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Deliverable 2
Clinical Research in Europe: interaction with ethics committees before, during and after a clinical trial.

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1 Abbreviations

AEMPS  Spanish Agency for Medicines and Medical Devices
AIFA  Agenzia Italiana del Farmaco (Italian National Drug Agency)
AMG  Arzneimittelgesetz (German Federal Drug Act)
AFSSAPS  Agence française de Securité Sanitaire des Produits de Santé (french competent authority)
ATU  Temporary Authorisation for Use
CA  Competent authority
CEIC  Clinical Research Ethics Committees
CRC  Clinical Research Centre
CTU  Clinical Trial Unit
CIC  Centre d’Investigation Clinique (Clinical Investigation Centre)
CNIL  Commission Nationale de l’Informatique et des Libertés
CCTIRS  Comité Consultatif sur le Traitement de l’Information en Matière de Recherche dans le Domaine de la Santé
CPP  Comité de Protection des Personnes (french research ethics committe)
CTA  Clinical Trial Authorisation
CTAA  Clinical trial authorisation application
DMA  Danish Medicine Agency
DGS  Direction Générale de la Santé (french General Direction of Heath)
DIMDI  Medical Documentation and Information
DK  Denmark
EC  Ethics committee
ECRIN  European Clinical Research Infrastructures Network
ECRIN-PPI  European Clinical Research Infrastructures Network and Biotherapy Facilities: preparation phase for the infrastructure
ECRIN-RKP  European Clinical Research Infrastructure Network – Reciprocal Knowledge
ECRIN-TWG  European Clinical Research Infrastructures Network- Transnational Working Groups
EMEA  European Medicines Agency
EU  European Union
EFCGP  European Forum for Good Clinical Practice
FP  Framework Programme
FR  France
GMP  Good Manufacturing Practice
GTAC  Gene Therapy Advisory Committee
Ger  Germany
GCP  Good Clinical Practice
HU  Hungary
IMP  Investigational Medicinal Product
IR  Ireland
ISS  Instituto Superiore della Sanita
It  Italy
KKS  Koordinierungszentrum für Klinische Studien (German national network)
MPA  Swedish Medical Products Agency
MS  Member State
NHS  National Health System
PEI  Paul- Ehrlich-Institute (German competent authority)
PI  Principal Investigator
PIAG  Patient Information Advisory Group
QA  Quality Assurance
QM  Quality Management
REC  Research Ethics committee
SOP  Standard Operating Procedure
SUSAR  Suspected Unexpected Serious Adverse Reaction
Sp  Spain
Sw  Sweden
2 Table of content

1 Abbreviations 3
2 Definitions 5
3 Introduction 8
4 Objectives 9
5 Methodology 9
5.1 ECRIN WP1 collaboration with ECRIN WP2 9
5.2 ECRIN WP1 methodology 10
6 Interaction with ethics committees for the conduct of a multinational clinical trial on medicinal products 11
6.1 Models of research ethics committees’ organisation system 11
6.1.1 Common models 11
6.1.2 Country specific models 12
6.2 Clinical Trial Submissions to ethics committees for approval 14
6.2.1 Common Regulatory Framework 15
6.2.2 Country specificities in relation to the clinical trials directive 16
6.2 Amendment Submissions to ethics committees 17
6.2.1 Common Regulatory Framework 17
6.2.2 Country specific elements 17
6.3 Notification of the end of trial to ethics committees 19
6.3.1 Common Regulatory Framework 19
6.3.2 Country specific elements 19
7 CONCLUSIONS 20
8 APPENDICES
8.1 Procedure chart on “Multinational clinical trials on medicinal products. Submission to an ethic committee. Common framework.” 22
8.2 Procedure chart on “Multinational clinical trials on medicinal products. Amendments and deviations application to an ethic committee. Common framework” 22
8.3 Procedure chart on “End of a multinational clinical trials on medicinal products. Notifications to an ethic committee“. Common framework” 22
8.4 Instructions per country: Practical aspects of interacting with authorities (ethics committee and competent authority) throughout the conduct of a multinational clinical trial on medicinal products. 26
2 Definitions

CA: Competent authority
Bodies having the power to regulate. In the ICH GCP guideline the expression Regulatory Authorities includes the authorities that review submitted clinical data and those that conduct inspections. These bodies are sometimes referred to as competent authorities. (ICH Harmonised Tripartite Guideline: Guideline For Good Clinical Practice E6).

Multicentre CT: Multicentre clinical trial
A clinical trial conducted according to a single protocol but at more than one site, and therefore by more than one investigator, in which the trial sites may be located in a single Member State, in a number of Member States and/or in Member States and third countries. (Directive 2001/20/EC)

CTA: Clinical trial authorisation
An authorisation of a clinical trial by the competent authority of a Member State will be a Clinical Trial Authorisation (CTA) and will only be valid for a clinical trial conducted in that EU Member State. This authorisation does not imply approval of the development programme of the tested IMP. (EU 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)

CTAA: Clinical trial authorisation application (often shortened to CTA)
According to Article 9(2) of the Directive the applicant must submit a valid request for authorisation to the competent authority. (EU 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)

EC: Ethics committee
An independent body in a Member State, consisting of healthcare professionals and nonmedical members, whose responsibility it is to protect the rights, safety and wellbeing of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, expressing an opinion on the trial protocol, the suitability of the investigators and the adequacy of facilities, and on the methods and documents to be used to inform trial subjects and obtain their informed consent. (Directive 2001/20/EC)

ECRIN: European Clinical Research Infrastructures Network
Based on the interconnection of national networks of academic clinical research infrastructures, the European Clinical Research Infrastructures Network (ECRIN) is designed to bridge the fragmented organisation of European clinical research and to develop an integrated EU-wide clinical research infrastructure.

EudraCT: Clinical trial data base for the Regulatory Authorities in EU

GMO: Genetically modified organism
Means an organism, with the exception of human beings, in which the genetic material has been altered in a way that does not occur naturally by mating
and/or natural recombination; (Directive on the Deliberate Release into the Environment of Genetically Modified Organisms 2001/18/EG).

**IMP**: Investigational medicinal product
A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorisation but used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form. (Directive 2001/20/EC)

However, as the transposition of this definition differs from one country to other, ECRIN SOPs use the term “Medicinal Product”. Please see the document "Deliverable 4: Clinical Research in Europe: national differences in legislative and regulatory framework” for further information.

**Informed Consent**
Decision, which must be written, dated and signed, to take part in a clinical trial, taken freely after being duly informed of its nature, significance, implications and risks and appropriately documented, by any person capable of giving consent or, where the person is not capable of giving consent, by his or her legal representative; if the person concerned is unable to write, oral consent in the presence of at least one witness may be given in exceptional cases, as provided for in national legislation. (Directive 2001/20/EC)

**Investigator**: a doctor or a person following a profession agreed in the Member State for investigations because of the scientific background and the experience in patient care it requires. The investigator is responsible for the conduct of a clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the leader responsible for the team and may be called the principal investigator. (Directive 2001/20/EC)

**MS**: Member State
Country involved in ECRIN.

**SOP**: Standard operating procedure
Detailed, written instructions to achieve uniformity of the performance of a specific function. (ICH Harmonised Tripartite Guideline: Guideline For Good Clinical Practice E6).

**Sponsor**: An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial. (Directive 2001/20/EC)

**Sponsor-Investigator**: An individual who both initiates and conducts, alone or with others, a clinical trial, and under whose immediate direction the investigational product is administered to, dispensed to, or used by a subject. The term does not include any person other than an individual (e.g., it does not include a corporation or an agency). The obligations of a sponsor-investigator include both those of a sponsor and those of an investigator. (ICH Harmonised Tripartite Guideline: Guideline For Good Clinical Practice E6).

**Subinvestigator**: Any individual member of the clinical trial team designated and supervised by the investigator at a trial site to perform critical trial-related procedures and/or to make important trial-related decisions (e.g., associates,
residents, research fellows). See also Investigator. (*ICH Harmonised Tripartite Guideline: Guideline For Good Clinical Practice E6*)

**Subject:** an individual who participates in a clinical trial as either a recipient of the investigational medicinal product or a control (*Directive 2001/20/EC*)
Within ECRIN framework, the term *participant* seems more adequate because it includes both patients (clinical trial subjects) and healthy volunteers.
3 Introduction

As a consequence of the unethical practices used and the low consideration of the participants’ rights in some of the first experiments in men, the interest for ethical issues of clinical research has significantly increased during the last decades raising the need of documents which guide throughout the investigation with humans. Those documents (The Nuremberg Code, the Belmont Report, the Declaration of Helsinki and the Oviedo Convention) are based in ethical values and human rights. The Nuremberg Code is the first written documents in which the right of the participants to freely consent to participate in a clinical trial is clearly recognised.

Afterwards, the importance of an independent evaluation and the need of harmonisation increased worldwide. The International Conference of Harmonisation issued the “Good Clinical Practices”, a set of rules which helped in harmonising practices in clinical research. However there was still lack of a European legislation to regulate the processes required by the ethics committees and competent authorities in order to perform a clinical trial.

In 2004, the 2001/20/EC Directive on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use came into force. To comply with this Directive, the sponsor is obliged to obtaining a favourable opinion of an ethical committee to start a clinical trial.

From a clinical research point of view, one of the main limitations of the 2001/20/EC Directive is that it only covers clinical trials with medicinal products. Moreover, transposition of the 2001/20/EC Directive to national laws varies from one country to another.

At present, 4 years after that, it is interesting to see how the different ECRIN Member States—Austria, Denmark, France, Germany, Hungary, Ireland, Italy, Spain, Sweden, UK—have chosen to implement the directive with regards to interacting with ethics committees, being the multicentre clinical trials the main concern.

We think that this has resulted in a mosaic of different ways of structuring the ethics committees. However, similarities may be drawn among them and two models of research ethics committee’s organisation system may be shaped and co-exist in Europe.

On one hand, there are countries like Austria, Denmark, France, Hungary, Ireland and Sweden, where a regional research ethics committee evaluates the protocol and gives its opinion. Some of them (Denmark and Sweden), moreover, have a national ethics committee which only gets involved if the regional can not come to a decision or if the investigator wants to appeal it.

And on the other hand, there are countries like Germany, Italy, Spain and UK which combine regional and local research ethics committees that share the same calendar and processes for the clinical trial ethics evaluation and make the decision collectively.
Implementation of the single opinion procedure has increased the overall process complexity for those countries which combine regional and local system, leading to longer procedures and some difficulties when a negative opinion is to be appealed.

This deliverable seeks to identify legislative and regulatory common framework as well as discrepancies in order to obtain the knowledge and tools to better conduct European-wide multi-national clinical research.

4 Objectives

• To identify a common regulatory framework regarding the interaction between the sponsor and the ethics committees during the conduct of clinical research.

• To describe the specific country procedures when varying from the common framework.

• To describe procedures for interaction with ethics committees in transnational studies.

5 Methodology

5.1 ECRIN WP1 collaboration with ECRIN WP2

The task of European Clinical Research Infrastructures Network (ECRIN) Working Package 2 is to describe the regulatory framework and how to interact with competent authorities in the different ECRIN countries. Thus, a survey in all ECRIN countries in order to collect relevant information on national regulation, rules, and, requirements for the different categories of clinical research was conducted.

ECRIN Working Package 1 helped to collect those data regarding ethics committees’ requirements, rules and national legislation/guidelines. The survey results showed that although many main areas of homogeneity were identified, some others varied substantially. The following list describes the main areas of heterogeneity:

• Although definitions for interventional and observational studies are on Directive 2001/20/CE, the consideration of interventional or observational studies varies from one country to another. Research ethics committee approval is not required for observational studies in some countries (i.e., France and Spain);

• National requirements regarding competent authority, sponsor, insurance, adverse event reporting are highly variable for interventional clinical research other than clinical trials on medicinal products. Insurance requirements and insurance systems covering participants in investigator-initiated clinical research are highly variable, with additional differences between public or private insurance for clinical research;

• Waiver of purchase cost of the investigational medicinal product for a non-commercial trial;

• Obligation to inform participants about the outcome of a clinical trial.
Therefore, it was agreed that ECRIN WP1 objectives (identification of a common framework, country specific divergences and bottlenecks for the interaction with ethics committees) should focus on clinical trials on medicinal products in a first step, as they represent the most homogeneous area. Afterwards, other clinical research areas will be assessed.

5.2 ECRIN WP1 methodology

The process of interaction with ethics committees when performing a multinational clinical trial on medicinal products was divided in three chronological periods (before, during and after the running of a clinical trial) as requirements, documentation and time periods differ substantially.

Interaction with ethics committees before the conduct of a multinational clinical trial on medicinal products processes are related to all the procedures which should be performed when submitting the initial clinical trial application to the ethics committees.

Interaction with ethics committees during the conduct of a multinational clinical trial on medicinal products processes are related to all the procedures which should be performed while the clinical trial is ongoing.

Such procedures include the submission of amendments of the initial clinical trial application to the ethics committees, any relevant safety event (in particular, SUSARs and annual safety reports), suspensions and infringements of a clinical trial. However, this document does not cover the interaction with EC regarding the SUSARs reporting, safety reports and other safety issues as this information is kept in the Deliverable 6.

Interaction with ethics committees after the conduct of a multinational clinical trial on medicinal products processes are related to all the procedures which should be performed when finalising the clinical trial.

For each period (before, during and after clinical trial), the different Member States were asked to represent graphically their national process in a flow chart. These flow charts were chosen as the ideal tool to get the relevant information in each country (WP1 survey). Flow charts are the best method to visualise and to get an overview of the sequential steps that comprise each national process when interacting with the ethics committees. This tool facilitates the detection of main discrepancies between the Member States and to establish a common regulatory framework as well. The information was extended upon and verified through teleconferences, meetings, and correspondence.

Moreover, and apart from the results obtained in the WP2 survey, other areas of heterogeneity could be explored:

- To deliniate competences between the main (concerned, reference, regional,...) and local ethics committees,
- To describe what is the role in the daily practice of the main ethics committees in the monitoring of the approved clinical trial (follow-up, amendments and final report),

Overall requirements, documentation and time periods regarding the common regulatory process of interaction with ethics committees when performing a
multinational clinical trial on medicinal products are described hereinafter. Moreover, diversities found between countries are detailed as well.

6 Interaction with ethics committees for the conduct of a multinational clinical trial on medicinal products

6.1 Models of research ethics committees’ organisation system

6.1.1 Common models
Although one of the key objectives of the clinical trials directive is to centralise the ethics committees’ decision through the single opinion process, the results of this survey show that the ‘single opinion’ process is understood differently in ECRIN countries. Most of the differences are probably due to the historical practice in each country or the previous and current political and legal situation.

Even so, among all ECRIN countries, there are similarities that could be gathered in two groups depending on how the ‘single opinion’ process is understood. This led to two models of research ethics committee’s organisation system:

1. In Austria, Denmark, France, Hungary, Ireland and Sweden, the ‘single opinion’ is considered to be the decision made by a single ethics committee for unicentre and multicentre clinical trials (i.e. it is not a collective decision). The deciding ethics committee informs the other committees according to the other trial sites involved about its decision, if applicable (i.e., France has one EC for all the trial sites).
In Denmark and Sweden the regional ethics committee to which the clinical trial application is made assesses the suitability of the investigators using the CVs, but they do not assess the suitability of the sites. However, in Austria, Ireland and Hungary local ethics committees assess the suitability of the investigators and the sites.

2. In Germany, Italy, Spain and UK the ‘single opinion’ is considered to be the decision made by a single ethics committee in cooperation with all ethics committees, which are competent for local study sites. In Italy and UK, the opinion of the local ethics committees is limited to the suitability of the site, investigator and facilities and does not constitute an additional ethical review (cannot ask major changes to the protocol). In Germany and Spain local ethics committees are allowed to comment on the protocol as well. In Germany, the lead ethics committee is exclusively responsible for the decision of the ‘single opinion’, which it takes independently, however in Spain the lead ethics committee provides its final ‘single opinion’ after assessing the comments from all the involved committees.

Thus, a single application for ethical review is made to a single ethics committee in Denmark, France, Ireland, and Sweden. However, in Austria, Germany, Italy, Spain and UK the clinical trial authorisation application (CTAA) needs to be submitted to all ethics committees involved in the trial. However, note that in Hungary the CTAA is submitted to the competent authority and it is the competent authority who forwards the CTAA to the ethics committee.
6.1.2 Country specific models
In **Austria** there are about 40 ethics committees implemented by all nine federal states, but also by universities, hospitals etc. Composition and obligations of ethics committees are regulated in the drug act (Arzneimittelgesetz AMG §41) and for hospitals in the hospital act (Krankenanstalten- und Kuranstaltengesetz KAKuG §8).

The sponsor has to submit the CTAA for a multi-site study to a reference EC, which has to be in the area of any site of the trial. If no site is in the area of one of the reference ECs, the sponsor can choose any reference EC in Austria. However, not all regional ECs are entitled to give a "single opinion" and can thus be a reference EC. The EC must be entitled by the health ministry to act as a reference EC ("Leitethikkommission" in german). Currently only 7 ECs in Austria are called "Leitethikkommission". The reference ethics committee has to adhere to special requirements for implementation (AMG § 41b).

The sponsor has to submit the CTAA to other EC involved in the trial. However, these ECs involved only give recommendations (at least 5 days before the EC meeting) concerning the suitability of the investigator and his staff and the suitability of the site to the reference EC (if objections rise). The reference EC makes the decision and does not actively involve other ECs but informs all other regional ECs.

Optional referral to the "Arzneimittelbeirat" (independent body comprising physicians, pharmacologists, etc.) is only done by the competent authorities. The sponsor has no official direct influence on this referral. This procedure is done only if there are huge discrepancies between competent authorities and ethics committees.

In **Denmark**, there are 9 regional ethics committees and a single national ethics committee, the Danish National Committee on Biomedical Research Ethics. The coordinating (or principal) investigator submits an application for a multi-site study to the regional scientific ethical committee for the area in which he/she is operating\(^1\). This regional committee must make its decision, which forms the basis for an opinion, and then inform the other regional committees and the Danish National Committee for Biomedical Research Ethics for the investigators at the other sites involved. The regional committee assess the suitability of the investigator and does not assess the suitability of the site.

If the regional ethics committee cannot decide whether to accept the application or not, then the national ethics committee will assess the application and decide. If a clinical trial application is rejected by the regional ethics committee to which it was submitted, then the decision can be appealed at the national ethics committee by the sponsor.

**France** has been divided in seven regional areas and the clinical trial application authorisation can be submitted by the sponsor to any Comité de Protection des Personnes (CPP) in the area where the principal investigator (or coordinator in multicentre Clinical trials) is located. This CPP is responsible of the single opinion and has to evaluate among other things the adequacy between objectives of the research and means used and to evaluate the qualification of the investigators. The list of the 40 French CPPs is available with their area of competence on the French Biomedical Research website.\(^2\) Only one CPP’s approval is requested either for a single- or multi-centre study.

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The approval of the EC is no longer valid after one year without beginning the study, except if justified before the deadline.

**In Germany,** there are about 52 ethics committees. They can be at the level of chamber of physicians (Ärztekammer) (EC-ÄK) in each federal state, at the level of the medical faculty (EC-MF), or at the ministry of health in some federal states (EC-HA).

The sponsor is responsible for the submission to the ethics committee. The application to the appropriate ethics committee is made depending on the location of the coordinating (or principal) investigator. This committee must achieve an assessment in cooperation with all ECs which are competent for local study sites. These local ECs comment on the qualification of investigators and suitability of the study sites. In these regards, their opinion should be respected in all points by the “lead EC”. Local ECs are allowed to comment on the protocol as well, but the lead EC is exclusively responsible for the decision on the content of the single opinion, which it creates independently.

**In Hungary,** there is one ethics committee.

The sponsor submits the clinical trial application to the competent authority (National Institute of Pharmacy) who is responsible of the transmission to the ethics committee (Committee for Clinical Pharmacology and Ethics of the Medical Council). The answer of the ethics committee is given to the sponsor via the competent authority. Local ethics committees (regional ethical committees and Institutional ethical committee) give only advices on the feasibility of the study and have no right to rewrite the central authorisation.

**In Ireland** there are 13 recognised ethics committee that have been certified by the Department of health and children as the only ethics committees that can give a single opinion in the case of IMP trials only.

The Principal Investigator (PI) is responsible for the submission to a recognised ethics committee (in practice this is usually carried out by the sponsor). The application to the appropriate single recognised ethics committee is made as a decision of the sponsor. Each local ethics committee must sign the Site Specific Assessment Form (SSA form) in order to confirm that a) local staff are suitable qualified and b) there are sufficient resources to carry out the trial locally. In practice, however two local ethics committees also carry out an additional ethical review of the study in relation to the hospital ethos and culture.

**In Italy** there are more than 300 ethics committees instituted by hospitals, local health agencies, clinical research institutions, according to a Legislative Decree issued on November 6, 2007.

The sponsor of the research interacts with the EC of the principal or coordinating centre of the clinical trial. This EC will give the single opinion. Then EC of all participating centres will be asked to evaluate the proposal of CT. These ethics committees are entitled to approve or reject the participation of investigators of their centre, and ask for modification for the informed consent to be delivered at these centres, but cannot ask major changes to the protocol.

**In Spain** there are 136 ethics committees that have been certified by the competent authorities to give its opinion in clinical research.

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3 [http://www.zentrale-ethikkommission.de/](http://www.zentrale-ethikkommission.de/)

4 [http://oss-sper-clin.agenziafarmaco.it/normativa_ing.htm](http://oss-sper-clin.agenziafarmaco.it/normativa_ing.htm)
The sponsor is responsible for the submission to all the ethics committees involved in the trial (between the 1st to the 5th day of the month). The application to the appropriate ethics committee is usually made depending on the location of the coordinating (or principal) investigator. This EC will act as a “Concerned Ethics Committee” and will give the single opinion. The sponsor should submit the application to all local EC involved in parallel. Local ethics committees will evaluate centre-specific aspects and are allowed to comment on the protocol as well. Finally, after assessing the comments from all the involved committees, the ‘concerned CEIC’ provides its final ‘single opinion’.

In Sweden, there are six independent regional Boards for Research Ethics Review (EC) as well as a (central) National Board for Research Ethics Review. Appeals can be made to this central committee. The coordinating (or principal) investigator submits an application for a multi-site study to the regional ethics committee for the area in which he/she is operating. This regional committee must make its decision, which forms the basis for an opinion. If there is uncertainty as to the necessity of ethics review for a certain project scientific advice at the EC is always possible.

In the UK, there are 117 REC. Any study that involves NHS participants or NHS time (ie, professionals working in the NHS) must seek research ethics committee approval. The NHS research ethics committees (REC) are coordinated by the National Research Ethics Service (NRES). The RECs are advisory bodies to the department of health. The NRES is part of the National Patient Safety Agency and provides help and leadership for REC by coordinating the development of operational and infrastructure arrangements in support of their work. For clinical trials on gene therapy product, the only ethics committee empowered to approve such trials is the Gene Therapy Advisory Committee (GTAC). The Patient Information Advisory Group (PIAG) provides advice on issues of national significance involving the use of patient information and to oversee arrangements created under the section 60 of the Health and Social Care.

The responsibilities of the sponsor can be accepted by an investigator, a single organisation or group of individuals and/or organisations. They may act as either co-sponsors or joint sponsors. Co-sponsors agree an allocation of blocks of the sponsor’s legal responsibilities between partners according to whichever is best placed to accept them. In the vast majority of cases for ethics applications of publicly funded research this will be the Chief Investigator to whom some of the sponsorship responsibilities are delegated. The Chief Investigator (coordinating investigator) is responsible for the application to a REC. The appropriate REC is chosen depending on the type of trial. All trials have to be submitted via a central allocation system to a ‘Concerned REC’. The local principal investigator is responsible for the application to the local EC (in parallel). Local EC is limited to the suitability of the site, investigator and facilities and does not constitute an additional ethical review. Approval for each site is then confirmed by the main REC to the chief investigator as part of the single opinion (the REC application has to be approved and signed by the Chief Investigator).

6.2 Clinical Trial Submissions to ethics committees for approval
6.2.1 Common Regulatory Framework

The **Directive 2001/20/EC** requires the ethics committee opinion for initial CT applications and for substantial amendments expressed as a single opinion per Member State and states maximum deadline periods to get that opinion. Therefore, the submission of a clinical trial authorisation application to an ethics committee is required in all the ECRIN countries involved in the trial.

The ethics committee shall give its opinion on specific topics, before a clinical trial commences, such as: the relevance of the clinical trial and the trial design, the anticipated benefits/risks ratio, the suitability of the investigator and supporting staff, the investigator's brochure, the quality of the facilities, the written information to be given and the procedure to be followed for the purpose of obtaining informed consent and the justification for the research on persons incapable of giving informed consent, provision for indemnity or compensation in the event of injury or death attributable to a clinical trial, any insurance or indemnity to cover the liability of the investigator and sponsor, the amounts for rewarding or compensating investigators and trial participants and the relevant aspects of any agreement between the sponsor and the site.

Each Member State can decide who is responsible (the ethics committee or the competent authority) for the assessments of provision for indemnity or compensation in the event of injury or death attributable to a clinical trial, and of any insurance or indemnity to cover the liability of the investigator and sponsor and the arrangements for compensations to investigators and trial participants.

The sponsor or delegated entity or person shall apply for a EudraCT number and submit a valid application for the ethics committee opinion.

In **Austria, France, Germany, Hungary, Italy, and Spain** the sponsor is responsible for the initial submission and updated documentation to the ethics committee(s). The application to the appropriate ethics committee (named reference, regional, concerned, etc.) is made depending on the site location of the coordinating (or principal) investigator.

In **Denmark, Ireland, Sweden** and **UK** the coordinating (or principal) investigator is responsible for the initial submission and updated documentation to the appropriate ethics committee. The application to the appropriate ethics committee is made depending on the site location of the coordinating (or principal) investigator, except for **UK and Ireland** where it is chosen depending on the type of trial and depending on the sponsor, respectively.

The sponsor is ultimately responsible for providing any other documentation needed or requested.

The ethics committee has 10 days for the validation of the adequacy of submitted documentation. The application is considered to be valid if all required documents are complete. If that is the case the applicant will be informed and the review period starts. If an application is not valid the ethics committee will inform the applicant of the deficiencies.

The ethics committee shall have a maximum of 60 days from the date of receipt of a valid application to give its reasoned opinion to the applicant and the competent authority in the Member State concerned. Within the period of examination, the ethics committee may send a single request for information.
supplementary to that already supplied by the applicant. The period shall be suspended until receipt of the supplementary information.

In the case of trials involving medicinal products for gene therapy or somatic cell therapy or medicinal products containing genetically modified organisms, an extension of a maximum of 30 days shall be permitted. For these products, this 90-day period may be extended by a further 90 days in the event of consultation of a group or a committee in accordance with national regulations and procedures. In the case of xenogenic cell therapy, there shall be no time limit to the authorisation period.

Written favourable opinion by the ethics committee is required before the commencement of clinical trials on medicinal products. Therefore, the sponsor may not start a clinical trial until the ethics committee has issued a favourable opinion and the competent authority of the Member State(s) concerned has not informed the sponsor of any grounds for non-acceptance. The procedures to reach these decisions can be run in parallel or not, depending on the sponsor.

If the ethics committee issues a negative opinion, the sponsor has the right to appeal.

In all countries except for UK, fees should be paid to the EC. The fees vary depending on the type of research and the centre.

6.2.2 Country specificities in relation to the clinical trials directive
The application submission to the ethics committee in parallel to the local ethics committees is mandatory in Austria, Hungary, Italy, Germany and Spain. In United Kingdom is optional.

In France, there is no legal calendar for validation of the adequacy of submitted documentation.

The period for the EC to give its reasoned opinion is 35 days in Austria and France. Although in France, this period can be extended up to 60 days in case the EC requests supplementary information.

There is no appealing procedure in Austria, Hungary and Spain.
6.2 Amendment Submissions to ethics committees

6.2.1 Common Regulatory Framework
Amendments may be made to the conduct of a clinical trial following the procedure described hereinafter:

The sponsor may make amendments to the protocol. The sponsor shall inform the ethics committee or committees concerned if those amendments are substantial and are likely to have an impact on the safety of the trial participants or to change the interpretation of the scientific documents in support of the conduct of the trial.

The ethics committee shall have 10 days for the validation of the adequacy of submitted documentation.

The ethics committee shall evaluate the authorised clinical trial amendments and shall give an opinion within a maximum of 35 days of the date of receipt of the proposed amendment in good and due form.

If this opinion is unfavourable, the sponsor may not implement the amendment to the protocol.

If the opinion of the ethics committee is favourable and the competent authorities of the Member States have raised no grounds for non-acceptance of the abovementioned substantial amendments, the sponsor shall proceed to conduct the clinical trial following the amended protocol.

Should this not be the case, the sponsor shall either take account of the grounds for non-acceptance and adapt the proposed amendment to the protocol accordingly or withdraw the proposed amendment.

The sponsor and the investigator shall take appropriate urgent safety measures to protect the participants against any immediate hazard which can affect the safety of the participants. Safety concerns and measures taken to the ethics committee should be notified.

The sponsor should enter in the European database (EudraCT via an update of the clinical trial application form) any amendments made to the protocol.

It should be noted that in Italy, Spain and UK, the ethics committees are required to monitor research with a favourable opinion. Thus, when the trial lasts longer than one year, the sponsor is required to submit an annual report on the progress of the trial (not only safety data). Annual progress reports should be submitted thereafter until the end of the study. Safety reports are also required annually.

6.2.2 Country specific elements

6.2.2.1 Country differences in relation to the clinical trials directive
In France, there is no legal calendar for validation of the adequacy of submitted documentation.

In Germany the ethics committee shall evaluate the authorised clinical trial amendments and shall give an opinion within a maximum of 20 days of the date
of receipt of the proposed amendment in good and due form. For trials with cell therapeutics or drugs from genetically modified organisms (GMO), the evaluation period is of 35 days of the date of receipt of the proposed amendment in good and due form.

For xenogenic cell therapeutics there is no time limit for the ethics opinion. Regarding the assessment of additional sites, if the EC does not express objections within 30 days after submission of application, agreement is granted.
6.3 Notification of the end of trial to ethics committees

6.3.1 Common Regulatory Framework
The sponsor shall notify the ethics committee that the clinical trial has ended within 90 days of the end of a clinical trial. If the trial has to be terminated early, this period shall be reduced to 15 days and the reasons clearly explained.

A final report should then be submitted 1 year after the end of trial.

If suspension of the trial or infringements is deemed necessary (by competent authorities), the ethics committee concerned should be informed as well as of the decision to suspend or prohibit the trial.

6.3.2 Country specific elements
No country specific elements were reported.
7 CONCLUSIONS

The recent Clinical Trials Directive has introduced a partial degree of harmonisation when performing clinical trials on medicinal products. However, bioethical evaluation of clinical research is a consensus process with moral implications. Thus, it should be a deliberative process between the ethics committees’ members. As this process is highly influenced by social and cultural aspects, it is very difficult to reach a complete harmonisation in Europe.

Moreover, historical practice or the previous and current political and legal situation in each country shaped the way of structuring the ethics committees in the different countries. Within ECRIN, there are countries with relatively few ethics committees, with a low EC/inhabitant ratio (i.e. Austria, Denmark, France, Germany, Hungary and Ireland), while others have many ethics committees with a higher EC/inhabitant ratio (i.e. Italy, Spain and UK).

In addition, some countries (Germany and Spain) have established ethics committees at different levels of the health system, with no clear-cut competences between them. In multicentre trials requiring a single opinion there is no clear distinction on their roles, i.e. general ethical and methodological issues in one hand (including informed consent and participants information sheet), and local aspects of the protocol implementation in the other.

Thus, the model of research ethics committees’ organisation system in place before the clinical trials directive came into force, has conditioned the way of understanding and transposing the ‘single opinion’ process in a determined country. Even though, the clinical trials directive partially complies with one of the key objectives: to centralise the ethics committees’ decision through the single opinion process.

In summary, the harmonisation process finally has led to a situation where two models of research ethics committee’s organisation system can be drawn.

In the first one (in Austria, Denmark, France, Hungary, Ireland and Sweden), the ‘single opinion’ is considered to be the decision made by a single ethics committee (i.e. it is not a collective decision). The deciding ethics committee informs the other committees according to the other trial sites involved about its decision.

In the second one, the ‘single opinion’ is considered to be the decision made by a single ethics committee in cooperation with all ethics committees, which are competent for local study sites (in Germany, Italy, Spain and UK). This results in a process more similar to a mutual recognition process than a ‘real single opinion’ process. This results in a multiplicity of protocol assessments and a considerable increase in bureaucratic work-load.

We think that the first model is more effective and simpler in terms of administrative and logistic work-load and, in a later step, reduces the costs. However, the consideration of proposals for harmonising the first model in all Europe is complex, as it should deal with historical practice, previous and current political and legal framework of the different Member States.
Another issue to be highlighted is that, although imperfect, a high degree of harmonisation has been achieved in the ethics committees procedures performed before the approval of the protocol. In some countries a specific appealing procedure has not been implemented so far.

The role of ethics committees during and after the conduct of the trial is in fact very weak. In all Member States, during the conduct of a trial their role is merely the appraisal of amendments. Often such amendments lead to great differences with the original protocol that can lead with important ethical consequences. This emphasizes the importance of the role of ethics committees in monitoring the trial.

During the trial an annual safety report, with information regarding adverse events is required in all Member States, while only in Italy, Spain and UK an annual report on the progress of the trial with a wider scope (number of participants entered, recruitment rates, etc.) is also mandatory.

After the end of the trial, the sponsor should submit a final report in all ECRIN countries. Ethics committees should reinforce the tasks related with the processes of monitoring clinical trials at the end (premature end, planned end, final reports).

Everyday interaction with ethics committees requires a deep knowledge of the general framework as well as Member States peculiarities. Therefore, ECRIN is in a good position to give support to clinical research projects across Europe, facilitating to overcome currently existing national barriers. This can be done through the National networks and the advice of the European correspondents. Moreover, the ECRIN website is a way to make public and update periodically the information in this regard.

In addition, ECRIN could act fostering a common European regulation on clinical research for observational and interventional clinical studies (other than on medicinal products).
8. APPENDICES

8.1 Procedure chart on “Multinational clinical trials on medicinal products. Submission to an ethic committee. Common framework.”

8.2 Procedure chart on “Multinational clinical trials on medicinal products. Amendments and deviations application to an ethic committee. Common framework”

8.3 Procedure chart on “End of a multinational clinical trials on medicinal products. Notifications to an ethic committee”. Common framework”

8.4 Instructions per country: Practical aspects of interacting with authorities (ethics committee and competent authority) throughout the conduct of a multinational clinical trial on medicinal products.
8.1 Procedure chart on “Multinational clinical trials on medicinal products. Submission to an ethic committee. Common framework”
8.2 Procedure chart on “Multinational clinical trials on medicinal products. Amendments and deviations application to an ethic committee. Common framework”
8.3 Procedure chart on “End of a multinational clinical trials on medicinal products. Notifications to an ethic committee”. Common framework”

*Notification of end clinical trial*
In case of early termination is 15 days
8.4 Instructions per country: Practical aspects of interacting with authorities (ethics committee and competent authority) throughout the conduct of a multinational clinical trial on medicinal products.
Instruction
Practical aspects of interacting with authorities (ethics committees and competent authorities) throughout the conduct of a multinational clinical trial on medicinal products
Austria

Code
ECRIN-EC-QCD002-AT-V0.1

Approval: Date: Revision:

FLOW CHART: Ethics committee and competent authority
Initial submission

Austria
Ethics committee interaction – before the trial

Application to EC
Study documents
EUDRACT-form
EC application form
(in German or English)

Multi-Center Study
Application to one
reference EC
Notification to local
ECs

Application to CA
Simultaneous or after
EC application. Not
before

Completeness check by EC (within 5 days of application)
by CA (within 35 days of application)

Observational study, Non-
interventional or
minimal intervention

Clinical trial with
IMP

Clinical trial with:
Somatic cell therapy
Gene therapy
Bioengineering

External Reviewer (optional)

EC Meeting

Approval by CA
if no objections raised (no written approval except
somatic cell therapy, gene therapy and bioengineering);
by EC (in writing)

Positive
Conditional
Approval
(clock-stop)

Major changes required
Re-discussion of revised
version at next meeting

Negative

Notification of non-approval
to sponsor within 60 days

Optional: Referral to
„Arzneimittelbeirat“

* In case of uncertainties

* Usually < 35 days

Expedited
review
by appointed
board (EC Chair)

Short notice at
EC Meeting

One clock stop
possible

* 35 days

90 days

Relevant legislation: The Medicines Act (Arzneimittelgesetz);
implementing Directive 2001/20/EC in 2004
The Genetic Act (Gentechnikgesetz) 1994
Where to find it: http://www.rie2.bka.gv.at
Austria
Ethics committee interaction – **during** the trial

**Annual (safety) report (ASR)**
to CA & EC includes:
- number of subjects enrolled and completed,
- SAEs
- SUSARs occurred in other trials with the IMP

**Change of Risk Benefit/Ratio**
of the trial
ENTR/CT 3, 5.1.1.2 und 5.1.6.5 b, ICH-GCP 4.10.2
Notification of CA & EC within 15 days

**Substantial Amendment**
Review by CA & EC within 35 days (approval in writing by EC not by CA)

**Other Amendments**
Only notification to CA & EC

**SUSAR**
AMG § 41e Abs. 1 und 2, ENTR/CT 3, 5.1.1.1

- **Death or Life-threatening**
  Notification of CA & EC within 7 days
  Follow-up 8 days

- **Other SUSARs**
  Notification of CA & EC within 15 days

**SAE**
AMG § 41e Abs. 3
Notification of CA & EC on a yearly basis only together with the ASR

Relevant legislation:
The Medicines Act (Arzneimittelgesetz); implementing Directive 2001/20/EC in 2004
The Genetic Act (Gentechnikgesetz) 1994
Where to find it: [http://www.ris2.bka.gv.at](http://www.ris2.bka.gv.at)
Declaration of the end of a clinical trial

Austria
Ethics committee interaction – after the trial

End of trial
Notification to CA & EC includes:
Number of subjects enrolled/completed
Number of SAE/SUSARs
Brief conclusion
Type of stop

Trial ended as planned
Notification of CA & EC within 90 days

Trial ended prematurely
Notification of CA & EC within 15 days

Final report
To CA & EC within one year

Relevant legislation: The Medicines Act (Arzneimittelgesetz); implementing Directive 2001/20/EC in 2004
The Genetic Act (Genetikgesetz) 1994
Where to find it: http://www.ris2.bka.gv.at
### COMPETENT AUTHORITY

<table>
<thead>
<tr>
<th>Competent authorities</th>
<th>Bundesamt für Sicherheit im Gesundheitswesen</th>
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<tbody>
<tr>
<td></td>
<td>AGES PharmMed</td>
</tr>
<tr>
<td></td>
<td>Schnirchgasse 9</td>
</tr>
<tr>
<td></td>
<td>A-1030 Vienna</td>
</tr>
<tr>
<td></td>
<td>Austria</td>
</tr>
<tr>
<td></td>
<td>Tel: +43 50 555-0; 050 555-DW</td>
</tr>
<tr>
<td></td>
<td><a href="http://www.ages.at">www.ages.at</a></td>
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Practical information: If you intend to contact someone at the AGES PharmMed the generic email `firstname.surname@ages.at` can be used

Language: German

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<td>Fees for amendments</td>
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### ETHICS COMMITTEES

<table>
<thead>
<tr>
<th>Ethics committee</th>
<th>REC EK Med.Universität Wien</th>
</tr>
</thead>
<tbody>
<tr>
<td>REC, here means a research ethics committee which is entitled to review a single opinion</td>
<td><a href="mailto:ethik-kom@meduniwien.ac.at">ethik-kom@meduniwien.ac.at</a></td>
</tr>
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<td></td>
<td><a href="http://www.meduniwien.ac.at/ethik">www.meduniwien.ac.at/ethik</a></td>
</tr>
<tr>
<td></td>
<td>Univ.Prof.Dr.Ernst Singer</td>
</tr>
<tr>
<td></td>
<td>Borschkegasse 8b/E 06</td>
</tr>
<tr>
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<table>
<thead>
<tr>
<th>REC EK der Stadt Wien gemäß KAG, AMG und MPG</th>
<th><a href="mailto:ethikkommission@m15.magwien.gv.at">ethikkommission@m15.magwien.gv.at</a></th>
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</tr>
<tr>
<td></td>
<td>SR Dr. Hans Serban LL.M.</td>
</tr>
<tr>
<td></td>
<td>TownTown, Thomas-Klestil-Platz 8</td>
</tr>
<tr>
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<tr>
<th>REC EK des Landes Niederösterreich</th>
<th><a href="mailto:post.ethikkommission@noel.gv.at">post.ethikkommission@noel.gv.at</a></th>
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<td><a href="http://www.noel.gv.at/ethikkommission">www.noel.gv.at/ethikkommission</a></td>
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<tr>
<td>Mag. Robert Bruckner</td>
<td></td>
</tr>
<tr>
<td>Abt. Sanitätsrecht u. Krankenanstalten, Landhausplatz 1, Haus 15B</td>
<td></td>
</tr>
<tr>
<td>A-3109</td>
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<tr>
<th>REC EK des Landes Oberösterreich</th>
<th><a href="mailto:johannes.fischer@gespag.at">johannes.fischer@gespag.at</a> bzw <a href="mailto:elgin.drda@ooe.gv.at">elgin.drda@ooe.gv.at</a></th>
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<td></td>
<td><a href="http://ooe-ethikkommission.at">http://ooe-ethikkommission.at</a></td>
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<tr>
<td></td>
<td>Univ.Prof.Prim.Dr. Johannes Fischer</td>
</tr>
<tr>
<td></td>
<td>Landesnervenklinik Wagner-Jauregg, Wagner-Jauregg Weg 15</td>
</tr>
<tr>
<td></td>
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<tr>
<th>REC EK f.d.Bundesland Salzburg</th>
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Instruction: Practical aspects of interacting with authorities (ethics committees and competent authorities) throughout the conduct of a multinational clinical trial on medicinal products - Austria ECRIN-EC-QCD002-AT-V0.1
ethikkommission@salzburg.gv.at
www.salzburg.gv.at/ethikkommission
HR Dr. Alois Grüner
Sebastian-Stief-Gasse 2
A-5010

REC EK Med.Universität Graz
ethikkommission@meduni-graz.at
www.meduni-graz.at/ethikkommission/Graz/index.htm
Univ.Prof.Dr. Dr. Peter H. Rehak
Auenbruggerplatz 2
A-8036

REC EK Med.Universität Innsbruck
Ethikkommission@i-med.ac.at
www.i-med.ac.at/ethikkommission
Univ.Prof.Dr. Dr. Peter Lukas
Geschäftsstelle, Innrain 43
A-6020

EK des Landes Burgenland gemäß KAG, AMG und MPG
r.peischl@krages.at
www.krages.co.at/ekomm/index.asp
PD Dr. DGKS Renate Peischl, MAS
Josef-Hyrtl-Platz 4
A-7000

EK des Landes Kärnten
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www.ethikkommission-kaernten.at
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Fadingerstrasse 1
A-4010

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kurt.lenz@bblinz.at
Prim.Univ.Prof. Dr. Kurt Lenz
Seilerstätte 2
A-4020

EK KH Barmh. Schwestern
ethik.linz@bhs.at
Univ.Prof. Dr. Peter Siostrzonek
Seilerstätte 4
A-4020

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HR Dr. Odo Feenstra
Amt d. Stmk.LR, FA Gesundheitswesen,
Paulustorgasse 4/II
A-8010
<table>
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<tr>
<th>Institution</th>
<th>Contact Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>EK KH Barmh. Brüder – Marschallgasse</td>
<td><a href="mailto:guenther.weber@bbgraz.at">guenther.weber@bbgraz.at</a> Prim.Univ.Doz. Dr. Günther Weber Marschallgasse 12 A-8020</td>
</tr>
<tr>
<td>EK KH Barmh. Brüder - Eggenberg</td>
<td><a href="mailto:peter.koeltringer@bbegg.at">peter.koeltringer@bbegg.at</a> Prof. Dr. Peter Költringer Bergstrasse 27 A-8020</td>
</tr>
<tr>
<td>EK des Landes Vorarlberg</td>
<td><a href="mailto:ethikkomm.vlbg@bregenznet.at">ethikkomm.vlbg@bregenznet.at</a> <a href="http://www.ethikkommission-vorarlberg.at">www.ethikkommission-vorarlberg.at</a> Mag.pharm. Dr. Helmut Grimm Geschäftsstelle, Rathausstrasse 15 A-6900</td>
</tr>
<tr>
<td>EK der Allgemeinen Unfallversicherungsanstalt</td>
<td><a href="mailto:helmut.koeberl@auva.sozvers.at">helmut.koeberl@auva.sozvers.at</a> Dr. Helmut Köberl Adalbert-Stifter-Strasse 65 A-1200</td>
</tr>
<tr>
<td>EK KH d. Barmh. Brüder Wien</td>
<td><a href="mailto:abteilung.interne@bbwien.at">abteilung.interne@bbwien.at</a> Doz. Dr. Stefan Kudlacek Große Mohrenasse 9 A-1020</td>
</tr>
<tr>
<td>EK Confraternität-Privatklinik Josefstadt</td>
<td><a href="mailto:dieter.volc@pkj.at">dieter.volc@pkj.at</a> Prim. Dr. Dieter Volc Skodagasse 32 A-1080</td>
</tr>
<tr>
<td>EK Privatklinik Döbling</td>
<td><a href="mailto:dieter.volc@pkj.at">dieter.volc@pkj.at</a> Prim. Dr. Dieter Volc Heiligenstädt. Strasse 57-63 A-1190</td>
</tr>
<tr>
<td>EK St. Anna Kinderspital</td>
<td><a href="mailto:gadner@acr.univie.ac.at">gadner@acr.univie.ac.at</a> <a href="http://www.stanna.at">www.stanna.at</a> Dr. Roland Lavaulx-Vrecourt Kinderspitalgasse 6 A-1090</td>
</tr>
<tr>
<td>EK KA des Göttlichen Heilandes</td>
<td><a href="mailto:michael.peintinger@meduniwien.ac.at">michael.peintinger@meduniwien.ac.at</a> OA Dr. Michael Peintinger Dornbacher Strasse 20-28 A-1170</td>
</tr>
<tr>
<td>EK Österreichische Arbeitsgemeinschaft für Klinische Pharmakologie und Therapie &amp; Institut für Hypertoniker</td>
<td><a href="mailto:office@ethikkommission-klinpharm.at">office@ethikkommission-klinpharm.at</a> <a href="http://www.ethikkommission-klinpharm.at">www.ethikkommission-klinpharm.at</a></td>
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Instruction: Practical aspects of interacting with authorities (ethics committees and competent authorities) throughout the conduct of a multinational clinical trial on medicinal products - Austria ECRIN-EC-QCD002-AT-V0.1
Univ.Prof.Dr.Gerhart Hitzenberger  
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A-1090  

EK Rheuma-Zentrum Wien-Oberlaa  
rheuma-zentrum@oberlaa.at  
OA Dr.Omid Zamani  
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A-1107  

EK Forschungsinstitut des Wiener Roten Kreuzes  
forschung@w.roteskreuz.at  
www.wrk.at/forschungsinstitut  
Mag.Alexander Lang  
Nottendorfer Gasse 21  
A-1030  

EK KH Barmh.Schwestern, Wien  
office.wien@bhs.at  
Prim.Dr.Boris Todoroff  
Stumpergasse 13  
A-1060  

EK Privatkrankenanstalt Rudolfinerhaus  
weissenhofer@rudolfinerhaus.at  
Univ.Prof.Dr.Fritz Paschke  
Billrothstrasse 78  
A-1090  

Fees for initial application  
Recomendation for all ECs in Austria – usually they stick to this:  
Monocenter studies:  
1500 € per application/protocol (incl. all SUSARS, amendments, etc.)  

Multicenter studies:  
Reference EC: 4000 € per application/protocol (incl. all SUSARS, amendments, etc.)  
Local EC: 500 € per application/protocol (incl. all SUSARS, amendments, etc.)  

Fee waiver for “academic” non-commercial studies 

Fees for amendments 

 Included in initial fee  

REGULATORY REFERENCES  

Law  
Österreichisches Arzneimittelgesetz (AMG):  
http://ris.bka.gv.at/  

Decree
Instruction

Practical aspects of interacting with authorities (ethics committees and competent authorities) throughout the conduct of a multinational clinical trial on medicinal products

Denmark

Code
ECRIN-EC-QCD002-DK-V0.1

Approval: Date: Revision:

FLOW CHART: Ethics committee and competent authority

Initial submission

Gene therapy or living genetically modified microorganisms require notification to Danish Working Environment Authority

Danish Forest & Nature Agency

EudraCT #

Sponsor/Investigator Submits Application

Danish Data Protection Agency

Notification to manufacturer of medicinal product

Ethics committee (EC)

Danish Medicines Agency (DMA)

Regular

Gene therapy, somatic cell therapy, genetically modified microorganisms

60 days

Consultation with other parties

+30 days

Xenogenic cell therapy

No time limit

If EC requests further information from applicant then time is suspended, the DMA must request further information within 35 days, applicant must respond within original time frame

Unceded or reject

EC decision

DMA decision

The Danish National Committee on Biomedical Research Ethics

Time scales as before

Decision final

Final approval

Notification of ethics committee and competent authority, clinical trials on medicinal products, Denmark
Submission of amendments during the conduct of the trial

Investigator

Wants to change experimental procedure, or terminate trial prematurely

Ethics committee (EC)

Requests amendment to protocol

Sponsor/investigator submits application for amendment

Danish Medicines Agency (DMA)

Danish Medicines Agency (DMA)

35 days

Decision

Decision

If terminated prematurely inform EC within 15 days. Urgent safety measures taken, immediately inform DMA and EC.

The Danish National Committee on Biomedical Research Ethics

Amendments to an approved clinical trial on medicinal products protocol, Denmark

Decision may be brought before the National Committee

If DMA stops the trial they announce decision to EC

Instruction: Practical aspects of interacting with authorities (ethics committees and competent authorities) throughout the conduct of a multinational clinical trial on medicinal products- Denmark ECRIN-EC-QCD002-DK-V0.1
Declaration of the end of a clinical trial

Sponsor/Investigator Notifies End of Trial

Premature end of trial

Planned end of trial

Changes to the final date should be notified to the Danish Data Protection Agency

Within 15 days sponsor informs DMA and investigator informs EC and states ground for premature termination

Within 90 days sponsor informs DMA and investigator informs EC

Investigator submits short report to the EC, including all serious adverse events as well as those reported during the trial. The EC may also request a final trial report or publication.

Within 1 year sponsor submits trial results to the DMA

Ethics committee (EC)

Danish Medicines Agency (DMA)

Notification of ethics committee and competent authority, end of trial on medicinal products, Denmark
### COMPETENT AUTHORITY

| Competent authorities | The Danish Medicines Agency  
| Axel Heides Gade 1  
| DK-2300 København S |
| **Phone:** +45 44 88 95 95  
| **Fax:** +45 44 88 95 99 |
| Telephone hours: Monday to Thursday at 8:30am - 16:00pm, Friday at 8:30am - 15:30pm |
| http://www.dkma.dk/1024/visUKLSArtikelBred.asp?artikelID=744 |
| **Practical information:** |
| **Language:** Danish or English |

| Local competent authority if applicable | N/A |
| Documents required (in addition to the general procedure) | |
| Fees for initial application | 7,010 DKK |
| Fees for amendments | 1,590 DKK |

### ETHICS COMMITTEES

| Ethics committee | Den Centrale Videnskabsetiske Komité  
| Slotsholmsgade 12  
| 1216 København K |
| **Phone:** +45 7226 9370  
| **Fax:** +45 7226 9380  
| **E-mail:** cvk@sum.dk |
| **Practical information:** The application needs to be submitted to one of the five regional ethics committees, according to where the investigator resides. |
| **Language:** Danish |

| Fees for initial application | 4,000 DKK  
| **Waiver of fee for initiating investigators from public hospitals.** |
| Fees for amendments | 1,500 DKK |
# REGULATORY REFERENCES

<table>
<thead>
<tr>
<th>Law</th>
<th>Relevant Legislation</th>
<th>Guidance</th>
<th>Where to find it</th>
</tr>
</thead>
</table>

### Instruction:
Practical aspects of interacting with authorities (ethics committees and competent authorities) throughout the conduct of a multinational clinical trial on medicinal products - Denmark ECRIN-EC-QCD002-DK-V0.1
Instruction
Practical aspects of interacting with authorities (ethics committees and competent authorities) throughout the conduct of a multinational clinical trial on medicinal products France

Code
ECRIN-EC-QCD002 – FR-V0.4

FLOW CHART: Ethics committee and Competent authority

Initial submission

Deliberative

REC (CPP)

Silence = refusal

Approval (avis favorable)

Parallel
Sequential

Beginning of the study

Authorisation
Silence = approval

End of the study
Sponsor must declare (REC & CA) within 90 days
Send abstract of the final report within 1 year

CA (AFSSAPS)

Consultative
60 days
(Gene or cellular therapy : 90 days)

Sponsor
1. n’EudraCT/AFSSAPS
2. Fees payment
3. Insurance
4. File

Interaction

Deliverative 35 days

The approval is no longer valid after 1 year without beginning, except if justified before the deadline

Clockstart
For the REC, the procedure starts when the full project is submitted, with a guarantee of a payment of the fees (taxes) and the insurance
However, the possibility of starting the clock with somewhat uncompleted file (guarantees waiting to come) can be discussed with the REC case by case

Clockstop
The REC can ask the sponsor either to provide additional information or to change his project. The deadline for advice is then delayed to 60 days, this delay can be shortened since the project has been improved
Only one clockstop is allowed
Only for Biomedical Research (see definition)
### Submission of amendments during the conduct of the trial

**Substantial amendments**

- **REC (CPP)**: Deliberative
  - 35 days
  - Silence = refusal
- **CA (AFSSAPS)**: Consultative
  - 60 days
  - Silence = approval (Gene or cellular therapy: 90 days)

### Declaration of the end of a clinical trial

Please see in the initial submission slide also the end of trial information.

### COMPETENT AUTHORITY

<table>
<thead>
<tr>
<th>Competent authorities</th>
<th>AGENCE FRANCAISE DE SECURITE SANITAIRE DES PRODUITS DE SANTE (AFSSAPS)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unités Essais Cliniques</td>
</tr>
<tr>
<td></td>
<td>143, 147 boulevard Anatole France</td>
</tr>
<tr>
<td></td>
<td>93285 Saint-Denis Cedex</td>
</tr>
<tr>
<td></td>
<td>Tel: 01.55.87.30.00</td>
</tr>
</tbody>
</table>

**Practical information:**
- Language: French or English (information and informed consent form should be provided in French)

### Local competent authority if applicable

| NA |

### Document required (in addition to the general procedure)

| Insurance attestation |
Fees for initial application: Only one fee for CA and EC (to be sent to competent authority) and reduced fee for academic sponsor. For the amounts please see: [http://agmed.sante.gouv.fr/htm/5/essclin/ind-essais-cliniques-med.htm](http://agmed.sante.gouv.fr/htm/5/essclin/ind-essais-cliniques-med.htm) (infos pratiques: montant de la taxe)


**ETHICS COMMITTEES**

Ethic committees: The Ethical review is performed by one of the 40 Ethics Committee (Comité de Protection des Personnes (CPP)). The sponsor applies to the CPP located in the region of the principal investigator. Practical information: List of Ethics committees at [http://www.recherche-biomedicale.sante.gouv.fr/pro/comites/coordonnees.htm](http://www.recherche-biomedicale.sante.gouv.fr/pro/comites/coordonnees.htm)

Fees for initial application: No specific fee (see previous paragraph)

Fees for amendments: No specific fee (see previous paragraph)

**REGULATORY REFERENCES**

**Law**

  - L1121-1, L1123-7, L1123-12, R1123-21, R1123-23, R1123-24, R1123-26: Definition and general conditions of biomedical research
  - L5311-1: Definition of medicinal products
  - L1121-4, L. 1123-1, L. 1123-12: Government(s), legal or authoritative body(s) implicated in clinical research
  - L1121-5 to 8: Special conditions for vulnerable populations
  - L1111-6, L1122-2 – I: Previous authorisation for vulnerable populations
  - L1121-13: Authorisation for the site of investigation
  - L1121-4, L. 1123-1, L. 1123-12, R1123-4, R1123-11 to 14, & 24, 28: French RECs (CPP)
  - R1123-24: Ways of submission to the REC
  - L1121-2, L1122-1, L1123-3, & L1123-7: Language for documents submitted to the REC
  - R1123-24 & 27: Refusal of a project by the REC
  - L1123-8 & 9, R1123-21, R1123-35: Amendments
  - L1121-16: Declaration of participants to the National file for Volunteers
  - R1123-28: Time limits for beginning the study
  - R1123-59, 60: End of the study

- Law n°2002-303 (04/03/2002)
  - Patients’ rights

- Law n°2004-800 (07/08/2004) related to bioethics
  - Biological collections

- Law n°1978-17 (06/01/1978) amended by
  - Electronic files and freedom

**Decree**

- Decision du 24 Novembre 2006 fixant les règles de bonnes pratiques cliniques pour les recherches biomédicales portant sur des médicaments à usage humain
  - Good clinical practices in biomedical research on drugs. Physical/moral persons responsible for the research
- Decree n°2006-477 (26/04/06) and decree n°2007-122 0 (10/08/07)
  - Biological collections

  - Documents and archives

- Order of the 09/03/2007 (22/03/2007)
  - Assessment of current care. Definition of medicinal products.
**Instruction**

**Practical aspects for interacting with authorities (ethics committees and competent authorities) throughout the conduct of a multinational clinical trial on medicinal products.**

**Germany**

**Code**

ECRIN-EC-QCDØØ2-DE-VØ.1

**Approval:** Date: Revision:

---

**FLOW CHART: Ethics committee(s) and Competent authorities**

**Initial submission**

- Clinical Trial acc. 2001/20/EC
  - Request for EudraCT-Number
  - Request for approval from Ethics Committee ²

- Mono-center
  - Application of approval at the local EC
  - Copy of the application to the local ECs (responsible for the local investigators)

- Multi-center
  - Application of approval at the reference EC (responsible for the coordinating investigator)
  - Copy of the application to the local ECs (responsible for the local investigators)

**Authority approval**

- EC approval
  - Notification of local authorities

**Non-interventional**

**Interventional**

**Clinical Trial acc. 2001/20/EC**

**Study Design**

- Registration ¹ & EC approval for the local investigator required in some federal states according to federal Medical Association’s professional code

---

1 „Kassenärztliche Bundesvereinigungen“, „Spitzenverbänden der Krankenkassen“ and competent authorities (BfArM or PEI)

2 Application to the competent authority (BfArM or PEI) and ECs can be done in parallel or one after the other. Responsible for the application is the sponsor or its legal representative (or delegate). EC and authority approval is essential before enrolment of patients. EC and authority act independently.

Timelines for approval vary depending on the type of trial and therapy.

For most trials implicit approval by the competent authority can be assumed after 30 days, for others explicit approval has to be awaited.
### Submission of amendments during the conduct of the trial

<table>
<thead>
<tr>
<th>Type of amendment</th>
<th>Request for approval to reference and concerned local Ethics Committee</th>
<th>EC approval</th>
<th>Notification of additional trial site to local authority</th>
</tr>
</thead>
<tbody>
<tr>
<td>Additional trial site</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amendment to Protocol or Procedures of a Clinical Trial</td>
<td>Request for approval to reference and concerned local Ethics Committees</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amendment to Protocol or Procedures of a Clinical Trial</td>
<td>Request for approval to competent authority</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3 Depending on the kind of amendment, request has to be sent to EC(s) or Authority or both, in which case it can be done in parallel.

### Declaration of the end of a clinical trial

The end of the trial has to be notified within 90 days to the authorities and the ethics committees. In case of premature termination of a trial the deadline is 15 days and the reason for termination has to be given.

### COMPETENT AUTHORITY

**Competent authorities**

For medicinal products and medical devices:

**Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM)**

Kurt-Georg-Kiesinger-Allee 3

D-53175 Bonn

Tel.: +49 (0)228 -99-307-30 (Zentrale)

Fax: +49 (0)228 -99-307-5207

E-Mail: poststelle@bfarm.de

http://www.bfarm.de

For biological medicinal products:

**Paul-Ehrlich-Institut (PEI)**

Bundesamt für Sera und Impfstoffe

Paul-Ehrlich-Straße 51-59

63225 Langen

Telefon: +49 6103 77 0

Fax: +49 6103 77 1234

E-Mail: pei@pei.de

http://www.pei.de

**Local competent authority if applicable**

Every investigator must be notified to the local authorities before the commencement of the trial. The investigator is responsible for the notification although this is usually delegated to the sponsor. The notification form and a list of local authorities can be found at www.zlg.de

**Document required (in addition to the general procedure)**

Cover letter has to be in German

The CTA must be submitted 4-fold (one original, 3 copies) with a CD-ROM containing the xml-file from the EudraCT database and a pdf file of the CTA.

**Fees for initial application**

Depends on the type of trial. See http://www.bfarm.de

**Fees for amendments**

Depends on the type of trial. See http://www.bfarm.de

### ETHICS COMMITTEES

**Ethics committees**

Practical information:

Contact the local EC regarding application for approval.

Contact details of the Ethics Committees can be found at: http://www.ak-med-ethik-komm.de
Application format for EC approval is mostly harmonized. Two paper and one electronic copy of the application need to be sent to the local ECs at the same time as to the reference EC. The local ECs give their opinion on suitability of the local site and staff to the reference EC. Although mostly harmonized the documentation requested on local site and staff may differ among the local ECs.

| Fees for initial application | Not harmonised. See the individual Ethics Committees. |
| Fees for amendments | Not harmonised. See the individual Ethics Committees. |

### REGULATORY REFERENCES

| Laws | German Drug Law (AMG, esp. §§ 40 – 42)  
http://bundesrecht.juris.de/amg_1976/  
A non authorized English translation of the German Drug Law (AMG) can be found on the English pages of www.bfarm.de or directly here:  
| Decrees | German Good Clinical Practice Decree (GCP-V)  
http://bundesrecht.juris.de/gcp-v/ |
Instruction
Practical aspects of interacting with authorities (ethics committees and competent authorities) throughout the conduct of a multinational clinical trial on medicinal products
Hungary

FLOW CHART: Ethics committee and Competent authority

<table>
<thead>
<tr>
<th>Initial submission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigational Medicinal Product Trial (phase I-IV)</td>
</tr>
<tr>
<td>Sponsor</td>
</tr>
<tr>
<td>NIP: National Institute of Pharmacy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Submission of amendments during the conduct of the trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsor</td>
</tr>
<tr>
<td>Essential changes, minor</td>
</tr>
<tr>
<td>Essential changes, major</td>
</tr>
<tr>
<td>Any other ethical and professional issues</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Minor: administrative or product quality issues</td>
</tr>
<tr>
<td>Major: scientific background, risk, IC, data handling, investigation site, any issues that basically influence the protocol</td>
</tr>
<tr>
<td>NIP: National Institute of Pharmacy</td>
</tr>
</tbody>
</table>
### Declaration of the end of a clinical trial

| Sponsor to report within 90 days to | NIP to inform within 8 days | Medical Research Council, Committee for Clinical Pharmacology and Ethics |

**NIP**: National Institute of Pharmacy

**Note**: if trial is stopped earlier than defined the sponsor is to report to NIP within 15 days

### COMPETENT AUTHORITY

| Competent authorities | Országos Gyógyszerészeti Intézet (OGYI)  
National Institute of Pharmacy (NIP) |
|-----------------------|----------------------------------------------------------------------------------|
| Zrínyi u. 3.  
1372 P.O. Box 450  
H-1051 Budapest  
Hungary  
Phone : +36 1 8869-300  
Fax : +36 1 8869-460  
ogyi@ogyi.hu  
http://www.ogyi.hu/ogyi/english/contact/ |
| Practical information :  
Language : Hungarian and English |

### Local competent authority if applicable

<table>
<thead>
<tr>
<th>Document required (in addition to the general procedure)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Fees for initial application</td>
<td></td>
</tr>
<tr>
<td>-----------------------------</td>
<td>---</td>
</tr>
<tr>
<td>Fees for amendments</td>
<td></td>
</tr>
<tr>
<td><strong>ETHICS COMMITTEES</strong></td>
<td></td>
</tr>
<tr>
<td>Ethics committees</td>
<td>Practical information: National Ethics Commissions within the Health Science Council</td>
</tr>
<tr>
<td></td>
<td>- Scientific and Research Ethics Commission (TUKEB)</td>
</tr>
<tr>
<td></td>
<td>- Clinical Pharmacology Ethics Commission (KFEB)</td>
</tr>
<tr>
<td></td>
<td>- Human reproduction commission</td>
</tr>
<tr>
<td></td>
<td>Regional Research Ethics Boards (RKEB)</td>
</tr>
<tr>
<td></td>
<td>- 12 regional research ethics boards throughout the country</td>
</tr>
<tr>
<td></td>
<td>Institutional research Ethics boards</td>
</tr>
<tr>
<td></td>
<td>- board set-up at each health care institution where research is carried out</td>
</tr>
<tr>
<td><strong>REGULATORY REFERENCES</strong></td>
<td></td>
</tr>
<tr>
<td>Law</td>
<td>XCV. Law 2005 on the modification on the laws regulating drugs for human use and on the regulation of drug market</td>
</tr>
<tr>
<td>Decree</td>
<td>Decree 35/2005. (VIII.26.) of the Ministry of Health on the clinical investigation of investigational medicinal products intended for human use and on the implementation of the Good Clinical Practice</td>
</tr>
</tbody>
</table>
Instruction
Practical aspects of interacting with authorities (ethics committees and competent authorities) throughout the conduct of a multinational clinical trial on medicinal products
Ireland

FLOW CHART: Ethics committee and competent authority

Initial submission

Clinical Trials on Medicinal Products Review Process - Ireland

- Study Documents
- EC Application Forms

15 days

Clinical Trials Sub Committee Meeting

- Clinical Trials Sub Committee Meeting
- Application validated on receipt

15 days

CA Review
- General Medicinal Products Biologics
- 15-16 days

Favourable Opinion
- CA Approval

ECRIN-EC-QCD002-IR-V0.1

Approval: Date: Revision:
Submission of amendment(s) during the conduct of the trial

Declaration of the end of a clinical trial
**COMPETENT AUTHORITY**

<table>
<thead>
<tr>
<th>Competent authorities</th>
<th>Irish Medicines Board website <a href="http://www.imb.ie">www.imb.ie</a></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Practical information:</td>
</tr>
<tr>
<td></td>
<td>Language: English</td>
</tr>
<tr>
<td>Local competent authority if applicable</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Documents required (in addition to the general procedure)</td>
<td>Form Additional National requirements for a clinical trial</td>
</tr>
<tr>
<td>Fees for initial application</td>
<td>From 256 to 2754 euros depending on agent (ie novel agent costs more than trial on drug used within its license)</td>
</tr>
<tr>
<td></td>
<td>In addition academic trials may be free of charge, if there is no financial support for trial</td>
</tr>
<tr>
<td>Fees for amendments</td>
<td>From 80 to 162 euros</td>
</tr>
</tbody>
</table>

**ETHICS COMMITTEES**

<table>
<thead>
<tr>
<th>Ethics committee</th>
<th>Practical information: there are 13 recognised ethics committees in Ireland that can review a drug clinical trial</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Language: English</td>
</tr>
<tr>
<td>Fees for initial application</td>
<td>1000 euros</td>
</tr>
<tr>
<td>Fees for amendments</td>
<td>250 euros</td>
</tr>
</tbody>
</table>

**REGULATORY REFERENCES**

<table>
<thead>
<tr>
<th>Law</th>
<th>SI 190 of 2004 and 374 of 2006</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decree</td>
<td></td>
</tr>
</tbody>
</table>
**Instruction**

Practical aspects of interacting with authorities (Ethics committee and competent authority) throughout the conduct of a multinational clinical trial on medicinal product **Italy**

**Code**
ECRIN-EC-QCDØØ2-IT-VØ.1

<table>
<thead>
<tr>
<th>Approval:</th>
<th>Date:</th>
<th>Revision:</th>
</tr>
</thead>
</table>

FLOW CHART: Ethics committee and Competent authority

Clinical Trial on Medicinal Products

Procedure for interacting with Ethical Committee

- OBSERVATIONAL STUDY
- CLINICAL RESEARCH STUDY
- CLINICAL TRIAL
- EudraCT Process

**Italy**

- Prospective Study
  - Coordinator Center EC 30 days
  - Collaborating Center EC 30 days
- No-prospective study
- AS NOTIFICATION
- Istituto Superiore di Sanità (ISS)

*only in case of products for gene therapy or somatic cell therapy or medicinal products containing genetically modified organisms*
Submission of amendments during the conduct of the trial

Clinical Trial on Medicinal Products

Amendments & Deviations Process

Day -7
Coordinator Center EC receive the documentation required

Day 0
Coordinator researcher submit the application and send the protocol to the LECs

EVALUATION PHASE
Possible suggestions from the Collaborating center’s EC to the Coordinator center’s EC

Day 30
Collaborating Center EC receive the documentation required

Day 60
Single Opinion and communication to the collaborating center’s ECs (OsSC)

Authorization and signment of the contract

Declaration of the end of a clinical trial

Clinical Trial on Medicinal Products

End of a clinical trial Process

OBSERVATIONAL STUDY

CLINICAL RESEARCH STUDY

CLINICAL TRIAL

EudraCT Process

FINAL CLINICAL STUDY REPORT

Local Ethical Committee

AIFA Agenzia Italiana del Farmaco

COMPETENT AUTHORITY

Competent authorities
Ministry of Health
Dipartimento del l'innovazione
Direzione Generale dei Farmaci e Dispositivi Medici
Piazzale dell'Industria 20
00144 Roma

ITALY
### Practical information:

- **Language**: Italian

<table>
<thead>
<tr>
<th>Local competent authority if applicable</th>
<th>NA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Document required (in addition to the general procedure)</td>
<td>Insurance attestation</td>
</tr>
<tr>
<td>Fees for initial application</td>
<td></td>
</tr>
<tr>
<td>Fees for amendments</td>
<td></td>
</tr>
</tbody>
</table>

#### ETHICS COMMITTEES

- **Ethics committees**
- **Fees for initial application**
- **Fees for amendments**

#### REGULATORY REFERENCES

- **Law**
  - D.G.R. n. 4049 del 22/12/04
  - D.P.R. n. 439 del 21/09/01

- **Decree**
  - Legislativa Decree n.211 of 24 June 2003
  - Decreto Ministeriale 12 Maggio 2006
  - Decreto Ministeriale 18 Marzo 1998
Instruction
Practical aspects of interacting with authorities (EC and CA) throughout the conduct of a multinational clinical trial
Spain

Code
ECRIN-EC-QCDØØ2-ES-VØ.2

Approval: Date: Revision:

FLOW CHART: Ethics committee and Competent authority

Initial submission

Ethical Submission of a Clinical Study (Before)
MEDICINAL PRODUCTS (MP) SPAIN

Clinical Trials

Multicenter in Spain
1 to 5 every month

MRCNTR IN SPAIN
MP 92.5

Other*: When a Complete MP dossier needs to be submitted (PS qualification), inform the Spanish National Organisations and Advanced Therapies.

Observational Studies

Non Authorised

Non approved conditions

Authorised MP

Approved conditions

Post-Authorisation Studies

Responsibility: Sponsor to investigator vs. Sponsor to Ethical Committee
Application to the competent authority and ECs can be done in parallel or sequentially

EC Approval

AEIPS (notification)

CCIA (notification)

AEPIS (notification)

Data Protection Law

*Approved indication AND dosage AND pharmaceutical form
Submission of amendments during the conduct of the trial

www.agemed.es

Declaration of the end of a clinical trial

Notification of the end of a clinical trial
90 days since final study date, unless anticipated ending 15 days
Periodic reports
Should be submitted yearly

COMPETENT AUTHORITY

Agencia Española de Medicamentos y Productos Sanitarios
Parque Empresarial "Las Mercedes", Edif 8, C/ Campezo 1 - 28022 MADRID
http://www.agemed.es/

Local competent authority if applicable
NA
Document required (in addition to the general procedure) | Insurance attestation
---|---
Fees for initial application | Fees are different depending on the type of submission (Clinical Trials vs. Clinical Trial with a Medicinal Product not authorised in Spain –PEI-) Please see [http://www.agemed.es/actividad/documentos/tasas/listadoTasasGp5.jsp](http://www.agemed.es/actividad/documentos/tasas/listadoTasasGp5.jsp)
Fees for amendments | There are no fees for an amendment procedure

**ETHICS COMMITTEES**

| Ethics Committees | Committee independent from the center, the sponsor or the investigator where the clinical trial is going to be carried out. This committee is formed by a multidisciplinary team: physician, pharmacologists, pharmacists and persons foreign to the sanitary profession, one of them graduated in law. The functions of the EC are to consider the methodological, ethical and legal aspects of the protocols, as well as the balance values risk - benefit of them. Practical information: In Spain there are 136 EC. They can act as reference EC or as local EC. Language: Spanish |
| Fees for initial application | Depending on the type of trial and on the centre (EC). Sponsor (or delegated entity) should contact each Ethics Committee before fees payment. |
| Document required (in addition to the general procedure) | Local document depending on the centre (EC) |
| Fees for amendments | Depending on the type of trial and on the centre (EC). Sponsor (or delegated entity) should contact each Ethics Committee before fees payment. |

**REGULATORY REFERENCES**

<table>
<thead>
<tr>
<th>Law/Decree/ Guidelines</th>
<th>RELEVANT LEGISLATION</th>
<th>GUIDANCE</th>
<th>WHERE TO FIND IT</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROSPECTIVE FOLLOW-UP POST-AUTORIZATION STUDY</td>
<td>RD 1344/2007 (PhV)</td>
<td>Local Guidance</td>
<td>At <a href="http://www.agemed.es">www.agemed.es</a></td>
</tr>
</tbody>
</table>

**Abbreviations:**
- AEMPS: Agencia Española de Medicamentos y Productos Sanitarios (Competent Authorities)
- CCAA: Comunidades Autónomas (local Competent Authorities)
- EC: Ethics Committee
- MP: Medicinal Product

**Observational Study Definition:**
“Estudio observacional: estudio en el que los medicamentos se prescriben de la manera habitual, de acuerdo con las condiciones normales de la práctica clínica (aquellas establecidas en la autorización de comercialización). La asignación de un paciente a una estrategia terapéutica concreta no está decidida de antemano por un protocolo de ensayo, sino que está determinada por la práctica habitual de la medicina, y la decisión de prescribir un medicamento determinado está claramente motivada de la decisión de incluir al paciente en el estudio. No se aplicará a los pacientes ninguna intervención, ya sea diagnóstica o de seguimiento, que no sea la habitual de la práctica clínica, y se utilizarán métodos epidemiológicos para el análisis de los datos recogidos. (Artículo 2, Definiciones, Real Decreto 223/2004, 6 de Febrero, por la que se regulan los ensayos clínicos con medicamentos).”

Comment: Article 2 defines observational studies. In summary, an observational study is a study where the MP is used following current clinical practice, according to approved conditions (indication, dosage and pharmaceutical form). No assignment of the patient to a particular therapeutic strategy is decided in advance in a study protocol (no randomisation). No intervention (diagnostic or follow-up intervention) is applicable to the patient if it is different from current clinical practice. Analysis used is based on epidemiologic methods.

Instruction
Practical aspects of interacting with authorities (Ethics committee and competent authority) throughout the conduct of a multinational clinical trial on medicinal product Sweden

Code
ECRIN-EC-QCD002-SW-V0.1

Approval: Date: Revision:

FLOW CHART: Ethics committee and Competent authority

Initial submission

SwedEn

Interventional research, Medicinal products

Reference Ethics Committee

Medical product agency MPA

EudraCT

* No time limit; Xenogeneric cell therapy; 90 days Gene therapy or genetically modified organisms

Interventional Research Med. products


* www.epn.se or www.riksdagen.se
Submission of amendments during the conduct of the trial

**Amendments of a clinical study on registered and investigational drugs**

**SWEDEN**

- **Interventional Research, medicinal products**
  - Send in letter and relevant documents
- **Substantial amendments**
  - Send in "Notification of amendment form" (EudraCT website) + Letter (specify EudraCT number and protocol code)
  - Approval
  - 35 days
  - For substantial amendments: always written letter from REC
- **Reference Ethics Committee**
- **Medicinal Products Agency**
  - Approval
  - 35 days
  - Fail

**Non-substantial amendments:**
Send in documents to MPA and REC for information only

- **COMPETENT AUTHORITY**
  - MEDICAL PRODUCT AGENCY
  - Läkemedelsverket
  - Box 26
  - SE-751 03 Uppsala

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**Declaration of the end of a clinical trial**

**Notification of end of a clinical study, registered and investigational drugs**

**SWEDEN**

- **Interventional Research, medicinal products**
- **End of trial according to protocol**
  - Within 90 days by investigator
  - Within 90 days by Sponsor
  - "Declaration of the End of Trial Form"
- **International multicentre trial**
- **Reference Ethics Committee**
  - Additional notification when trials at all participating centres are terminated.
- **Medicinal products agency MPA**

- "If the trial is completed or prematurely terminated, the "Declaration of the End of Trial form" must be submitted within 15 days.

- **COMPETENT AUTHORITY**
  - MEDICAL PRODUCT AGENCY
  - Läkemedelsverket
  - Box 26
  - SE-751 03 Uppsala

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www.lakemedelsverket.se
Sweden
Tel: +46 18 17 46 00
http://www.lakemedelsverket.se/
Practical information:
Language: Swedish or English (information and informed consent forms should be provided in Swedish)

<table>
<thead>
<tr>
<th>Local competent authority if applicable</th>
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<th>Document required (in addition to the general procedure)</th>
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<tr>
<th>Fees for initial application</th>
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<tbody>
<tr>
<td>URL source: <a href="http://www.lakemedelsverket.se/Tpl/NormalPage____1282.aspx">http://www.lakemedelsverket.se/Tpl/NormalPage____1282.aspx</a></td>
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<tr>
<td>Fee for initial application: 30,000 SEK. (Academic research without economic support from external sponsor may submit application free of charge.)</td>
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<tr>
<th>Fees for amendments</th>
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<tr>
<td>No fee for amendments.</td>
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**ETHICS COMMITTEES**

Ethics Committees: Sweden has six independent regional boards for research ethics review (Reference Ethics Committees), and one Central Ethics Committee (in Stockholm). Each committee is chaired by a judge. The other 15 members of each committee are appointed by the Government (5 should represent public interests and 10 should have a scientific expertise).

Practical information: The Reference Ethics Committees are situated in Stockholm, Uppsala, Lund, Umeå, Linköping and Gothenburg.

- Regionala etikprövningsnämnden i Göteborg
  Box 100
  405 30 Göteborg, Sweden

- Regionala etikprövningsnämnden i Linköping
  c/o Hälsouniversitetets kansli
  Sandbäcksgatan 7
  581 83 Linköping, Sweden

- Regionala etikprövningsnämnden i Lund
  Box 133
  221 00 LUND
  [Hämtställe 27], Sweden

- Regionala etikprövningsnämnden i Stockholm
  Postadress: Box 289
  171 77 STOCKHOLM, Sweden

- Regionala etikprövningsnämnden i Umeå
  Samverkanshuset
  Universitetsområdet
  901 87 Umeå, Sweden

- Regionala etikprövningsnämnden i Uppsala
  Box 1964
  751 49 UPPSALA, Sweden

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<th>Fees for initial application</th>
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<tr>
<td>URL source: <a href="http://www.epn.se">www.epn.se</a></td>
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<tr>
<td>The fees for initial application may vary from 5,000 SEK to 16,000 SEK (Medicinal Products, or multicenter trial).</td>
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<tr>
<th>Fees for amendments</th>
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<tr>
<td>URL source: <a href="http://www.epn.se">www.epn.se</a></td>
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<tr>
<td>Fee for amendments: 2,000 SEK.</td>
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**REGULATORY REFERENCES**

Law: Medicinal Products Act (SFS 1992:859), Medicinal Products Ordinance (SFS 2006:272), Act
<table>
<thead>
<tr>
<th>Decree</th>
<th>Läkemedelsverkets föreskrifter och allmänna råd (LVFS 2003:6) om klinisk prövning av läkemedel för humant bruk.</th>
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</table>
Instruction
Practical aspects of interacting with authorities (Ethics committee and competent authority) throughout the conduct of a multinational clinical trial on medicinal product
United Kingdom

FLOW CHART: Ethics committee and Competent authority

Initial submission

- It is the responsibility of the sponsor to ensure a scientific review, proportionate to the scale and importance of the research, has been undertaken before submitting an application to a REC.

- Submit study to R&D office at each site: www.clintrials.nhs.uk.

- Studies involving an IMP or a device also require authorisation from the MHRA.

- Submit SSI Forms to relevant local REC’s.

- Local RECs to advise main REC on site specific issues.

Complete Parts A + B of the REC application form, and if applicable Part C.

Phone the Central Allocation System (CAS) or your local REC to book the application.

Submit Part A + B of the application form and supporting documentation direct to the REC within 4 working days of booking.

Application received by the main REC office (60 day clock starts).

REC Co-ordinator validates application (5 working days).

Valid Application – Chief Investigator invited to REC meeting, or to be available by phone.

Application reviewed by the main REC.

Favourable Opinion (within 60 days).

Provisional opinion (60 days clock stops).

Unfavourable opinion (within 60 days).

- REC seeks advice from specialist referee (60 day clock does not stop).

- Modifications reviewed by Chair or Sub-committee.

- Modify and resubmit application.

- Appeal.

- YOU CAN NOW START!

Approval: [ ]
Date: [ ]
Revision: [ ]
**ECRIN SOPs**

Practical aspects of interacting with authorities (ethics committees and competent authorities) throughout the conduct of a multinational clinical trial on medicinal products – United Kingdom ECRIN-EC-QCD002-UK-V0.1

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**Submission of amendments during the conduct of the trial**

- **Legal responsibility to decide whether an amendment is substantial lies with sponsor.**
  - Sponsor requires authorisation from competent authority only
  - Sponsor requires favourable opinion from ethics committee

- **Sponsor submits EU Notification of Amendment Form to MHRA. Copy to main REC for information.**
  - Co-ordinator acknowledges receipt within 30 days by sending SL29 to sponsor

- **Amendment notified by Chair.**
  - Main REC sends copy of letter from MHRA to sponsor giving a decision on the request for authorisation of the amendment. Letter placed on file.
  - Amendment reviewed by main REC within 30 days of receiving valid Notice of Amendment.

- **Valid Notice of Amendment**
  - Co-ordinator notifies sponsor using SL27

- **Invalid Notice of Amendment**
  - Co-ordinator notifies sponsor using SL29

- **Favourable Opinion**
  - Co-ordinator notifies sponsor and CI of committee’s decision using SL32
  - Copy sent to MHRA

- **Unfavourable Opinion**
  - Co-ordinator notifies sponsor and CI of committee’s decision using SL33
  - Copy sent to MHRA

- **Sponsor may submit a modified amendment.**
  - Sponsor submits a modified amendment and modified supporting documents to main REC at least 14 days before it is planned to implement the amendment.

- **Main REC to review modified amendment (Sub-committee or Chairman/Chair under delegated authority) and notify sponsor of decision within 14 days of receiving modified amendment.**

- **Main REC notifies sponsor and CI of favourable opinion using SL34**

- **Main REC notifies sponsor and CI of unfavourable opinion using SL35.**
  - **AMENDMENT CANNOT BE RESUBMITTED.**

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Notification and reports can be submitted by Sponsor; Sponsor’s Legal Representative, Chief Investigator (CI) or another person or organisation authorised by the Sponsor.

**REC Standard Letters**

- **SL21** Extension of favourable opinion to additional site(s) - re-issue of site approval form (SF1)
- **SL27** Valid notice of a substantial amendment for ethical review
- **SL26** Valid notice of a substantial amendment for no form
- **SL25** Invalid notice of a substantial amendment
- **SL30** Notification of substantial amendment to CTIMP notified for information only
- **SL32** Favourable opinion of a substantial amendment
- **SL35** Unfavourable opinion of a substantial amendment
- **SL34** Favourable opinion of a modified amendment
- **L35** Unfavourable opinion of a modified amendment
- **SL38** End of study declaration form
Declaration of the end of a trial

**Conclusion of a trial**

- **Trial terminated early**
  - Sponsor submits "Notification of the conclusion of a clinical trial" form to main REC and MHRA within **15 days** of the conclusion of the trial. Form to be accompanied with explanatory note stating reason for early termination.
  - Main REC coordinator returns **SL39** to acknowledge receipt of notification. MHRA acknowledges receipt of notification.
  - Sponsor submits final study report within 12 months of the conclusion of the trial. Note: Details of arrangements for publication and dissemination including feedback to participants to be provided to main REC.
  - Main REC coordinator returns **SL40** to acknowledge receipt of final study report.

- **Trial concludes as specified in the protocol**
  - Sponsor submits "Notification of the conclusion of a clinical trial" form to main REC and MHRA within **90 days** of the conclusion of the trial.
  - Main REC coordinator returns **SL39** to acknowledge receipt of notification. MHRA acknowledges receipt of notification.
  - Sponsor submits final study report within 12 months of the conclusion of the trial. Note: Details of arrangements for publication and dissemination including feedback to participants to be provided to main REC.
  - Main REC coordinator returns **SL40** to acknowledge receipt of final study report.

The date and/or event that indicate the conclusion of the trial should be specified in the study protocol. Any changes to this definition should be notified as a substantial amendment.

Notification and reports can be submitted by Sponsor, Sponsor’s legal representative, Chief Investigator (CI) or another person or organisation authorised by the Sponsor.


REC Standard Letters
SL39 Acknowledgement of declaration of end of study
SL40 Acknowledgement of declaration of end of study
### COMPETENT AUTHORITY

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<thead>
<tr>
<th>Competent authorities</th>
<th>Medicines and Healthcare products Regulatory Agency (MHRA)</th>
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|                       | 10-2 Market Towers  
1 Nine Elms Lane  
London  
SW8 5NQ |
|                       | Tel: +44 (0) 20 7084 2000 (weekdays 0900 -1700)  
Tel: +44 (0) 20 7210 3000 (other times)  
Fax: +44 (0) 20 7084 2353  
Email: info@mhra.gsi.gov.uk |
|                       | MHRA Clinical Trials Unit  
Fax: + 44 (0) 20 7084 2443  
E-mail: clintrialhelpline@mhra.gsi.gov.uk |
|                       | http://www.mhra.gov.uk/Contactus/SpecificenquiriesbyMHRADivision/Licensing/index.htm |
|                       | Practical information: http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Clinicaltrials/MakingclinicaltrialsubmissionstotheMHRA/index.htm |
|                       | Language : English |

| Local competent authority if applicable | Not applicable |

| Document required (in addition to the general procedure) | UK specific instructions in relation to the format of trial submissions are available at http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Clinicaltrials/MakingclinicaltrialsubmissionstotheMHRA/index.htm. |

| Fees for initial application | Information on fees can be accessed at the following link: http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Clinicaltrials/Fees/index.htm |
| Fees for amendments          | Information on fees can be accessed at the following link: http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Clinicaltrials/Fees/index.htm |

### ETHICS COMMITTEES

| Ethics committees | National Research Ethics Service  
4-8 Maple Street,  
London W1T 5HD,  
United Kingdom.  
Tel: + 44 (0) 20 7927 9898  
Fax: + 44 (0) 20 7927 9899  
Email: queries@nres.npsa.nhs.uk  
Website: http://www.nres.npsa.nhs.uk/ |
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### REGULATORY REFERENCES

**Law**
- The Medicines for Human Use (Clinical Trials) Regulations 2004 SI 2004/1031
- The Medicines for Human Use (Clinical Trials) Amendment Regulations 2006 (SI 2006/1928)
  [http://www.opsi.gov.uk/si/si2006/20061928.htm](http://www.opsi.gov.uk/si/si2006/20061928.htm)
- The Medicines for Human Use (Clinical Trials) Amendment (No.2) Regulations 2006 (SI 2006/2984)
- The Medicines for Human Use (Clinical Trials) and Blood Safety and Quality (Amendment) Regulations 2008 (SI 2008/941)

**Decree**
- Not applicable