



# Ethical issues in innovative clinical research

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In today's world, medical science has entered an era of rapid development. Numerous new drugs, devices, technologies, and diagnosis and treatment methods continue to emerge, bringing great benefits to our human health. However, there are potential risks in the above innovative research and development process, and some can even endanger the health or life of the test subjects. As a result, medical ethics plays an increasingly important role during the rapid development of innovative clinical research, acting as a “brake” on this high-speed vehicle. This article will illustrate some medical problems and solutions that are common in today's clinical research in the following aspects.

## Development and principles of medical ethics

The word ethics originates from the Greek “*ethos*”, which means character/personality. Ethics is a subject that studies the value of human beings within the scope of morality, while medical ethics concerns the moral norms that doctors should follow in the process of practicing medicine. In the ancient Greek period, Hippocrates, the father of medicine, proposed the ethical standard of doctors, “first do no harm to the patient”, which has become a moral code that practitioners need to abide by for thousands of years. On the other hand, the development of medical technology requires continuous exploration and innovation, which is a process of “trial and error”, bringing potential risks and pain to patients. How to balance the “benefit” and “risk” is a long-standing problem faced by medical workers.

Many of the great discoveries in the history of medicine that we are familiar with bear huge ethical shadows. William Beaumont (1785–1853) is the first person who revealed the digestive function of the stomach, but he obtained his finding from Alexis St. Martin, a patient

who suffered from an untreated external gastric fistula for 8 years after his abdominal injury. The American surgeon J. Marion Sims (1813–1883), conducted long-term surgical experiments on black women to explore the treatment of vesicovaginal fistula, causing them to suffer tremendous physical and mental torture. Years of court debates have led to a comprehensive and profound reflection in the legal and medical circles, in which the Nuremberg Code came into being. As the first international ethical guide on clinical research in history, the Nuremberg Code particularly emphasizes the protection of patient volunteers who undergo clinical research. The Code lays a legal foundation for the ethical principles of clinical research.

In this regard, Henry K. Beecher published an article “ethics and clinical research” in *The New England Journal of Medicine*, which stated the ethical requirements of clinical research: (I) informed consent: fully informed and respect the choice of the patient (subject); (II) researchers with responsibility, compassion and conscience improve the reliability of research outcome; (III) the ethical attributes of research depend on the inception, the results do not justify means; (IV) whether to publish data obtained by unethical means is arguable. These statements established a solid foundation for 45 CFR Subpart A (the Common Rule), which is a compilation of the US Federal Regulations to protect research subjects. In 1964, the World Medical Association (WMA) adopted this declaration at its eighth congress in Helsinki. The Common Rule stated that all animal experiments, laboratory data, and research protocols should be submitted to institutional review boards (IRB) for preview. Patient rights and privacy should override societal and scientific interests and research should be suspended when risks outweigh potential benefits. Informed consent should be signed by the research subject or the subject's

legally authorized representative, and exceptions should be reviewed by the IRB. Each patient, including those in the control group, should be assured of optimal treatment. Research should not be published if its measures violate the principles of this declaration. Thus far, the ethical principles in clinical research were preliminarily established.

### The development of clinical research methods

Early clinical studies were merely summaries of physicians' personal experiences. "Shennong's courage to taste hundreds of herbs" may be the earliest clinical drug test in human history. With the development of modern natural science, clinical medicine has transitioned into evidence-based medicine since the middle of the last century. The level of evidence becomes the decisive basis for the clinical decision-making process, and the top-level evidence is from multicenter, randomized, controlled studies.

In the field of new drug development, there is the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The ICH, established in 1990, is an organization that brings together regulatory agencies and the pharmaceutical industry to discuss the scientific and technical issues of drugs and formulate guidelines. In 2017, the Food and Drug Administration of China officially joined ICH and China subsequently published the "Good Clinical Practice (GCP)", which strengthened the regulation of clinical research before drug marketing. The scientific principles followed by drug clinical trials globally mainly depended on evidence-based medicine. In 2017, an article named "the changing face of clinical trials—pragmatic trials" was published in *The New England Journal of Medicine*, suggesting that clinical research should shift from evidential trials, which primarily focus on evidence-based research, to pragmatic trials, which concurrently take science, safety, and cost-effectiveness into account (1). This article opened a new world of clinical research facing to the era of precision medicine and innovation.

### Ethical issues in innovative research

In many clinical studies, the development path of surgical techniques has its uniqueness. The surgical operation usually involves high risk, high difficulty, and is highly technology dependent, clinical research in the surgical field cannot strictly follow the GCP-based research

guidelines. Therefore, Oxford University started up the IDEAL Collaboration (Idea, Development, Exploration, Assessment, and Long-term follow-up), which consists of surgeons, clinical epidemiologists, statisticians, and academic editors. As a global surgical innovative academic organization, the IDEAL Collaboration has researchers from all over the world (2). Through countless practices, researchers found that the IDEAL research mode is not only applicable to surgical technology but also can be extended to improve new treatment plans. Its recommendation to have different plans at each stage is completely in line with the current thinking of pragmatic trials.

The so-called IDEAL divides research into five stages: idea, development, exploration, assessment, and long-term follow-up. As the research continues, researchers gradually increase the number of cases, improve the level of evidence, and consolidate the research background by adopting different clinical designs (3). In innovative research, besides the clinical research mode mentioned above, a pre-ideal stage is also very substantial. Pre-ideal stage integrates the results of preclinical research, including *in vitro* experiments, animal experiments, and results from mechanical and material science into the overall clinical research. Strict ethical review is required to ensure the safety and interests of subjects to the maximum extent before each step of clinical trials (4). To disclose the research process, researchers are required to register their research designs at all stages to maintain the impartiality of the research, which simultaneously protects the rights and interests of researchers (5). Under the guidance of the IDEAL Collaboration in recent years, numerous innovative medical research findings combined, which greatly promoted the development and prosperity of the medical health field (6).

Medicine today is in a stage of rapid development. With the continued development of our social civilization, medical ethical issues become more prominent. Every clinician and researcher should keep ethical principles in mind when pursuing their research fields, discovering new clinical technologies, and solving complicated clinical problems. By doing so, our patients can be treated fairly and effectively, so that our medical science will carry a healthy and bright future.

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