

Roche FAQ on Clinical Research

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1. What are clinical trials?

A clinical trial is a research study conducted in human beings with the goal of answering specific questions about new therapies, vaccines or diagnostic procedures, or new ways of using known treatments. Clinical trials are used to determine whether new drugs, diagnostics or treatments are both safe and effective. Carefully conducted clinical trials are the fastest and safest way to find treatments that work in people.

Ideas for clinical trials usually come from researchers. After researchers test new therapies or procedures in the laboratory and in animal studies, the treatments with the most promising results are moved into clinical trials. Clinical trials are broken down into different phases of trials. During a trial, more and more information is gained about the new treatment, its risks and how well it may or may not work.

2. What are the different phases of a clinical trial?

Clinical trials are categorized as Phase I to IV trials. Roche defines Phase I to IV clinical trials as follows:

- **Phase I** (*small number, normally between 6-100, of healthy volunteers; for life-threatening conditions where suitable treatment options are lacking, i.e. virology/oncology, also patients*)

Phase I studies are designed to allow scientists and medical doctors to understand what effects an investigational compound has in human subjects. The goal is to study what happens to the compound in the body from the time it is swallowed or injected until it is excreted, when it is excreted and how the human body reacts to the new compound from a safety and tolerability point of view. Study participants are monitored for the occurrence and severity of any side effects that they may experience.

- **Phase II** (*once the initial safety of the study drug has been confirmed in Phase I trials, Phase II trials are performed on larger groups, 20-300 in number, of patients*)

Phase II studies are designed to evaluate the safety and efficacy of an investigational compound in patients with a specific disease or condition. Phase II trials are typically conducted in a small group of patients usually selected on the basis of similarities in their disease, e.g., the disease has progressed to a certain stage or they share a genetic mutation¹. The patients are given various doses of the compound and closely monitored to compare the effects and to determine the safest dosing regimen. In many instances, multiple Phase II studies are conducted to test the compound in a variety of patient populations or indications.

- **Phase III** (*carried out on large patient groups, 300–3,000 or more depending upon the disease/medical condition studied*)

Phase III studies are designed to confirm the safety and efficacy of an investigational compound, and the dosage regimen chosen, in large numbers of patients with a specific disease or condition. These studies, as in the earlier phases, may involve one or more ‘treatment arms’, which allow for the safety and efficacy of the new investigational drug to be compared to other available treatments, or to be tested in combination with other therapies. Information obtained from Phase III studies is used to determine how the compound is best prescribed to patients in the future.

- **Phase IV** (*also known as Post-Marketing Surveillance Trials*)

Phase IV studies take place after the drug has received market authorization and are designed to provide broader experience in evaluating the safety and effectiveness of the new medicine in larger numbers of patients, subpopulations of patients, and to compare and/or combine it with other available treatments. These studies are designed to evaluate the long-term effects of the drug. Under these circumstances, less common adverse events may be detected.

3. Why does Roche conduct clinical trials?

Clinical trials are an integral part of the drug and diagnostics discovery and development process. Before a new medicine or diagnostic assay 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 patients consenting to participate.

4. What are the ethical principles that govern clinical trials?

Ethical clinical research is guided by the principles of nonmalificence, respect, beneficence and justice.

- *Nonmalificence* is the duty to cause no harm. This principle has its roots in the Hippocratic Oath. The ethical issue at the core of clinical research is whether the

¹ The patient population is defined in the Eligibility Criteria against which the subjects are recruited into the study

outcome of the research can be reasonably expected to provide benefit to society without doing any harm to the individuals 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.
- *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 individuals 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 participating person 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 individuals who may be likely to benefit.

5. Which legal and ethical standards does Roche apply for its clinical trials?

The basic right of every person is to be treated with respect as an independent moral being. The dignity, rights, safety, and well-being of individuals participating in clinical research must be promoted and protected at all times and in any part of the world where clinical trials take place. Since participants in clinical research 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 a number of times to be adapted to the progress in modern medical science.² This document is the foundation of modern ethics in clinical research. The Declaration, which was originally based on the Nuremberg code, remains the closest document 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 participants of the clinical research study 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 and the well-being of the research participants

² Amendments: October, 1975 (Tokyo), October, 1983 (Venice), September, 1989 (Hong Kong), October, 1996 (Somerset West, Republic of South Africa), October, 2000 (Edinburgh) and October, 2008 (Seoul).

as well as the responsibilities of physicians to make clear the risks and benefits of the research.

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, in its version of Seoul 2008, 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, whichever affords greater protection to the individual. In other countries where Guidelines for Good Clinical Practice exist Roche and the investigators will strictly ensure adherence to the stated provisions.

Whenever Roche conducts new trials in the field of transplantation, Roche adheres to the Declaration of Istanbul on Organ Trafficking and Transplant Tourism (first published on July 5, 2008) and the WHO guiding Principles on Human Cell, Tissue and Organ Transplantation. Roche will not support any activity (e.g. clinical trials and conferences) that violate these Principles.

Basic ethical principles are applied independently of the location where Roche conducts the clinical trial.

6. How is the adherence to legal and ethical standards controlled externally?

Roche respects human rights, human dignity, patient safety, and ethical principles. The company 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. 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. Consequently, the company welcomes external controls of its clinical trials.

The concept of independent oversight requires 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 beings. 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 participating individuals. Thus, there is a system in place that strives to provide scientific validity while protecting patients’ interests through meaningful informed consent, justice and independent oversight and review.

7. How does Roche ensure that clinical trials are carried out according to legal and ethical standards?

Roche has developed internal standards and systems to ensure that we comply with or exceed all guidelines, regulations, and legal requirements. 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 integrity, and apply the highest standards of medical care and respect for patients at all times.

To ensure this compliance, Roche will ensure that Good Clinical Practice (GCP) training is provided to employees working in clinical research and related areas. In addition, Roche has established internal processes to facilitate early discussion of and consultation on issues. This support mechanism allows employees to obtain independent advice if they need it. In addition, Roche staff is obligated to report any suspected issue of noncompliance with regulatory or ethical standards.

Roche has also established a process for discussing and resolving potential ethical issues that may arise during the course of everyday work in drug development. This framework incorporates a central point of contact for Roche staff and an escalation process to facilitate the consideration of alternative perspectives when appropriate.³ Any Roche employee, who is faced with an ethical dilemma or question can contact the Science and Ethics Advisory Group (SEAG) which is independent of the clinical teams. The SEAG will help clinical teams to find an appropriate answer or will escalate the issue, first, to an internal committee of experts. If need be, advice may be requested from an independent external advisory group composed of ethicists and experts from academia and the patient community.⁴

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.

8. What are the rights of participants in a clinical trial?

Participants are entitled to a clinical trial that adheres to all legal and ethical standards. In addition, participants have a right to:

- A clear, transparent Informed Consent process before they agree to join the trial
- Withdraw from the trial at any point in time

The Informed Consent process aims at answering any and all questions that might be relevant to a participant's decision to agree or decline to join a trial. Only participants who, after having all their questions answered, sign an Informed Consent form can enter the trial. With their signature, participants confirm that they believe they have been given

³ This process was formalized within Pharma Development in July 2003

⁴ For further information see Resolving Ethical Issues in Human Subject Research:
http://www.roche.com//corporate_responsibility/csr_research_and_development/ethical_standards.htm

all the important facts about a trial, that they understand them, and that they decided to take part in the trial of their own free will.

An Informed Consent document is not a contract. Therefore, a participant may change his or her decision – any participant has the right to withdraw at any point of the trial. A withdrawal will not affect the participant's relationship with their doctor nor will it result in a loss of benefits to which the participant is otherwise entitled. Potential medical risks of a sudden withdrawal from the trial should be detailed in the Informed Consent document.

9. How is the privacy of participants protected?

If a patient agrees to join a trial, some people will need to be told about the participation. These people are:

- The patient's GP, who is responsible for their healthcare on a day-to-day basis
- The doctor and research team looking after the patient in the trial

The fact that someone is taking part in a trial will be written in that patient's medical notes. Investigators cannot tell anyone else about a participation in a trial unless the patient gives his or her permission.

During the trial, all of the information collected about the participants will be kept confidential, as with any other medical records. When investigators publish the results of a trial, they are not allowed to include any information that would identify people – a patient's name will not be used in any reports or publications.

The clinical trial protocol will define what is to be done with samples and information of participants. Specific sections within this document will detail for how long samples and information must be kept before they are destroyed. If samples and/or information are to be used further, then this will be either:

- included in the original trial protocol
- be part of the informed consent a patient signs prior to his participation in the trial
- be written up in a specific informed consent which the patient will also be asked to sign.

10. What kind of information does Roche publish on clinical trials?

Roche is committed to communicate information about clinical trials, including both positive and negative results, to ensure that a balanced view is readily available to the medical community and to the general public. Therefore, Roche commits to publishing the results of Roche sponsored clinical trials.

This commitment is reflected in the Roche Policy on Transparency in Clinical Trials, which governs Roche's *Clinical Trial Protocol Registry* and *Clinical Trial Results Database* (<http://www.roche-trials.com/>). This global, public database was launched on April 15, 2005. The registry and the results database both contain information on all Roche-sponsored clinical trials in patients, worldwide, for marketed products, as well as

interventional clinical studies sponsored by Roche Diagnostics. For further information see Registration of Clinical Trial Protocols and Publication of Clinical Trial Results Policy.⁵ For access to Roche's Clinical Trial Protocol Registry and Clinical Trial Results Database, visit <http://www.roche-trials.com/>. Information on Roche clinical trial protocols can also be accessed via <http://clinicaltrials.gov/>.

11. What does the end of a trial mean for participants?

Roche is obliged by law to store the records of its clinical trials for a certain period of time, typically 15-20 years. The end of a trial has no impact on the confidentiality of those documents; they will still be protected from accidental disclosure to third parties.

In terms of treatment, the end of a trial doesn't necessarily mean patients will have to fall back on their previous healthcare. If a new treatment proves to be superior, Roche will typically discuss the question of whether to continue on with that new treatment even after the trial has ended.

There are certain circumstances when, for the well-being of patients participating in a trial, continued access to the Roche investigational medicinal product is necessary. Examples are serious, life-threatening or disabling diseases such as cancer or lupus, when no alternative treatment is commercially available. In these situations, following termination of the Roche Sponsored Clinical Trial, an adequate supply of treatment will be assured for all the Roche Sponsored Clinical Trial participants, until the Roche investigational medicinal product becomes available commercially.

12. Does Roche work with contractors to carry out clinical trials?

Roche will work with qualified Contract Research Organizations (CROs) and other types of contractors whenever needed. In this context, Roche will apply the Roche Guidelines on Dealing with Suppliers and Service Providers (in force since October, 2004). In particular, the 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.

13. Clinical trials in developing countries – why?

The greatest contribution Roche can make to society is to continue developing innovative medicines and diagnostics that respond to medical needs, as well as save and improve quality of life. But for many reasons, not everyone has equal access to healthcare. Some patients are able to live longer, healthier lives than others with the same disease because the same level of medical care is not available in all countries – often because of cost or lack of healthcare infrastructure.

The development and improvement in the provision of healthcare is the responsibility of governments. However, the healthcare sector can contribute through a number of mechanisms. Healthcare resources and needs vary widely from country to country and

⁵ http://www.roche.com//corporate_responsibility/csr_research_and_development/clinical_trials.htm

cannot be provided for with a single approach. Roche has developed different strategies and programs for improving global access, reflecting the needs of the different regions and providing benefits to the countries.

As one part of that, Roche provides free medicines and tests to patients in phase I-IV clinical trials that take place in developing countries. This often includes additional treatment and tests other than those being trialled. Hospitals and clinics are compensated for hosting the trials, and often use the money to fund additional nursing staff, education centres and research. Phase IV trials familiarise clinicians with new drugs before they become widely available.

14. Are the standards for clinical trials in developing countries different?

Conduct of clinical trials in developing countries presents a unique set of ethical issues. Where Roche undertakes clinical trials in developing countries, 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. For further information see Clinical Trials in Low and Middle Income Developing Countries.⁶

For Roche sponsored trials Roche commits to provide the investigational product, as required by GCP, and in accordance with the regulatory requirements of the country. Roche commits to provide the investigational medicinal product free for the duration of the study, and in certain cases also after the trial has ended (**see Q 11**). Roche will make every effort to support the local healthcare infrastructure where appropriate. However as a research based pharmaceutical company it is not in a position to provide such infrastructure where none exists.

Where the results from a Roche Sponsored Clinical Trial in a low or middle income country are used for the purposes of registering the Roche medicinal product in another country, Roche commits to apply for marketing authorization of the medicinal product in the low or middle income country in which the trial was conducted.

Links:

Declaration of Helsinki:

<http://www.wma.net/e/policy/pdf/17c.pdf>

Declaration of Istanbul:

<http://www.declarationofistanbul.org/>

IFPMA website:

<http://clinicaltrials.ifpma.org/>

Roche website:

<http://roche-trials.com/glossary.action>

US website:

<http://www.clinicaltrials.gov/ct/info/glossary>

⁶http://www.roche.com/clinical_trials_policy_in_low_and_middle_income_developing_countries.pdf and <http://www.roche.com/sust-access.pdf>

UK website:

<http://www.imperial.nhs.uk/research/clinical-trials/research-glossary/index.htm>

EGAN website (FAQ on clinical trials and glossary):

<http://www.biomedinvo4all.com/en/publications/faq-on-clinical-trials-various-languages/>

<http://www.biomedinvo4all.com/en/publications/glossary-of-terms/>