

Guidelines to the Regulation of 30 October 2009 relating to clinical trials on medicinal products for human use

Introduction

Requests for authorisation to conduct clinical trials shall be sent to the Norwegian Medicines Agency (hereafter called NoMA). NoMA shall evaluate the requests pursuant to the provisions of the Regulation on clinical trials on medical products for human use, with legal basis in the Medicines Act (Act no. 132 of 4 December 1992 relating to medicines etc.) and laid down by the Norwegian Ministry of Health and Care Services on 30 October 2009. The regulation incorporates international guidelines for good clinical practice ("Note for Guidance on Good Clinical Practice, CPMP/ICH/135/95") (hereinafter called GCP). The request shall also be sent to the Regional Committee for Medical and Health Research Ethics (hereafter called the Ethics Committee), see Chapter 3, Section 3-1, 3-2 and 3-3 and the remarks to these subsections.

NoMA has supervisory authority for clinical trials and for performing inspections. See Chapter 6. Inspection of health services provided in connection with the trials is carried out by the Norwegian Board of Health.

The Ministry of Health and Care Services is the appeals authority for decisions taken by NoMA pursuant to the regulation. The National Committee for Medical and Health Research Ethics (NEM) is the appeal authority for decisions taken by the regional ethics committees.

The address of the Norwegian Medicines Agency is Sven Oftedals vei 6, 0950 Oslo (telephone +47 22 89 77 00, fax +47 22 89 77 99).

The aforementioned regulation repeals regulation no. 1202 of 24 September 2003 on clinical trial of medicinal products for human use. Efforts have been made to harmonise the regulation with EU Directives 2001/20/EC and 2005/28/EC. The purpose of the directives is to harmonise the requirements relating to clinical trials on medicinal products in the EU/EEA in order to prepare the way for synchronised start-up of international multi-centre trials. The intention is also to ensure protection of susceptible groups, to increase the insight of the authorities, to harmonise adverse event reporting and to implement good clinical practice (GCP) and good manufacturing practice (GMP). Directive 2005/28/EC is also intended to harmonise the manufacture and import of medicinal products for clinical trials, archiving and documentation in connection with clinical trials, inspection procedures in connection with GCP inspections, and the requirements to be made of GCP inspectors. The guidelines for the directives – The Rules Governing Medicinal Products in the European Union, [Volume 10](#) – have been drawn up by the European Commission and are to be found on the [Commission's website](#).

Efforts have also been made to harmonise the regulation as far as possible with the Norwegian Health Research Act, but where there are divergent provisions the Regulation relating to clinical trials shall prevail (see Section 2 of the Health Research Act).

In the following, we will comment on the various chapters and some of the sections in the regulation.

Chapter I – General provisions

Section 1-1. Scope

Pharmacogenetic surveys that are not a part of a clinical trial do not require approval by NoMA, but are covered by the provisions of the Health Research Act and if relevant by the Biotechnology Act (see Section 1-13 of the guidelines). Questions regarding this type of study can be posed to the Ethics Committee or the Directorate of Health.

Section 1-2 Good clinical practice and the Helsinki Declaration

In this regulation, 'standard for good clinical practice' means GCP as described in Note for Guidance on Good Clinical Practice, CPMP/ICH/135/95.

Section 1-4. Conditions for initiating a clinical trial

Requests for authorisation may be sent in parallel to the Ethics Committee and NoMA. Both authorities must approve the trial before it can start. The trial can start at the individual centre when:

- Both the Ethics Committee and NoMA have approved the trial.
- Documents as described in Chapter 8.2 of ICH/GCP have been generated.

Section 1-5. Definitions

a) serious adverse event (SAE), serious adverse reaction (SAR)

Any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening,
- requires inpatient hospitalisation or prolongation of existing hospitalisation,
- results in persistent or significant disability/incapacity,

or

- is a congenital anomaly/birth defect

b) adverse reaction (AR): an adverse reaction is an adverse event (AE) where a causal connection with the investigational medicinal product (IMP) cannot be excluded (possible or probable connection).

c) CRO: contract research organisation, consulting company which can undertake tasks for sponsor according to agreement.

f) good clinical practice – GCP: ("[Note for Guidance on Good Clinical Practice, CPMP/ICH/135/95](#)") which has been adopted by CHMP.

g) principal investigator: a physical person with responsible for the day-to-day running of the trial, and who has the necessary research qualifications and experience to be able to fulfil project manager's responsibilities pursuant to this regulation. Principal investigator has the same responsibility as a project manager according to the Health Research Act. Principal investigator should have qualifications in GCP. It is the national coordinating investigator who undertakes this responsibility in connection with multi-centre trials.

l) clinical trial:

The definition does not apply to retrospective studies. Trials involving a substance or medicinal product, but in which it is not intended studying its properties as a medicinal product as such, need not be reported to NoMA. In such cases a positive assessment from the Ethics Committee is sufficient. An application for approval by NoMA and the Ethics Committee must be made for a clinical trial of a medicinal product for an approved indication, with approved dosage and with an approved means of administration, for the purpose of providing further information about efficacy and/or safety.

In the event of disputes, NoMA should be contacted for a clarification. Requests can be submitted by sending an e-mail with a brief description of the trial to klut@legemiddelverket.no. NoMA can also be contacted by phone.

See also the Commission's [Question & Answers](#) documents – last two pages.

s) sponsor: sponsor may be an institution or other legal or physical person who has the ultimate responsibility for the research project and who has the necessary qualifications for fulfilling the obligations of the person or body responsible for research pursuant to this regulation and to GCP. Sponsor and principal investigator (national coordinating investigator in the case of multi-centre trials) may be one and the same physical person. Normally, however, sponsor and principal investigator will not be the same person, since a clinical trial will normally be so extensive that sponsor ought to be an institution or similar in order to have at its disposal the resources, expertise and means necessary to ensure proper follow-up.

Sponsor has ultimate responsibility for quality assurance and systemic responsibility for organisation, execution and reporting on the trial in question. Sponsor shall also comply with the requirements made of sponsor in GCP.

Sponsor has the same responsibility as the person or body responsible for research according to the Health Research Act.

w) adverse event (AE): an adverse event may be any untoward and unintended sign (including abnormal laboratory values), symptom or illness that is temporarily associated with the use of an IMP, whether it is related to the trial product or not.

Section 1-7. Sponsor's location

There is no requirement that sponsor or sponsor's authorised representative be located in Norway provided that they are located within the EEA. There shall only be 1 sponsor.

Section 1-9. Financing of the trial product

Sponsor shall ensure that the investigational medicinal product (IMP), including the comparator, are made available free of charge to patients.

NAV (the Norwegian Labour and Welfare Organisation) can be contacted about relevant financing schemes.

Section 1-10. Permission to process personal data

The authorisation requirement pursuant to the Health Research Act must be clarified with the Ethics Committee.

Section 1-11. Investigator's brochure

In cases where an approved summary of product characteristics is used instead of an investigator's brochure, the approved SmPC shall be available in English or Norwegian. For more information, see the guidelines for Section 4-1.

The investigator's brochure shall be sent to NoMA for information purposes only if there are substantial amendments to the document. An account shall be given of what the substantial amendments concern. This can be given in the form of a summary in the cover letter. It is sponsor's responsibility to decide whether the changes in the investigator's brochure are substantial or not. See also Section 5-1.

Section 1-12. Transfer of ownership

Transfer of ownership shall be documented in writing to NoMA. If transfer of ownership takes after the trial has begun, an update of the EudraCT form shall be sent to NoMA for information purposes.

Section 1-13. Further duty of notification for special studies

Clinical trials that involve gene therapy also require approval from the Directorate of Health pursuant to Section 6-3 of the Biotechnology Act.

Clinical trials that involve predictive, presymptomatic or carrier-diagnostic genetic examinations, including pharmacogenetic testing, require the approval of the Directorate of Health pursuant to Section 7-1, cf. Section 5-3 of the Biotechnology Act, if the trial has diagnostic or treatment-related consequences for the participant, or if information about the participant can be traced back to the individual concerned. Written consent to such testing is required from the participant, and genetic guidance shall be provided before, during and after the testing.

The Gene Technology Act regulates the production and use of genetically modified organisms (GMO). Medicinal products that consist of or contain GMOs are covered by the Act. Medicinal products that have already been approved centrally in the EU are exempt. Clinical trials on medicinal products that are covered by the Gene Technology Act may be conducted either in a confined space or as deliberate release of GMOs. Trials in a confined space shall proceed in facilities approved by the Directorate of Health, and also require notification to the Directorate of Health with a description of the organism. The conduct of clinical trials according to the deliberate release rules presuppose circulation for comment and require the approval of the Directorate for Nature Management.

Clinical trials that entail the collection, storage, processing, destruction, introduction into Norway or transport out of Norway of human biological material also require the approval of the Ethics Committee, pursuant to the Health Research Act.

Clinical trials that entail the use of cells that stem from surplus fertilised eggs also require the approval of the Ethics Committee pursuant to the Biotechnology Act.

Chapter 2 – Protection of trial subjects

Section 2-2. Requirement of informed consent

The Ethics Committee, the Data Inspectorate, the National Research Ethics Committee for Medicine and NoMA have jointly recommended a template for information and consent in connection with trial of medicinal products. The template should be used for getting the best possible information to patients and for achieving the smoothest possible case processing by the Ethics Committee and NoMA. The contents of the patient information are also required to be in compliance with international GCP guidelines (CPMP/ICH/135/95). If the template is followed, there is also a greater probability that the GCP requirements are followed. For more information about the template, see the information on the [Ethics Committee's website](#).

An important principle of GCP, Chapter 2.9 and 4.8 ([CPMP/ICH/135/95](#)) is that all those considering taking part in clinical trials shall have access to certain basic information which is not dependent on the view of the individual investigator or pharmaceutical manufacturer. NoMA's most important task in connection with administration of the regulation in question is to safeguard the patients' safety. We therefore consider the patient information to be very essential in this connection.

Approval shall be "informed" in the sense that it is given on the basis of relevant information about the trial. A trial nurse, or another doctor who is well informed about the trial and has appropriate qualifications in the therapy area in question, may inform the trial subjects on behalf of the principal investigator about the trial and obtain consent to their participation if the trial subject wants to take part in the trial. The principal investigator or the person who has headed the information process shall date and sign that the information has been provided.

Personal data can be freely transferred to countries within the EU and EEA. It may also be transferred to countries that the European Commission has approved, and to individual companies in the US that observe "safe harbor" rules. There are, however, other possibilities for transfer to third countries that fall outside these agreements, such as the EU standard contract or consent from the person whose data are registered. The rules for transfer of personal data to other countries are also to be found in the Personal Data Act, Chapter IV, Sections 29 and 30.

Section 2-3. Withdrawal of consent

In the event of withdrawal of consent to take part in the trial, all trial-related procedures shall cease. Patient data and biological material that have been collected up to the time when the consent is withdrawn cannot be required to be deleted or destroyed. No further data shall be collected. Nor may any analyses be carried out on the biological material beyond those that were planned up to the time when the patient withdraws. It can be required that pharmacogenetic samples be destroyed.

The wording of the new regulation is in line with current practice. NoMA wishes to emphasise this, to prevent safety information being lost. The biological material may potentially contain information about new side effects of an IMP. NoMA is aware that the provisions of this regulation are in conflict with the provisions of the new Health Research Act, but at the same time the latter makes it clear that in cases where there is divergence between the Regulation relating to clinical trials on medicinal products and the Health Research Act, the provisions of the Clinical Trials Regulation shall prevail.

The right to require destruction, deletion or surrender does not apply if material or data have been anonymised, or if the material forms part of another biological product after processing, or if the information has already been incorporated in scientific work, cf. the Health Research Act.

Section 2-4. Insurance of trial subjects

Special drug liability insurance must be subscribed to in connection with the execution of clinical trials of medicinal products. This is the only valid insurance for clinical trials of medicinal products. This is laid down in Act no. 104 of 23 December 1998 relating to product liability, last amended on 30 August 2002. Liability which is insured pursuant to the Product Liability Act cannot be limited by agreements or provisos of any kind, and the scope of the Act is not affected by the manner in which the harm occurs. Insurance through the Drug Liability Association is the only valid insurance.

Sponsor is responsible for ensuring that necessary insurance is subscribed to via the Drug Liability Association.

If a consultant or a consulting firm (CRO) is to be responsible for conducting the study on behalf of a pharmaceuticals manufacturer, it is sufficient that the pharmaceuticals manufacturer has subscribed to insurance in the Pharmaceuticals Liability Association. An ordinary compensation for injuries to patients scheme is in other words not sufficient. **Nor is ordinary hospital insurance sufficient.** The aforementioned insurance must be subscribed to irrespective.

In non-commercial multi-centre trials it is sufficient for the national coordinating investigator (if this party is sponsor) to sign insurance for the whole trial. The principal investigators at individual centres and their patients are insured through the national coordinating investigator's insurance.

Further information about insurance can be obtained from the secretary of the Drug Liability Association, P.O. Box 15, 1524 Vika, 0117 OSLO, tel. +47 22 83 02 70 or by sending an e-mail to post@bahr.no.

Section 2-6. Requirements regarding the doctor's or dentist's qualifications

In addition to being a qualified doctor or dentist, the investigator should be familiar with and conduct the trial in compliance with GCP guidelines, this regulation and other relevant rules and regulations.

Section 2-7. Requirement regarding a point of contact

The patient shall have access to a person that he/she can ask for advice on the trial. This information shall be provided in the patient information. A telephone number should be supplied. See also the guidelines to Section 2-2.

Section 2-8. Clinical trials on persons aged under 18

The provision stipulates special rules for the obtaining and giving of consent on behalf of persons aged under 18.

Directive 2001/20/EC encourages more clinical trials to be performed on children in order to improve the treatment of this group. The fact that the trial is intended to be for the good of the patient group does not preclude placebo-controlled or non-therapeutic trials.

Parents/guardians shall normally consent on behalf of their children. As a general rule, both parents/guardians shall consent to participation when both have parental responsibility. All children shall be given information that is aimed directly at them. As a general rule, separate patient information shall be prepared for children aged from 12 and up which the child himself or herself can be given the option of signing.

The possibility of preparing written information for children aged under 12 to read should be considered.

Children shall always be given such information as they are capable of understanding. In cases where children refuse to take part in a trial, this should as a general rule be respected, provided that it does not have serious consequences for their own state of health. Trial subjects should be given a copy of the patient information and informed consent statement.

Trial subjects who become able to give consent during the course of the trial shall be provided with information about the trial pursuant to the guidelines in Section 2-2, and shall then give an informed consent statement if they wish to continue taking part in the trial.

According to Section 5-7 of the Biotechnology Act, predictive, presymptomatic or carrier-diagnostic genetic examinations, including pharmacogenetic testing, shall not be carried out on children aged under 16, unless the testing can reveal conditions where treatment can prevent or reduce harm to the child's health.

Section 2-9. Trials on persons unable to or with limited capacity to give informed consent

As far as possible, persons with limited capacity shall give consent on their own behalf.

Persons who are included in the trial as a result of consent from next-of-kin and who are later capable of giving consent, shall be provided with information about the trial pursuant to the guidelines in Section 2-2, and then give an informed consent statement if they wish to take part in the trial.

Defined as kin in the Patients' Rights Act are persons who: persons whom the patient states to be kin and next-of-kin. If the patient is not capable of indicating kin, the next-of-kin shall be the person who has had the most regular and constant contact with the patient.

However, in principle the following order shall apply: spouse, registered partner, person who cohabits in a marriage-like or partnership-like manner with the patient, children over the age of 18, parent or others with parental responsibility, siblings aged over 18, grandparents,

other members of the family who are close to the patient, patient's guardian or conservator. In the case of mandatory observation or mandatory psychiatric care, the person who has had the most regular and constant contact with the patient has the same rights as the next-of-kin pursuant to the Mental Health Care Act and law in Norway, unless special circumstances dictate otherwise.

It will be possible to apply to the Ethics Committee for permission to conduct a clinical trial when it is neither possible nor advisable to obtain consent.

The objective of the regulation is not to preclude clinical trials on patients in acute situations (e.g. unconscious patients). It should be possible to conduct clinical trials without consent if the following criteria are met:

- The patient is in a life-threatening condition.
- It is not possible to obtain consent
- There is no time to obtain representative consent
- There is no known therapy that is better or has a greater probability of saving the patient's life

Nor is it the intention of the regulation to preclude placebo-controlled clinical trials when the risk must be weighed up against the benefit to the individual trial subject.

Chapter 3 – The Ethics Committee

Section 3-1. Application to the Ethics Committee for approval of a clinical trial

See the [Ethics Committee's website](#) for further information.

Please see also the Commission's guidelines on "[Detailed guidance on the application format and documentation to be submitted in an application for an Ethics Committee opinion on the clinical trial on medicinal products for human use](#)" for submitting an application to the Ethics Committee.

Chapter 4 – The Norwegian Medicines Agency

Section 4-1 Request to initiate a clinical trial

A request for authorisation to conduct a clinical trial shall meet requirements issued by the Commission and applying to all EU/EEA countries. The application form (EudraCT form) to NoMA is the same one that is used for the rest of the EU/EEA area, and can be downloaded from the Norwegian Medicines Agency's website, from the Commission or from the EMEA's website (<http://www.emea.europa.eu/>), and can be completed in Norwegian or English. The application form to be sent to NoMA must bear a unique number, the EudraCT number, which can be obtained from the EudraCT public website or from the Norwegian Medicines Agency's website. The number is obtained through a two-step process. First, a security code is applied for by going onto EMEA's website (<http://www.emea.europa.eu/>), and supplying name and e-mail address. The security code, identification of the trial (Trial title and protocol

number) identification of sponsor and a description of the trial product are requirements for being given a EudraCT number. The EudraCT number is sent by e-mail. A copy of the e-mail with the EudraCT number must be attached to the application. The data concerning the clinical trial that must be available are specified in the Commission's guidelines on the European database "[Detailed guidance on the European clinical trials database](#)". The EudraCT number must be used in all correspondence concerning the trial in question. An application form must be sent electronically in xml-format, full version (on CD ROM or a USB memory chip) to NoMA

Since 1 October 2008, NoMA has had fully electronic case processing and archiving of clinical trials material. This means that most of the correspondence between NoMA and external contacts is electronic. When an electronic communication is sent to us, **we do not want a paper version in addition.**

To avoid delays in case processing, electronic correspondence must fulfil our format requirements. The following file formats are standardised in the EU and/or the Norwegian National Archives and are therefore to be preferred for submitting material to us:

- Pure text (UTF-8 or ISO 8859)
- TIFF
- PDF/A (ISO 19005)
- XML
- All formats used in Windows software (get converted here)

The files can be sent on CD or a USB memory stick with a cover letter that briefly indicates what the submission is about (the cover letter to the documentation itself should only be sent electronically). We do not accept diskettes. The files may be either zipped or divided up into folders organised by content. We request that the files be given names that unambiguously describe the contents – for example "Protocol", "Investigator's brochure", "IMPDP" etc. The EudraCT form should be sent in scanned with signature.

Files may also be sent by e-mail to post@legemiddelverket.no.

There is a charge of NOK 10 0000 for requests for authorisation to conduct clinical trials. Trials with non-commercial (investigator-initiated) sponsors are free of charge.

Cover letter:

In cases where sponsor has information about earlier trials conducted on the IMP, NoMA requests that this be stated in the cover letter.

Documents that must be submitted:

- Protocol
- Patient information with informed consent form
- Documentation of the IMP (see below)
- Copy of the notification to the Regional Committee for Medical Research Ethics
- Copy of the Regional Committee for Medical Research Ethics' assessment of the trial if it is available.

- Copy of the insurance certificates of the trial subjects. Only insurance with the Drug Liability Association is valid.
- Labelling of the product package(s) – copy of label, or detailed description of the actual inscription on the individual package. See Section 4-4 of the guidelines.
- Curriculum Vitae (CV) for national coordinating investigator and for the principal investigator at each centre. As well as being a doctor or dentist it is required that the investigator also be qualified in terms of practice and experience in the discipline in question. As documentation, NoMA requests that the principal investigator at each centre send an updated (not more than 2 years old) dated and signed CV for each trial. The CV shall be sent to NoMA for their information.

The protocol: The requirements regarding the contents of the protocol are listed briefly and can be used as a list for those writing protocols. The requirements are harmonised with, but not restricted to, [CPMP/ICH/135/95, "Note for Guidance on Good Clinical Practice"](#). In accordance with the ICG-GCP guidelines, the protocol shall contain a description of the following:

- general administrative information (protocol code, date and protocol version)
- background information (including description of the product, summary of preclinical and clinical findings which may have a bearing on the trial in question, rationale for choice of dose and treatment programme, confirmation that the trial will be in accordance with GCP)
- the purpose of the trial
- procedures for monitoring compliance
- trial design/type (with end-points, description of any randomisation and blinding, description of the treatment and the trial visits, duration, how long the patient is expected to be in the trial, criteria for when a patient must be withdrawn from the trial, how the drug accountability records are to be kept, maintenance of randomisation and any procedures for breaking the randomisation code, identification of data that are to be registered directly in CRF and which will be regarded as source data)
- inclusion and exclusion criteria
- assessment of efficacy
- assessment of safety, compiling of adverse events, both side effects and events that cannot with certainty be said to be related to the trial product
- choice of method and statistical reasons for the number of trial subjects and assessment of results
- how direct access to source data/documentation is to be protected
- how to ensure that the quality of data and procedures is assured
- ethical considerations
- data processing and archiving – how the results are to be processed after the trial has been concluded
- reporting of suspected unexpected serious adverse reactions (SUSARs) to the authorities

Supplementary information: In accordance with the GCP guidelines, [Chapter 6](#), the following points are not required to be included in the protocol. If this information is not in the protocol, it should be described in other documents or in the cover letter:

- How the trial is to be financed
- Plan for publication of results (publication plan).
- Plan for termination of earlier treatment, if relevant. NoMA also requests a plan for termination of previous treatment, where relevant, with emphasis on safety and ethical aspects.
- Follow-up of subjects after the trial. NoMA requests a plan for follow-up of the patients after the trial, with emphasis on the safety and ethical aspects. It should be specified who is responsible for follow-up of the patient after the trial has been concluded, and how long the patient is to be followed up.
- Plan for information to personnel concerned. NoMA requests information on how, for example, trial nurses and others who will be involved in the trial will receive adequate information about the trial and the guidelines that are to apply to handling of the IMP.
- Preparedness in the event of complications. If it is not described in the protocol, a description should be provided of the plan for the eventuality that something serious should happen to the patient in the course of the trial.
- Plan for handling medicinal products
- Account of how a separate list of subjects and a trial subject form are going to be kept for each trial subject in the study. NoMA does not wish to be sent a trial subject case report form (CRF), but merely to receive confirmation that this form will be used. The data that are to be recorded must be indicated in the protocol
- For medicinal products that are under development: In order to facilitate assessment, it is important that it be made clear where in the overall development plan the trial belongs. The manufacturer will often have trials running in a number of countries. It may be difficult for the national authorities to adopt a position on whether the trial in question is relevant if the overall development plan for the product is not known.

Documentation - general

As a general rule, the rules applying are those set out in Eudralex, Volume 10 in ["Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial"](#) Attachment 1 to the document provides an overview of what must be sent in to the pharmaceuticals authorities.

As a general rule simplified documentation (simplified IMPD) of the product can be sent in if the IMPD has been assessed earlier as part of an application for a marketing authorisation in an EU/EEA country or has been assessed in connection with a clinical trial in Norway. See Table 1 in ["Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial"](#)

Guideline requirements for documentation of the various parts are as follows, and for practical reasons NoMA requests that the different parts of the documentation be submitted separately:

Documentation of the quality of the IMP

A general reference is made to NoMA's guidelines "Requirements regarding pharmaceutical and chemical documentation for medicinal products for clinical trials" and "[Guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials](#)" (CHMP/QWP/185401/2004 final).

If sponsor has not prepared a separate dossier with a summary for the trial substance (as described in Section 4.1.6 in "Detailed guidance..." above), the summary can be made using NoMA's template "Summary of pharmaceutical and chemical documentation".

Preclinical documentation for the IMPs

Documentation shall be submitted if no similar studies have been conducted on the product in Norway previously (with respect to stage in trial plans, dosage, duration and patient group) or a request for marketing authorisation of the product has not been submitted to NoMA. The documentation shall be in accordance with the [Guidelines to the Maintenance of the ICH Guideline on Non-Clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals](#)

Clinical documentation of the IMPs

Documentation shall be submitted of clinical experience of the medicinal product. This information can be compiled in the IMPD, or in the investigator's brochure. If there is marketing authorisation for the trial substance in Norway and it is to be used as described in the SmPC, reference can be made to this. If the trial is to be conducted on a substance that has not been approved in Norway, but in another EEA country, this SmPC can be appended. It should be translated into English or Norwegian if English is not the original language of the SmPC in question.

The trial protocol is also regarded as part of the clinical documentation for the trial.

In clinical trials it is sponsor or sponsor's authorised representative who has the overall responsibility for the application to NoMA and signing of the application form. NoMA makes an assessment only when a valid application is at hand.

When the first patient in Norway has signed the informed consent statement, NoMA shall be informed. NoMA requests that this information be submitted within about 14 days.

Section 4-2. Time periods for considering a valid request for authorisation

NoMA will initially review the submitted documentation to ensure that the request is valid (validation phase). This is an administrative check that all documents specified on the request form have been submitted. If any documents have been omitted, the reasons for this shall be specified separately. This review is estimated to take 3-5 days after the request has been received by NoMA. If there is anything missing, NoMA will inform the sponsor of what is missing. When the request is valid, sponsor will be informed that the assessment is beginning, i.e. that the clock is starting to tick in relation to the time limits. If sponsor fails to submit supplementary documentation, the request is regarded as denied.

When a request is regarded as valid, the assessment is normally estimated to take place in the course of 30-35 days, during which time any deficiencies/weakness in the application will

be identified. NoMA gives written notice of any reason that the trial cannot start and gives sponsor the opportunity to supplement the application once, with a time limit of 15 days for a response. The reason given for this time limit is that NoMA cannot “stop the clock” and in order that a final assessment can be given within a maximum of 60 days. NoMA can give an extended deadline in exceptional cases if there are special reasons for doing so. If sponsor cannot supplement the application, the documentation submitted does not answer our questions satisfactorily or the documentation is not in the hands of NoMA within the specified time limit, the request may be denied.

Section 4-3. The Norwegian Medicines Agency’s decision

NoMA considers fundamental questions concerning the pharmaceutical/chemical, preclinical and clinical documentation for the trial substance(s). In addition the trial programme’s scientific value and patient information are assessed.

The fourth paragraph, litra a) covers medicinal products developed by means of one of the following biotechnological processes:

- recombinant DNA technology
- controlled expression of genes as codes for biologically active proteins in prokaryotes and eukaryotes, including transformed mammalian cells
- hybridoma technology and methods based on monoclonal antibodies

The trial start can be denied for reasons of patient safety. The trial start can also be denied when it has not been planned in compliance with currently applicable provisions. By currently applicable provisions is meant first and foremost this regulation with appurtenant guidelines, in particular current ICH/GCP guidelines, and guidelines associated with Directive 2001/20/EC and any guidelines to Directive 2005/28/EC. NoMA can also refuse to allow the trial to commence if NoMA finds it necessary for other special reasons. Special reasons may, for example, be that NoMA disagrees with the design, age of the trial subjects, criteria for participation, choice of control substance, inadequate preclinical documentation or inadequate documentation about the quality of the IMP.

Section 4-4 Labelling of the IMP

It is stressed that also substances with marketing authorisation that are involved in trials shall be labelled in accordance with the rules (cf. therapeutic tests, comparative tests in which marketed substances are involved etc.). The labelling rule is important because it will be apparent from the label that the trial subject/patient is taking part in a clinical trial, for example when they bring medicines with them on admission to hospital, in connection with dispensing of reimbursable medicines, etc. The labelling rule for marketed substances can be complied with by the prescribing doctor writing what is not already on the packaging on the prescription.

In principle, the labelling on the external and the internal packaging shall be identical. The label shall in principle be in Norwegian and be in compliance with ["Annex 13 of the EC Guide to Good Manufacturing Practice", July 2003, Chapters 26-33.](#)

The label shall in principle contain the information given below. Exceptions from the rules can be made pursuant to ["Annex 13 of the EC Guide to Good Manufacturing Practice", July 2003, Chapters 26-33](#)

- a) name, address and telephone number of sponsor, CRO or investigator (main contact for information on the product, the trial and emergency unblinding)
- b) pharmaceutical dosage form, route of administration, dosage, and for open trials the name/identifier and strength/potency of the product shall also be given.
- c) batch number and/or code number, to identify contents and packaging operation,
- d) a trial reference code allowing identification of the trial, trial site, investigator and sponsor if not given elsewhere
- e) subjects' identification number/treatment number,
- f) name of principal investigator if not included in a) or d)
- g) directions for use (if necessary, reference may be made to a leaflet or other explanatory document intended for the trial subject or other user),
- h) "For clinical trial use only"
- i) storage conditions
- j) expiry date ("use by date"/"expiry date") (month/year)
- k) "Keep out of the reach of children", except when the product is for use in trials where the product is not taken home by the subject

If the products are handled exclusively by health personnel, an exception from the requirement of Norwegian labelling can be applied for. In the case of a reasoned request NoMA will also be able to accept that the following information, for example, is on the patient card instead of on the label:

- telephone number of sponsor, CRO or investigator (main contact for information about the product, the trial and unblinding)
- dosage, if this is space-consuming

Section 4-5 Dispensing of medicinal products

It is assumed that the IMPs are stored, distributed, handled and destroyed in accordance with the GCP guidelines and Annex 13 to the GMP guidelines.

Chapter 5 – Rules during the trial

Section 5-1. Protocol amendments

Sponsor may make changes in the clinical trial. Changes may for example be made in the protocol, the investigator's brochure, the patient information, or the documentation of the IMP (IMPD =Investigational Medicinal Product Dossier). The changes may be divided into **substantial and non-substantial amendments**. It is sponsor's responsibility to determine whether an amendment is to be regarded as substantial or non-substantial.

There is a charge of NOK 5000 for substantial amendments. There is no charge for non-commercial sponsors (investigator-initiated). Non-substantial amendments are free of cost for both commercial and non-commercial sponsors.

There is a table on the website of the Norwegian Medicines Agency of what is required to be sent for approval and what is required to be sent for information purposes:

<http://www.legemiddelverket.no/upload/26154/Skjema%20for%20amendments%20juli2009.pdf>

Substantial amendments

By substantial amendments is meant changes which will probably have a major effect on:

- the safety or physical/mental integrity of the trial subjects
- the scientific value of the trial
- the execution and handling of the trial or
- The quality and safety of the IMP (see below)

All substantial amendments shall be submitted to NoMA on the standard application form that is to be found in Eudralex, Volume 10 in "[Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial](#)", **Annex 2, Substantial Amendment Form.**

If the substantial amendment entails changes in the original EudraCT form, an updated EudraCT form shall be submitted in addition to the amendment form.

Along with the application form, NoMA requires a cover letter that describes clearly what the amendment concerns and the reason for the amendment(s).

More information about substantial amendments and requirements concerning the documentation to be appended is given in "[Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial](#)" EudraLex Volume 10.

If NoMA has presented reasoned objections to an application to make an amendment, sponsor shall take account of the objections and adapt the proposed amendment in the light of these comments or refrain from making the amendment.

Substantial amendments to the pharmaceutical documentation

The actual documentation shall be submitted with the request form. Information about changes in the quality of the IMP and whether these changes are to be regarded as substantial or not is to be found at the end of "[Guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials](#)" (CHMP/QWP/185401/2004 final).

Substantial amendments to the preclinical pharmacological/toxicological documentation

New preclinical/toxicological tests must be sent for approval. We request that a summary of the documentation be submitted. It must be clear what the amendment concerns.

Substantial amendments to the clinical documentation

We request that a summary of the documentation be submitted. It must be clear what the amendment concerns. When there are substantial amendments to the protocol, an updated

protocol or protocol supplement shall be submitted. It must be clear what the amendment concerns.

Amendments to investigator's brochure (IB)

Updated information in the IB which can change the initial risk-benefit assessment of the trial or the safety profile of the IMP shall be sent to NoMA for assessment. Other amendments shall be sent to NoMA for information purposes. In both cases there shall be a summary of the changes in the cover letter, and it is recommended that old and new text be marked.

Non-substantial amendments

Documentation of non-substantial amendments shall be kept by sponsor and included in the next update of the investigator's brochure, protocol or documentation in question. Amendments shall be kept in the sponsor's trial documentation and be available in the event of an inspection.

Information about amendments that only require the approval of the Ethics Committee may be sent to NoMA for information purposes in connection with the next submission of a substantial amendment.

Amendments to patient information

If new information emerges during or after the trial, for example information about new side effect findings, patients must be informed of these, preferably in writing in the form of revised patient information with informed consent, or as a supplement to existing patient information. The supplement shall also contain an informed consent form. Amendments concerning new safety information are to be regarded as a substantial amendment and shall be submitted for approval. NoMA requests that the changes be marked clearly in the revised document. Other changes are regarded as non-substantial amendments and can be sent to NoMA for information purposes when a request to make a substantial amendment is submitted.

Trials that are not initiated

NoMA requests that notification be sent as soon as it is clear that the trial is not going to be initiated, or as soon as the decision to halt the trial is taken. The standard form for declaration of the end of the trial shall be used for this (cf. Annex 3 of [Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial](#))

Chapter 6 – Supervision and inspection

Section 6-1. Supervisory authority

NoMA will exercise supervision to verify compliance with the provisions of this regulation. In addition to this, NoMA may conduct inspections of biobank activities associated with clinical trials of medicinal products.

NoMA requests to be informed of cases where foreign supervisory authorities are going to conduct GCP inspections of sponsor and/or investigator in Norway.

Section 6-2. Inspection

Notification of GCP inspections will be sent to the parties that are to be inspected. After the inspection is over, NoMA will write an inspection report.

Chapter 7 – duty to report adverse events and reactions

Section 7-3. Sponsor’s duty to report unexpected serious adverse reactions

Suspected unexpected serious adverse reactions (SUSAR) that occur during trials on patients in Norway shall be reported in the form of individual reports (reports for individual patients) to NoMA. In the event of adverse events that are serious, fatal or life-threatening, and unexpected, where the causal relationship has not yet been determined, NoMA requests that a report be submitted in accordance with the time limits described in the regulation. Causal relationships shall be determined and an updated report submitted to NoMA as soon as it is available. As a general rule the reports shall be unblinded. (cf. [CPMP/ICH/377/95 Topic E2A](#)).

The time limits in Section 7-3 apply from the day on which sponsor learns of the event. Individual reports on SUSARs that have occurred in Norway shall be sent electronically to EMEA’s EudraVigilance database and to NoMA. NoMA requests that these adverse event reports be sent electronically in an E2B-compatible format. The requirements regarding time limits and the content of the reports will not be changed as a result of this request, but we request that the language used be English, since the reports shall now be available to all the pharmaceuticals authorities in Europe.

SUSARs are no longer required to be reported to the Ethics Committee. The committees find it sufficient that SUSARs be reported to NoMA.

Duty to report on trials in Norway

We request that individual reports on SUSARs that have occurred in Norway be sent electronically to EMEA’s EudraVigilance Clinical Trial Module (EVCTM) and to NoMA (NOMACT profile). Identical reports shall be sent to both places, and NoMA will not forward the reports it receives to EVCTM.

Events outside Norway

NoMA does not wish to receive SUSARs that have occurred in other countries in connection with the same trial or with the same IMP as individual electronic reports. The duty to report will be complied with in that they will be reported to EVCTM, where NoMA will have access to them. The list with an overview of all SUSARs that have occurred with the same IMP in all countries shall be sent to NoMA every six months.

For non-commercial trials

NoMA understands that non-commercial sponsors (i.e. for trials that are not carried out with the sponsorship of a pharmaceuticals company) may have difficulty in meeting the

requirement relating to electronic reporting of SUSARs. If products with marketing authorisation are used in these trials, we recommend that a dialogue be broached with the company that has the marketing authorisation as to whether this company can help with electronic reporting. It may also be possible for the larger institutions/health trusts to establish separate units that can be responsible for this reporting for all trials at the institution/health trust. If these proposals for a solution are not possible, NoMA can help to find a solution. In the event, contact the Section for Clinical Trials:

klut@legemiddelverket.no.

Sponsor shall inform all investigators of the IMP in question of suspected adverse reactions that are serious and unexpected. For more detailed information on this subject, please see Eudralex, Volume 10, "[Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use](#)" and "[Detailed guidance on the European database of Suspected Unexpected Serious Adverse Reactions](#)".

Section 7-4 Annual report

For trials that are in progress for more than 1 year (1 year between first patient in and last patient out), an annual report shall be submitted to NoMA on a special form drawn up by NoMA. The form can be downloaded from NoMA's website. The report shall be submitted annually once the trial has been approved by the Ethics Committee and NoMA. The annual report shall be submitted as long as the trial is in progress in Norway, i.e. until the last patient in Norway leaves the trial. The national coordinating investigator is no longer required to sign the form.

Chapter 8 – Documentation (Master File) and final report

Section 8-1. Final report

Sponsor shall notify NoMA within 90 days of the trial ending (last follow-up visit of last patient) at the last centre (internationally). The standard form for declaration of end of trial shall be used to report that the trial is finished (cf. Annex 3 of [Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial](#))

The final report that is to be submitted within one year at the latest of the conclusion of the trial in all participating countries shall be in compliance with the guidelines in [CPMP/ICH/137/95 Topic E3](#) as regards structure and contents.

In addition NoMA requests notification that the trial has been concluded in Norway.

The absolute requirement for notification is 90 days after the trial has ended in all countries. We are flexible with respect to when notification is sent in as to when the trial ended in Norway. If these dates coincide, it can be sent in at the same time.

Section 8-2. Sponsor's and investigator's storage of documentation

All equipment that is used in the trial shall be available as long as the trial is in progress at the individual centre. If the equipment is replaced during the course of the trial, the old equipment shall be retained and be available in the event of a GCP inspection or audit, as far as possible. If the equipment is jettisoned, information about when the equipment was in use and calibration/validation documentation shall be kept. The trial is regarded as ended at the individual centre when the last patient is finished with the last trial visit.

There is no requirement that source data be stored at the trial site, but it must be possible to produce source data in the event of an audit or GCP inspection.