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Deliverable 1
Securing participant's autonomy and interacting with ethics committees

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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 Securité Sanitaire des Produits de Santé (french competent authority)
ATU	Temporary Authorisation for Use
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
DMA	Danish Medicine Agency
DGS	Direction Générale de la Santé (french General Direction of Heath)
DIMDI	Medical Documentation and Information
DK	Denmark
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
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: Multicenter 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 no medical 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

Ethical considerations have been part of the conduct of studies with humans for several decades. However, it is only since the Second World War and several abusive trial situations coming to attention that ethical considerations have become a prominent and critical part of the conduct of clinical trials.

One of the elements that should be noted is that the nature of ethics is such that there is never one single answer to any question, but a series of dilemmas for debate and consensus built sometimes within the context of widely-divergent opinions.

Ethical evaluation has a multiplicity of considerations during the conduct of clinical trials. These ethical considerations span from matters related to the design of a study, to the conduct and even to the reporting of the results obtained. Each of these needs to be carefully considered and explained in the shape of international and national principles and guidelines.

The Clinical Trial Directive 2001/20/EC came to set the standards of good clinical practice in clinical trials on medicinal products throughout Europe. It is very important to note that each country had different jurisdictions and an established governance of ethics committees in place, when the Directive came into force.

Therefore in order to conform to, and follow the same guidance and processes in it described, there had to be an adaptation in the form of a national transposition. This has resulted in a wide variety of situations, mostly described in deliverable 2, some of which unfortunately incurred in redundancy of tasks, role overlapping, and other unnecessary day to day tasks.

This deliverable seeks to identify the common elements and main differences of the Informed Consent (General and Vulnerable Population), the differences and common elements in the composition of ethics committees in each country (including the involvement and role of Patient's Associations) and the current problems of the ECRIN countries when interacting with ethics committees as well as provide recommendations to improve current guidelines.

4 Objectives

- Describe the common elements of the Informed Consent (General and Vulnerable Population)
- Describe the country-specific elements of the Informed Consent (General and Vulnerable Population)
- Describe the composition of ethics committees in each country, including the involvement and role of Patient's Associations
- Describe the identified bottlenecks in interacting with the ethics committees in each country, especially in fields not covered by the 2001/20/EC Directive

- Proposals and recommendations to harmonise the processes and reduce any heterogeneity

5 Methodology

5.1 Patient Information Sheet

The Spanish Society of Clinical Pharmacology created a template for the patient information sheet. This template was used as an initial proposal for the patient information sheet for ECRIN developed by the WP1. Throughout several teleconferences and correspondence via email, a final agreement on the patient information sheet was reached.

This patient information sheet was the source, together with information from European and national legislation, to identify and describe the common and country–specific elements of the informed consent in general and vulnerable population.

However, one of the main concerns was related to the terminology used in order to guarantee that on equal terms all members involved understand the same concepts. In fact, during the Brussels meeting in 2008, throughout an oral questionnaire, the WP1 realised that there are relevant differences from one country to another in the populations considered *"vulnerable populations"* or *"incapacitated person"*. Therefore, a considerable amount of effort had been done in clarifying those terms which require special attention as they have implicit sensitive legal interpretations (which may also vary between countries).

As a result a common glossary of definitions was built, in an attempt to include definitions from European legislation and from Good Clinical Practice. In those cases where a term was not defined here, a consensus was reached between the different countries in order to reflect the minimal requirements applicable to all ECRIN countries. The glossary is used for all SOPs and in each SOP those definitions which were essential for the comprehension of each particular SOP were kept.

5.2 Composition of ethics committees, bottlenecks and proposals

A survey was conducted in order to collect information on the composition of ethics committees in each country and to identify the bottlenecks in interacting with the ethics committees, especially in fields not covered the EU Directive

All ECRIN countries were requested to complete the following questions:

1. Composition of the ethics committees
2. Type of evaluation
3. Involvement and role of patient's associations
4. Bottlenecks when interacting with ethics committees

5.3 Proposals and recommendations

All ECRIN countries, except for Italy, answered the survey.

6 Informed Consent (General and Vulnerable Population)

6.1 Introduction

There has been an evolution in the way that health-care providers and patients make most medical decisions. Paternalism has slowly gone and it has emerged a consent process in which the patient is a more fully informed and active participant. Enhancing patient choice is a central theme of medical ethics and law. Informed consent is the legal process used to promote patient autonomy; shared decision making is a widely promoted ethical approach[1].

This process of ensuring informed consent for participating in a clinical trial involves three phases, all of which involve information exchange between investigator (who can be a physician or another health professional) and participant and are a part of participant education. First, in words the participant can understand, the investigator must explain the details of a treatment or procedure, its potential benefits and serious risks, and any feasible alternatives. The participant should be presented with information on the most likely outcomes of treatment(s). Second, the investigator must evaluate whether or not the person has understood what has been said, must ascertain that the risks have been accepted, and that the participant is giving consent to proceed with the treatment with full knowledge. Finally, the participant must sign the consent form, which documents the major points of consideration. Participants have the right to refuse treatment and to be given all available information relevant to the refusal.

A participant's autonomy is part of the informed consent process, but also the essential objective element, which is, information. The duty to inform the participant lies with the person performing the procedure. Participant's comprehension of the information given is a very important issue because without it, the participant cannot achieve true autonomy in making decisions.[2]

Moreover, it should be taken into consideration that the informed consent process may be conditioned by religion with the moral aspects and the accelerated deontological evolution with pathways parallel to the needs and the progress offered by new forms of treatment and novel biotechnological applications.[3]

This process takes time and for the busy investigator there is often the temptation to simply hand the participant a consent form to sign. It is important to realise that signing a consent form does not constitute informed consent[1].

However, there is no reasonable way to control how the informed consent process is done. We should be confident of the investigators desire to achieve a proper informed consent, nevertheless, we should reinforce the fact that demonstration of a well-conducted process not only protects the investigator from exposure to liability, but also increases the patient's autonomy in decisions concerning health.

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[1] Terry PB.Informed consent in clinical medicine.Chest. 2007 Feb;131(2):563-8. Review.
[2] Pape T.Legal and ethical considerations of informed consent.AORN J. 1997 Jun;65(6):1122-7. Review.
[3] Mallardi V. Acta Otorhinolaryngol Ital. 2005 Oct;25(5):312-27. The origin of informed consent.

6.2 Describe the common elements of the Informed Consent (General and Vulnerable Population)

See the following appendices:
Appendix 1 Patient Information Sheet,
Appendix 2 SOP on "*How to write an Information and Informed Consent form for a multinational trial on medicinal products",*
Appendix 3 SOP on "*How to prepare an information and Informed Consent form for a multinational trial on medicinal products with Vulnerable Populations"*

6.3 Describe the country-specific elements of the Informed Consent (General and Vulnerable Population)

See the following appendices:
Appendix 1 Patient Information Sheet,
Appendix 2 SOP on "*How to write an Information and Informed Consent form for a multinational trial on medicinal products",*
Appendix 3 SOP on "*How to prepare an information and Informed Consent form for a multinational trial on medicinal products with Vulnerable Populations"*

7 Composition of ethics committees

Note that we are referring solely to the composition of ethics committees that review clinical trials on medicinal products.

7.1 Common aspects

The results showed that all ECRIN countries reported covering ethical, methodological and legal aspects in their ethics committee evaluation of the trial documents.

Although composition of ethics committees varies substantially from one country to another, all of them comply with the minimal requirements described in Good Clinical Practices (ICH E6 (R1)3.2 Composition, Functions and Operations).
In this regard, the proportion of the involvement of members with a scientific background and members with other background is of relevance. Two countries have a proportion inferior to one half (Denmark and France) with 3/7 and 4/11 respectively. Three others (Austria, Sweden and UK) have a proportion of one half. And other three (Hungary, Ireland and Spain) have a proportion superior to a half. Hungary 21/27, Ireland with 2/3 and Spain with 7/9. In addition, four out of nine countries have representatives of patients associations and five do not.

There are only three countries which require a specific background for the scientific/medical members by law (Austria, Hungary and Spain). Moreover, in the UK is a recommendation.

7.2 Country specific aspects

In Austria the ethics committees have at least 9 members and 9 substitutes. Of which one is a clinician, one is a clinician with expertise in the required filed, one

is a nurse, one is a lawyer, one is a pharmacist, one is a patients representative, one is a representative of a handicapped persons organisation, one is a biometrician and one is a priest or minister.
Patient's associations are involved in the ethics committee's activities as members.

In Denmark each ethics committee must be composed of at least 7 members, with 3 medical members and 4 lay members. If it is deemed necessary to have more members then the composition of medical to lay persons must be as follows 4:5; 5:6; 6:7; and 7:8, until a maximum of 15 members.
Within each research ethics committee there is an elected chair and an elected deputy chair, one must be a medical member and the other must be a lay member.
The members with a medical background are appointed upon recommendation of medical research organisations and the lay members are members of the county council. All ethics committee members are elected every 4 years (this corresponds to the election period for county councils), and can only be re-elected once.
There is no involvement of patient's associations.

In France the ethics committee is made up of two colleges. The first college or scientific college has four persons with qualification and extensive experience with biomedical research. Of these four, two or more must be medical doctors, and one to be well versed in biostatistics or epidemiology; one should be a general practitioner; one a hospital pharmacist; one a nurse.
The second college consists of lay members, of which one is an ethicist; one a psychologist; one a social worker; two are lawyers; and two are representatives of associations of patients / users of the health system.
Quorum is set when at least 7 members or more reach an agreement. Three of which must be from the 1st college, of which at least one should be competent in biostatistics or epidemiology. And three others should be from the 2nd college, of which at least one should be representing associations.
The French law states that "associations with this aim of representing both patients and users of the health system" must have local representatives in the ethics committees. Such associations are conditioned by a legal agreement.
Local representatives are involved in the evaluation of the informed consent form and the global philosophy of the project; their advice is helped by the information given by the scientific members of the ethics committee and the experts.
Associations take part of the federation of French Research Ethics Committee (*CNCPP*)

In Germany the ethics committee composition is regulated according to federal state law which it is different in every German federal state.
There is involvement of patient's associations as ethics committee members, which is required by law in several federal states.

In Hungary, there are three central ethics committee for the whole country, of which only one, the KFEB (Clinical Pharmacological and Ethics Committee) is dealing with medicinal products. It has 27 members, 4 of which should be clinical pharmacologist and 6 should be lay members (two lawyers, one head of patient's association and the rest paramedical professionals).

Patient's associations are involved in the ethics committee's activities reviewing ethical and legal issues.

In Ireland, the ethics committees have a maximum of 18 members of which 1/3 are lay. Minimum quorum for a valid committee is 7 members.
There is no involvement of patient's associations.

In Spain, the ethics committee should be composed of at least 9 members, of which: one should be a clinical pharmacologist, one a pharmacist, one a nurse, one and independent doctor from the centres involved and 2 lay members. One of which should be a lawyer.
There is no involvement of patient's associations.

In Sweden, there is one national body of ethics committees consisting of 12 Regional ethics committees (located at 6 medical universities/faculties) and one central ethics committee (Stockholm). The regional ethical committees consist of one Chairman (a lawyer), 10 senior scientist elected by the medical university / faculty and 5 laymen elected by the county council. The Central ethics committee has also a Chairman who is a lawyer, 4 senior scientists and 2 laymen. All members are appointed by the government.
There is no involvement of patient's associations.

In United Kingdom, the ethics committees should have no more than 18 members. They should be constituted by expert and lay members. At least half of the total memberships must be lay members and at least half of the lay members must be "lay +" members.
"Lay+" member is a person who is not an never has been a health care professional; a person involved in the conduct of clinical research other than as a research subject; and a chairman, member or director of a health service body or any other body providing health care.
Although there is no exact statuary requirement or guideline for the exact compositions of the IEC expert members in UK, most will consider essential to have a statistician, a pharmacist or pharmacologist and a relevant medical doctor.
There is no involvement of patient's associations.

8 Bottlenecks in interacting with the ethics committees, especially in fields not covered by the 2001/20/EC Directive

8.1 Common bottlenecks

In general, Clinical Trials Directive reached a partial harmonisation in the different EU Member States. However, there is still a heterogeneous administrative burden independently of the type of research ethics committees' organisation system in the country (i.e., different requirements for applications, number of copies and the fees to be paid) (see deliverable 2).

Moreover, there is no harmonisation in other fields of research not involving medicinal products (non interventional or interventional). Therefore a wide range of problematic situations exist, ranging from the variety of the local requirements for

the application process to the way of how to handle clinical trials on medical devices combined with medicinal products.

Another common bottleneck raised by most of ECRIN countries is regarding the ethics committee specific expertise (i.e., advanced, genetic therapies, prison research, etc.). The majority of ethics committees find themselves with no sufficient scientific knowledge to evaluate studies in those areas.

8.2 Country specific bottlenecks

In Austria, the need for a "single opinion" by the ethics committee before the start of any trial applies only for trials with medicinal products. There is no need for a "single opinion" for other type of studies. This situation becomes problematic for combination-products, e.g. drug eluted stents.
There is no mandatory expertise within the ethics committees for advanced, genetic therapies and no appeal mechanism for a "negative opinion" foreseen for the sponsor.

In Denmark, the committee shall decide on the approval of a project within sixty days of receiving a valid application, however there is no time limit for a decision with respect to projects using xenogenic cell therapy, and the time limit is suspended if the committee requests supplementary information from the investigator.

In France the timelines, specifically the time to deliver the final decision, is rather long especially when revision or question is requested. Also, there is a lack of expertise of the members of ethics committees in case of specific research.
In addition, the specific field of "evaluation of usual care" that is proposed in France for research in which the usual care (except drugs) is assessed with an additional follow-up, is a puzzling topic in which the ethics committees are involved to give an advice; the first experiences about this issue showed that some projects are very hard to classify in this field or in the one of biomedical research.

In Germany, there are different requirements for applications in every federal state (e.g. number of copies and the fees to be paid still vary remarkably).
For trials not involving medicinal products (e.g. medical devices or surgical procedures) there is no harmonisation and a wide range of local requirements for the application process exist.

In Hungary, there is one ethic committee meeting per month, which means too many protocols to discuss on a meeting. From 2008 it will change to every three weeks.
There is no direct link between the sponsor and the ethical committee, the sponsor has contact only with the competent authority. This is time consuming and not effective enough. Also, there are many problems with the layout and content of the Informed Consent (length, formulation, local legal, insurance discrepancies).

In Ireland, the local sign off of Site Specific Assessment (SSA) is a heterogeneous administrative burden, some sites require full local approval for this whilst other just require hospital Chief Executive Officer sign off.

In Spain, the local ethic committee involvement in the evaluation produces discrepancies of the interpretation of the "single opinion" concept; heterogeneity in the requirements; increases the administrative burden and end up resulting in an insufficient time for submission (1st to 5th day every month).
Also, the ethical committees have stop clock during their evaluation period whilst competent authorities do not. The parallel submission may lead to competent authorities' non-authorisations due to absence of an ethical opinion by the time the competent authorities' evaluation time runs out.
In addition, there is no existence of a specialised advanced therapy ethics committee, which may induce to inaccurate protocol evaluation.
Finally, co-sponsorship is not allowed in Spain; as a result a sponsor with different legal entity depending on the country may face problems when submitting documentation to the ethics committee and to the competent authorities.

In Sweden, there are no obvious bottlenecks.

In United Kingdom, bottlenecks from the past have now been streamlined and there are no major problems at present. However, some small problems still exist, like the ethics committees may not be able to accommodate all ethics applications and there may be one-two month's waiting list which could be frustrating for some researchers.

Another capacity problem is that in certain areas of research such as prison research, research falling under the human tissue act and mental capacity act require that the ethics committee have specific expertise. Not all ethics committees have this expertise and this may lead to one-two month's waiting list before the study is approved by an appropriate committee.

Obtaining approval from R&D personnel in hospital is another issue to mention. Sometimes there is uncertainty whether a project requires ethical approval. Research which is considered audit or service development, service evaluation does not require ethical approval. Nevertheless, researchers are under pressure from the R&D personnel to obtain approval for their research or themselves apply for ethics approval (i.e. believe that this will have a positive effect if they intend to publish their results).

9 Proposals and recommendations to harmonise the processes and reduce any heterogeneity

9.1 Common proposals and recommendations

A European legislation other than on medicinal products seems a recurrent general proposal reported by most of ECRIN countries along standardized training and updates for ethics committee's members.

Equally, a set of a standard of minimal requirements to reach accreditation in Europe and the introduction of an expert ethic committee at national level for the evaluation of advance therapies studies, are shared recommendations among ECRIN.

Another relevant proposal is the use of standardised and harmonised electronic application which may result in sharing databases.

9. 2 Country specific proposals and recommendations

In Austria they propose the harmonization of laws and ethical procedures for clinical studies (IMP, medical devices, others)

In Denmark they propose to share databases, a consolidation of the committees' specialist expertise and the introduction of controls on approved trials.

In France they advocate for specific resources to compensate for time allocated by EC members and suggests providing training to EC members, as the application of the EU directive (in 2006 in France) was not associated with enough support from the government in terms of education.

In Germany, the standardisation regarding documents to be submitted, fees to be paid and an application process for study types different than those on medicinal products (e.g. medical devices, surgical procedures) harmonised with that of the medicinal products.

In Ireland they propose a harmonised electronic application form and a harmonised process for ethical review of all interventional clinical trials as at the moment only drug clinical trials have single opinion. Also a timeline for SSA sign-off at each site.

In Spain they suggest to place into the Reference Ethics Committee the main scientific evaluation, leaving local aspects to the Local ethic committees. And the creation of a coordination centre for Reference Ethic Committees in Spain or Europe to standardize evaluation methodology and have updates on new and advanced therapies though a similar training.

In United Kingdom there is big input on quality. The Ethics community is trying to standardise the review in different areas and to improve the quality of the ethical review by focusing on continuous training.

10 Conclusions

Looking at the broader picture, it can be stated that the process to obtain an informed consent in the different ECRIN countries follows almost exactly the same principles and conditions described in the European Clinical Trial Directive 2001/20/EC. Therefore it can be said that the different national transpositions did not result in major divergences among them. And that harmonisation in that respect has been achieved.

However looking deeper into it, one can see that the ethical evaluation in Europe is not as ideal as one might initially believe. There is no reasonable way to control how the informed consent process is performed and which steps should be taken to issue a favourable or negate e opinion. Directive 2001/20/EC states that national legislation for those matters should prevail and the national

legislations go no further than describing the composition of ethics committees and how to reach a quorum.

Informed consent is an open process in which there should be an interchange of information between the investigator and the participant, based on mutual confidence, in order to ensure participant's autonomy. The signature of the consent form is a written proof of the agreement on the information provided, given the fact that the process itself cannot be effectively monitored. Exhaustive long and complex consent forms are currently being proposed as a way to safeguard sponsors in case of litigation. However, an inadequate length of the patient information sheet complicates its comprehension and they do not prove that the process has successfully been achieved.

It should be reinforced the fact that demonstration of a well-conducted process, not only protects the investigator from exposure to liability, but increases the participant's autonomy in decisions concerning their health.

The European regulation should take into account all types of clinical research, not only studies on Medicinal Products. European ethics committees, being competent in all areas of research, are under the scope of European Directive 2001/20/EC for clinical trials on Medicinal Products, remaining orphan for all other types of research. There is a shared need for a common regulation regarding all other types of research.

The role of ethics committees does not come to an end when the protocol and the participant's information sheet are approved, as it is often the case. They should have an iterative and proactive role throughout the time the study is active and during the period of follow-up. The importance of protocol amendments evaluation should be strengthen as well as the assessment of post-study arrangements such as the access by study participants to interventions identified as beneficial in the study or access to other appropriate care or benefits.

The composition, structure and registration of ethics committee's members are currently responsibility of a single national body in most ECRIN Member States (Austria, Denmark, France, Hungary, Ireland, Sweden and UK) and of different national bodies within the country in others (Germany, Spain). For example, in the later ones, the ethics composition varies intra-nationally as it is not regulated according to national laws but according to federal or regional laws. A general consensus on obtaining registration and the minimal requirements for obtaining registration should be effectively worked out.

A major heterogeneity is still present in numerous and varied aspects of the ethical processes across ECRIN. Although the European Directive is clear in the timelines allowed for specific purposes, they are to the maximum and not to the minimum. Therefore for the same process one country may have shorter timelines than other probably being more efficient in the approval of protocols. This is the case of France and Austria, versus the rest of ECRIN countries, where the time for the initial protocol evaluation is shortened to 35 days.

Administration resources, fees, education and training of the ethics committee's members are another source of heterogeneity. The ethics committee member's training and education should be based on a common syllabus.

Similarly, there is no harmony in the involvement of patient's associations. In Austria, Germany (depending on the federal state), France and Hungary, the patient's associations take part in the ethics committees meetings whilst in Denmark, Ireland, Spain, Sweden and UK they do not. Thus, the involvement of Patients' Association in everyday European ethics committees work should be further discussed, trying to reach a consensus agreement between Member States.

Finally, the proportion of lay members is also a significant weak point of harmonization. Some countries have significantly bigger proportion of lay members than others. In Austria, Denmark, France, Sweden and UK at least half of the total memberships must be lay members. However, in Hungary, Ireland and Spain this proportion varies from one forth to a third of the total.

As these examples shows, there is still room for improvement in the activity of ethics committees in Europe. It is recommended major harmonisation of the activity of ethics committees through more detailed guidances. Implementation of an appeal procedure and an accreditation system for ethics committees, ensuring appropriate training and quality assurance based on EU-wide specification would also be an asset. In addition, a European coordination of ethics committees should promote harmonised training, tools, and practice, including a common template for the informed consent requirements in the EU.

A guidance is needed to further define the respective tasks of ethics committees (protection of participants) and of competent authorities (assessment of the medicinal product), and how ethics committees and competent authority (either national, or a single EU competent authority) should cooperate in the clinical trial application process and during the conduct of the trial. This could reduce redundant work and increase clarity and responsibility.

For advanced therapies, gene therapies, tissues bioengineering and other specialized fields, a single ethic committee per Member State with enough expertise in its members should be in place.

A European harmonized electronic application valid for the different types of Clinical Research handled by ethics committees might also be an interesting proposal to give consideration.

Although most of the ethical procedures are deliberative in nature, and thus require time and a bottom up approach, ECRIN is in a good position to foster the harmonisation of ethics committees practice in Europe. This deliverable intends to promote such an important goal.

11 Appendices

Appendix 1- Patient Information Sheet,

Appendix 2- SOP on "*How to write an Information and Informed Consent form for a multinational trial on medicinal products",*

Appendix 3- SOP on "*How to prepare an information and Informed Consent form for a multinational trial on medicinal products with Vulnerable Populations"*

Appendix 1- Patient Information Sheet

PATIENT INFORMATION SHEET

APPROVED VERSION

23/10/2007

PATIENT INFORMATION SHEET

Note: Within this document you will find regular text, *italic text* and **bold text**. Regular text applies for all studies, *italic text applies for variable aspects depending on the study characteristics but which should be fulfilled obligatory* and, finally, **bold text applies for instructions and for variable aspects depending on the study characteristics but without the necessity to be fulfilled in all cases.**

PROTOCOL TITLE: If not explicit, it could be of interest to explain the title in some words
SPONSOR:
PROTOCOL NUMBER:
PRINCIPAL INVESTIGATOR[1]:
CENTRE:

[1] Study doctor. *Name, address and department, telephone number are needed.* **It should be specified if the PI is a professional other than a physician.**

Information on the authorisation of the REC, authorisation of the AC should be added, as well as a sentence stating that the consent does not discharge the medical doctor from his own responsibility.

INTRODUCTION

We would like to inform you about a clinical research study in which you are being asked to take part. An Ethics Committee and appropriate regulatory Authorities approved the clinical research study, according to country's regulations.

Our intention is to provide you with sufficient information to let you decide whether or not you wish to take part in this study. Please take time to read the following information carefully. This information sheet or the consent form may contain words that you do not understand. Please ask the study doctor or the study staff to explain any words or information that you do not understand.

STUDY PARTICIPATION

Taking part in this study is voluntary. You have the right to choose not to take part in it. If you decide not to participate in the study, this will not affect your medical treatment. You will not lose any benefits or medical care to which you are entitled to. If you choose to participate, you have the right to stop at any time; you may withdraw at any time if you wish, without having to explain the reason to your doctor and without putting at risk the treatment that you will need to receive. You will be informed in a timely manner of any new findings during the study that may affect your decision to continue to take part.

The study doctor may remove you from the study in certain circumstances. For example, you may be withdrawn for the study if it is considered that your participation could be harmful to you, if you require a treatment that is not permitted in the study, if you fail to follow the study instructions, if you are a woman and become pregnant or if the study is cancelled.

The study Sponsor may stop the study if considered necessary for reasons related to the project or to safety.

Any withdrawal or suspension will be based on documented arguments and explained to you.

Before you make a decision, you may want to take this document home with you to discuss it with others, for example, your relatives or GP.

A comment on the results of the study should be mentioned. (e.g., Are the results going to be published? ,…). It should be specified that in case of publication results are anonymous.

GENERAL DESCRIPTION OF THE STUDY[2]:

*Definition, **objectives**, **methodology[3]**, **duration**, **advantages/risks[4]**, total number of participants to be included and the participants' responsibilities (in relation to procedures but also to adverse events and medication changes notification) should be included in this section. Non technical words must be used as far as possible*

[2] **This section should not be more than 2 pages long. The content should be relevant, expressed in a comprehensive and clear way for participants. Selection criteria and each visit detailed description should be avoided.**
Describe first the context in 5 lines maximum.

[3] *The study design should be defined and explained in a clear way to the participant. Special effort should be done when equivalent or non-inferiority (a non-inferiority trial aims to demonstrate that the test product is not worse than the comparator by more than a pre-specified, small amount. This amount is known as the non-inferiority margin, or delta (Δ)) studies are proposed. The randomisation process should be defined (when needed) as well as the possibilities of receiving each of the treatments (i.e. 2:2; 2:1; etc.). If the study design is double blind a sentence like "Neither you nor your study doctor will know what dose of study drug you are taking during the study." should be included. The appropriateness of the use of a placebo arm and its definition (pharmaceutical form, same aspect as active treatment but without active substance) should be also included in this section.*

Add whenever possible and especially when children are involved a scheme to explain the study.

Insert a specific paragraph entitled "constraints".

[4] *Number of visits and extra tests reflecting clearly which ones are extra because of the participation in the study. A sentence reflecting the blood sample amount should be specified (*e.g., *"the blood sample amount would correspond to about 2 table spoons").*

POSSIBLE BENEFITS AND RISKS OF PARTICIPATING IN THIS STUDY

The expected health benefit for the participant and for the society (participation in this research study may be of benefit to other subjects in the future) should be commented in this section. Moreover, a sentence noting that there is no guarantee that participants will receive any health benefit in this research study must be included.

Previous experience with the compound should be briefly stated, as well as possible adverse events in a concise and comprehensive way for the participant (percentages should be included, if known).

A sentence regarding the status of the medicinal product should be added (whether or not the Competent Regulatory Authorities have approved the medicinal product).

Any risk related to study tests should also be described in this section.

In these trials which the treatment arm assignment may be guessed due to the adverse events presented (e.g., riphampicin), an appropriate trial design should be considered (e.g. double blind).

In those cases where female participants of childbearing potential can participate in the study, a specific section regarding Pregnancy and Birth Defects should be included.

When children are involved in trials (e.g., pharmacogenetics), a sentence should be included in the P.I.S to let parents know that their children will receive his/her own P.I.S and will be asked to sign his/her own consent form.

The fact that there is no charge for any procedures or tests required by the study, test results, or study medication, should not be considered as a benefit of participating in the study and, therefore, should not be included in this section.

ALTERNATIVE TREATMENTS

A sentence stating that the participant does not have to participate in the study to receive treatment for his/her condition should be added. Alternative treatments should be briefly described, if any.

If a Phase IV study the possibility that the participant may receive the same treatment as in the study should be highlighted.

You should talk about other treatments with your study doctor. Make sure that you understand all of your choices before you decide whether or not to take part in the study. You may decide not to have any treatment.

INSURANCE (according to local applicable law)

If you are injured as a result of study procedures, the study doctor will treat you and inform the Sponsor. If the injury is found to be caused by the study drug (or procedure administered in accordance with the study protocol), the sponsor has insurance (according to applicable local legislation) and will be financially responsible for the costs of necessitated medical treatment as well as for any compensation as a result of such injury.

CONFIDENTIALITY

Your identity will be kept confidential according to the professional standards and applicable laws and/or regulations. **A cross reference to national regulation/law should be included.** According to law, you have the right to modify, oppose and revoke your consent for personal data, if necessary. In that case, you should contact the study doctor.

A code will identify personal study records. Your study doctor or approved collaborators are the only persons who can relate (**link**) the data with you and your medical history. Thus, your identity will remain confidential. There may be very rare exceptions to this, but these are governed by professional codes and legislation.

If you withdraw from the trial or the study, all data already collected will continue to be kept confidential.

There may be a need to release information to third parties possibly in other countries. However, your identity (name, surname, initials, address, National Health System number, etc…) will not be disclosed, and only information that is directly related to the study aims will be released.

Your study doctor/s or approved collaborators, Competent Authorities, Ethics Committees and agent/s from the sponsor are permitted to access your personal information in order to check data and study procedures when necessary, but will always maintain confidentiality according to laws and/or regulations.

ECONOMIC ASPECTS

The sponsor is responsible for all costs related to the study. A contract has been signed with the centre and the study doctor involved.

There is no cost to you for participating in this study. You may be reimbursed for some travel expenses associated with study participation (**If it is not necessary because of the characteristics of the study, it will be eliminated. However, a justification should be provided**). *You will not have to pay for study treatment, unless Member States have established precise conditions for*

exceptional circumstances (**It also should be described in this section when compensation to participants because of time dedicated or trouble because of the study characteristics**).

OTHER RELEVANT INFORMATION

You will be informed as soon as possible of any significant new information about risks associated with participation in this study, as well as other information that may affect your decision to continue to participate.

If you choose to stop participation before the end of the study for any reason, any new data will not be included in the database. Moreover, you can demand that any identifiable sample of yours that has been retained in the study is destroyed.

When you sign the consent form you are agreeing to comply with study procedures.

Once the study ends, your treatment will be decided by your clinical team. It is possible that study medication will not be available any longer after the study ends. Please remember that taking part in the study does not mean you will get the study drug in the future.

ACKNOWLEDGEMENT

Thank you for reading this document that provides information on the clinical trial. Please, take your time to decide whether you wish to participate. If you decide to take part in the trial, please sign the consent form. You will be given a copy of this document and the consent form to keep.

If at any time during the trial you wish to ask a question about the treatment or your condition, or in the event of an emergency, you should contact:

Dr. _____ Phone:_____

Dr. _____ Phone:_____

PATIENT CONSENT FORM

Participant's identification:
Study title:

I, …… (full name)

I have read the information sheet provided
I have been able to ask questions about the study
I have received sufficient information about the study

I have spoken to…… (investigator's name)

I understand that my participation is voluntary.
I understand that I can withdraw from the study:

1. Whenever I wish
2. Without having to provide an explanation
3. Without it affecting my medical care

I authorize the use and disclosure of my health information for the purposes described above to the parties listed in this consent form.

I authorise my study doctor to inform my GP that I am participating in this study

I freely consent to participate in the study.

Date: ____/____/____ Participant's signature: _____

Date: ____/____/____ Investigator's signature : _____

Appendix 2- SOP on "How to write an Information and Informed Consent form for a multinational trial on medicinal products"

How to prepare an information and Informed Consent form for a multinational trial on medicinal products
Reference: ECRIN-EC-SOP ØØ1-VØ.4
Version number: draft VØ.4

APPROVAL
Author(s): Nuria Sanz, Raquel Hernández
Validated by Working group leader: Xavier Carné Date: Signature:
Validated by QA Unit representative: Antonio Portoles, Peggy Houben Date: Signature:
Effective date
Supersedes version number (if applicable):
REVISION
Version number: not applicable
Date: not applicable
Reason for change: not applicable
Main modifications: not applicable
COUNTRIES
Valid in: Austria, Denmark, Finland, France, Germany, Hungary, Ireland, Italy, Spain, Sweden, United-Kingdom

PURPOSE

The purpose of this SOP is to describe the general procedure and the role of the ECRIN team and their cooperation with the sponsor for the development of oral and written information and the participant consent form for multinational clinical trials to be performed within the network.

SCOPE

All participants entering into a clinical trial with medicinal product must have given informed consent prior to participating in any procedures. This SOP relates to participants able to give informed consent.

This SOP does not cover vulnerable population nor incapacitated patients. There is a specific SOP on "*Informed consent in vulnerable populations and incapacitated patients".*

This procedure will cover all clinical trials selected by the ECRIN scientific board which will be performed within the ECRIN network.

DEFINITIONS AND ABBREVIATIONS

ICF: 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*)

Participant Information Sheet (PIS)
This document informs the participant about a clinical research study in which he/she is being asked to take part. The intention is to provide the participant with sufficient information to let him/her decide whether or not he/she wish to take part in this study.

RESPONSIBILITY

Common elements	Country specific elements
The sponsor (or delegated entity or person) is responsible for the development of the patient information sheet and consent form for multinational clinical trials	
The sponsor (or designated person/ entity) should develop the information and consent form based on the information and minimal requirements described in the template provided in appendix 1	
The European Correspondent supports the sponsor in providing the national information and consent form.	
The sponsor is responsible for providing each ECRIN Member State with the validated version	
The European Correspondent supports the sponsor in arranging for translation.	
The PI (or designated person) is responsible for obtaining the written informed consent from the potential study participant, or participant's legally acceptable 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.	Italy: the oral information is considered illegal.
If staff other than the PI are to assigned responsibility for the informed consent process and/or being the sole signatory on the Informed Consent Form, it is important to guarantee compliance with ICH GCP Guidelines	
The PI (or designated person) is responsible for explaining	

study procedures, benefits, risks, alternatives to study participation, voluntary nature of research participation, confidentiality issues, and ability to withdraw from study participation	
The PI (or designated person) is responsible for answering all questions from the subject. If additional information is needed to answer the question(s), this should be obtained to resolve any questions or concerns prior to completion of the consent process	Denmark: It is possible for the participant to bring a relative or a friend as an observer during the information session/interview by the researcher.
The PI (or designated person) is responsible for using only the currently approved, most recent version of the ICF for obtaining written informed consent	
The Participant and PI (or designated person) must sign and date the ICF. The original stays on file with the study documents, and the participant or the participant's legally acceptable representative should receive a copy of the signed and dated written informed consent form and any other written information provided to the subjects.	Hungary: two original and signed ICFs mandatory: one for files and one for participant.
The PI (or designated person) is also responsible for informing the participant of any information, which may be of relevance, arising during the trial. If information arises regarding the effects, risks, side effects, complications or drawbacks of the trial, or if the trial design is considerably changed, the participant shall be informed and renewed consent is needed. If new knowledge about side effects and risks means that the trial procedure will be changed immediately, a revised version of the written patient information shall be prepared and forwarded to the committee on biomedical research ethics for approval. The participants shall then be informed and, on the basis of the new information, renewed written shall be obtained.	Denmark: The participant may have previously declined to receive information about his or hers own state of health i.e. the participant would have written a clear statement declining to receive such information before being included in the trial. UK: It would be the decision of the Ethics Committee whether or not it was necessary / appropriate to provide updated consent when a new version of the ICF was approved. E.g. patients on the control arm of a trial may not need updated information if this relates to side effects of treatment on the experimental arm of the trial (in an open label design).
The PI (or designated person) is responsible for obtaining a new signed informed consent form from any participants actively participating in the study at the earliest possible opportunity (typically the next clinic visit), if during the course of the study, the ICF is revised (not including routine annual renewals).	

DESCRIPTION

Common elements	Country specific elements
The minimal requirements for the patient information sheet should contain: - Introduction - Study participation - General description of the study - Possible benefits and risks of participating in this study - Alternative treatments - Insurance - Confidentiality - Economic aspects - Other relevant information - Patient consent form For further information consult appendix 1	Denmark: The written information should clearly state the financial support that the investigator receives for carrying out the research project including whether the subsidy is paid as a fixed sum or as a remuneration per trial person, and whether the subsidy is paid directly to the investigator or to a research fund or otherwise, and any financial connection between the investigator and the funding body of the project. If any biological material from the participant is to be stored in a biobank, then this has to be stated and consented to, electronic signatures are acceptable. All participants will be given a folder called: “The rights of a trial subject in a biomedical research project” Finland: For further information, see Medical Research Degree (986/1999).

(in compliance with ICH-GCP E6, chapter 4.8.10).	France: In case of treatment of electronic data, the information document as to mention that the participant - accepts the electronic support for the data extracted from the research, - accepts this electronic support if the data extracted from the research belong to the intimacy, such as ethnical origins, behaviour… - has at any time the right to access to the data and to eventually alter them, via a medical doctor of his/her choice. and The law n°2004-801 (06/01/1978). Hungary: 1. Description of indemnification 2. Further care after having finished the study participation UK: The ICF should include: 1. Notification of the patients General Practitioner 2. Translational research 3. What will happen to the results of the research 4. Who is organising and funding the study There is also a standard consent form template provided by the National Research Ethics Service.

SPECIFIC REFERENCES

Common elements	Country Specific elements
Good Clinical Practice : Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95 - adopted July 96)	**Austria**: Austrian Medicines Act (Arzneimittelgesetz) http://www.ris2.bka.gv.at **Denmark**: Danish Medicines Act http://lms-lw.lovportaler.dk/ShowDoc.aspx?docId=lov20051180uk-full Act on the Biomedical Research Ethics Committee System http://www.cvk.im.dk/cvk/site.aspx?p=150 **Finland:** Act on Medical Research (488/1999). Medical Research Decree (986/1999). http://www.finlex.fi TUKIJA's instructions for researchers and ethics committees http://www.etene.org/e/tukija/documents/checkle4.pdf TUKIJA's instructions on patient information concerning DNA tests http://www.etene.org/e/tukija/documents/DNAengl2.pdf **France:** L1122-1 about the information to the participant in biomedical research (in Code de la Santé Publique), from : - Law nº 2002-303; 4 March 2002 (published in: Journal Officiel du 5 mars 2002, art. 15 I.) - Law nº 2004-806; 9 August 2004 (published in: Journal Officiel du 11 août 2004, art. 89 I, II.) Law n°1978-17 (06/01/1978) about electronic data. **Spain**: RD 223/2004, Ley 29/2006, de 26 Julio de Garantías y Uso

	Racional de los Medicamentos y Productos Sanitarios **Hungary**: Law CLIV/1977 Decree Min. Health 23/2002 Decree Min. Health 35/2005 Decree Min. Health 1/2007 **UK:** Medicines for Human Use (Clinical Trials) Regulations http://www.uk-legislation.hmso.gov.uk/si/si2004/20041031.htm National Research Ethics Service Guidance http://www.nres.npsa.nhs.uk/rec-community/guidance/#InformedConsent
Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 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 (*Official Journal L 121, 1/5/2001 p. 34 - 44*)	
Declaration of Helsinki. http://www.wma.net/e/ethicsunit/helsinki.htm	

ECRIN REFERENCES

- ECRIN-EC-SOPØØ5 "*Informed consent in vulnerable populations and incapacitated patients".*

APPENDICES

Appendix 1: Patient Information Sheet and Consent Form (Approved by WP1 on 23/10/2007).
This appendix describes the minimal requirements for the patient information sheet in ECRIN countries.

Appendix 1: Patient Information Sheet and Consent Form (Approved by WP1 on 23/10/2007)

Sponsor
Protocol number

PATIENT INFORMATION SHEET

APPROVED VERSION

23/10/2007

Document version
Date XX/XX/XXXX

Page 1 of 7

Sponsor
Protocol number

PATIENT INFORMATION SHEET

Note: Within this document you will find regular text, *italic text* and **bold text**. Regular text applies for all studies, *italic text applies for variable aspects depending on the study characteristics but which should be fulfilled obligatory* and, finally, **bold text applies for instructions and for variable aspects depending on the study characteristics but without the necessity to be fulfilled in all cases.**

PROTOCOL TITLE: If not explicit, it could be of interest to explain the title in some words
SPONSOR:
PROTOCOL NUMBER:
PRINCIPAL INVESTIGATOR[1]:
CENTRE:

[1] Study doctor. *Name, address and department, telephone number are needed.* **It should be specified if the PI is a professional other than a physician.**

Information on the authorisation of the REC, authorisation of the AC should be added, as well as a sentence stating that the consent does not discharge the medical doctor from his own responsibility.

INTRODUCTION

We would like to inform you about a clinical research study in which you are being asked to take part. An Ethics Committee and appropriate regulatory Authorities approved the clinical research study, according to country's regulations.

Our intention is to provide you with sufficient information to let you decide whether or not you wish to take part in this study. Please take time to read the following information carefully. This information sheet or the consent form may contain words that you do not understand. Please ask the study doctor or the study staff to explain any words or information that you do not understand.

STUDY PARTICIPATION

Taking part in this study is voluntary. You have the right to choose not to take part in it. If you decide not to participate in the study, this will not affect your medical treatment. You will not lose any benefits or medical care to which you are entitled to. If you choose to participate, you have the right to stop at any time; you may withdraw at any time if you wish, without having to explain the reason to your doctor and without putting at risk the treatment that you will need to receive. You will be informed in a timely manner of any new findings during the study that may affect your decision to continue to take part.

The study doctor may remove you from the study in certain circumstances. For example, you may be withdrawn for the study if it is considered that your participation could be harmful to you, if you require a treatment that is not permitted in the study, if you fail to follow the study instructions, if you are a woman and become pregnant or if the study is cancelled.

The study Sponsor may stop the study if considered necessary for reasons related to the project or to safety.

Any withdrawal or suspension will be based on documented arguments and explained to you.

Sponsor
Protocol number

Before you make a decision, you may want to take this document home with you to discuss it with others, for example, your relatives or GP.

A comment on the results of the study should be mentioned. (e.g., Are the results going to be published? ,…). It should be specified that in case of publication results are anonymous.

GENERAL DESCRIPTION OF THE STUDY[2]:

*Definition, **objectives**, **methodology[3]**, **duration**, **advantages/risks[4]**, total number of participants to be included and the participants' responsibilities (in relation to procedures but also to adverse events and medication changes notification) should be included in this section. Non technical words must be used as far as possible*

[2] **This section should not be more than 2 pages long. The content should be relevant, expressed in a comprehensive and clear way for participants. Selection criteria and each visit detailed description should be avoided.**
Describe first the context in 5 lines maximum.

[3] *The study design should be defined and explained in a clear way to the participant. Special effort should be done when equivalent or non-inferiority (a non-inferiority trial aims to demonstrate that the test product is not worse than the comparator by more than a pre-specified, small amount. This amount is known as the non-inferiority margin, or delta (Δ)) studies are proposed. The randomisation process should be defined (when needed) as well as the possibilities of receiving each of the treatments (i.e. 2:2; 2:1; etc.). If the study design is double blind a sentence like "Neither you nor your study doctor will know what dose of study drug you are taking during the study." should be included. The appropriateness of the use of a placebo arm and its definition (pharmaceutical form, same aspect as active treatment but without active substance) should be also included in this section.*

Add whenever possible and especially when children are involved a scheme to explain the study.

Insert a specific paragraph entitled "constraints".

[4] *Number of visits and extra tests reflecting clearly which ones are extra because of the participation in the study. A sentence reflecting the blood sample amount should be specified (e.g., "the blood sample amount would correspond to about 2 table spoons").*

POSSIBLE BENEFITS AND RISKS OF PARTICIPATING IN THIS STUDY

The expected health benefit for the participant and for the society (participation in this research study may be of benefit to other subjects in the future) should be commented in this section. Moreover, a sentence noting that there is no guarantee that participants will receive any health benefit in this research study must be included.

Previous experience with the compound should be briefly stated, as well as possible adverse events in a concise and comprehensive way for the participant (percentages should be included, if known).

A sentence regarding the status of the medicinal product should be added (whether or not the Competent Regulatory Authorities have approved the medicinal product).

Any risk related to study tests should also be described in this section.

Sponsor
Protocol number

In these trials which the treatment arm assignment may be guessed due to the adverse events presented (e.g., riphampicin), an appropriate trial design should be considered (e.g. double blind).

In those cases where female participants of childbearing potential can participate in the study, a specific section regarding Pregnancy and Birth Defects should be included.

When children are involved in trials (e.g., pharmacogenetics), a sentence should be included in the P.I.S to let parents know that their children will receive his/her own P.I.S and will be asked to sign his/her own consent form.

The fact that there is no charge for any procedures or tests required by the study, test results, or study medication, should not be considered as a benefit of participating in the study and, therefore, should not be included in this section.

ALTERNATIVE TREATMENTS

A sentence stating that the participant does not have to participate in the study to receive treatment for his/her condition should be added. Alternative treatments should be briefly described, if any.

If a Phase IV study the possibility that the participant may receive the same treatment as in the study should be highlighted.

You should talk about other treatments with your study doctor. Make sure that you understand all of your choices before you decide whether or not to take part in the study. You may decide not to have any treatment.

INSURANCE (according to local applicable law)

If you are injured as a result of study procedures, the study doctor will treat you and inform the Sponsor. If the injury is found to be caused by the study drug (or procedure administered in accordance with the study protocol), the sponsor has insurance (according to applicable local legislation) and will be financially responsible for the costs of necessitated medical treatment as well as for any compensation as a result of such injury.

CONFIDENTIALITY

Your identity will be kept confidential according to the professional standards and applicable laws and/or regulations. **A cross reference to national regulation/law should be included.** According to law, you have the right to modify, oppose and revoke your consent for personal data, if necessary. In that case, you should contact the study doctor.

A code will identify personal study records. Your study doctor or approved collaborators are the only persons who can relate (**link**) the data with you and your medical history. Thus, your identity will remain confidential. There may be very rare exceptions to this, but these are governed by professional codes and legislation.

If you withdraw from the trial or the study, all data already collected will continue to be kept confidential.

Sponsor
Protocol number

There may be a need to release information to third parties possibly in other countries. However, your identity (name, surname, initials, address, National Health System number, etc...) will not be disclosed, and only information that is directly related to the study aims will be released.

Your study doctor/s or approved collaborators, Competent Authorities, Ethics Committees and agent/s from the sponsor are permitted to access your personal information in order to check data and study procedures when necessary, but will always maintain confidentiality according to laws and/or regulations.

ECONOMIC ASPECTS

The sponsor is responsible for all costs related to the study. A contract has been signed with the centre and the study doctor involved.

There is no cost to you for participating in this study. You may be reimbursed for some travel expenses associated with study participation (**If it is not necessary because of the characteristics of the study, it will be eliminated. However, a justification should be provided**). *You will not have to pay for study treatment, unless Member States have established precise conditions for exceptional circumstances* (**It also should be described in this section when compensation to participants because of time dedicated or trouble because of the study characteristics**).

OTHER RELEVANT INFORMATION

You will be informed as soon as possible of any significant new information about risks associated with participation in this study, as well as other information that may affect your decision to continue to participate.

If you choose to stop participation before the end of the study for any reason, any new data will not be included in the database. Moreover, you can demand that any identifiable sample of yours that has been retained in the study is destroyed.

When you sign the consent form you are agreeing to comply with study procedures.

Once the study ends, your treatment will be decided by your clinical team. It is possible that study medication will not be available any longer after the study ends. Please remember that taking part in the study does not mean you will get the study drug in the future.

Sponsor
Protocol number

ACKNOWLEDGEMENT

Thank you for reading this document that provides information on the clinical trial. Please, take your time to decide whether you wish to participate. If you decide to take part in the trial, please sign the consent form. You will be given a copy of this document and the consent form to keep.

If at any time during the trial you wish to ask a question about the treatment or your condition, or in the event of an emergency, you should contact:

Dr. _____ Phone:_____

Dr. _____ Phone:_____

Sponsor
Protocol number

PATIENT CONSENT FORM

Participant's identification:
Study title:

I, ... (full name)

I have read the information sheet provided
I have been able to ask questions about the study
I have received sufficient information about the study

I have spoken to..... (investigator's name)

I understand that my participation is voluntary.
I understand that I can withdraw from the study:

1. Whenever I wish
2. Without having to provide an explanation
3. Without it affecting my medical care

I authorize the use and disclosure of my health information for the purposes described above to the parties listed in this consent form.

I authorise my study doctor to inform my GP that I am participating in this study

I freely consent to participate in the study.

Date: ____/____/____ Participant's signature: _____

Date: ____/____/____ Investigator's signature : _____

Appendix 3- SOP on "How to prepare an information and Informed Consent form for a multinational trial on medicinal products with Vulnerable Populations"

Informed consent in vulnerable populations and incapacitated patients
Reference: ECRIN-EC-SOP ØØ5
Version number: draft VØ.1

APPROVAL
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COUNTRIES
Valid in: Austria, Denmark, Finland, France, Hungary, Ireland, Spain, Sweden, United-Kingdom

PURPOSE

The purpose of this SOP is to describe the general procedure and the role of the ECRIN team and their cooperation with the sponsor for the development of oral and written information and the participant consent form for multinational clinical trials to be performed within the network. This SOP relates to vulnerable population and participants not capable to give informed consent themselves.

SCOPE

All participants entering into a clinical trial with medicinal products must have given informed consent prior to participating in any procedures.

This procedure will cover all clinical trials selected by the ECRIN scientific board and which will be performed within the ECRIN network.

DEFINITIONS AND ABBREVIATIONS

Emergency Situations

Situations where the participants may be included into a trial before giving his/her own legally informed consent. Such situations are:

- the participant is unable by virtue of physical (such as extreme pain or weakness, incapacity to sign a form…) or mental (such as coma, unconsciousness, dementia…) incapacity to give informed consent, but the participation cannot wait for either a relief from incapacitance or a legal protection,
- the time available to include the participant does not allow either to obtain an informed consent, or to proceed to a legal protection,
- the field of the research is in accordance with the inclusion of such patients,
- there is no indication that the patient would refuse the clinical trial,
- informed consent should be given accordingly with the hierarchy of consent (see section 5.3)
- informed consent has to be obtained when the study participant is able to consent (for example: regain of consciousness).

Incapacitated adults

Common elements	Country specific elements
An adult unable by virtue of physical or mental incapacity to give informed consent. *(UK NRES guidance on informed consent in CTIMPs)*. Physical incapacity can be considered as someone suffering extreme pain with myocardial infarction. Mental incapacity can be considered as someone with mental retardation or someone unconscious.	**Austria:** According to the Austrian drug act (§43) a person who is mentally incapacitated as a result of a psychological disease or mental disability and thus appointed a legal representative for medical treatments. **France:** Incapacitated adults are sorted into two different categories : 1. "Legal" incapacitated adults (*incapables majeurs*) are major participants under legal protection, because their personal faculties are altered in such a way that they cannot manage on their own their personal interests. This goes for persons "who, by prodigality, intemperance or idleness, expose themselves to be in the need or compromise their family duties". They can be considered as "adult minors" and have a legal representative designed by a judge. 2. "Medical" incapacitated adults: see "emergency situations".

Informed Consent Form

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)*

Oral consent
Oral consent is not expressed by signing a written document.

Minor

Common elements	Country specific elements
The Clinical Trials Directive refers to children as minors. When quoting or referencing the Clinical Trials Directive in relation to legal competence, the term "minor" will be used, and it applies to all individuals from birth until the legal age of adulthood, which may differ from each member state. *(Guideline –EMEA/ 286712/2007ethical_considertations_children)* A minor is considered those children younger than 18 years of age.	**Denmark**: A minor is considered those children being 15-17 years old. Ministerial Order No. 806 of 12/07/04: In view of his/her age and maturity and the type of illness and research, is capable of understanding the importance of the research procedure and the research is likely to be of direct benefit to the minor's health, it shall be sufficient for the minor to give his/her informed consent in writing. In such cases the guardian shall be informed of this. In other cases minors may be research participants only where written consent for this has been given by their guardian or legal representative after being provided with the information. **Finland**: Same as for Denmark. **Spain**: The minor (12-18 years old) can give his/her informed consent following an "Assent process" ("Procedimiento de asentimiento del menor"). **Sweden:** Same as for Denmark. **UK**: In Scotland minor are considered younger than 16 years old. In the rest of the UK a minor is considered younger than 16 where the clinical trial regulations apply, otherwise it is younger than 18 (although there can be debate as to competence between 16 and 18).

Legal representative

Common elements	Country specific elements
The definition of a legal representative is a matter for national legislation in each member state. Common to the definition of the legal representative in any scenario is that the individual concerned must not be "a person connected with the conduct of the trial". This is defined as: a) the sponsor of the trial, b) a person employed or engaged by, or acting under arrangements with, the sponsor and who undertakes activities connected with the management of the trial, c) an investigator for the trial, d) a health care professional who is a member of an investigator's team for the purposes of the trial, or e) a person who provides health care under the direction or control of a person referred to in paragraphs c) and d) above, whether in the course of the trial or otherwise. *(UK NRES guidance on informed consent in CTIMPs)*	**Denmark**: the legal representative is composed of two physicians, who in emergency situations can give surrogate consent on behalf of the incapacitated trial participant. The legal representative shall attend the interests of the trial participant. **France:** Minors: the two parents (see derogation for one parent in flowchart annex) or somebody designed by a judge; Total trusteeship: the tutor; Partial trusteeship: the curator.

Vulnerable populations

Common elements	Country specific elements
The definition of vulnerable populations is a matter for national legislation in each member state. Within ECRIN framework, the term vulnerable populations refer to: minors, pregnant/lactating women and incapacitated adults.	**Austria:** Other vulnerable populations according to $45 (Austrian drug act) in which clinical trials on IMP can not be conducted: - Persons in military service - People who lost their freedom after a legal or administrative act **Denmark**: vulnerable populations are considered to be minors (below 18 years old), individuals under personal guardianship or, legally incompetent adults. **Finland:** Prisoners are also considered as vulnerable population. **France:** in addition to minors and incapacitated adults, add: - Patients hospitalised against their will (excluding patients under legal protection) according the the law's articles L. 3212S-1 & L. 3213-1, for example psychiatric disorders leading to a high danger for the participant or the surrounding people. - People who lost their freedom after a legal or administrative act. - Patients admitted in a social or sanitary institution with aims different from research. **Sweden:** in addition to minors (under 18 years), and incapacitated adults, also: people in emotional crisis and people who lost their freedom after a legal or administrative act.

Witness
A person, who is independent of the trial, who cannot be unfairly influenced by people involved with the trial, who attends the informed consent process if the subject or the subject's legally acceptable representative cannot read, and who reads the informed consent form and any other written information supplied to the subject. (*ICH E6-GCP*)

4. RESPONSIBILITY

Common elements	Country specific elements
Ethics committees are responsible for considering the adequacy and completeness of 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 as regards the specific restrictions laid down in Article 3 of the Clinical Trials Directive 2001/20/EC	
In clinical trials on minors, the Ethics Committee must have a paediatric expertise otherwise it must seek advice in clinical, ethical and psychosocial problems in the field of paediatrics	

In clinical trials on incapacitated adults, the Ethics Committee must have expertise in the relevant disease and the patient population concerned otherwise it must seek advice in clinical, ethical and psychosocial problems in the field of the relevant disease and patient population concerned	
The sponsor (or delegated entity or person) is responsible for the development of the patient information sheet and consent form for multinational clinical trials	
The **Sponsor** (or delegated entity or person) is responsible for providing the national information and consent form	
The **Sponsor** (or delegated entity or person) is responsible for arrenging the translation of the patient information sheet (PIS) and the consent form	
European Correspondent supports the sponsor in providing the national information and consent form	
The **European Correspondent** supports the sponsor in arranging for translation	
Principal Investigator (or designated person) is responsible for obtaining the written informed consent	
Principal investigator (or designated person) is responsible for: • Explaining study procedures, benefits, risks, alternatives to study participation, voluntary nature of research participation, confidentiality issues, and ability to withdraw from study participation, • Answering all questions from the subject, • Using only the currently approved, most recent version of the ICF for obtaining written informed consent, • Obtaining the written informed consent from the potential study participant, or participant's legally acceptable representative, • Informing the participant of any information, which may be of relevance, arising during the trial, • Obtaining a new signed informed consent form from any participants actively participating in the study at the earliest possible opportunity, if during the course of the study, the ICF is revised (not including routine annual renewals).	
In clinical trials on minors, the principal investigator is responsible for informing the minor, according to its capacity of understanding, by staff with experience in minors, about the trial, the risks and the benefits	
The principal investigator (or designated person) is responsible for considering the explicit wish of a minor who is capable of forming an opinion to refuse participation or to be withdrawn from a clinical trial at any time	
In clinical trials on incapacitated adults, the principal investigator is responsible for informing the person not able to give informed consent, according to his/her capacity of understanding, about the trial, the risks and the benefits	
The principal investigator (or designated person) must consider the explicit wish of a person not able to give informed consent who is capable of forming an opinion to refuse participation or to be withdrawn from a clinical trial at any time	

5. DESCRIPTION

5.1 Process description & General Conditions and Principles

General conditions and principles must prevail but each country must follow its own national legislation in relation to data protection in clinical trials.

PROCESS DECRIPTION FOLLOWING THE CONCERNED POPULATION AND THE MEMBER STATE	MINORS	INCAPACITATED ADULTS	PREGNANT/ LACTATING WOMEN
Member State	COUNTRY	COUNTRY	COUNTRY
The *parent or legal representative has had an interview with the investigator, or with the co-investigator, in which opportunity has been given to understand the objectives, risks and inconveniences of the trial and the conditions under which it is to be conducted	AT, DK, ES, FR, FI, HU, SE, UK	AT, DK, ES, FR, FI, HU, SE, UK	
The *parent or legal representative has been provided with a contact point where further information about the trial may be obtained	AT,ES, FR, IE, FI, HU, SE, UK	AT, ES, FR, IE, FI, HU, SE, UK	
The *parent or legal representative has been informed of the right to withdraw the participant from the trial at any time	AT, DK, ES, FR, IE, FI, HU, SE, UK	AT, DK, ES, FR, IE, FI, HU, SE, UK	
The *parent or legal representative has given informed consent to the participant taking part in the trial	ES, FR, FI, HU, SE, UK	ES, FR, FI, HU, SE, UK	
The *parent or legal representative may, without the participant being participant to any resulting detriment, withdraw the participant from the trial at any time by revoking the informed consent	DK, ES, FR, FI, HU, SE, UK	DK, ES, FR, FI, HU, SE, UK	
The participant has received information, according to his or her capacity of understanding, about the trial and its risks and benefits	AT, DK, FR, IE, FI, HU, UK	AT, DK,ES, FR, IE, FI, HU, SE, UK	
*The information must be given by staff with experience with minors	DK, FR, FI, HU, SE, UK		
The investigator must consider the explicit wish of a participant capable of forming an opinion and assessing the information provided. This applies both to the wish of a participant to refuse to take part, or to withdraw from the trial at any time	AT, DK, ES, FR, IE, FI, HU, SE, UK	AT, DK, ES, FR, IE, FI, HU, SE, UK	
No incentives or financial inducements are given either to the participant or to the *parent or legal representative, except the provision of compensation for injury or loss	AT, ES, FR, IE, FI, HU, SE, UK	AT, ES, FR, IE, FI, HU, SE, UK	FI
The clinical trial relates directly to a condition from which the participant suffers or is of such a nature that it can only be carried out on this concerned vulnerable population	AT, ES, FR, IE, FI, HU, SE, UK	AT, ES, FR, IE, FI, HU, SE, UK	AT, ES, FR, FI, HU, SE
Some direct benefit for the group of patients involved in the trial is to be obtained from the trial	AT,ES, FR, IE, FI, HU, SE, UK	AT, ES, FR, IE, FI, HU, SE, UK	AT, ES, FR, FI, SE
The trial is necessary to validate data obtained (a) in other clinical trials involving persons able to give informed consent	FR, HU, SE, UK	FR, HU, SE, UK	FR

The corresponding scientific guidelines of the European Medicines Agency (EMEA) are followed	ES, FR, FI, HU, SE, UK	ES, FR, FI, HU, SE	ES, FR, FI, HU, SE
PRINCIPLES			
Informed consent by a *parent or legal representative shall represent the participant's presumed will	AT, DK, ES, FR, IE, FI, HU, SE, UK	AT, DK, ES, FR, IE, FI, HU, SE, UK	
The trial has been designed to minimise pain, discomfort, fear and any other foreseeable risk relation to the disease and the cognitive abilities or stage of development of the Participants	ES, FR, FI, HU, SE, UK	ES, FR, FI, HU, SE, UK	ES, FR, FI
The risk threshold and the degree of distress have to be specially defined and constantly mo	ES, FR, FI, HU, SE, UK	ES, FR, FI, HU, SE, UK	ES, FR, FI
The interests of the participant always prevail over those of science and society	AT, DK, ES, FR, IE, FI, HU, SE, UK	AT, DK, ES, FR, IE, FI, HU, SE, UK	ES, FR, IE, FI, SE

* Applies only to clinical trial on minors

AT	Austria
DK	Denmark
FI	Finland
FR	France
DE	Germany
HU	Hungary
IE	Ireland
IT	Italy
ES	Spain
SE	Sweden
UK	United-Kingdom

5.2 Emergency Situations

Common elements	Country specific elements
Exceptional provision relating to trials involving incapacitated adults must apply in emergency situations. Where the investigational medicinal product needs to be administered urgently to a patient who is unconscious, time may not allow for the written consent of a legal representative to be obtained first. Incapacitated adults are allowed to be entered into a trial prior to consent being obtained from a legal representative provided that: 1. Having regard to the nature of the trial and the particular circumstances of the case, it is necessary to take action for the purpose of the trial as a matter of urgency but 2. It is not reasonably practicable to obtain informed consent prior to entering the participant, and The action to be taken is carried out in accordance with a procedure approved by the ethics committee.	**Austria:** There is no need to obtain consent from a legal representative; the participant is asked for consent after he or she regains consciousness. **Denmark**: If a clinical trial involving an investigational medicinal product can only be implemented in emergency situation where the participant is unable to give informed consent, then surrogate consent is sought from the parent or guardian, the holder of custody, the closest relative and general practitioner, medical officer of health, or finally a legal representative. If consent is obtained from the legal representative, then the investigator shall subsequently seek either participant informed consent or surrogate consent from the aforementioned, as soon as possible. If no surrogate consent is possible, then the clinical trial may be implemented if it may improve the long-term health of the participant, and the investigator shall subsequently seek surrogate consent.

5.3 Hierarchy of consent

5.3.1 Hierarchy of informed consent for a minor

	Person who may give consent	*Definition*	*Commentary*	*National differences*
1.	Parent	A parent or person with parental responsibility.	Should always be approached if available.	**France**: consent of both parents is required unless only one legal representative or exception as stated in flow chart
2.	Personal Legal representative	A person not connected with the conduct of the trial who is: (a) suitable to act as the legal representative by virtue of their relationship with the minor and, (b) available and willing to do so.	May be approached if no person with parental responsibility can be contacted prior to the proposed inclusion of the minor by reason of the emergency nature of the treatment provided as part of the trial.	**Ireland**: Ethics committee must determine this in advance **France**: a previously judge-designed representative in replacement of the parents.
3.	Professional legal representative	A person not connected with the conduct of the trial who is: (a) the doctor primarily responsible for the treatment of the minor, or (b) a person nominated by the relevant health care provider	May be approached if no person suitable to act as personal legal representative is available. Informed consent must be given before the minor is entered into the trial.	**Ireland** Ethics committee must determine this in advance **France**: no possibility of representation by someone different from the parents or the judge-designed legal representative **Germany**: A professional legal representative by law is needed

5.3.2 Hierarchy of informed consent for an incapacitated adult

	Person who may give consent	*Definition*	*National differences*
1.	Personal Legal representative	A person not connected with the conduct of the trial who is: (c) suitable to act as the legal representative by virtue of their relationship with the adult and, (d) available and willing to do so.	**Ireland:** Ethics committee must determine process in advance. **France**: a previously judge-designed tutor or curator.
2.	Professional legal representative	A person not connected with the conduct of the trial who is: (c) the doctor primarily responsible for the adult's medical treatment, or	**Denmark**: In emergency situations, the professional legal representative is composed of two physicians, they shall attend the interests of the trial participant. **France**: no possibility of representation

		(d) a person nominated by the relevant health care provider A professional legal representative may be approached if no suitable personal legal representative is available.	by someone different from the judge-designed legal representative. *Informed consent in emergency situations:* 1. Personal confident representative: A person not connected with the conduct of the trial who: - has previously been designed by the participant to act as the representative for health issues in case of incapacity, - is available and willing to do so. 2. Rescue personal representative: A person not connected with the conduct of the trial who: - belongs to the participant's family or has a close and stable relationship with the participant - is available and willing to do so. A rescue personal representative may be approached if no suitable personal confident representative is available. **Germany**: A professional legal representative by law is needed

5.3.3 Hierarchy of informed consent in emergency situations

Same as above. See 5.3.2

5.4 Oral consent

If the individual 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.

In **Ireland**, two witnesses must attest that the participant was give the written information orally, and consented to their participation.

6 SPECIFIC REFERENCES

Common references	Country Specific references
International Conference on Harmonisation -ICH E6 Good Clinical Practices (1996)	
EU directive 2001/20/EC	
Declaration of Helsinki.	
National Legislation on Informed Consent in Clinical Trials	**Austria** : Arzneimittelgesetz (Austrian drug act) **Denmark:** Act on the Biomedical Research Ethics Committee System. http://www.cvk.im.dk/cvk/site.aspx?p=150 Act No. 272 of 01/04/06 Act amending the act on the biomedical research ethics committee system and treatment of biomedical research projects. Ministerial Order No. 806 of 12/07/04 on Information and Consent at Inclusion of Trial Participants in Biomedical Research Projects http://www.cvk.im.dk/cvkEverest/Publications/cvkx2

	Eimx2Edk%20x2D%20dokumenter/English/20061130094532/CurrentVersion/MinisterialOrder806r.pdf **Finland:** - Medical Research Act (No. 488/1999) - Medical Research Degree (No. 986/1999) **France:** - Law n°2004-806 (09/08/2004) related to politics in public health. *JORF*, 11/08/2004 Articles: L1111-6, L1121-5 to 8, L 1122-1 & 2. Code for public health (*Code de la Santé Publique)*. - *Code Civil*, 488 ; *Code de Procédure Civile*, 199. **Hungary**: 35/2005 Order of Ministry of Health
Other legislation	**UK:** UK NRES guidance on informed consent in CTIMPs

7. ECRIN REFERENCES

ECRIN-EC- SOP ØØ1- How to prepare an information and Informed Consent form for a multinational trial on medicinal products.

8. APPENDICES

Not applicable.