners, who were motivated and trusted to do what they thought best for the patients. Fraud and abuse were minimized through peer censorship rather than reviewership. There was no specific code of ethics, laws, or regulations governing the conduct of scientific research. Early in the 19th century after the development of Penicillin by Alexander Fleming and other antibiotics, drugs were required to prove evidence of safety by law before being marketed. This stipulation has given immense attention to scientific research particularly from regulating bodies and pharmaceutical industry and also led to distinguishing the clinical practitioner from the clinical researcher.

Generally, clinical practice refers to activities and interventions that are designed solely to enhance the well being of an individual patient and have a reasonable expectation of success. However, the goal of the research is to develop a general knowledge to better understand health and improve health care with similar disorders or risk profiles as well as for future patients and the society.<sup>1</sup> Therefore, clinical practice consists of activity to diagnose, prevent, treat or care for an illness or condition in a particular individual in order to benefit that individual whereas, clinical research is designed to answer a question and generate knowledge useful to others. Hence, it is paramount to distinguish between conducting biomedical and behavioral research on one hand and the practice of medicine on the other for several reasons. These relate to ethical, professional, financial and other issues that can generate potential conflicts of interest when physicians conduct research involving people, and particularly their own patients. Clinical

research uses human subjects with the goal to generate knowledge and does not necessarily have the best interest of the designated subjects.<sup>2</sup>

*Regulations and codes of ethics in clinical research.* Several influential documents have helped to shape our sense and the contours of ethical research throughout recent history. Most were written in response to specific crises or historical events. Yet, all are built on the belief that research is a valuable means towards progress in medical care and health. It is worthwhile reviewing briefly some important historical events that helped to shape and continue to influence current efforts to protect research subjects. The Nuremberg code, a 10-point code of ethics of human experimentation, was written at the conclusion of the Nuremberg trials of the Nazi doctors (1949). The Nuremberg code recognizes the potential value of research knowledge to society but introduces and emphasizes the absolute necessity of the voluntary consent of the subject as well as a scientifically valid research design that could produce fruitful results for the good of the society (Table 1). The Nuremberg code established that in order to be ethical, the conduct of research must have the rights and welfare of the subject as its utmost priority.

The World Medical Assembly developed the declaration of Helsinki in 1964 as a guide to the world's physicians involved in human subject research (Table 1). The declaration emphasizes that patients' participation in research should not put them at a disadvantage with respect to medical care. The declaration of Helsinki also recognizes as legitimate, the possibility of including people in research who cannot give their own informed consent, but for whom permission is obtained from a legal guardian. This declaration had considerable influence on the formulation of international, regional, and national legislations and regulations for research and was revised most recently in October 2002. Abuse of human subjects in scientific research in North America led to intense scientific and public scrutiny, reflection, and debate on the scope of limitation of research involving human subjects (Table 1).<sup>3</sup> This has primarily occurred in the accounts of the hepatitis B studies at Willowbrook, and the natural history of syphilis studies at Tuskegee and others. This was followed by the Belmont report published by the United States of America (USA) national commission for the protection of human subjects of biomedical and behavioral research in 1974. This document stated the 3 broad principles that guide the conduct of research and form the basis on which specific rules could be formulated, criticized, and interpreted (Table 1). The 3 principles are respect for person, beneficence and justice.

The Council of International Organizations of Medical Sciences (CIOMS) in conjunction with the World Health Organization (WHO) in 1982, issued international guidelines for biomedical research involving human subjects, that explore the application of the Helsinki principles to the special circumstances of many technologically developing countries (Table 1). The CIOMS guidelines, noting the increase in international research, acknowledge deferring circumstances in developing and developed countries stressing the vulnerability of less privileged populations.

The USA federal law's common role regulates research funded by the Department of Health and human services stresses the importance of and stipulates both the membership and the function of institutional review boards (IRBs) and specifies the criteria any IRB should employ when reviewing a research protocol to determine whether or not to approve it (Table 1). Furthermore, the common role also delineates the types of information that should be included in an informed consent document and how a consent should be documented. It also describes additional protection for fetuses, pregnant women, prisoners and children. The International Conference on Harmonization (ICH) published guidelines for good clinical practice in 1996 in order to provide a unified standard for the European Union, Japan and USA and allow for mutual

acceptance of clinical data by the regulatory authorities in those areas of jurisdictions (Table 1). The ICH guidelines are an international ethical and scientific quality fold standard for designing, conducting, recording and reporting trials that involves the participation of human subjects.

**Principles of research ethics.** Regulations and guidelines related to the conduct of research established fundamental and ethical principles that are relevant to all research involving human subjects and demonstrate how they are applied to the conduct of research.<sup>4-7</sup> Based on synthesis of various ethical codes, guidelines and literature, 7 principles are required to make clinical research ethical including value, validity, fair subject selection, favorable balance of risk and benefits, independent review, informed consent, and respect for the enrolled subject. Value requires that questions asked through research aim at developing useful and generalizable knowledge. It is unethical to spend resources or to subject individuals to risk or inconvenience for no socially valuable purpose. Validity requires that the design and method of the research be such that the study is feasible, the question is answered and the information is reliable and generalizable. Poorly designed research studies that have inadequate power, insufficient data, or inappropriate methods are harmful because human and material resources are wasted for no real

**Table 1** - Codes and guidelines related to the conduct of reserach involving humans.

Item	Year	Main feature
Nuremberg code <sup>9</sup>	1949	Voluntary consent
Declaration of Helsinki <sup>10</sup>	1964	Interest of subjects...over...interest of science Recognized the consent of legal guardian
The Belmont report <sup>11</sup>	1974	Triad of respect, beneficence and justice Written consent
International ethical guidelines <sup>12</sup>	1982	Application of principles to developing countries and vulnerable populations
The common role <sup>13</sup>	1991	Institutional review board (membership and function)
International conference on harmonization <sup>14</sup>	1996	Unified standard for EU, the USA and Japan

benefit. Fair subject selection requires that the primary basis for selecting subjects be the scientific question, balanced by consideration of what the risks and benefits are, how they will be fairly distributed, and that special attention is given to those who might be vulnerable. Research should be designed so that risks to subjects are minimized and benefits maximized so that the unavoidable risk of doing the study are justified or outweighed by the anticipated benefits. Independent review by individuals unaffiliated with the research study help minimize the potential impact of multiple conflicts of interest and commitment of investigators, and at the same time assures the public that subjects who are enrolled in trials will be treated ethically. Informed consent is a process that allows each individual subject to make an informed, considered, and voluntary willful decision regarding participation in a research study; demonstrating respect for the autonomy of the individual. Respect does not stop with the informed consent alone, but should extend throughout the individual participation in various segments of research and beyond. Respect is also demonstrated to enrolled subjects by maintaining confidentiality and monitoring their well being.

**Medical research ethics in the Kingdom of Saudi Arabia (KSA).** To address problems in medical research ethics the authors researched existing literature utilizing the key words, medical research, ethics and KSA and 7 publications were obtained of which none was relevant to the discussion. This is quite surprising given that the KSA is the highest producing nation for scientific publication in the Eastern Mediterranean region by WHO standards.<sup>7,8</sup> This may reflect absence of problems or more realistically represent under reporting. Although codes for regulating medical research ethics may exist in the official bodies of the Ministry of Health and Saudi Council for Health Specialties and others, the medical professionals through widely available refereed scientific journals should discuss such publications.

In conclusion, it is the vulnerability of human subjects that challenges the ethical conduct of research. Unfortunately, in human history all too often this vulnerability was of pre-condition to compromise and lead to investigator action that culminates in abuses and grievous harm. Awareness of these abuses has generated a collective response whereby there has been an increasing recognition of due heightened custodial responsibility. This has led to the establishment of high standards of ethical propriety that seeks to balance the real need to conduct research and the

need to protect subjects from the exploitation of their vulnerability. It is by embracing these high standards that we will sustain the scholarly activity of clinical research and beneficence to humans. By doing so we will transcend the researcher-subject relationship to that of a physician-patient relationship, that maintains the integrity, professionalism and valued ethics of clinical research.

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