Roche FAQ on Clinical Research

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 medicines, vaccines, or diagnostics, or new ways of using known medicines. Clinical trials are used to determine whether new medicines, 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 medicines or procedures in the laboratory and in animal studies (as required by regulatory authorities), the medicines 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 0 to V trials. There is also the possibility of combining different trial phases. For example, combining phases II and III may allow research questions to be answered more quickly or with fewer patients. Roche defines Phase 0 to V clinical trials as follows:

- **Phase 0 (not a regulatory requirement, usually less than 15 participants)**

The purpose of this phase is to help speed up and streamline the approval process for new medicines. Phase 0 studies may help researchers find out if the investigational medicines do what they're expected to do. This may help save time and money that would have been spent on later phase trials. Phase 0 studies use only a few small doses of an investigationall medicine in a few people. They might test whether the medicine reaches the tumor, how the medicine acts in the human body, and how cancer cells in the human body respond to the medicine.

- **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 physicians to understand what effects an investigational medicine has in humans. The goal is to study what happens to the medicine in the body from the time it is swallowed or injected until it is removed from the body. In addition, the study will find out when the medicine is removed from the body, how the human body reacts to the new medicine, and if it is well tolerated and safe. 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 medicine 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 mutation.[1] The patients are given various doses of the medicine 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 medicine in a variety of different types of patients 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 medicine at a dose that has been selected, 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 medicine 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 medicine is best prescribed to patients in the future.

- **Phase IV**

  Phase IV studies investigate the side effects caused over time by a new medicine after it has been approved and is available in hospitals/pharmacies. These trials look for side effects that were not seen in earlier trials and may also study how well a new medicine works

over a long period of time. Phase IV clinical trials may include thousands of people. These studies may also look at other aspects of the medicine, such as quality of life, patient subgroups, or cost effectiveness. Postmarketing requirements (PMRs) include studies and clinical trials that sponsors are required to conduct under one or more laws or regulations. Postmarketing commitments (PMCs) are studies or clinical trials that a sponsor has agreed to conduct, but that are not required by a law or regulation.

- **Phase V**

  These are large-scale, long-term studies that, for example, explore expanding the use of an approved medicine to treat other groups of patients (e.g., children, elderly) or different diseases.

3. Why does Roche conduct clinical trials?

Clinical trials are an important part of developing new medicines, devices, or tests for diagnosis of diseases. Before a new medicine, medical device, or diagnostic test is made available, evidence of its safety and effectiveness must be provided by well-designed, well-conducted and controlled, and carefully monitored clinical studies in healthy volunteers and patients consenting to participate.

Importantly, clinical trials are not the same as standard medical care and they are not a replacement for medical care provided by a personal physician using medicines and other therapies that are already approved by regulatory agencies like the US Food and Drug Administration (FDA). The purpose of clinical trials is to test an experimental medicine or other medical product.

4. What are the ethical principles that govern clinical trials? Ethical clinical research is guided by the principles of nonmaleficence, respect, beneficence and justice.

- Nonmaleficence is the duty to avoid and minimize harm. This principle has its roots in the Hippocratic Oath. The ethical issue at the core of clinical research is whether the outcome of the research can be reasonably expected to provide benefit to society while avoiding and minimizing harm to the individuals enrolled in the trial. Study risks are considered in physiologic, psychological, and socioeconomic terms. For a clinical trial to be considered ethical, there must exist sufficient scientific/medical evidence to justify exposure of individuals to the risks of the trial.
- Respect for persons is a key feature of informed consent, requiring that information is thorough and provided in a manner that is understandable, that the participant's cooperation is voluntary, and that privacy protections are robust.
- Beneficence is demonstrated by a thorough risk/benefit assessment, recognizing that benefits can be direct, collateral, and/or altruistic. 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 deserve the gratitude and respect of society.

The *Declaration of Helsinki*.[2] 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 clinical research 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 bioethics. Roche contributes to this debate through collaboration in interdisciplinary working parties of various partners in various 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 as well as the responsibilities of investigators to make clear the goals, 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*, 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* 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, publications, 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, 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 personal data protection rights to help reduce the risk of 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) or Research Ethics Committees (REC). 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 participants' 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 participants at all times.

To ensure this compliance, Roche provides Good Clinical Practice (GCP) training 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] 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 a 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 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. When withdrawal is requested, the research team will create a safe pathway for leaving the clinical trial. 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?

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

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

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

During the trial, personal 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 participant's name or identifiable image 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 will 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 form a participant signs prior to participation in the trial
- Be written up in a specific informed consent form that the participant will also be asked to sign.

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

We seek to share our data in four important ways:

- We publish information from our protocols and clinical study results on clinical trial databases.
- We disclose clinical study documentation in clinical trial databases (e.g., study protocol or ICF).
- We publish in peer-reviewed journals and share data in scientific meetings.
- We provide qualified researchers access to individual participant data.

Learn more about Roche's approach to data sharing by reading the company's Global Policy on Sharing of Clinical Study Information

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 treatment. 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 (see Q13).

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

Roche works with qualified Contract Research Organizations (CROs) and other types of contractors when 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 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. Under which conditions does Roche provide continued access to investigational medicinal product?

Roche offers patients who participate in Roche-sponsored clinical studies continued access to the investigational medicinal product that they received after study completion when:

- The patient has a life threatening or severe medical condition and their wellbeing requires continued administration of the investigational medicinal product;
- There are no appropriate alternative treatments available to the patient;
- The patient and their doctor comply with and satisfy applicable legal or regulatory requirements.

Roche will not provide continued access to investigational medicinal product as described above if:

1. The investigational medicinal product is commercially available in the patient's country and is reasonably accessible to the patient (e.g., is covered by the patient's insurance or wouldn't otherwise create a financial hardship for the patient);
2. Roche has discontinued development of the investigational medicinal product or data
suggest that the investigational medicinal product is not effective for the relevant indication;
3. Roche has safety concerns regarding the investigational medicinal product and/or the benefit risk ratio for the concerned indication is deemed negative; or
4. Provision of investigational medicinal product would not be permitted under the laws and regulations of the patient's country.

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

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 robust results at the conclusion of the clinical research.

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.

Roche commits to apply for marketing authorization of the medicinal product in countries in which the trial was conducted.

15. Do these ethical research standards in principle also apply for diagnostics and medical devices?

Yes, they do.

16. Can research participants have access to their clinical trial data?

If the person participated anonymously it is not possible to return any personal clinical trial data because the data is not traceable to the person. If the data was collected with links to their personal information, data sharing will be according to the provisions detailed in the corresponding informed consent form.

Notes

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

[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).

[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