A responsible approach to clinical trials

Bioethics in action
What is bioethics?

At Novo Nordisk bioethics is the expression used for all ethical issues related to the use of life science technologies in the discovery, development and production of pharmaceutical products. This covers the ethical aspects of the use of human biological material, animals and gene technology in research, and clinical trials.

Novo Nordisk Bioethics Policy

In Novo Nordisk we will continuously improve our bioethical performance. This means that we will:

- Promote bioethical awareness throughout the company
- Establish and ensure high ethical standards for:
  - Experiments on live animals
  - Clinical trials and use of human material
  - Gene technology
  - Our external partners, contract research organisations and suppliers, and monitor their performance
- Engage in stakeholder dialogue and partnerships, and report on our performance
- Live up to the spirit, values and principles and content of relevant conventions, laws and requirements
Novo Nordisk’s approach to clinical trials

Clinical trials are one of the last steps in the long process of bringing a new pharmaceutical product to the market. Before such a product can be approved by the regulatory authorities, it must be proven to be efficacious and safe in the targeted patient population.

In 2007, more than 20,000 people in 46 countries were involved in Novo Nordisk-sponsored clinical trials. It is of paramount importance to us that we can ensure the safety and well-being of these volunteers and that all trials are conducted in accordance with universal ethical principles. These involve respecting the rights, integrity and dignity of people participating in clinical trials.

Clinical trials follow a pre-set protocol approved by national health authorities and ethics committees. Our global standards are not to be compromised. Trials must be conducted in the same way, no matter where in the world and by whom they are carried out. Doctors (investigators) must carefully select participants so that they have the right profile, and they must obtain informed consent from each individual and ensure their well-being throughout and after the trial. Investigators and research teams must be offered fair reimbursement for their costs and labour. Trials must undergo independent scientific and ethical review and approval and are subject to random audit by authorities during or after their execution. And the results, irrespective of the outcomes, must always be made publicly available.

Principles have value only when they are put into action. At Novo Nordisk, all employees involved in clinical trials receive training in ethical standards and a governance structure is in place to specify clear roles and responsibilities. We only conduct trials in countries where our standards can be met, where ethics committees are established, and where we intend to market the new pharmaceutical product once it is approved. In this brochure you can read more about the ethics of clinical trials and our efforts to continuously improve our performance.

Mads Krogsgaard Thomsen
Executive vice president and chief science officer
Novo Nordisk
An introduction to clinical trials

The route for a new pharmaceutical product from idea to patient is highly complex and time consuming. Out of 10,000 ideas that begin in the laboratory, just 10 will ever reach the stage where they are tested in humans. Of these, only one may prove to be efficacious and safe enough to be approved by authorities as a new treatment.

A clinical trial is a controlled research investigation carefully designed to evaluate the efficacy and safety of a pharmaceutical product. Clinical trials are an important – and legally required – step in the research and development process to make new treatments available for particular conditions. The clinical development programme for a new product involves many clinical trials and includes many thousands of trial participants.

“Clinical trials enable us to evaluate and assess the effectiveness of a pharmaceutical product in the treatment of a particular condition and also help to disclose possible side effects. Clinical trials are the most expensive part of drug development and it typically takes 7–12 years from initiation of the first clinical trial until the product reaches the market,” explains Peter Kristensen, senior vice president in Global Development.

Clinical trials begin once a drug candidate has been tested in animals with regard to its pharmacology and toxicity. Only then will it be tested in humans. A pharmaceutical company may sponsor a clinical trial, while a doctor (investigator) conducts the trial.

Trials are usually randomised and blinded, so that participants, and in most trials also the doctors, do not know if the treatment participants are receiving is the new drug or the control treatment. Trials may be placebo controlled, which means that participants are randomised to receive either the new drug candidate or placebo, to establish the real effect of the trial drug. A placebo will only be used if ethically acceptable. If the new treatment is given in addition to the existing treatment, a placebo can be used to mask if the participant is receiving the new treatment and the existing treatment, or just the existing treatment.

There are four main phases of clinical trials (see chart opposite).
| Phase 1 trial | 100–200 healthy volunteers and/or patients | Tests how well the drug is tolerated in single then multiple dosing trials | Usually placebo controlled |
| Phase 2 trial | 200+ patients, lasting for several months | Tests the efficacy of the drug and obtains information on dose-response relationships | Usually includes an active comparator |
| Phase 3 trial | 2,000+ patients, lasting 1+ years in chronic diseases | Confirms the effectiveness and safety of the drug over a longer period of time and detects even potentially rare adverse effects | Usually includes an active comparator |
| **Market authorisation** |
| Phase 4 trial/post-marketing trial | 2,000+ patients | Takes place after market authorisation is given, determines the effectiveness and safety of the product in an even wider variety of patients. May also be conducted on request from authorities as a condition for market authorisation approval, for example to address specific safety issues |
Novo Nordisk has the same ethical standards wherever it conducts clinical trials and will only conduct trials in countries where these standards can be met.
Global ethical standards

When clinical trials are performed on behalf of Novo Nordisk, the company operates according to a common global standard which is in compliance with international guidelines and regulations. Two fundamental international guidelines form the basis for clinical research and drug development worldwide. These are the Declaration of Helsinki and the ICH guidelines on Good Clinical Practice (GCP). The Declaration of Helsinki, developed by the World Medical Association in 1964 and revised several times since, is a standard of ethical principles for human rights for participants in clinical trials. The GCP guidelines were subsequently drawn up by the International Conference on Harmonisation (ICH), consisting of health authority representatives from Europe, the US and Japan, to ensure the rights, safety and well-being of trial participants and validity of compiled data.

“All Novo Nordisk clinical trials are performed in accordance with the Declaration of Helsinki and the ICH GCP guidelines, in addition to a number of other international guidelines such as the Belmont report, Code of Federal Regulation (US), the CIOMS and the EU Clinical Trials Directive, The Nuremberg Code and UNESCO’s Universal Declaration on Bioethics and Human Rights. These are integrated into our global Standard Operating Procedures which ensure that we are in compliance with these guidelines when sponsoring clinical trials. Novo Nordisk is furthermore committed to complying with national regulations in the countries where trials are performed,” explains Anders Dejgaard, chief medical officer in Global Development at Novo Nordisk.

The company has taken further steps to ensure a continuous focus on ethical issues during new drug development. An internal governance system involving senior management addresses ethical issues in the development of new pharmaceutical products and related clinical trial activities. External investigators are involved in the establishment of clinical trial protocols, and the company discusses development programmes and individual protocols with representatives from global health authorities.

All clinical trials are subject to quality audits from national and international health authorities. Novo Nordisk’s own quality organisation also audits trial sites and processes to ensure that the conduct of the clinical trials the company sponsors meet the company’s requirements.
Novo Nordisk’s position regarding clinical trials

To ensure uniform ethical standards globally, Novo Nordisk has developed a position statement for clinical trials that the company sponsors. This can be found at novonordisk.com/sustainability/positions. The following is a summary of this statement.

- Clinical trials sponsored by Novo Nordisk will always be conducted according to the Declaration of Helsinki and similar international ethical guidelines such as the Nuremberg code, the Belmont report and the International Conference on Harmonisation (ICH) guidelines for Good Clinical Practice.
- These guidelines are the foundation for our Standard Operating Procedures which work to ensure the safety, rights, integrity, confidentiality and well-being of persons involved in Novo Nordisk trials globally.
- Novo Nordisk will apply the same procedures wherever we sponsor clinical trials. We will only conduct clinical trials for drug development in countries where we intend to market the investigational drug.
- The interest and well-being of the trial participants will always prevail over the interest of science, society and commerce.
- Clinical trials will only be conducted if they can be scientifically and medically justified, and potential benefits outweigh potential risks.
- No trial activity will start before approval is obtained from external local ethics committees and health authorities, and informed consent is obtained from the participants.
- In cases where participants are incapable of giving consent, or if the person is a minor, informed consent is obtained from the legally authorized representative in accordance with national laws. Such study participants are only included in trials if there is no research alternative.
- Participants can withdraw from a clinical trial at any time without giving any reason.
- Novo Nordisk conducts site monitoring to ensure that the study is executed according to the study protocol.
- Any adverse events are monitored and actions taken when necessary.
- Patients participating in clinical trials will, after the study has finished, be offered the best possible treatment, at the discretion of the investigator.
- Novo Nordisk ensures proper indemnification of trial participants in case a product or procedures in a trial cause bodily harm.
- Novo Nordisk strives to publish all clinical trial results according to accepted international guidelines and timelines. The company ensures transparency of clinical trials by registering protocol information and trial results on external websites.
Novo Nordisk has established a comprehensive global position statement regarding clinical trials based on a series of international guidelines and recommendations.
Novo Nordisk must ensure that the pharmaceutical product being tested, in the right volumes, is supplied to each investigational site involved in a clinical trial.
Sponsoring a clinical trial

During the execution of a clinical trial all parties involved – including the company sponsoring the trial – have specific responsibilities to ensure adherence to ethical principles. For every trial sponsored by Novo Nordisk, the company writes a clinical trial protocol which is a detailed description of all activities related to the clinical trial.

The protocol includes the number and type of healthy or patient volunteers which need to be enrolled, which treatment they will receive based on a randomised process, when they should visit the investigational site and which procedures and blood samples they will be subject to during the study. The protocol also includes a detailed description of which statistical analysis will be conducted and the endpoints for the trial. Furthermore, the protocol provides a detailed description of the trial in layman’s terms including any potential risks, which will be given to the participants as part of the informed consent procedure.

According to GCP, pharmaceutical companies who sponsor clinical trials, including Novo Nordisk, are not allowed to have direct contact with trial participants throughout a trial, in order not to bias their response to the tested treatment. The company therefore collaborates with investigators and clinical research organisations who conduct the trials for the company. It is Novo Nordisk’s responsibility to ensure that the investigators are skilled in the relevant therapeutic areas and trained in the regulation and ethical principles governing the conduct of clinical trials. The company must ascertain that the investigators have the time, resources and access to any necessary equipment needed to conduct the trial. Furthermore, the company must ensure supply of the pharmaceutical product being tested to each investigational site involved in the trial.

Once the trial is underway, employees from Novo Nordisk (clinical trial monitors), frequently visit the trial sites ensuring that the trial is executed according to the protocol and that data collected for the trial is consistent with data from the patient records.

For every clinical trial it sponsors, Novo Nordisk establishes safety committees that follow the reporting of adverse events globally, make appropriate reports to health authorities and take action as required.

When the trial finishes it is the responsibility of Novo Nordisk to do the preplanned statistical analysis and write the clinical trial report based on this analysis of the data collected.
Conducting and participating in a clinical trial

A doctor (investigator) conducts a clinical trial on behalf of the sponsoring pharmaceutical company. The main role of the investigator is to serve and protect the interests of the trial participants and ensure their safety, rights and privacy are maintained.

When an investigator agrees to conduct a clinical trial on behalf of Novo Nordisk, they confirm that the trial has been planned and will be conducted according to local requirements and scientific and ethical guidelines. The investigator is responsible for submitting the trial protocol to ethics committees for approval, including informed consent documents and information about the financial agreement between the investigator and the sponsoring company.

The investigator ensures potential participants are eligible to take part in the trial based on the criteria detailed in the protocol. This involves obtaining a signed informed consent from the volunteer, performing a detailed medical examination, obtaining blood sample(s) and reviewing their full medical history. “We have established procedures to ensure a person’s full understanding of the trial and consequences of participation. The investigator informs the volunteers verbally and in writing in their native language about the planned research procedures, treatment after trial and the risk of participating, including possible side effects, before they decide whether to take part,” explains Ole Molskov Bech, vice president, International Operations Clinical Development Centre at Novo Nordisk. Participation in a clinical trial is always voluntary and participants may withdraw at any time, without providing a reason.

The investigator ensures that trial participants receive the examinations and treatment as described in the protocol through regular visits to the clinic. If a trial participant experiences a serious adverse event (unfavourable medical occurrence), the investigator must report the event to Novo Nordisk and the health authorities, irrespective of whether the event is considered to be related to the pharmaceutical product being tested or not.

Once the trial is completed the investigator informs participants about the outcomes of the trial.
Participants in clinical trials must freely give their consent after both verbal and written information about the trial has been given to them by the investigator. The investigator’s role is to serve and protect the interests of the participants.
To share knowledge and ensure transparency, Novo Nordisk communicates clinical trial results through scientific journals, at conferences and via publicly available websites.
Clinical trials disclosure
Novo Nordisk is committed to sharing knowledge and being transparent. The company communicates the results of clinical trials, regardless of outcome, through the publication of papers in scientific journals, abstract submissions at scientific meetings or by other means. The company adheres to guidelines and legislation regarding when and what information should be made available. On a global scale the requirements on clinical trials disclosure are subject to constant change and Novo Nordisk’s policy is updated accordingly. Since 2005, the company has provided public access to the results of all their sponsored phase 1–4 clinical trials for marketed products, and protocol information on all phase 2–4 clinical trials for drugs and devices in development. In addition, similar information on phase 1 trials initiated after 1 July 2008 is included. To meet US legal requirements on clinical trials disclosure, information is also available at www.ClinicalTrials.gov, a US government site, according to their standards.

To provide easier access to information about Novo Nordisk-sponsored trials, the company launched its clinical trials website in 2007. The site, novonordisk-trials.com provides an overview of all phase 2–4 clinical trials initiated after October 2002 and, since July 2008, phase 1 clinical trials.

Access to a post-trial drug
Clinical trial participants should have access to best proven and available treatment after a trial has stopped. Treatment after participation in a Novo Nordisk-sponsored trial is described in the protocol and the informed consent document.

Novo Nordisk submits marketing approval applications to authorities in the US (FDA), the EU (EMEA), Japan (PMDA) and all other countries where the company intends to market a pharmaceutical product following the completion of the clinical trial programme. Many countries require their own national approvals with country-specific trial requests.

The product is not available for patient use until national authorities have approved the application. Consequently, patients participating in phase 1–3 trials can not be offered the trial drug immediately after the trial stops, but will be offered a marketed drug at the discretion of the investigator. In phase 4 trials participants can have the trial drug prescribed after the trial stops if the investigator finds it appropriate.
Dealing with specific issues

Trials in developing countries
National health authorities are continuously asking for greater numbers of participants in clinical development programmes. In addition, an increasing number of countries require that trials are performed in their own population before a pharmaceutical product can be marketed in their country. In 2007, more than 20,000 people in 46 countries were involved in clinical trials sponsored by Novo Nordisk and approximately 40% of the people live in developing countries. Trials in developing countries can be a challenge due to the potential immaturity of the ethical governance system in such countries. Novo Nordisk only conducts trials in countries where ethics committees’ systems are established, where health authorities act according to international guidelines and where the company’s global clinical trial standards can be met. Furthermore, Novo Nordisk will only conduct trials in countries where the company intends to market the new pharmaceutical product being tested.

Novo Nordisk develops one common protocol for every clinical trial so ensuring the same ethical standards for the recruitment of participants and the same procedures are followed, irrespective of the country in which the trial takes place. In trials sponsored by Novo Nordisk, all medical staff have documented training to ensure they have the necessary competences, and they must adhere to the Declaration of Helsinki, ICH Good Clinical Practice, Novo Nordisk policies and clinical trial procedures. Novo Nordisk clinical trial monitors frequently visit the trial sites to ensure that the trial is executed according to the protocol.

Minimising conflicts of interest
Investigators performing clinical trials on behalf of Novo Nordisk receive reimbursement only for their work associated with a given trial. Payments are usually made to a research fund at the hospital and not directly to the doctor. It is Novo Nordisk’s policy to fairly compensate volunteers for their participation in clinical trials and to ensure that such compensation does not influence their decision to participate. When appropriate, trial participants are compensated for their time or the inconvenience of trial procedures. Information on these financial agreements with investigators and trial participants is always included in the protocol application to the national health authorities and ethics committees.
Novo Nordisk ensures the same ethical standards are followed, irrespective of the country in which the trial takes place.
The governance system of Novo Nordisk-sponsored trials

All clinical trials are subject to random audits by health authorities. This is completely independent of where the trial is executed geographically. This means, for example, that a trial performed in Asia can be audited by the Food and Drug Administration (FDA) from the US. Such audits will assess if international ethical guidelines and GCP are adhered to. At the same time these authorities are the bodies that eventually approve documentation of the new pharmaceutical product and in that process they will further evaluate if the clinical trials have been performed properly. The review and approval of protocols by health authorities and ethical committees are further examples of external assessment of the way clinical trials are performed.

Internally, Novo Nordisk has developed a dedicated and systematic approach to deal with all bioethical issues related to the discovery and development of new pharmaceutical products including clinical trials to ensure a continuous focus on these issues. The company’s Bioethics Management department is responsible for a virtual cross-functional team of between 50–70 employees who ensure that Novo Nordisk’s research activities are ethically sound.

The company’s bioethical work is governed by the Novo Nordisk Environment, Bioethics and Occupational Health and Safety Committee, mandated and chaired by Novo Nordisk’s Executive Management. The Committee is responsible for the company’s policy and strategy on bioethics. The Novo Nordisk Research & Development Bioethics Board strengthens the co-ordination of the bioethical activities across research and development, and ensures synchronicity, knowledge and information sharing. The board prepares and suggests new initiatives, develops and implements new policies and guidelines, and supervises the company’s handling of bioethical issues worldwide. The Clinical Trial Ethics focus group is a subgroup to the board and deals with specific issues related to ethical performance in clinical trials sponsored by Novo Nordisk.

From a project perspective, specialist boards and committees (see table opposite) with representatives from Novo Nordisk’s top management and regional and local operations, review and approve work connected with clinical trials to ensure bioethical standards are maintained at all stages of the clinical development programme.
<table>
<thead>
<tr>
<th><strong>Novo Nordisk specialist boards and committees</strong></th>
<th><strong>Responsibility</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Project Management Committee</strong></td>
<td>Reviews entire project portfolio and individual development projects. Mandated and chaired by Executive Management.</td>
</tr>
<tr>
<td><strong>CDP Challenge Board</strong></td>
<td>Approves clinical development plan (CDP) for each project including potential ethical issues. Chaired by the company’s chief medical officer and consists of management from the regional development organisation.</td>
</tr>
<tr>
<td><strong>Protocol Review Committee</strong></td>
<td>Reviews and approves each clinical trial protocol before it is sent to the national ethics committees and health authorities in participating countries. Members are senior managers, regional representatives and academic and technical employees.</td>
</tr>
<tr>
<td><strong>Global Development Operational Management</strong></td>
<td>Endorses country allocation of trials to ensure countries are competent to do the requested trial and that trials are only conducted in countries where the company intends to market the new product.</td>
</tr>
<tr>
<td><strong>Clinical Issues focus group</strong></td>
<td>Surveys and assesses new regulation to ensure all guidelines from health authorities and other relevant bodies are properly implemented.</td>
</tr>
<tr>
<td><strong>International SOP Committee</strong></td>
<td>Updates standard operating procedures (SOPs) with relevant changes from Clinical Issues focus group.</td>
</tr>
<tr>
<td><strong>Clinical trial monitors</strong></td>
<td>Visit the trial sites frequently to ensure that the trial is executed according to the protocol and that data collected for the trial is consistent with data from the patient records.</td>
</tr>
<tr>
<td><strong>Clinical Quality Assurance</strong></td>
<td>Randomly audits ongoing clinical trials on a regular basis for compliance with GCP and Novo Nordisk SOPs.</td>
</tr>
<tr>
<td><strong>Safety Committee</strong></td>
<td>Surveys all safety aspects in relation to the clinical trials programme for each product and takes appropriate action if necessary.</td>
</tr>
<tr>
<td><strong>Report Review Committee</strong></td>
<td>Reviews and approves all clinical trial reports.</td>
</tr>
</tbody>
</table>

Note: local phase 4 trials are subject to local governance systems.
Stakeholder engagement

For decades, Novo Nordisk has been meeting with stakeholders to discuss bioethical issues. The company recognises the value and importance of input from external stakeholders and in the field of clinical trials the company appreciates the role it can play in supporting the training of healthcare professionals:

Involving healthcare professionals
Novo Nordisk welcomes advice from healthcare professionals whose knowledge is invaluable. The company has established advisory boards comprised of investigators from around the world whose expertise provides input to the design of a product’s clinical trial programme and protocols. Other examples of such engagement include the Novo Nordisk Nurse Steering Committee in the UK. “The nurses have a wealth of experience of dealing with patients on a daily basis and their expertise is used to ensure participants have the best possible experience of the clinical trials. Their input is used in the design, materials and organisation of clinical trials.” explains Henrik Schou, clinical research director, Novo Nordisk Northern Europe. The committee also organises an annual Research Nurse Symposium, open to all research nurses, which includes training and development for a wider group of research nurses and is an important forum for the profession.

Training for healthcare professionals
Novo Nordisk ensures that all investigators working on its clinical trials are trained in GCP. When necessary, the company offers such training for doctors, nurses and pharmacists at clinical research sites. In this way, the company ensures that the rights and well-being of trial participants are given priority and that the clinical trial data generated is reliable, of high quality and trustworthy in a global perspective.

Industry associations and regulatory authorities
Novo Nordisk is a member of several industry associations, including the European Pharmaceutical Industry Association (EFPIA) and the Pharmaceutical Research and Manufacturers of America (PhRMA), through which the company works with regulatory authorities to improve and harmonise the requirements for clinical trials conduct, such as the revision of the Declaration of Helsinki. Harmonised requirements enable clinical trials conducted in one country to provide acceptable evidence for a drug approval in other countries, thereby avoiding almost identical trials to be performed in several different countries.
Novo Nordisk frequently meets with various stakeholders such as non-governmental organisations (NGOs), inter-governmental organisations (IGOs), governments and regulators, researchers, students and journalists to discuss bioethical issues. The company participates in seminars, symposiums and conferences to share knowledge and views.
Access to information

three days
– searching for
better treatment
Bioethical challenges
within research and development
of new pharmaceuticals

Take a closer look
Bioethical considerations are part of everyday life in research and development (R&D) at Novo Nordisk. Now a film provides a closer look at the company’s search for better treatments. The documentary *Three days – searching for better treatment* follows three employees on a pivotal day for their projects and shares their reflections on the spirit of R&D at Novo Nordisk. The film explains the long and difficult road from idea to patient, where ethical issues are an inevitable part of the journey. Read more or request the film and accompanying booklet at Novo Nordisk’s bioethics website novonordisk.com/science/bioethics

Clinical trials online
Novo Nordisk’s approach to ethical issues in relation to clinical trials can be found at its clinical trials website, which provides an overview of all the company’s clinical trial programmes worldwide. On the website potential trial participants and interested parties can find general information about clinical trials, see which trials are taking place in their country and get further insight into the company’s projects in clinical development within diabetes, haemostasis and other areas of biopharmaceutical drugs and devices. For more information visit novonordisk-trials.com
“Stakeholder dialogue and partnerships are invaluable for the development of research programmes and clinical trial protocols at Novo Nordisk.”

Mads Krogsgaard Thomsen
Executive vice president and chief science officer, Novo Nordisk
Novo Nordisk welcomes feedback, comments and suggestions on this brochure as part of our ongoing dialogue and engagement with stakeholders.

Send your comments to:
Lise Holst, director, Bioethics Management
bioethics@novonordisk.com

Novo Nordisk A/S
Novo Allé
2880 Bagsværd
Denmark
Tel +45 4444 8888

novonordisk.com