

Roche Global Position on Human Subject Research

Adopted by CEC in February 2004

Roche is committed to producing safe and effective medicines and diagnostics that benefit patients and physicians by addressing unmet medical needs. To do this, the company makes use of the most recent advances in science and technology to understand diseases as well as to identify and test novel medicines and diagnostics.

Clinical trials are an integral part of the new drug discovery and development process. Before a new medicine can be made available, evidence of its safety and effectiveness must be provided by well-designed, well-controlled, and carefully monitored clinical studies in healthy volunteers and/or patients consenting to participate. We recognize the importance of including diverse patient populations in our clinical trials. All studies using Roche pharmaceutical products, where Roche is the trial sponsor, are conducted according to international standards of Good Clinical Practice, as well as according to local legislation.

Roche respects human rights, human dignity, patient safety, and ethical principles. The company has its own internal standards and systems to ensure that we comply with or exceed all guidelines, regulations, and legal requirements. Roche is committed to act ethically and to provide the highest standards of care to individuals participating in Roche sponsored clinical trials.

Roche commits to protect the privacy of all individuals participating in Roche trials, as much as possible within the constraints of local laws and international guidelines. This commitment aims at safeguarding all personal data protection rights and will ensure that no patients suffer any emotional or physical harm because of having participated in a Roche clinical trial.

All Roche employees who work on clinical trials for Roche products, as well as external contractors working with Roche, are required to strictly adhere to local laws and international guidelines, conduct their research with compassion, and apply the highest standards of medical care and respect for patients at all times. Roche is fully committed to ensuring compliance with these standards and monitors this process on a continuous basis. Roche has a system in place for review and resolution of any ethical issues that may arise during the normal course of business. Roche will ensure that Good Clinical Practice (GCP) training is provided to employees working in clinical research and related areas.

Roche commits to presenting and / or publishing the results of Roche sponsored pivotal clinical trials conducted in any country, and in all other cases of trials where the results or the methodology applied are of a quality and importance warranting publication in a peer-reviewed scientific journal.

Background

1. History of clinical research

To a large extent the high standard of living and lengthy life expectancy we enjoy today in the developed world can be attributed directly to the power of clinical research. Clinical trials are an integral part of new drug development, they and provide the basis for evidence-based medicine.

Our modern systems for clinical research have their roots in ancient times. From the early healers, who used observational data, a formal framework for clinical research has evolved, which uses statistically significant differences to confirm improvements in medical practice. Development of ethical standards required for human subject protection has proceeded in parallel with the scientific/medical breakthroughs seen during the last century. The strength of the resulting process facilitates the discovery, development and delivery of novel medicines with a high level of safety and efficacy, while simultaneously providing unprecedented levels of protection for the rights of human subjects.

2. Patients' rights

The basic right of every human subject is to be treated with respect as an independent moral being. The dignity, rights, safety, and well-being of research subjects must be promoted and protected at all times. Since human study subjects willingly provide information that cannot be obtained in any other way, they clearly deserve the gratitude and respect of the world community.

The Declaration of Helsinki was first adopted by the 18th World Medical Association General Assembly in Helsinki, Finland in June, 1964. It has subsequently been amended in October, 1975 (Tokyo), October, 1983 (Venice), September, 1989 (Hong Kong), October, 1996 (Somerset West, Republic of South Africa), and October, 2000 (Edinburgh). This document is the foundation of modern ethics in clinical research. The Declaration, which was originally based on the Nuremberg code, remains the closest thing to an international "human subjects' bill of rights" in existence today. It is reviewed periodically and modified as needed so that it always reflects the most up to date thinking in clinical ethics. Roche contributes to this debate through collaboration in interdisciplinary working parties of various partners in different regions of the world. An especially important aspect of the Declaration is informed consent. The informed consent process should be one of shared information and decision making in which physicians and human subjects openly discuss the research to be done and communicate their goals and values to each other. In this way, the process accommodates both the personal values of subjects as well as the responsibilities of physicians to make clear the risks and benefits of the research while considering the well-being of their human subjects.

3. Ethical principals in clinical trials

Ethical clinical research is guided by the principles of non-malificence, respect, beneficence and justice. *Non-malificence* is the duty to cause no harm. This principle

has its' roots in the Hippocratic Oath. The ethical issue at the core of human subject research is whether the outcome of the research can be reasonably expected to provide benefit to society without doing any harm to the subjects enrolled in the trial. *Respect for persons* is embodied in informed consent, dictating that information is exhaustive and provided in a manner that is understandable, that the subject's cooperation is voluntary, and that all information pertaining to the subject is held in confidence; these concepts represent the modern age of medical ethics. *Beneficence* is demonstrated by a thorough risk/benefit assessment, recognizing that benefits can be direct, collateral, and/or altruistic. Similarly, risks are considered in physiologic, psychological, and socioeconomic terms. For a clinical trial to be considered ethical, there must exist a sufficient body of scientific/medical evidence to justify exposure of human subjects to the risks of the trial. There must be clear medical need, and the potential benefits to be gained by the research must be weighed against the possible risks to the human subjects in both safety and effectiveness of the drug or intervention being studied. The principle of *justice* takes into account all the processes by which populations are selected for study to ensure that the results benefit the community, avoid exploiting vulnerable populations, and include subjects who may be likely to benefit.

The concept of independent oversight is a central ethical principle requiring the review of proposed clinical research projects by qualified individuals independent from the investigators and sponsors. Independent review boards approve and provide oversight to studies involving human subjects. In the US, these are known as Institutional Review Boards (IRBs), and in other parts of the world, they are called Independent Ethics Committees (IECs). These boards are composed of researchers, ethicists, legal experts, and community members. Such independent oversight helps ensure the integrity of the clinical research, both from the standpoint of scientific validity and the protection of human subjects.

Thus, we have a system in place that strives to provide scientific validity while protecting patients' interests through meaningful informed consent, justice and independent oversight and review. This approach allows those faced with serious illnesses to have access to promising new treatments while minimizing their exposure to those that are futile or potentially harmful.

Roche has established a process for discussing and resolving potential ethical issues that may arise when planning or conducting clinical research. Any Roche employee, who is faced with an ethical dilemma or question, can contact the Global Ethics Liaison who is independent of the clinical teams. The Global Ethics Liaison will help the clinical teams in finding an appropriate answer or will escalate the issue, first, to the Head of Pharma Development and his advisors and, if need be, eventually to an independent external advisory group composed of ethicists and experts from academia and the patient community.

4. Roche adheres to all laws, regulations, guidelines and standards

There is a deep understanding of, and belief in high ethical standards by all members of the Roche community. This translates into the practical application of these high ethical standards by each employee in his daily work responsibilities.

Roche is committed to following all international guidelines as well as local laws and regulations in the conduct of its clinical research programs. All Roche clinical studies are conducted in full conformance with the principles of the Declaration of Helsinki and with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. All Roche clinical studies must fully adhere to the principles outlined in "Guideline for Good Clinical Practice" ICH Tripartite Guideline (January 1997) or with local law if it affords greater protection to the subject. In other countries where Guidelines for Good Clinical Practice exist Roche and the investigators will strictly ensure adherence to the stated provisions.

5. Research in genetics and other innovative technologies

Research using genetic and other innovative approaches, such as genomics and proteomics, is an essential part of Roche's endeavors to provide better health care. Roche recognizes the importance of genetic predisposition as one of the risk factors for common complex disorders, as well as the necessity and promise of using genetic information for the discovery and delivery of new and improved diagnostics and therapeutics.

Roche views genetic data and information as part of the spectrum of private medical information, all of which must be afforded the highest possible standards of data protection and confidentiality. Given current public perceptions that genetic data is potentially more sensitive, and current ethical committee requirements for added steps in protecting this information, the company has developed an additional set of guidelines directed specifically at the collection and use of genetic data. Thus, Roche is committed to prevent the misuse of genetic information obtained during the course of its research activities for discrimination or exploitation of individuals and/or groups. Moreover, we recognize it as our duty to integrate the principles to which we adhere into a program of scientifically sound and socially responsible use of genetic information for the development of new diagnostics and therapeutics. Finally, Roche is dedicated to communicate research results to the scientific community in a timely fashion, and supports general educational activities in the areas of genetics and other innovative research fields.

Roche has established an independent Science and Ethics Advisory Group (SEAG) consisting of recognized outside experts representing the fields of biology, ethics, sociology, and law, as well as of community and patient representatives. The mandate of this advisory group is to offer independent guidance and advice related to genetics and other innovative research areas which Roche is involved in.

6. Clinical trials in developing countries

Conduct of clinical trials in developing countries present a unique set of ethical issues. Where Roche undertakes such studies, the same high standards of ethical conduct and scientific integrity will be adhered to, with the ultimate goal of delivering credible results at the conclusion of the clinical research.

The standard of care provided to people participating in Roche Sponsored Clinical Trials in low and middle income developing countries will be according to accepted standards of therapy for the treatment of the disease as defined in WHO treatment guidelines for resource poor settings, where such guidelines exist. In the absence of such guidelines, international treatment guidelines will apply. Roche will support the local healthcare infrastructure, although as a private research based company, is not in a position to provide such infrastructure where none exists.

Roche commits to provide clinical trial material, as required by GCP (e.g. investigational products, supportive care, diagnostic kits, etc) free of charge for patients participating in Roche Sponsored Clinical Trials. Roche commits to provide free drug for the duration of the study and in accordance with the regulatory requirements of the country. Continuity of drug supply following termination of the Roche Sponsored Clinical Trial will be assured for all Roche Sponsored Clinical Trial participants for as long as they continue to receive medical benefit from the Sponsored Clinical Trial medication, provided that the benefit-risk ratio for the product continues to support such use. As such, Roche commits to work within the framework of local healthcare systems or with other third parties to provide continued supply of the medication following the termination of the study or will agree to provide such medication free of charge or at reduced costs to be agreed in advance of commencing the Roche Sponsored Clinical Trial if alternative options are not available.

Roche commits to register and, provided registration is granted by the national Health Authorities, market a new medicine in any country where Roche has sponsored a clinical trial with the medicine.

Roche commits that in conducting clinical studies in low and middle income developing countries that Roche will work with local investigators and will respect local laws and customs, provided such laws and customs do not compromise patients safety, human rights and dignity, ethical principles, or Good Clinical Practice of the Roche sponsored clinical trials.

Roche commits that in conducting clinical trials in low and middle income developing countries it will work within local healthcare systems in a manner that does not overburden such systems or take precedence over local healthcare priorities.

7. Work with contractors

Roche will work with qualified Contract Research Organizations (CROs) and other types of contractors whenever needed. These external organizations will be audited regularly to assure compliance with all Roche policies and procedures. All contractors with which Roche collaborates, will be held to the same high ethical standards to which Roche adheres, and their work will be carefully supervised by Roche employees.