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

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Work package 1: **Transnational working group on ethics and
interaction with ethics committees**

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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 Sécurité 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	Comite 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
EMA	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

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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 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 arise). 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 operating¹. 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.

¹ <http://www.cvk.im.dk/cvk/site.aspx?p=513>

² <http://www.recherchebiomedicale.sante.gouv.fr/pro/comites/coordonnees.htm#>

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 committees³. They can be at the level of chamber of physicians (Ärzttekammer) (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.⁴

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

³ <http://www.zentrale-ethikkommission.de/>

⁴ 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

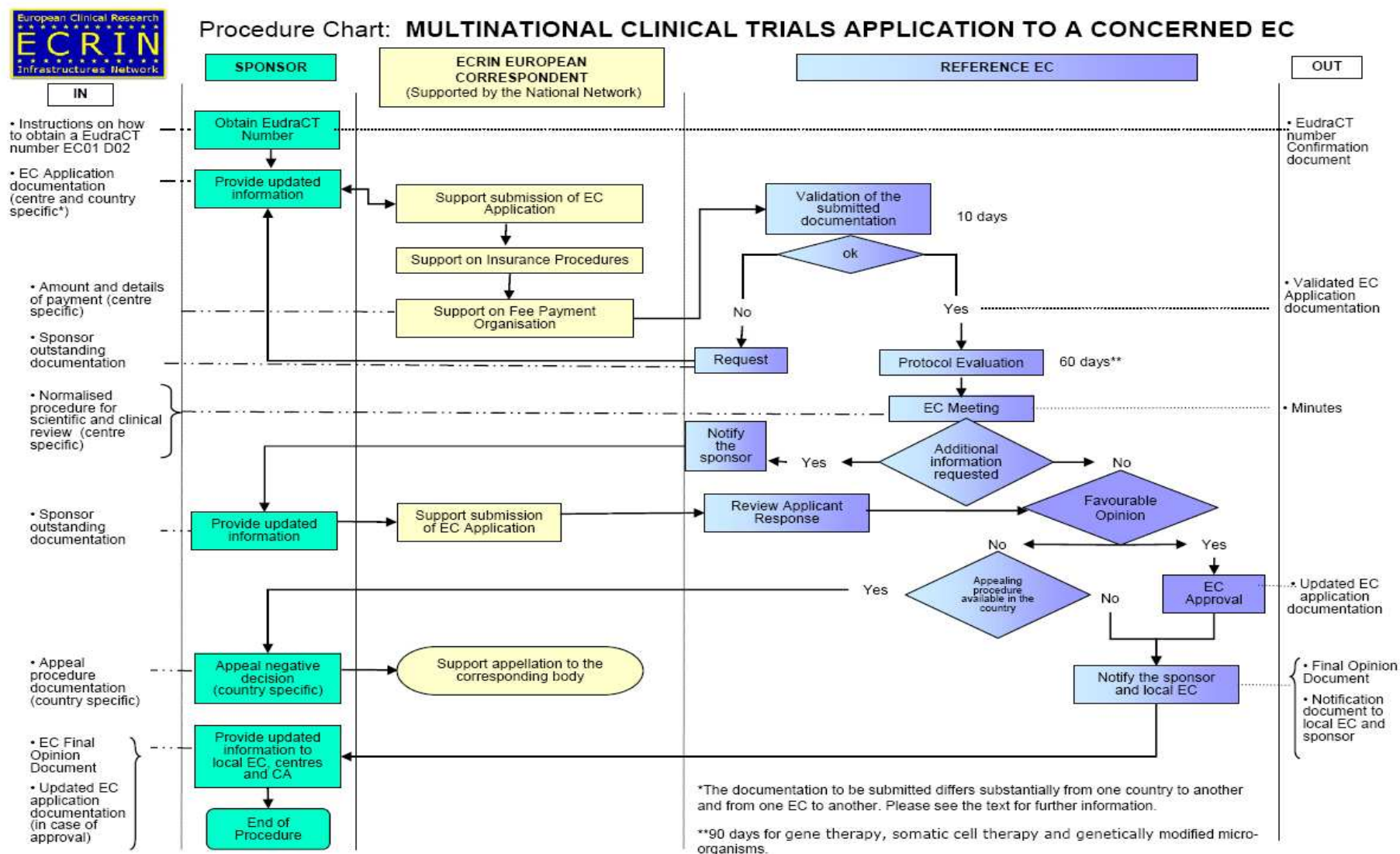
8.1 Procedure chart on "Multinational clinical trials on medicinal products. Submission to an ethic committee. Common framework."

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

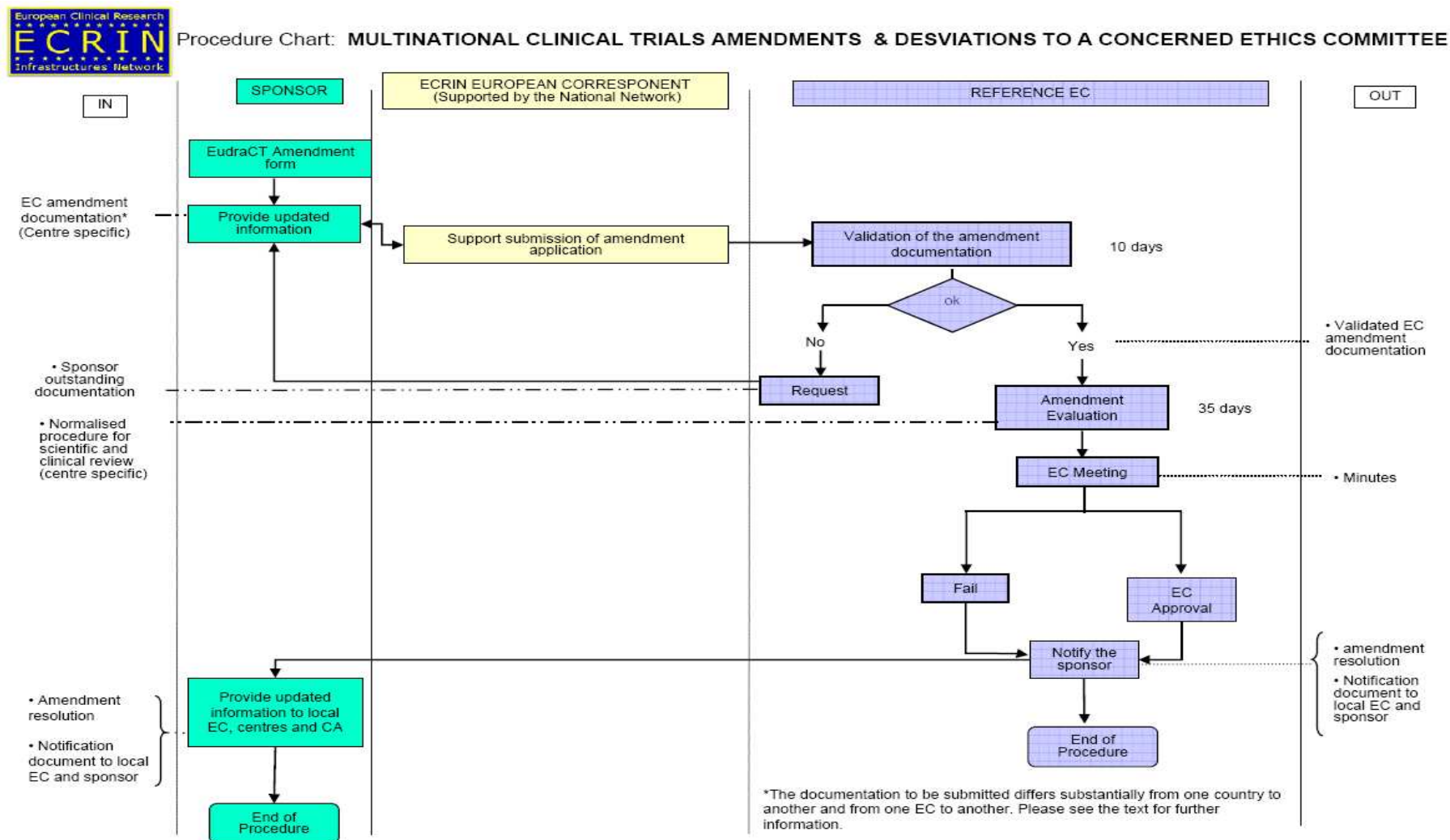
8.3 Procedure chart on "End of a multinational clinical trials on medicinal products. Notifications to an ethic committee". Common framework"

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"

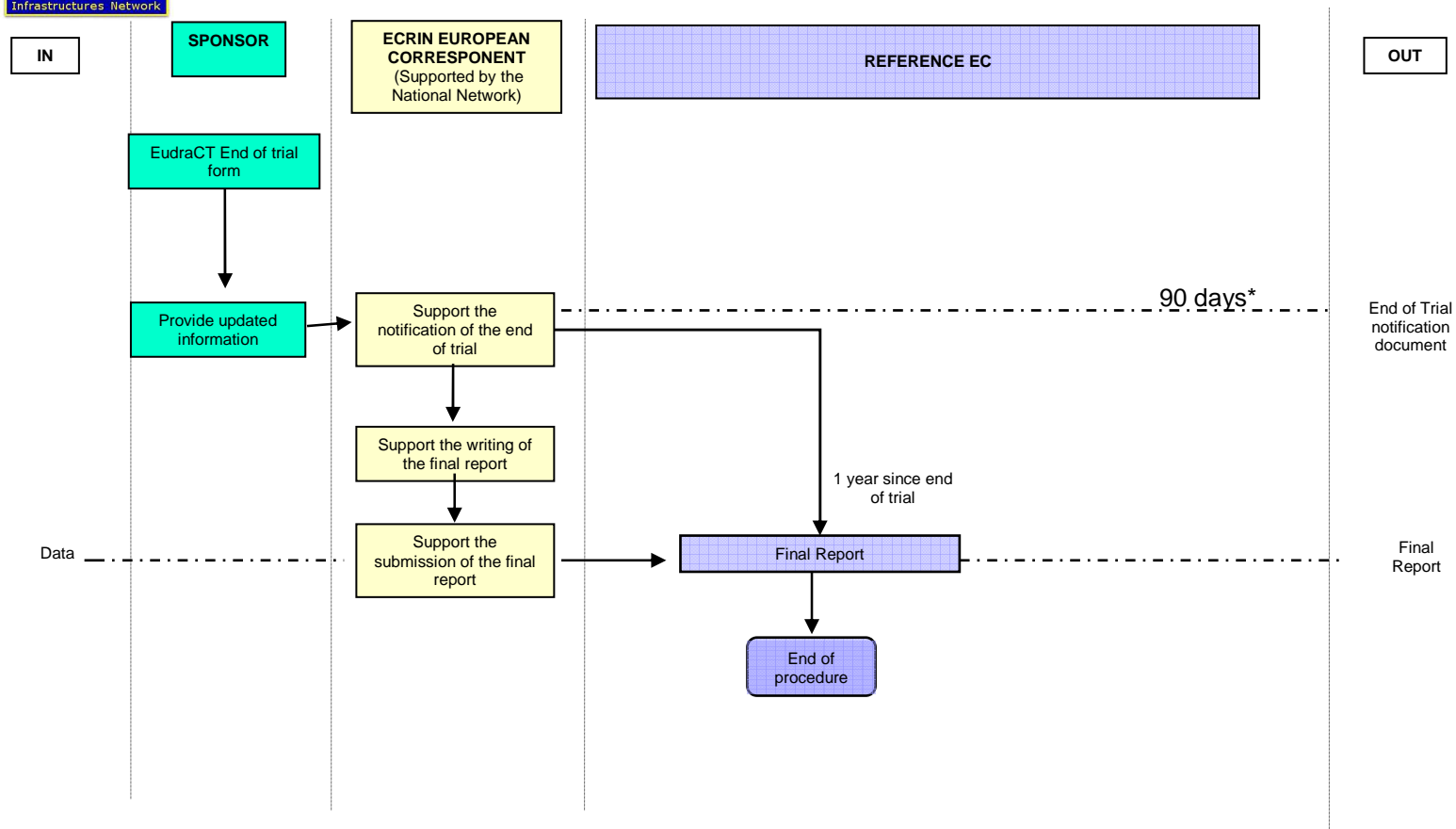


8.2 Procedure chart on "Multinational clinical trials on medicinal products. Amendments and deviations application to an ethic committee. Common framework"




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

Procedure Chart: **END OF A MULTINATIONAL CLINICAL TRIAL**



*** 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

Usually < 35 days

Expedited review
by appointed board (EC Chair)

* 35 days

External Reviewer (optional)

90 days



One clock stop possible

Short notice at EC Meeting

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

* In case of uncertainties

Notification of non-approval to sponsor within 60 days

Optional: Referral to „Arzneimittelbeirat“

Notification to CA

atcrin
austrian clinical research infrastructures network

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>

Submission of amendments during the conduct of the trial

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

atcrin

austrian clinical research infrastructures network

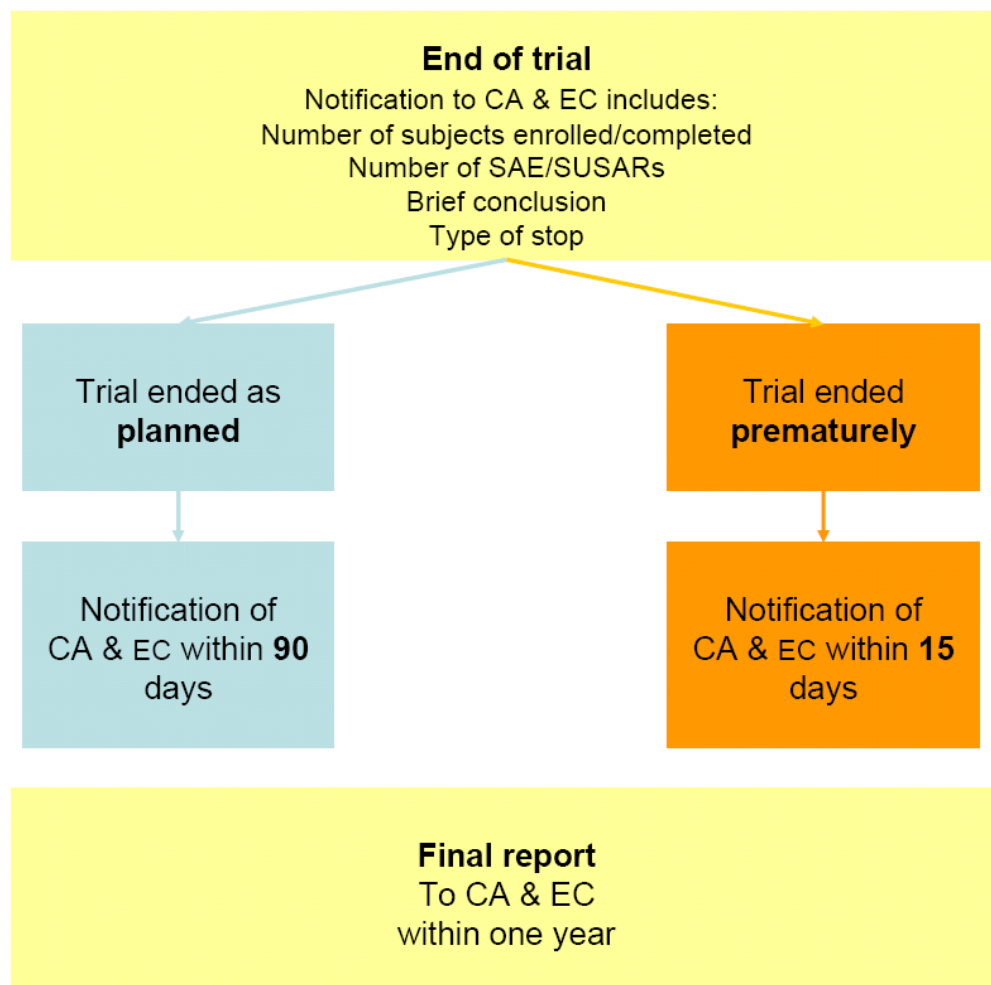
Relevant legislation: The Medicines Act (Arzneimittelgesetz); implementing Directive 2001/20/EC in 2004
The Genetic Act (Gentechnikgesetz) 1994

Where to find it: <http://www.ris2.bka.gv.at>

Declaration
of the end of
a clinical
trial

Austria

Ethics committee interaction – **after** the trial



COMPETENT AUTHORITY	
Competent authorities	<p>Bundesamt für Sicherheit im Gesundheitswesen AGES PharmMed Schnirchgasse 9 A-1030 Vienna Austria Tel: +43 50 555-0; 050 555-DW www.ages.at</p> <p>Practical information: If you intend to contact someone at the AGES PharmMed the generic email firstname.surname@ages.at can be used</p> <p>Language: German</p>
Local competent authority if applicable	None
Documents required (in addition to the general procedure)	None
Fees for initial application	None There is one for medical devices (2500 € if you submit before initiation of the study, 7500€ thereafter)
Fees for amendments	None

ETHICS COMMITTEES	
Ethics committee REC, here means a research ethics committee which is entitled to review a single opinion	<p>REC EK Med.Universität Wien ethik-kom@meduniwien.ac.at www.meduniwien.ac.at/ethik Univ.Prof.Dr.Ernst Singer Borschkegasse 8b/E 06 A-1090</p> <p>REC EK der Stadt Wien gemäß KAG, AMG und MPG ethikkommission@m15.magwien.gv.at www.magwien.gv.at/ma15/ethikkommission/index.htm SR Dr.Hans Serban LL.M. TownTown, Thomas-Klestil-Platz 8 A-1030</p> <p>REC EK des Landes Niederösterreich post.ethikkommission@noel.gv.at www.noel.gv.at/ethikkommission Mag.Robert Bruckner Abt. Sanitätsrecht u. Krankenanstalten, Landhausplatz 1, Haus 15B A-3109</p> <p>REC EK des Landes Oberösterreich johannes.fischer@gespag.at bzw elgin.drda@ooe.gv.at http://ooe-ethikkommission.at Univ.Prof.Prim.Dr.Johannes Fischer Landesnervenklinik Wagner-Jauregg, Wagner-Jauregg Weg 15 A-4020</p> <p>REC EK f.d.Bundesland Salzburg</p>


	<p>ethikkommission@salzburg.gv.at www.salzburg.gv.at/ethikkommission HR Dr.Alois Grüner Sebastian-Stief-Gasse 2 A-5010</p> <p>REC EK Med.Universität Graz ethikkommission@meduni-graz.at www.meduni-graz.at/ethikkommission/Graz/index.htm Univ.Prof.DI.Dr.Peter H. Rehak Auenbruggerplatz 2 A-8036</p> <p>REC EK Med.Universität Innsbruck Ethikkommission@i-med.ac.at www.i-med.ac.at/ethikkommission Univ.Prof.DI Dr.Peter Lukas Geschäftsstelle, Innrain 43 A-6020</p> <p>EK des Landes Burgenland gemäß KAG, AMG und MPG r.peischl@krages.at www.krages.co.at/ekommm/index.asp PDir.DGKS Renate Peischl, MAS Josef-Hyrtl-Platz 4 A-7000</p> <p>EK des Landes Kärnten Ethik@lkh-klu.at www.ethikkommission-kaernten.at OA Dr.Gerhard Kober LKH Klagenfurt, St.-Veiter-Strasse 45-47 A-9020</p> <p>EK KH Elisabethinen rainer.schoefl@elisabethinen.or.at Univ.Doiz.Dr.Rainer Schöfl Fadingerstrasse 1 A-4010</p> <p>EK KH Barmh.Brüder Linz kurt.lenz@bblinz.at Prim.Univ.Prof.Dr.Kurt Lenz Seilerstätte 2 A-4020</p> <p>EK KH Barmh.Schwestern ethik.linz@bhs.at Univ.Prof.Dr.Peter Siostrzonek Seilerstätte 4 A-4020</p> <p>EK f.d.Bundesland Steiermark FA8B@stmk.gv.at www.verwaltung.steiermark.at/cms/ziel/442986/DE/ HR Dr.Odo Feenstra Amt d. Stmk.LR, FA Gesundheitswesen, Paulustorgasse 4/II A-8010</p>
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	<p>EK KH Barmh.Brüder – Marschallgasse guenther.weber@bbgraz.at Prim.Univ.Doiz.Dr.Günther Weber Marschallgasse 12 A-8020</p> <p>EK KH Barmh.Brüder - Eggenberg peter.koeltringer@bbegg.at Prof.Dr.Peter Költringer Bergstrasse 27 A-8020</p> <p>EK des Landes Vorarlberg ethikkomm.vlb@bregenznet.at www.ethikkommission-vorarlberg.at Mag.pharm.Dr.Helmut Grimm Geschäftsstelle, Rathausstrasse 15 A-6900</p> <p>EK der Allgemeinen Unfallversicherungsanstalt helmut.koeberl@auva.sozvers.at Dr.Helmut Köberl Adalbert-Stifter-Strasse 65 A-1200</p> <p>EK KH d. Barmh. Brüder Wien abteilung.interne@bbwien.at Doz.Dr.Stefan Kudlacek Große Mohrengasse 9 A-1020</p> <p>EK Confraternität-Privatklinik Josefstadt dieter.volc@pkj.at Prim.Dr.Dieter Volc Skodagasse 32 A-1080</p> <p>EK Privatklinik Döbling dieter.volc@pkj.at Prim.Dr.Dieter Volc Heiligenstädter Strasse 57-63 A-1190</p> <p>EK St.Anna Kinderspital gadner@acrl.univie.ac.at www.stanna.at Dr.Roland Lavaulx-Vrecourt Kinderspitalgasse 6 A-1090</p> <p>EK KA des Göttlichen Heilandes michael.peintinger@meduniwien.ac.at OA Dr.Michael Peintinger Dornbacher Strasse 20-28 A-1170</p> <p>EK Österreichische Arbeitsgemeinschaft für Klinische Pharmakologie und Therapie & Institut für Hypertoniker office@ethikkommission-klinpharm.at www.ethikkommission-klinpharm.at</p>
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	<p>Univ.Prof.Dr.Gerhart Hitzenberger Kinderspitalgasse 10/15 A-1090</p> <p>EK Rheuma-Zentrum Wien-Oberlaa rheuma-zentrum@oberlaa.at OA Dr.Omid Zamani Kurbadstrasse 10 A-1107</p> <p>EK Forschungsinstitut des Wiener Roten Kreuzes forschung@w.roteskreuz.at www.wrk.at/forschungsinstitut Mag.Alexander Lang Nottendorfer Gasse 21 A-1030</p> <p>EK KH Barmh.Schwestern, Wien office.wien@bhs.at Prim.Dr.Boris Todoroff Stumpergasse 13 A-1060</p> <p>EK Privatkrankenanstalt Rudolfinerhaus w.weissenhofer@rudolfinerhaus.at Univ.Prof.Dr.Fritz Paschke Billrothstrasse 78 A-1090</p>
Fees for initial application	<p>Recommendation for all ECs in Austria – usually they stick to this: Monocenter studies: 1500 € per application/protocol (incl. all SUSARS, amendments, etc.)</p> <p>Multicenter studies: Reference EC: 4000 € per application/protocol (incl. all SUSARS, amendments, etc.) Local EC: 500 € per application/protocol (incl. all SUSARS, amendments, etc.)</p> <p>Fee waiver for “academic” non-commercial studies</p>
Fees for amendments	Included in initial fee

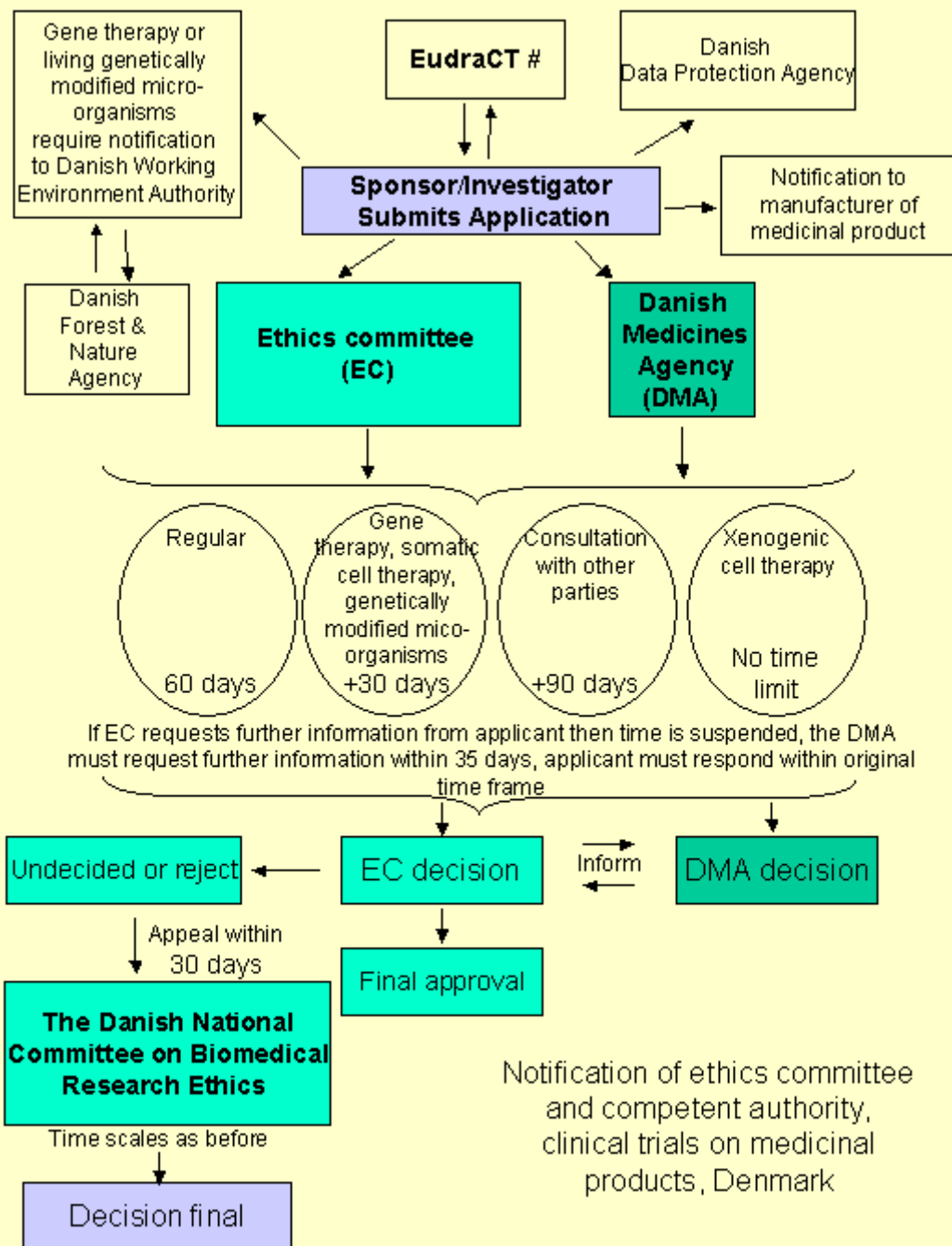
REGULATORY REFERENCES

Law	<p>Austrian Law for medicinal products</p> <p>Österreichisches Arzneimittelgesetz (AMG): Bundesgesetz vom 2. März 1983 über die Herstellung und das Inverkehrbringen von Arzneimitteln (Arzneimittelgesetz) BGBl. Nr. 185/1983 in der geltenden Fassung. Für Klinische Prüfungen relevante Novellen: BGBl. I Nr. 35/2004, Nr. 107/2005 und Nr. 153/2005 http://ris.bka.gv.at/</p>
Decree	

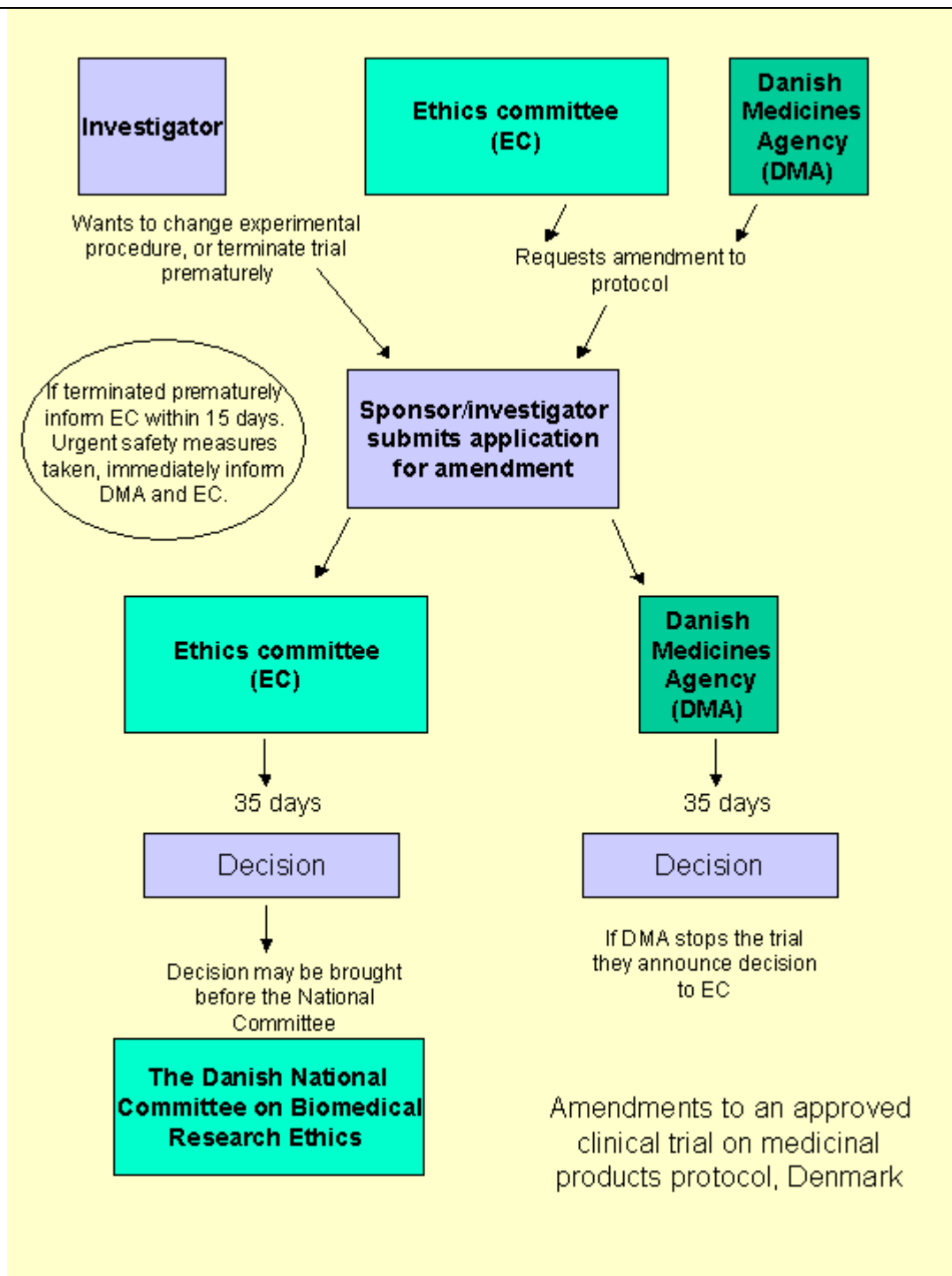
	Instruction Practical aspects of interacting with authorities (ethics committees and competent authorities) throughout the conduct of a multinational clinical trial on medicinal products Denmark	Code ECRIN-EC- QCD002-DK-V0.1
Approval:	Date:	Revision:

FLOW CHART: Ethics committee and competent authority

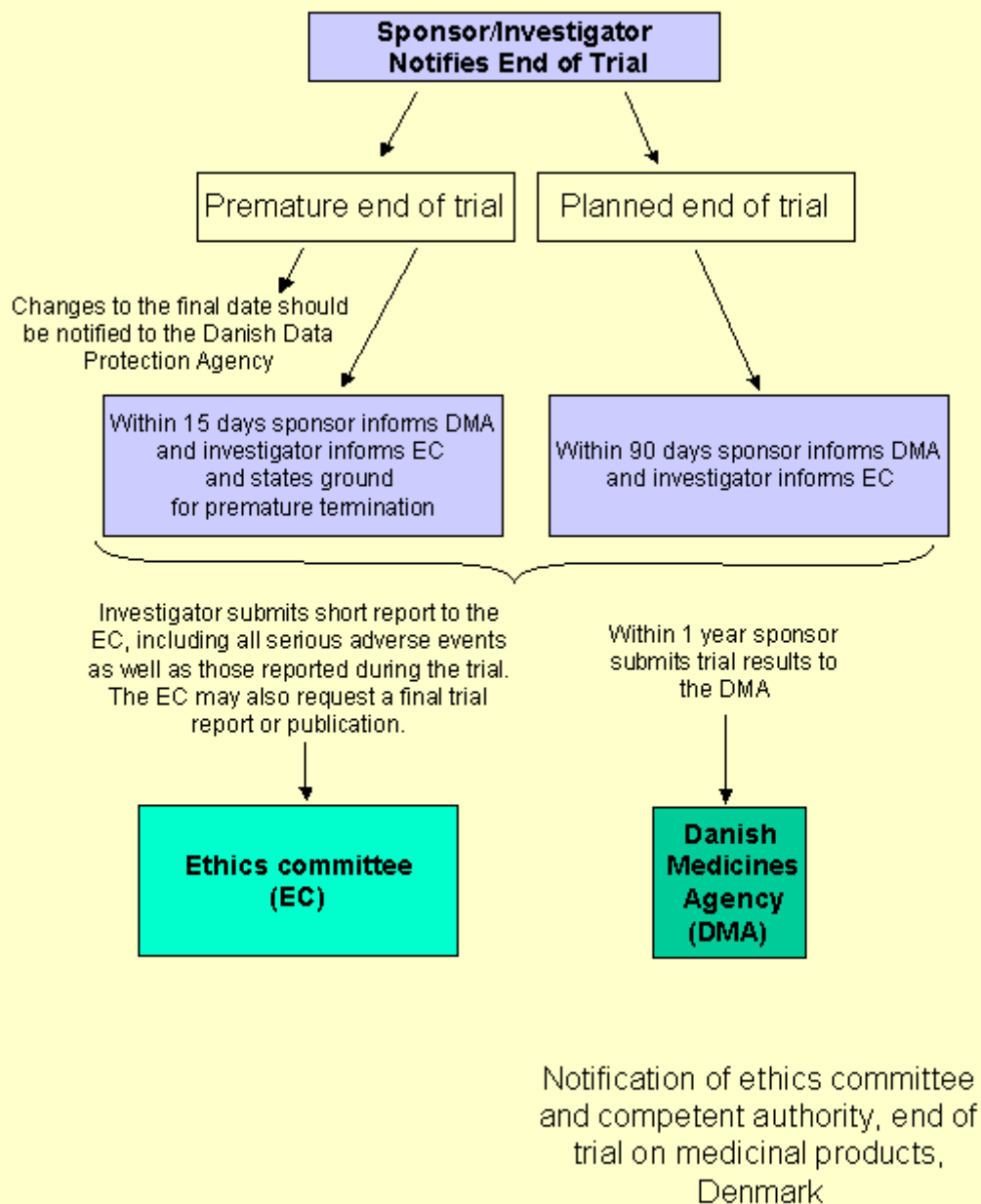
Initial submission



Submission of amendments during the conduct of the trial



Declaration
of the end of
a clinical
trial



COMPETENT AUTHORITY	
Competent authorities	<p>The Danish Medicines Agency Axel Heides Gade 1 DK-2300 København S</p> <p style="text-align: center;">tlf.: +45 44 88 95 95 fax +45 44 88 95 99</p> <p>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</p> <p>Practical information:</p> <p>Language: Danish or English</p>
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	<p>Den Centrale Videnskabsetiske Komité Slotsholmsgade 12 1216 København K</p> <p>Tlf. +45 7226 9370 Fax +45 7226 9380 E-mail cvk@sum.dk</p> <p>Practical information: The application needs to be submitted to one of the five regional ethics committees, according to where the investigator resides.</p> <p>Language: Danish</p>
Fees for initial application	4,000 DKK Waiver of fee for initiating investigators from public hospitals.
Fees for amendments	1,500 DKK

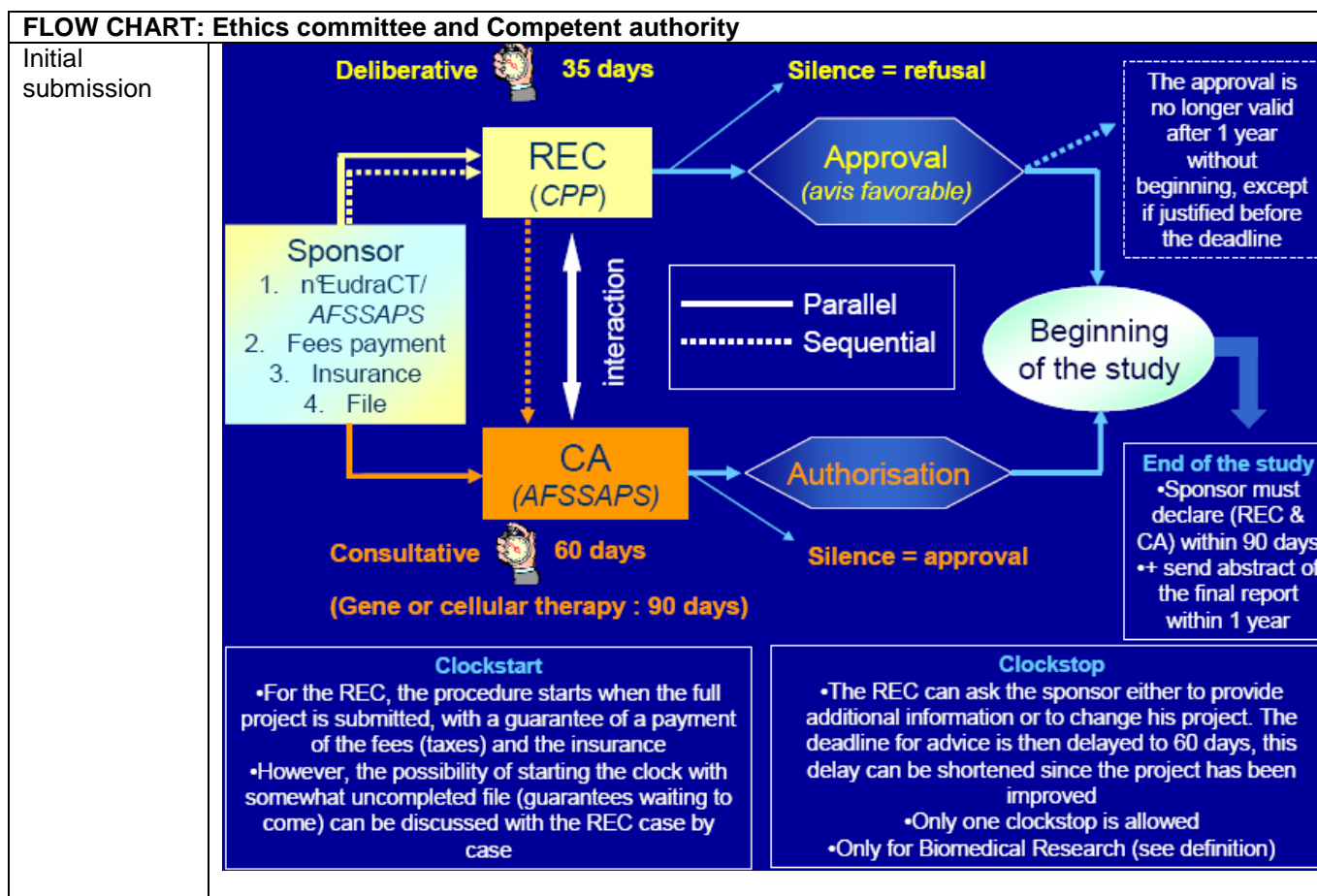
REGULATORY REFERENCES

Law

	Relevant Legislation	Guidance	Where to find it
Act on the Biomedical Research Ethics Committee System	Act 402 of 28/05/2003	Guidelines on the Biomedical Research Ethics Committee System	http://www.cvk.sum.dk/cvk/site.aspx?p=150 http://www.cvk.im.dk/cvk/site.aspx?p=513
Danish Medicines Act	Section XI, Act 1180 of 12/12/2005	Guideline for applications for authorisation of clinical trials of medicinal products on humans, October 2006	http://ms-lw.livportaler.dk/ShowDoc.aspx?schultzlink=ov20051180uk#pkt88 http://www.dkma.dk/1024/visUKLSArtikel.asp?artikelID=6181
Act amending the act on a biomedical research ethics committee system and treatment of biomedical research projects	Act 272 of 01/04/2006		http://www.cvk.im.dk/cvkEverest/Publications/cvk%20Eim%20Edk%20%20%20dokumenter/Englis h/20061129155844/CurrentVersion/ovaending UK.pdf
The Act on Processing of Personal Data	Act 429 of 31/05/2000		http://www.databl synet.dk/english/the-act-on-processing-of-personal-data/
European legislation, Clinical trial on medicinal product	Directive 2001/20/EU L 121/34		http://europa.eu/eur-lex/pr/en/obj/dat2001/1121/112120010501en00340044.pdf


Decree

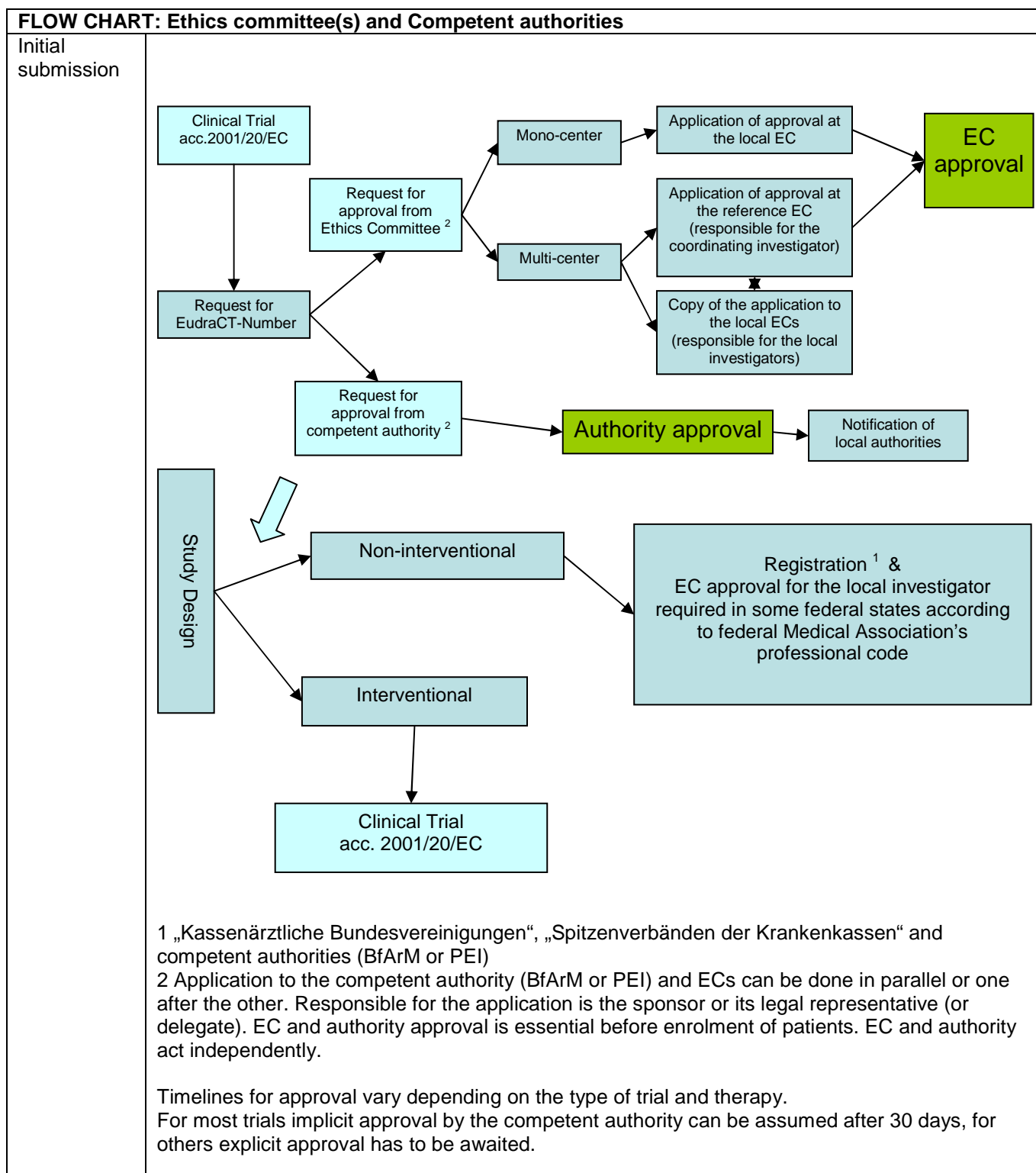
	Instruction Practical aspects of interacting with authorities (ethics committees and competent authorities) throughout the conduct of a multinational clinical trial on medicinal products France	Code ECRIN-EC-QCD002 – FR-V0.4
Approval:	Date:	Revision:



<p>Submission of amendments during the conduct of the trial</p>	<div data-bbox="347 152 1497 1008"> <h3 style="color: cyan;">Substantial amendments</h3> <div style="border: 1px solid black; padding: 5px; margin-bottom: 10px;"> Definition: every change in the research protocol that have a relevant consequence on <ul style="list-style-type: none"> • the safety or physical or mental integrity of the subjects; • the scientific value of the trial; • the conduct or management of the trial; or • the quality or safety of any IMP used in the trial. </div> </div>
<p>Declaration of the end of a clinical trial</p>	<p>Please see in the initial submission slide also the end of trial information.</p>
<p>COMPETENT AUTHORITY</p>	
<p>Competent authorities</p>	<p>AGENCE FRANCAISE DE SECURITE SANITAIRE DES PRODUITS DE SANTE (AFSSAPS) Unités Essais Cliniques 143, 147 boulevard Anatole France 93285 Saint-Denis Cedex Tel: 01.55.87.30.00 http://agmed.sante.gouv.fr/</p> <p>Practical information: Language: French or English (information and informed consent form should be provided in French)</p>
<p>Local competent authority if applicable</p>	<p>NA</p>
<p>Document required (in addition to the general procedure)</p>	<p>Insurance attestation</p>


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 (infos pratiques: montant de la taxe)
Fees for amendments	For the amounts please see : 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
Fees for initial application	No specific fee (see previous paragraph)
Fees for amendments	No specific fee (see previous paragraph)
REGULATORY REFERENCES	
Law	<p>Law n°2004-806 (9 août 2004) Code de la Santé Publique</p> <ul style="list-style-type: none"> • 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 • L1123-59, 60: End of the study <p>Law n°2002-303 (04/03/2002)</p> <ul style="list-style-type: none"> • Patients 'rights <p>Law n°2004-800 (07/08/2004) related to bioethics</p> <ul style="list-style-type: none"> • Biological collections <p>Law n°1978-17 (06/01/1978) amended by</p> <ul style="list-style-type: none"> • Electronic files and freedom
Decree	<p>Decision du 24 Novembre 2006 fixant les règles de bonnes pratiques cliniques pour les recherches biomédicales portant sur des médicaments à usage humain</p> <ul style="list-style-type: none"> • Good clinical practices in biomedical research on drugs. Physical/moral persons responsible for the research <p>Decree n°2006-477 (26/04/06) and decree n°2007-122 0 (10/08/07)</p> <ul style="list-style-type: none"> • Biological collections <p>Order of the 08/11/2006 (22/11/2006)</p> <ul style="list-style-type: none"> • Documents and archives <p>Order of the 09/03/2007 (22/03/2007)</p> <p>Assessment of current care. Definition of medicinal products.</p>

	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-QCD002- DE-V0.1
Approval:	Date:	Revision:

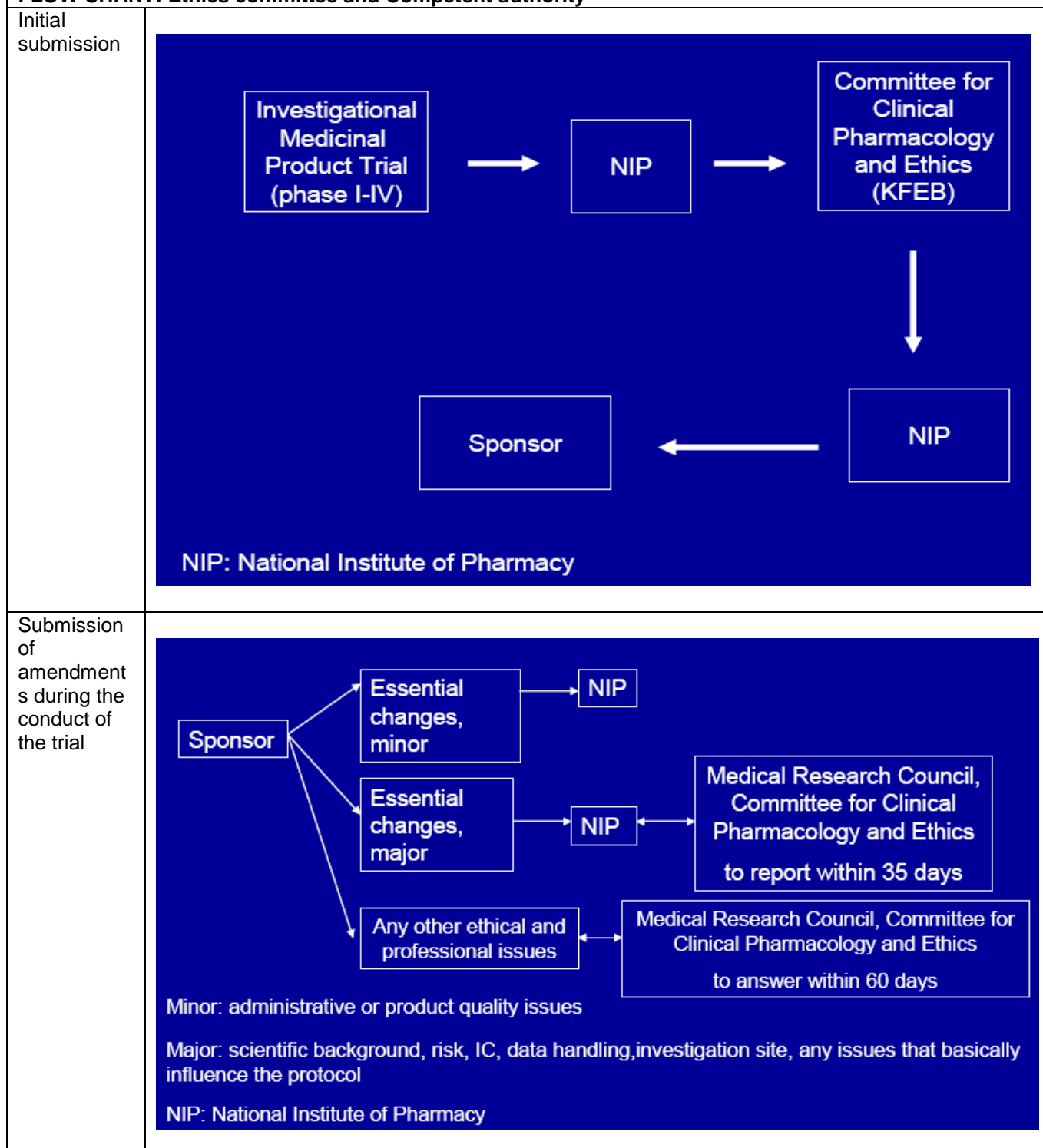


Submission of amendments during the conduct of the trial	<pre> graph TD A[Type of amendment] --> B[Additional trial site] A --> C[Amendment to Protocol or Procedures of a Clinical Trial 3] B --> D[Request for approval to reference and concerned local Ethics Committee] C --> E[Request for approval to reference and concerned local Ethics Committees] C --> F[Request for approval to competent authority] D --> G[EC approval] E --> G F --> H[Authority approval] G -.-> I[Notification of additional trial site to local authority] </pre> <p>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</p>
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	<p><u>For medicinal products and medical devices:</u> 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</p> <p><u>For biological medicinal products:</u> 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</p>
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

	<p>Application format for EC approval is mostly harmonized</p> <p>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.</p> <p>Although mostly harmonized the documentation requested on local site and staff may differ among the local ECs.</p>
Fees for initial application	Not harmonised. See the individual Ethics Committees.
Fees for amendments	Not harmonised. See the individual Ethics Committees.
REGULATORY REFERENCES	
Laws	<p>German Drug Law (AMG, esp. §§ 40 – 42) http://bundesrecht.juris.de/amg_1976/</p> <p>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: http://www.bmg.bund.de/cln_110/nn_1200354/SharedDocs/Downloads/EN/health/AMG-pdf.templateId=raw.property=publicationFile.pdf/AMG-pdf.pdf</p>
Decrees	<p>German Good Clinical Practice Decree (GCP-V) http://bundesrecht.juris.de/gcp-v/</p>


	Instruction Practical aspects of interacting with authorities (ethics committees and competent authorities) throughout the conduct of a multinational clinical trial on medicinal products Hungary	Code ECRIN-EC-QCD002-HU-V0.3
Approval:	Date:	Revision:

FLOW CHART: Ethics committee and Competent authority



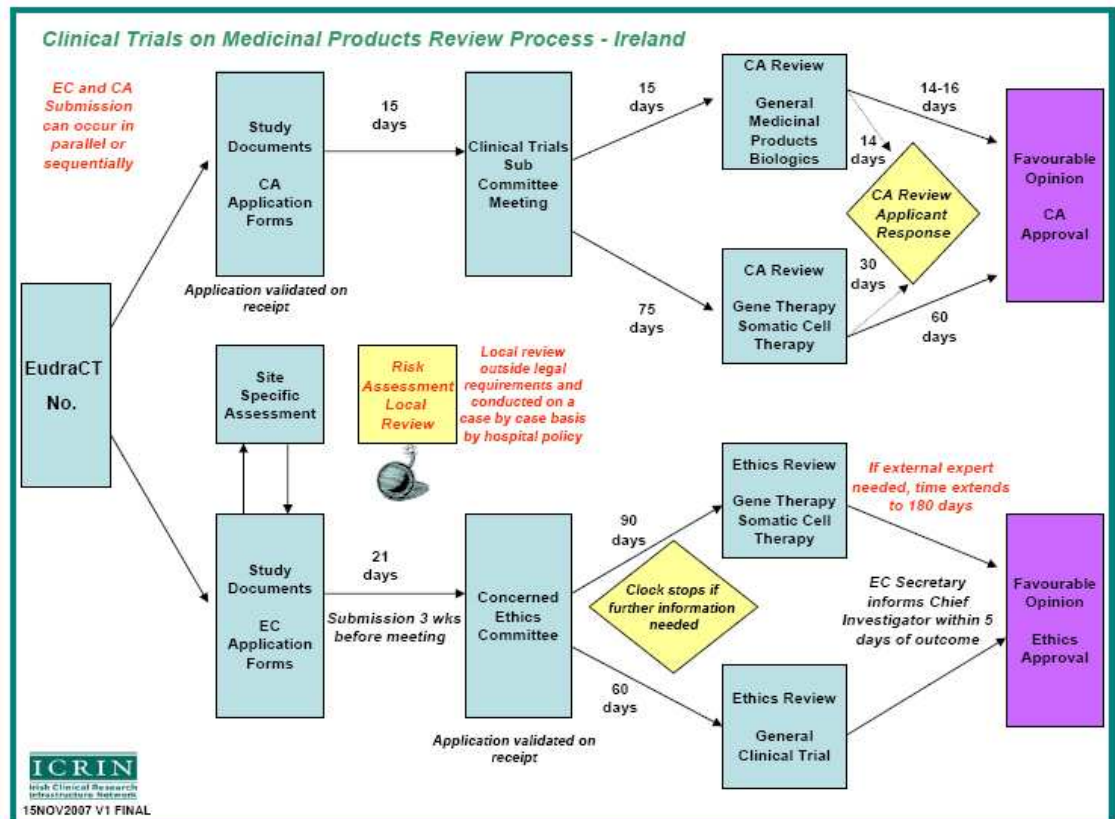
Declaration of the end of a clinical trial	<div data-bbox="363 197 1460 383"> <pre> graph LR A[Sponsor to report within 90 days to] --> B[NIP to inform within 8 days] B --> C[Medical Research Council, Committee for Clinical Pharmacology and Ethics] </pre> </div> <p>NIP: National Institute of Pharmacy</p> <p>Note: if trial is stopped earlier than defined the sponsor is to report to NIP within 15 days</p>
COMPETENT AUTHORITY	
Competent authorities	<p>Országos Gyógyszerészeti Intézet (OGYI) National Institute of Pharmacy (NIP)</p> <p>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/</p> <p>Practical information : Language : Hungarian and English</p>
Local competent authority if applicable	
Document required (in addition to the general procedure)	

Fees for initial application	
Fees for amendments	
ETHICS COMMITTEES	
Ethics committees	<p>Practical information : National Ethics Commissions within the Health Science Council</p> <ul style="list-style-type: none"> - Scientific and Research Ethics Commission (TUEB) - Clinical Pharmacology Ethics Commission (KFEB) - Human reproduction commission <p>Regional Research Ethics Boards (RKEB)</p> <ul style="list-style-type: none"> - 12 regional research ethics boards throughout the country <p>Institutional research Ethics boards</p> <ul style="list-style-type: none"> - board set-up at each health care institution where research is carried out <p>Language:</p>
Fees for initial application	
Fees for amendments	
REGULATORY REFERENCES	
Law	XCV. Law 2005 on the modification on the laws regulating drugs for human use and on the regulation of drug market
Decree	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

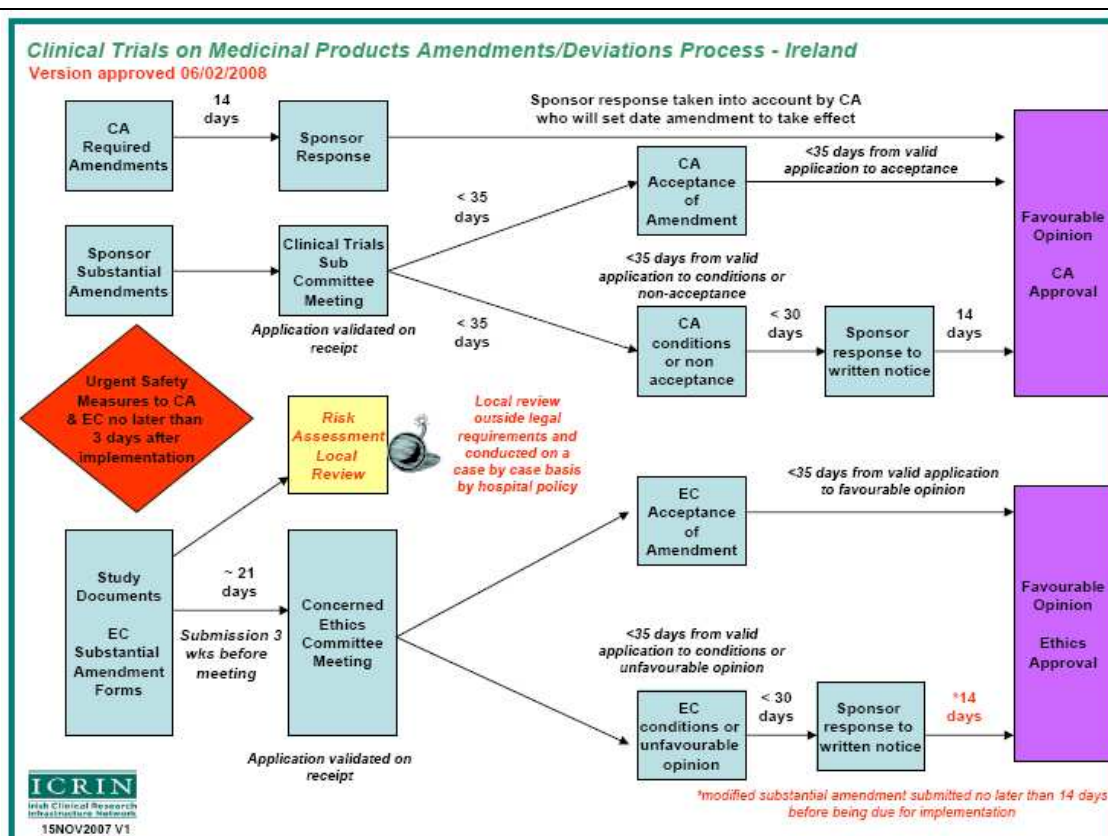
	<p align="center">Instruction</p> <p align="center">Practical aspects of interacting with authorities (ethics committees and competent authorities) throughout the conduct of a multinational clinical trial on medicinal products Ireland</p>	<p align="center">Code ECRIN-EC- QCD002-IR-V0.1</p>
Approval:	Date:	Revision:

FLOW CHART: Ethics committee and competent authority

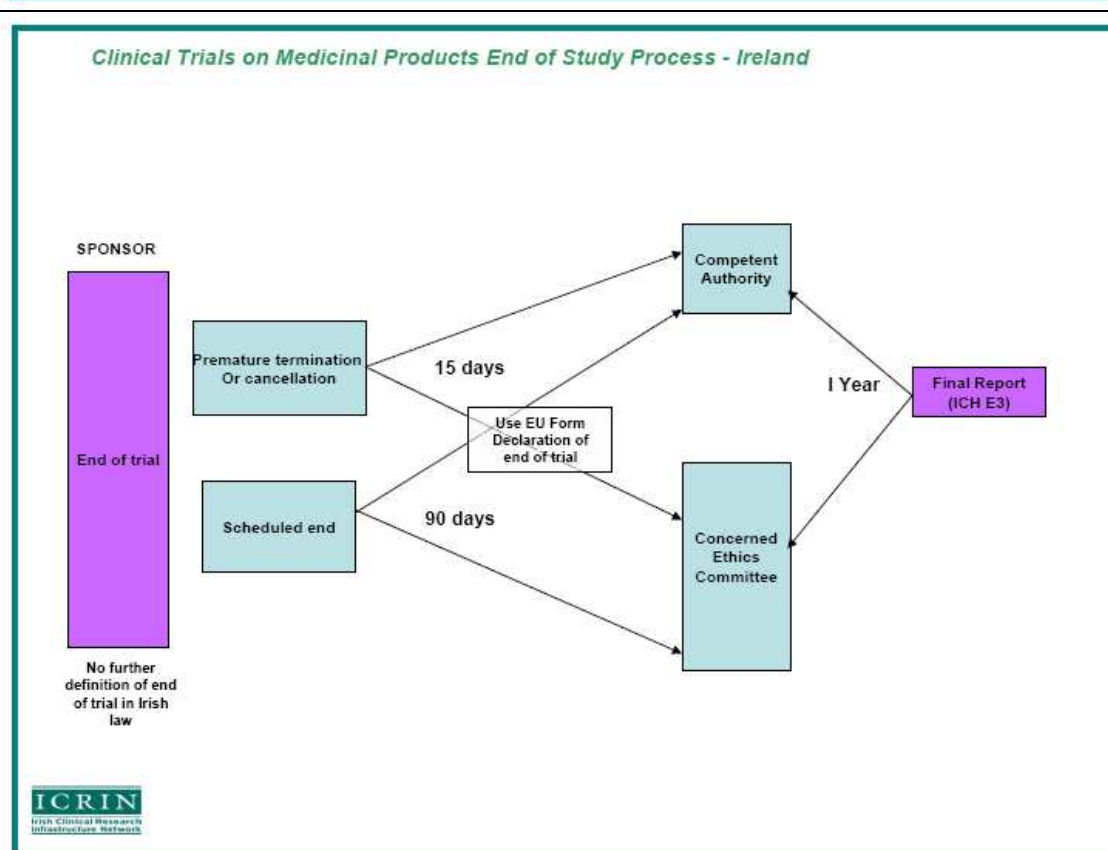
Initial
 submission



Submission of amendments during the conduct of the trial



Declaration of the end of a clinical trial



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

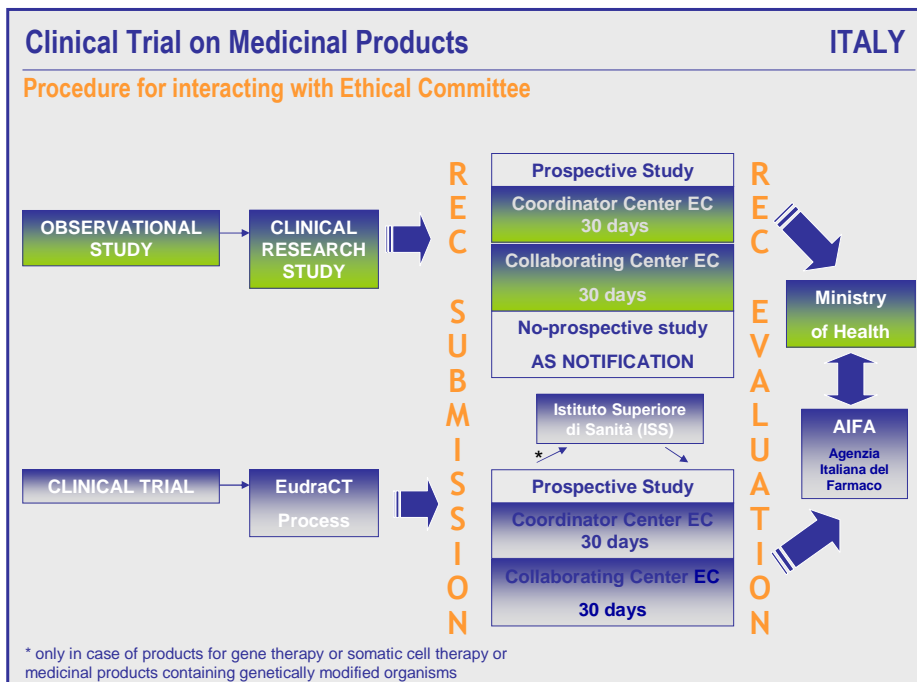
ETHICS COMMITTEES	
Ethics committee	Practical information: there are 13 recognised ethics committees in Ireland that can review a drug clinical trial Language: English
Fees for initial application	1000 euros
Fees for amendments	250 euros

REGULATORY REFERENCES	
Law	SI 190 of 2004 and 374 of 2006
Decree	

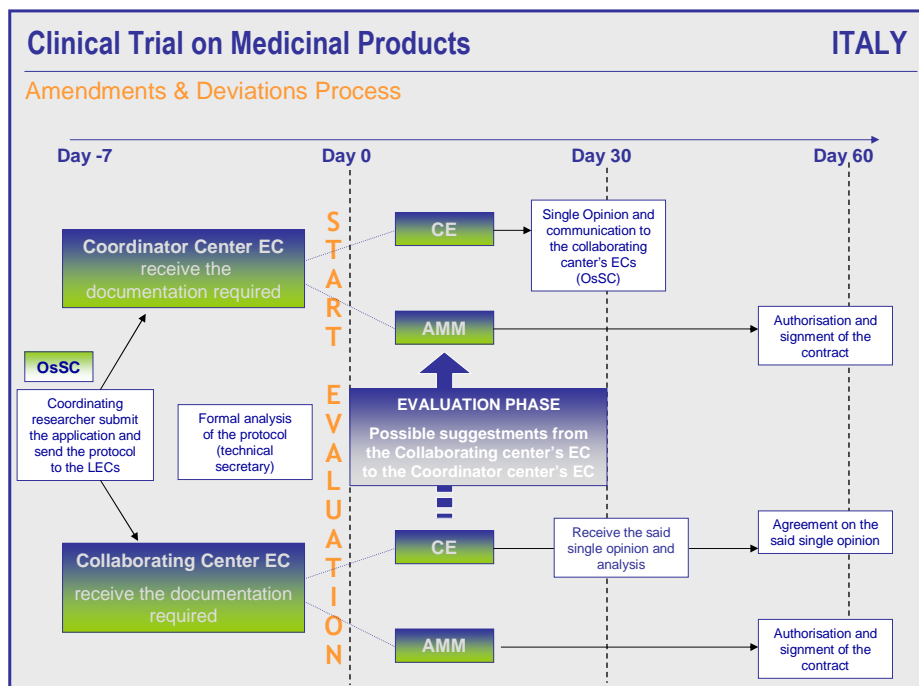
Code
ECRIN-EC-QCD002-
IT-V0.1

Revision:

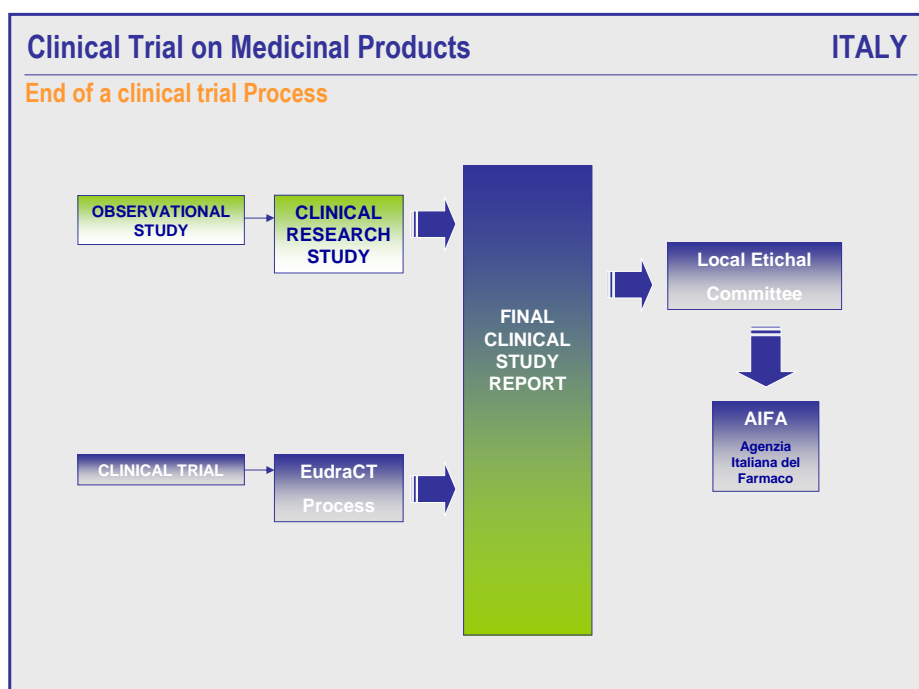
Initial submission



Submission of amendments during the conduct of the trial



Declaration of the end of a clinical trial




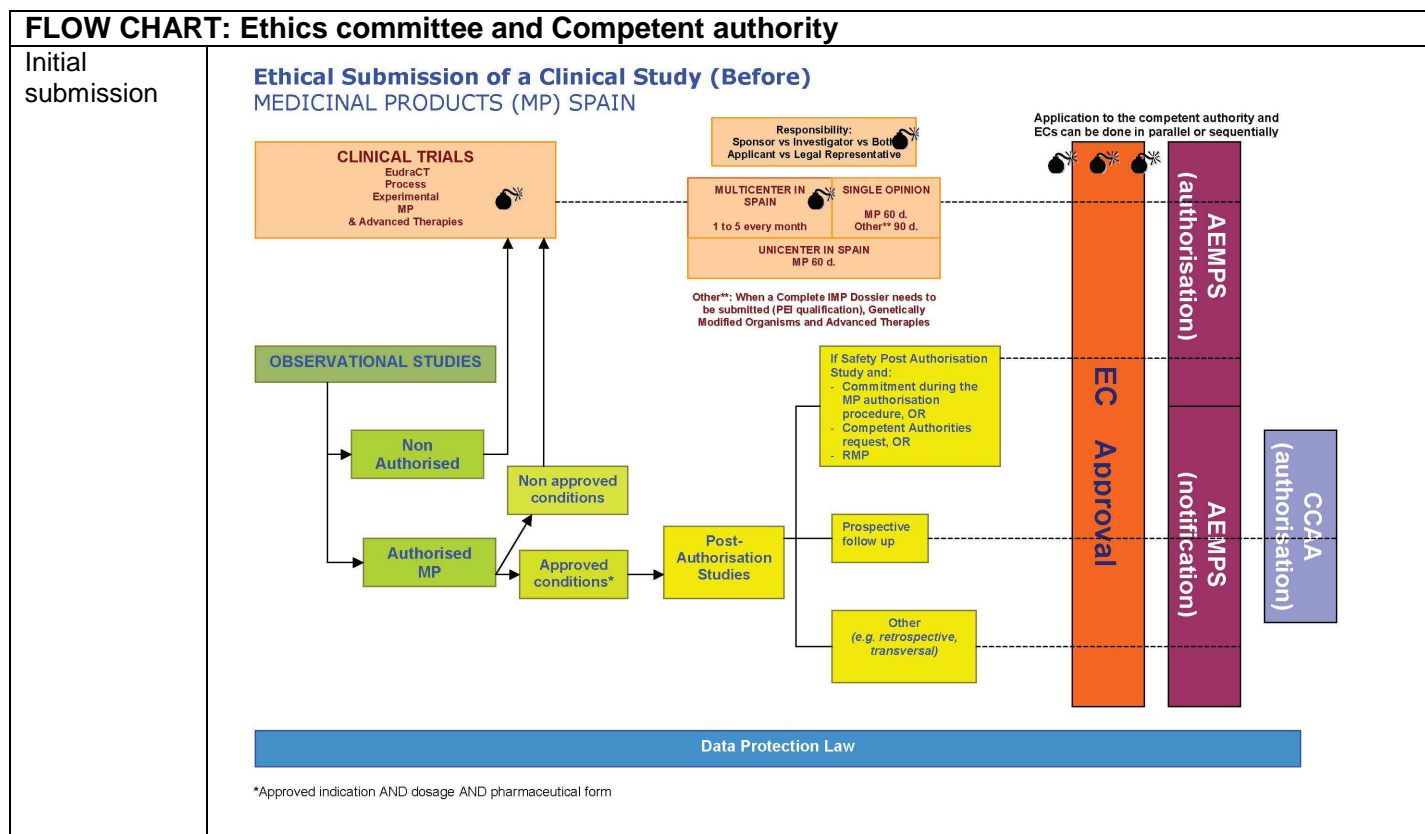
COMPETENT AUTHORITY

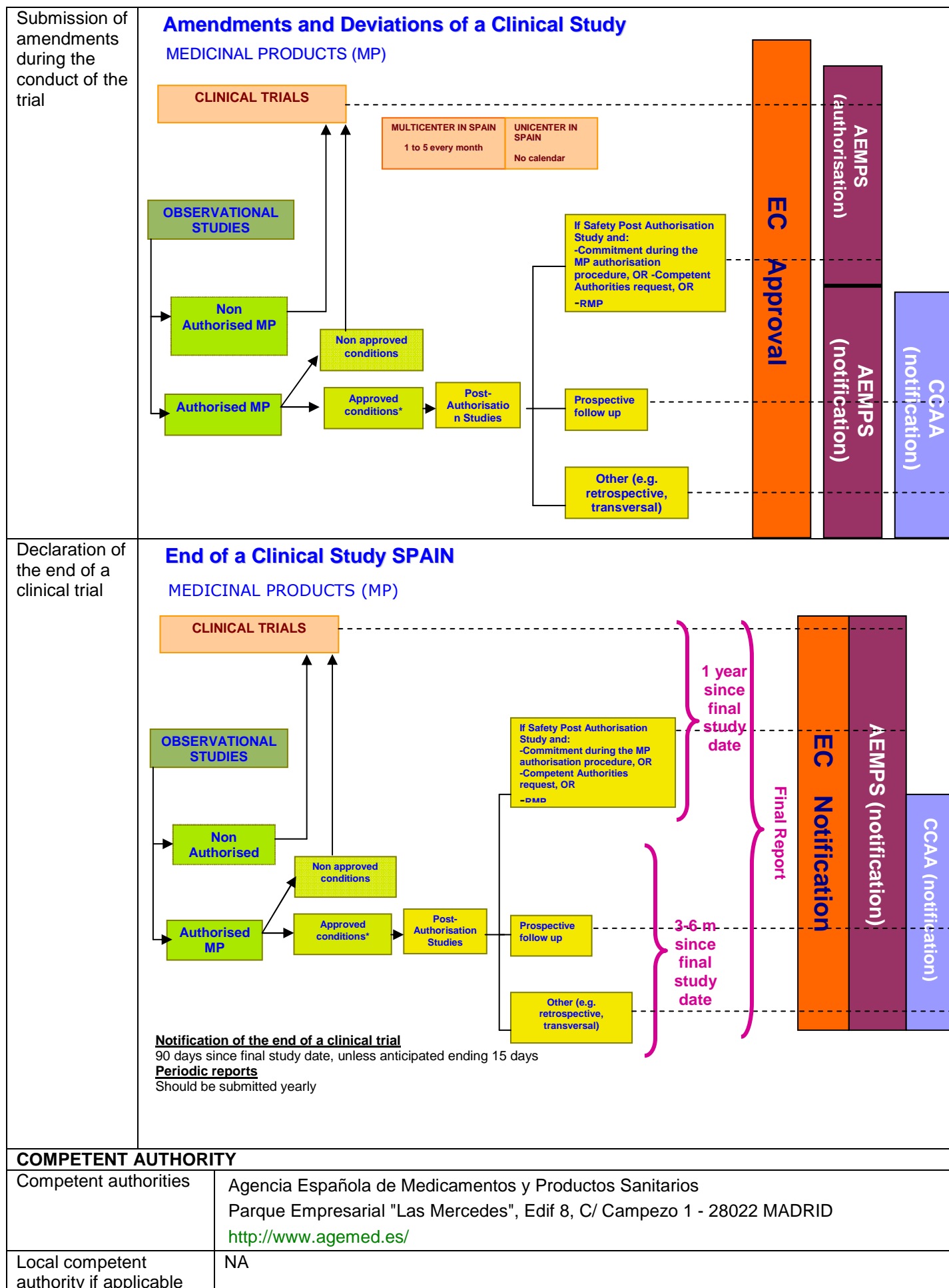
Competent authorities

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


	<p>Tel: + 39 06 59943809</p> <p>http://www.ministerosalute.it/</p> <p>http://www.iss.it/</p> <p>Practical information:</p> <p>Language : Italian</p>
Local competent authority if applicable	NA
Document required (in addition to the general procedure)	Insurance attestation
Fees for initial application	
Fees for amendments	
ETHICS COMMITTEES	
Ethics committees	
Fees for initial application	
Fees for amendments	
REGULATORY REFERENCES	
Law	<p>D.G.R. n. 4049 del 22/12/04</p> <p>D.P.R. n. 439 del 21/09/01</p>
Decree	<p>Legislative Decree n.211 of 24 June 2003</p> <p>Decreto Ministeriale 12 Maggio 2006</p> <p>Decreto Ministeriale 18 Marzo 1998</p>

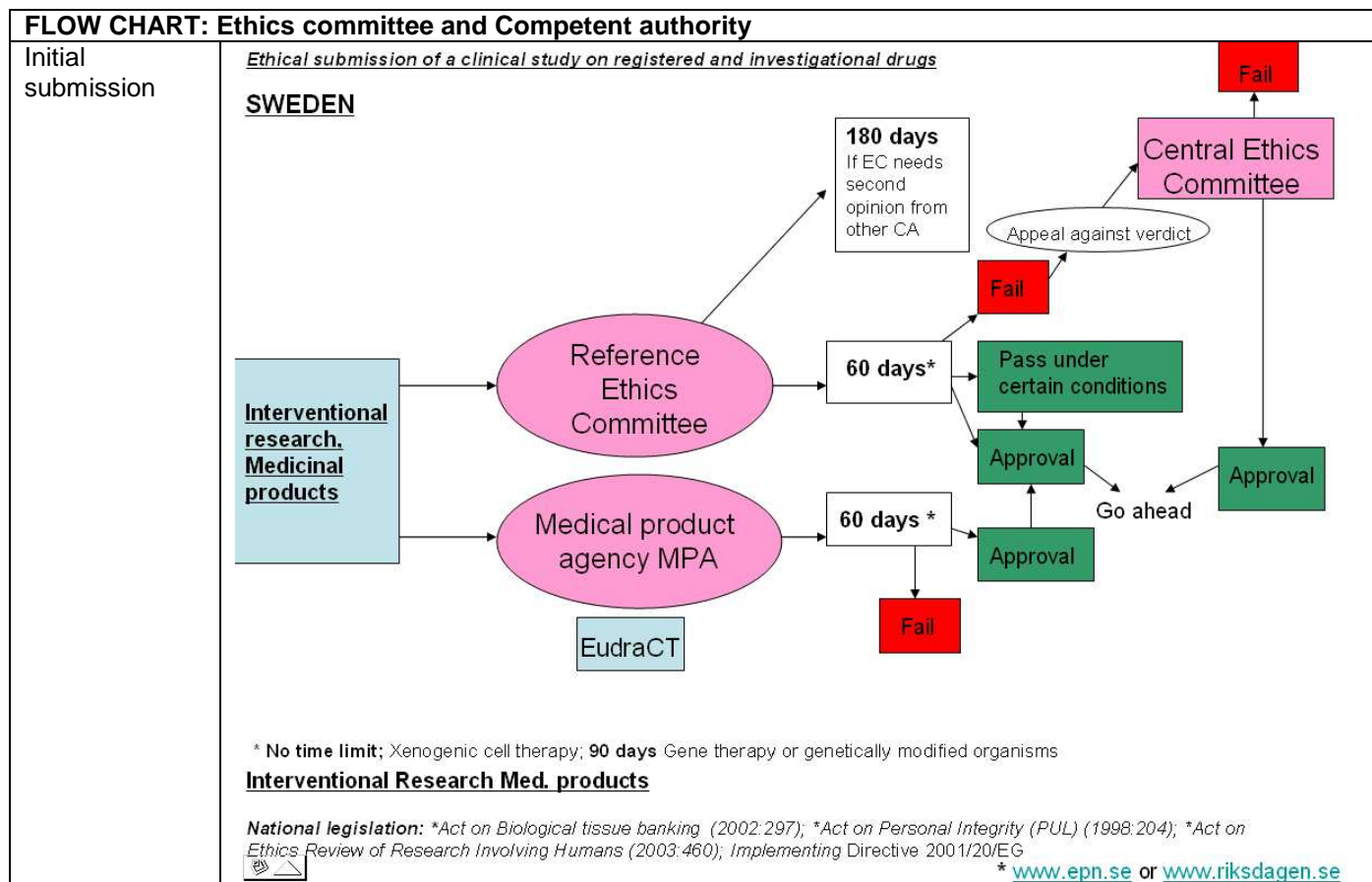
	Instruction Practical aspects of interacting with authorities (EC and CA) throughout the conduct of a multinational clinical trial Spain	Code ECRIN-EC-QCD002-ES-V0.2
Approval:	Date:	Revision:

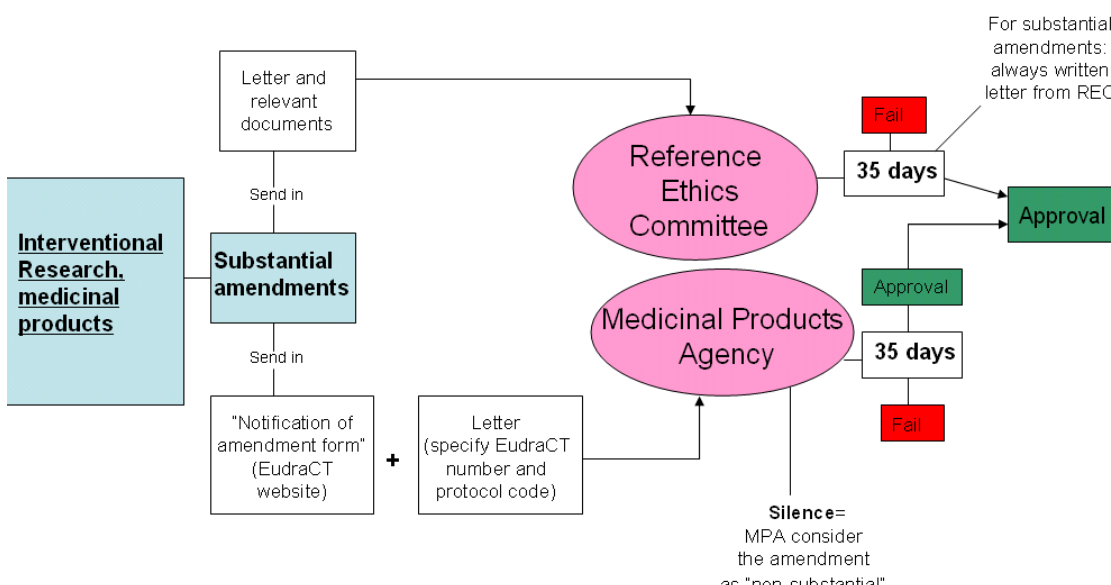
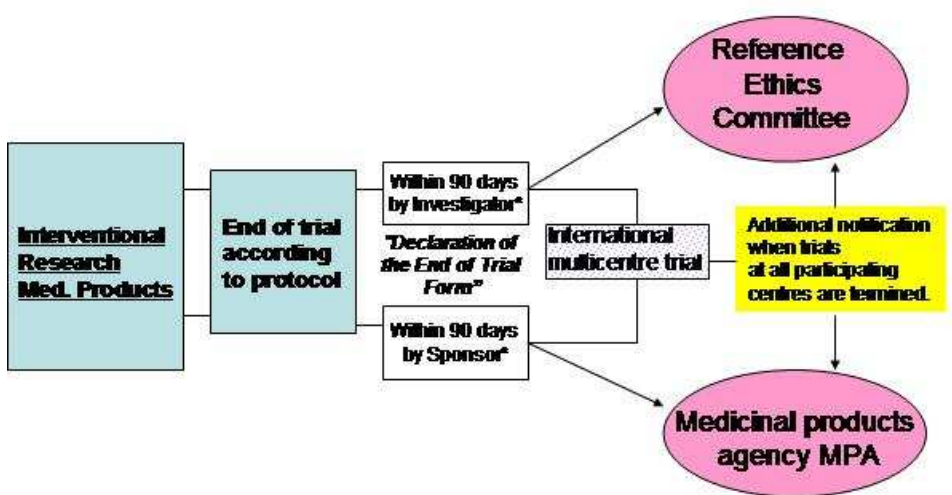




Document required (in addition to the general procedure)	Insurance attestation											
Fees for initial application	Fees are different depending on the type of submission (Clinical Trials vs. Clinical Trial with a Medicinal Product not authorised in Spain –PEI-) Please see http://www.agemed.es/actividad/documentos/tasas/listadoTasasGrp5.jsp											
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												
Law/Decree/ Guidelines	<table><tr><td></td><td>RELEVANT LEGISLATION</td><td>GUIDANCE</td><td>WHERE TO FIND IT</td></tr><tr><td>PROSPECTIVE FOLLOW-UP POST-AUTHORIZATION STUDY</td><td>RD 1344/2007 (PhV)</td><td>Local Guidance</td><td rowspan="2">At www.agemed.es</td></tr><tr><td>CLINICAL TRIALS</td><td>Directive 2001/20/EU RD 223/2004</td><td>Detailed Guidance Dec 2007 "Aclaraciones 12/2007"</td></tr></table> <p>Abbreviations: AEMPS: Agencia Española de Medicamentos y Productos Sanitarios (Competent Authorities) CCAA: Comunidades Autónomas (local Competent Authorities) EC: Ethic Committees MP: Medicinal Product</p> <p>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 estará decidida de antemano por un protocolo de ensayo, sino que estará determinada por la práctica habitual de la medicina, y la decisión de prescribir un medicamento determinado estará claramente disociada 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 lo que se regulan los ensayos clínicos con medicamentos)".</p> <p>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.</p> <p>http://www.boe.es/boe/dias/2004/02/07/pdfs/A05429-05443.pdf</p>		RELEVANT LEGISLATION	GUIDANCE	WHERE TO FIND IT	PROSPECTIVE FOLLOW-UP POST-AUTHORIZATION STUDY	RD 1344/2007 (PhV)	Local Guidance	At www.agemed.es	CLINICAL TRIALS	Directive 2001/20/EU RD 223/2004	Detailed Guidance Dec 2007 "Aclaraciones 12/2007"
	RELEVANT LEGISLATION	GUIDANCE	WHERE TO FIND IT									
PROSPECTIVE FOLLOW-UP POST-AUTHORIZATION STUDY	RD 1344/2007 (PhV)	Local Guidance	At www.agemed.es									
CLINICAL TRIALS	Directive 2001/20/EU RD 223/2004	Detailed Guidance Dec 2007 "Aclaraciones 12/2007"										

	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:

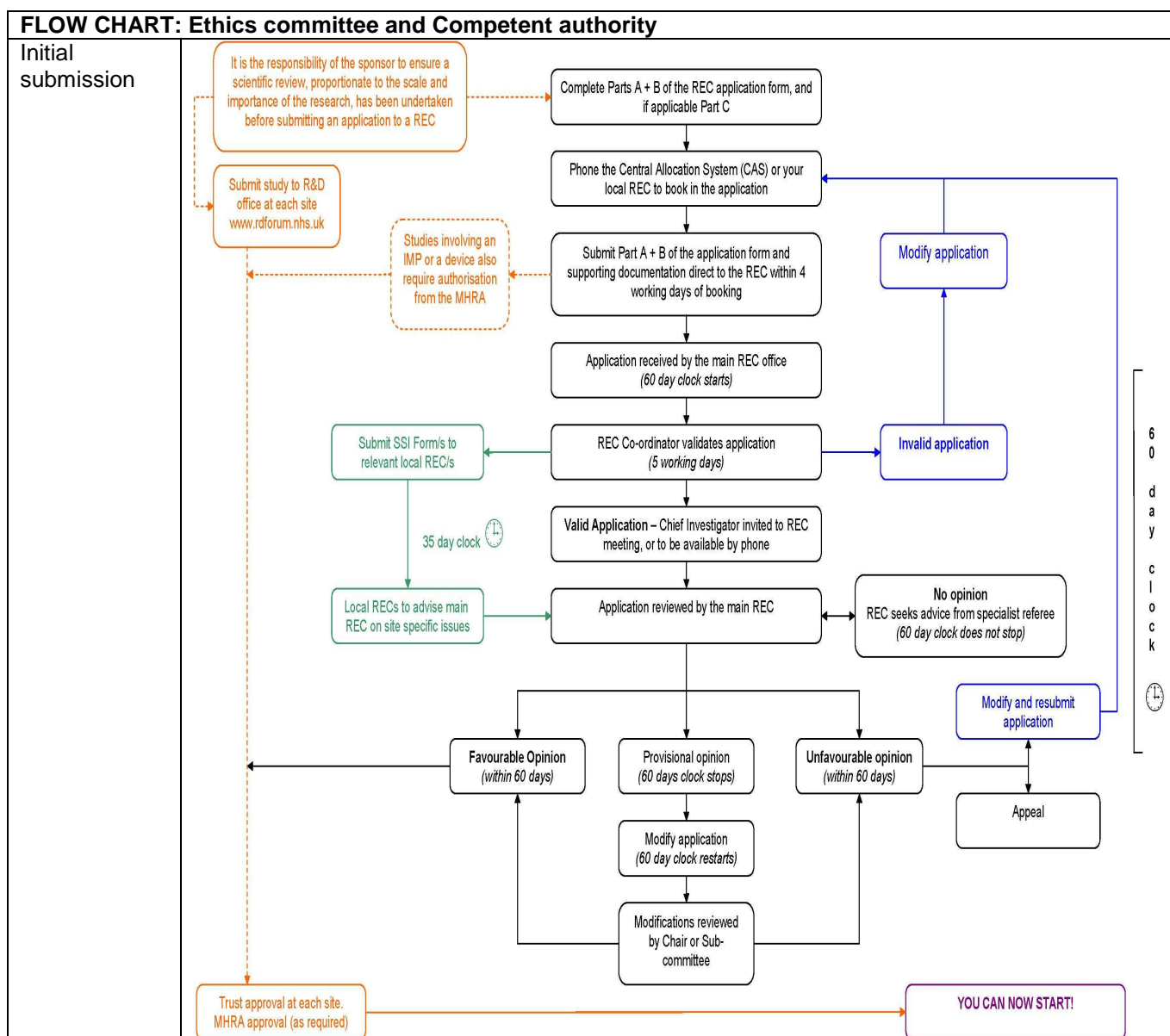


<p>Submission of amendments during the conduct of the trial</p>	<p><i>Amendments of a clinical study on registered and investigational drugs</i> SWEDEN</p>  <p>Interventional Research medicinal products</p> <p>Letter and relevant documents</p> <p>Send in</p> <p>Substantial amendments</p> <p>Send in</p> <p>"Notification of amendment form" (EudraCT website)</p> <p>Letter (specify EudraCT number and protocol code)</p> <p>Reference Ethics Committee</p> <p>Medicinal Products Agency</p> <p>35 days</p> <p>Fail</p> <p>Approval</p> <p>35 days</p> <p>Approval</p> <p>Fail</p> <p>Silence = MPA consider the amendment as "non-substantial"</p> <p>For substantial amendments: always written letter from REC</p> <p>Non-substantial amendments: Send in documents to MPA and REC for information only</p> <p>National decree: LVFS 2003:6, implementing Directive 2001/20/EG www.lakemedelsverket.se</p>
<p>Declaration of the end of a clinical trial</p>	<p><i>Notification of end of a clinical study, registered and investigational drugs</i> SWEDEN</p>  <p>Interventional Research Med. Products</p> <p>End of trial according to protocol</p> <p>Within 90 days by Investigator*</p> <p>"Declaration of the End of Trial Form"</p> <p>Within 90 days by Sponsor*</p> <p>Reference Ethics Committee</p> <p>Medicinal products agency MPA</p> <p>Additional notification when trials at all participating centres are terminated.</p> <p>*If the trial is completed or prematurely terminated, the "Declaration of the End of Trial form" must be submitted within 15 days.</p> <p>National decree: LVFS 2003:6, implementing Directive 2001/20/EG www.lakemedelsverket.se</p>
<p>COMPETENT AUTHORITY</p>	
<p>Competent Authorities</p>	<p>MEDICAL PRODUCT AGENCY</p> <p>Läkemedelsverket Box 26 SE-751 03 Uppsala</p>

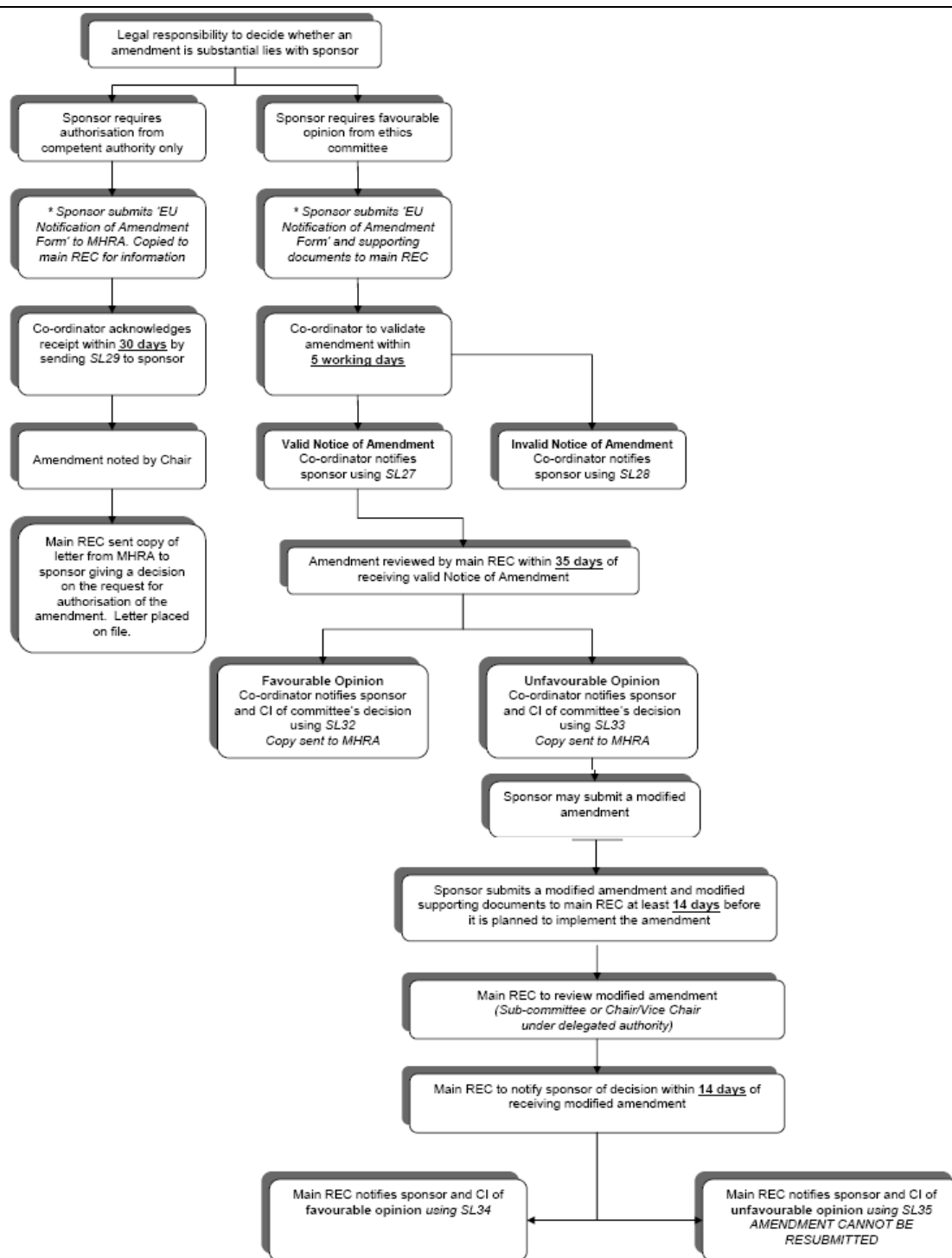
	<p>Sweden Tel: +46 18 17 46 00 http://www.lakemedelsverket.se/ Practical information: Language : Swedish or English (information and informed consent forms should be provided in Swedish)</p>
Local competent authority if applicable	
Document required (in addition to the general procedure)	
Fees for initial application	<p>Url source: http://www.lakemedelsverket.se/Tpl/NormalPage_1282.aspx Fee for initial application: 30.000 SEK. (Academic research without economic support from external sponsor may submit application free of charge.)</p>
Fees for amendments	No fee for amendments.
ETHICS COMMITTEES	
Ethics Committees	<p>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.</p> <p>Regionala etikprövningsnämnden i Göteborg Box 100 405 30 Göteborg, Sweden</p> <p>Regionala etikprövningsnämnden i Linköping c/o Hälsouniversitetets kansli Sandbäcksgatan 7 581 83 Linköping, Sweden</p> <p>Regionala etikprövningsnämnden i Lund Box 133 221 00 LUND [Hämtställe 27], Sweden</p> <p>Regionala etikprövningsnämnden i Stockholm Postadress: Box 289 171 77 STOCKHOLM, Sweden</p> <p>Regionala etikprövningsnämnden i Umeå Samverkanshuset Universitetsområdet 901 87 Umeå, Sweden</p> <p>Regionala etikprövningsnämnden i Uppsala Box 1964 751 49 UPPSALA, Sweden</p>
Fees for initial application	<p>Url source: www.epn.se The fees for initial application may vary from 5.000 SEK to 16.000 SEK (Medicinal Products, or multicenter trial).</p>
Fees for amendments	<p>Url source: www.epn.se Fee for amendments: 2.000 SEK.</p>
REGULATORY REFERENCES	
Law	Medicinal Products Act (SFS 1992:859), Medicinal Products Ordinance (SFS 2006:272), Act

	on Biological tissue banking (2002:297), Act on Personal Integrity (PUL) (1998:204), Act on Ethics Review of Research Involving Humans (2003:460), (Implementing Directive 2001/20/EG)
Decree	Läkemedelsverkets föreskrifter och allmänna råd (LVFS 2003:6) om klinisk prövning av läkemedel för humant bruk.

<p>European Clinical Research ECRIN Infrastructures Network</p>	<p align="center">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</p>	<p align="center">Code ECRIN-EC-QCDØØ2- UK-VØ.3</p>
<p>Approval:</p>	<p>Date:</p>	<p>Revision:</p>



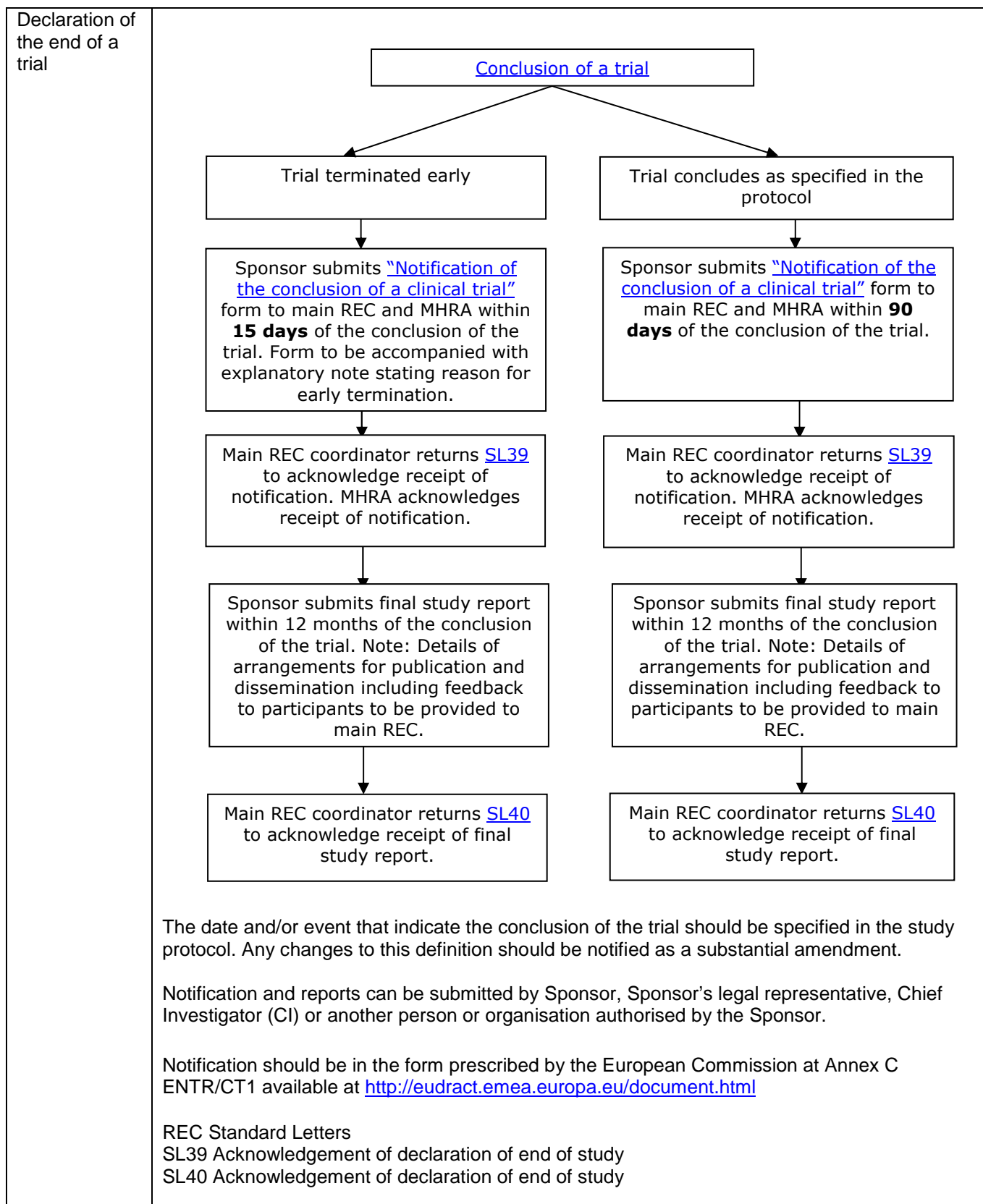
Submission of amendments during the conduct of the trial



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
- SL28 Invalid notice of a substantial amendment for no form
- SL28 Invalid notice of a substantial amendment
- SL29 Acknowledgement of substantial amendment to CTIMP notified for information only
- SL30 Minor amendment to CTIMP
- SL32 Favourable opinion of a substantial amendment
- SL33 Unfavourable opinion of a substantial amendment
- SL34 Favourable Opinion of a Modified amendment
- L35 Unfavourable opinion of a modified amendment
- SL39 End of study declaration form



COMPETENT AUTHORITY	
Competent authorities	<p>Medicines and Healthcare products Regulatory Agency (MHRA)</p> <p>10-2 Market Towers 1 Nine Elms Lane London SW8 5NQ</p> <p>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</p> <p>MHRA Clinical Trials Unit</p> <p>Fax: + 44 (0) 20 7084 2443</p> <p>E-mail: clintrialhelpline@mhra.gsi.gov.uk</p> <p>http://www.mhra.gov.uk/Contactus/SpecifcencquiriesbyMHRADivision/Licensing/index.htm</p> <p>Practical information: http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Clinicaltrials/MakingclinicaltrialsubmissionstotheMHRA/index.htm.</p> <p>Language : English</p>
Local competent authority if applicable	Not applicable
Document required (in addition to the general procedure)	<p>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.</p>
Fees for initial application	<p>Information on fees can be accessed at the following link: http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Clinicaltrials/Fees/index.htm</p>
Fees for amendments	<p>Information on fees can be accessed at the following link: http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Clinicaltrials/Fees/index.htm</p>
ETHICS COMMITTEES	
Ethics committees	<p>National Research Ethics Service</p> <p>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/</p> <p>Language: English</p>

Fees for initial application	None
Fees for amendments	None
REGULATORY REFERENCES	
Law	<p>The Medicines for Human Use (Clinical Trials) Regulations 2004 SI 2004/1031 http://www.opsi.gov.uk/si/si2004/20041031.htm</p> <p>The Medicines for Human Use (Clinical Trials) Amendment Regulations 2006 (SI 2006/1928) http://www.opsi.gov.uk/si/si2006/20061928.htm</p> <p>The Medicines for Human Use (Clinical Trials) Amendment (No.2) Regulations 2006 (SI 2006/2984) http://www.opsi.gov.uk/si/si2006/uksi_20062984_en.pdf</p> <p>1 <i>The Medicines for Human Use (Clinical Trials) and Blood Safety and Quality (Amendment) Regulations 2008 (SI 2008/941)</i> http://www.opsi.gov.uk/si/si2008/pdf/uksi_20080941_en.pdf</p>
Decree	Not applicable