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Standard Operating Procedures on Regulation and interaction with competent authorities

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Work package 6: **Transnational working group on standard operating procedures**

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1 Introduction

The SOPs were developed by the WP2 on regulation and interaction with competent authorities. The group was also involved in the development of SOP with the WP1 (Ethics and interaction with ethics committees) (see deliverable 18).
All the SOPs were validated by the WP2 and by the WP6 but will be discussed at the beginning of the next ECRIN project to comply with the objectives of the Quality Unit and the different delegation models to be used for the pilot projects.

2 List of SOPs

SOP Reference	SOP Title	WP
ECRIN-CA-SOPØØ1	Interaction with competent authorities before the conduct of a multinational clinical trial on medicinal products	WP2
ECRIN-CA SOPØØ2	Submission of amendments to competent authorities during the conduct of a multinational clinical trial on medicinal products	WP2
ECRIN-CA-SOPØØ3	Interaction with competent authorities after the conduct of a multinational clinical trial on medicinal products	WP2
ECRIN-CA SOPØØ4	Archiving in ECRIN studies	WP2
ECRIN-EC QCDØØ 1	EudraCT: obtention of a trial number and management of the authorisation request form	WP1/WP2
ECRIN-EC-QCDØØ2 AT/ DK/FI FR/DE HU/IT/IE/ES/SE/GB	Practical aspects of interacting with authorities (ethics committees and competent authorities) throughout the conduct of a multinational clinical trial on medicinal products	WP1/WP2
ECRIN-CA-SOP ØØ4	Insurance in multinational clinical trials on medicinal products	WP2
ECRIN-GE-SOP ØØ2	Personal data protection	WP1/WP2
Guidance document	Logistics of the Investigational Medicinal Products within ECRIN multinational clinical trials	WP2
Guidance document	Blood and tissue samples: collection, circulation, storage	WP2

ECRIN-CA-SOPØØ1

Interaction with competent authorities before the conduct of a multinational clinical trial on medicinal products

Interaction with competent authorities before the conduct of a multinational clinical trial on medicinal products

Reference: ECRIN-CA-SOPØØ1-VØ.3
Version number: VØ.3

APPROVAL
Author(s): Kate Whitfield, Christine Kubiak
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Validated by QA Unit representative: Date: Signature:
Effective date:
Supersedes version number (if applicable):
REVISION
Version number: not applicable
Date: not applicable
Modifications: not applicable
COUNTRIES
Valid in: Denmark, Finland, France, Germany, Hungary, Ireland, Italy, Spain, Sweden, United-Kingdom

1 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 submission of a clinical trial authorisation to a competent authority for a multinational clinical trial on a medicinal product.

Additional or specific requirements are described in the section 'Country specific elements' of this SOP and in the instructions "Practical aspects of interacting with authorities (ethics committee and competent authority) throughout the conduct of a multinational clinical trial on medicinal products".

2 SCOPE

Any research that fulfils the definition of a clinical trial (CT) on a medicinal product, as described by the EU Directive 2001/20/EC, will require a clinical trial authorisation (CTA) from the competent authority in the Member States in which the trial is being carried out. The CTA is required in each Member State involved in the CT.

Applications to the competent authority and to the ethics committee can be made in parallel or sequentially, depending on the legal framework or the wishes of the sponsor.

This SOP only covers the initial application to the competent authority. The initial application to the ethics committee, submitting amendments to the competent authority and ethics committee, and the interactions with competent authority and ethics committee after the conduct of a multinational clinical trial with medicinal products are described in other SOPs (see paragraph 7 ECRIN references).

This procedure covers all clinical trials performed within the network and applies to all clinical trials on medicinal products (chemical entities, biotechnology products, cell therapy products, gene therapy products, plasma derived products, other extractive products, immunological medicinal products, herbal medicinal products, radiopharmaceutical products, homeopathic products) selected by ECRIN scientific board and applies to all clinical trials involving human participants.

3 DEFINITIONS AND ABBREVIATIONS

Common elements	Country specific elements
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*). **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) **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*).	***Denmark :*** LMS: Lægemiddelstyrelsen (DMA: Danish Medicines Agency) ***Finland:*** LL: Lääkelaitos (NAM: National Agency for Medicines) ***France:*** AFSSAPS: Agence française de Sécurité Sanitaire des Produits de Santé ***Germany:*** BfArM: Bundesinstitut für Arzneimittel und Medizinprodukte PEI: Paul Ehrlich Institute ***Hungary*:** OGYI: (NIP: national Institute of Pharmacy) ***Ireland:*** IMB: Irish Medicines Board ***Spain:*** AEMPS: Agencia Española de Medicamentos y Productos Sanitarios ***Sweden:*** Läkemedelsverket (MPA: Medical Products Agency) ***UK:*** MHRA: Medicines and Healthcare Products Regulatory Agency

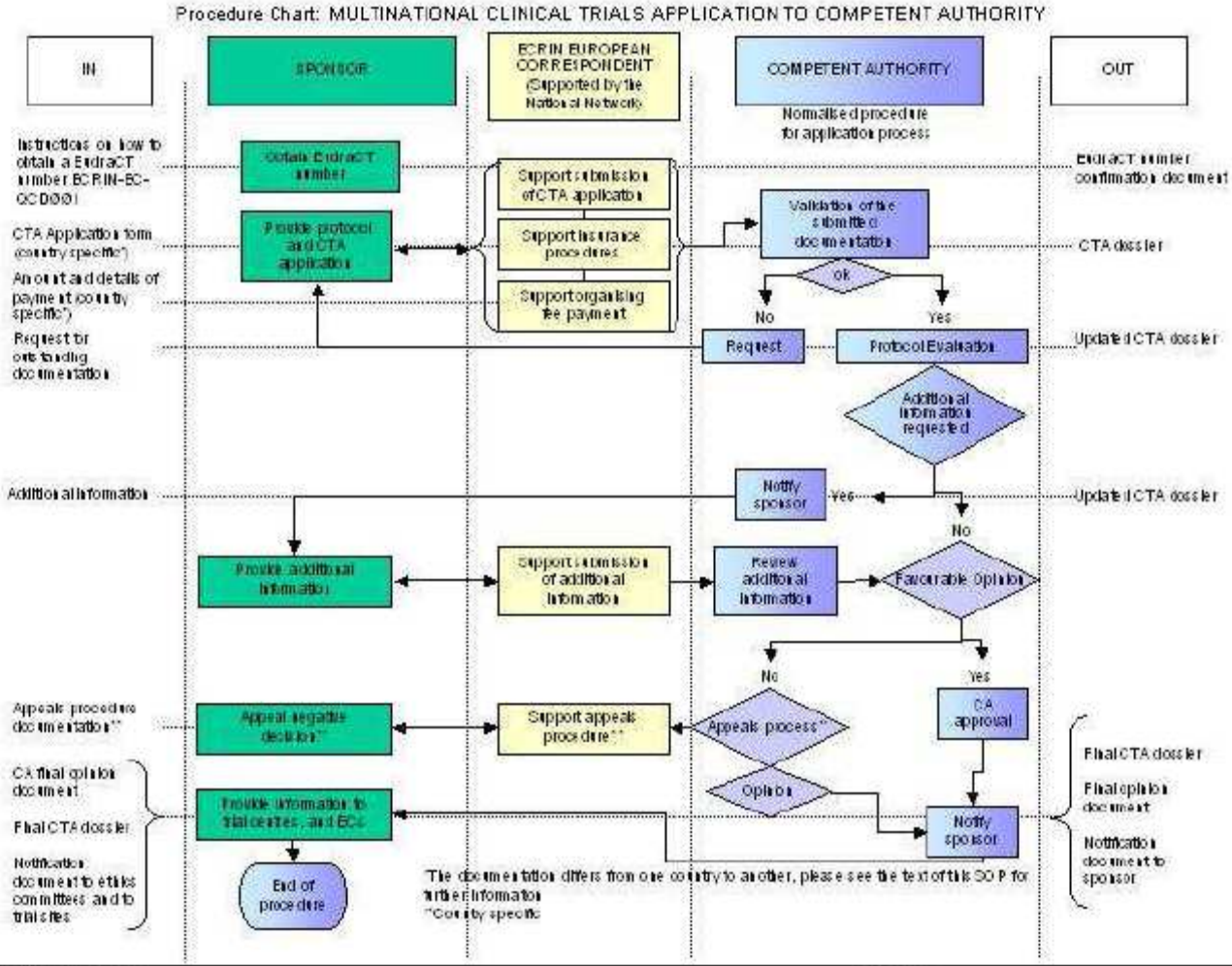
4 RESPONSIBILITY

Common elements	Country specific elements
Sponsor (or delegated entity or person): is responsible for submitting a valid request for authorisation to the competent authority and to provide the necessary documents. **European Correspondent**: is the contact point and the local support to the sponsor in his/her country and is responsible for facilitating the interaction between the sponsor and the national competent authority.	

5 DESCRIPTION

5.1 Process Flow chart

The following flow chart describes a common framework for submitting a clinical trial authorisation application on medicinal products to the competent authority.


Procedure Chart: MULTINATIONAL CLINICAL TRIALS APPLICATION TO COMPETENT AUTHORITY
IN
SPONSOR
ECRIN EUROPEAN CORRESPONDENT (Supported by the National Network)
COMPETENT AUTHORITY
Normalised procedure for application process
OUT
Instructions on how to obtain a EudraCT number ECRIN-EC-QCD00I
Obtain EudraCT number
Support submission of CTA application
Support insurance procedures
Support organising fee payment
Provide protocol and CTA application
CTA Application form (country specific)
Amount and details of payment (country specific)
Request for outstanding documentation
Validation of the submitted documentation
OK
No
Yes
Request
Protocol Evaluation
EudraCT number confirmation document
CTA dossier
Updated CTA dossier
Additional information requested
Additional information
Notify sponsor
Yes
No
Updated CTA dossier
Provide additional information
Support submission of additional information
Review additional information
Favourable Opinion
No
Yes
Appeals procedure documentation**
Appeal negative decision**
Support appeals procedure**
Appeals process**
CA approval
CA final opinion document
Final CTA dossier
Notification document to ethics committees and to trial sites
Provide information to trial centres, and EC
Opinion
Notify sponsor
Final CTA dossier
Final opinion document
Notification document to sponsor
End of procedure
The documentation differs from one country to another, please see the text of this SOP for further information
**Country specific

5.2 Obtaining a EudraCT number

To request a EudraCT number please refer to ECRIN-EC-QCD ØØ1.

5.3 Initial request for a clinical trial authorisation to competent authorities

Application to ethics committee can be done in parallel or sequentially, and is described in the ECRIN-EC-SOPØØ2 "Interaction with ethics committees before the conduct of a multinational clinical trial on medicinal products"

Common elements	Country specific elements
Completing the CTA Application form	
The CTA application form and guidance documents can be obtained through the website of EMEA (https://eudract.emea.europa.eu/eudract/index.do) or from each national competent authority (list of websites in Instructions 'Practical aspects of interacting with authorities throughout the conduct of a multinational clinical trial on medicinal products ') Once completed in English, the CTA form should be saved as an .xml file and sent electronically as well as on paper to the competent authorities.	**Germany:** All documents as pdf-file. CTA in quadruplicate. **Italy:** the sponsor or representative must fill in the form directly on the Italian trial website: https://oss-sper-clin.agenziafarmaco.it **Sweden**: All documents, one original and five copies. Only one complete application should be submitted where all sites are listed for multicentre trials. See: http://www.lakemedelsverket.se/Tpl/NormalPage____4115.aspx **UK**: Applicants are required to submit electronic documents as one PDF file for each document. In exceptional cases where the use of PDF files is not feasible, (for example, in the case of small, non-commercial clinical trials) electronic documents using Word are acceptable and will be processed to the same target timescales. Disks should be submitted with no subdirectory structure. The portal is not available for clinical trial submissions at this time. Updates on portal availability will be provided in due course.
Content of the application	
The request for clinical trial authorisation requires a number of documents, including: • Receipt of confirmation of EudraCT number (see ECRIN- EC -QCD ØØ 1) • Covering letter (should contain the EudraCT number, the title of the trial with the sponsor protocol number and any special issues related to the application such as specific trials population) • Application form (CTA form in .xml file) • Clinical trial protocol with all current amendments • Investigator's brochure or summary of product characteristics (for product with marketing authorisation and used in accordance with this marketing authorisation) • Investigational Medicinal Product Dossier • (IMPD) or simplified IMPD for known products • List of competent authorities (CA) to which the application has been submitted and details of decisions • Copy of ethics committee opinion in the MS concerned when available (if not available	**Germany:** The covering letter must be in German with the confirmation that paper and electronic version are identical (According to " 3.Bekanntmachung " (which is a Guideline of the BfArM and the PEI regarding clinical trials on medicinal products for human use) http://www2.bfarm.de/bekanntmachungen/3bk_kp.pdf) Additional documents: • Reasons for any gender specific inclusion/exclusion decision • Data protection: participant's consent to transfer and analyse data in pseudo-anonymous form • If investigator not a physician give reasons and qualifications to perform research • Statement if it is a new trial or a following-up trial **Ireland:** Additional requirements for clinical trial applications: http://www.imb.ie/EN/Publications/Medicines/Clinical-Trials/Clinical-TrialApplication-Form.aspx?categorypageid=1739&categorytypeid=-1 **Spain:** The covering letter should be in Spanish. There are templates of the documentation needed (e.g. cover letter) at www.agemed.es

should be forwarded to the CA upon receipt) • Authorisation letter from sponsor if the applicant is not the sponsor • Participant information and informed consent form (in local language) • Copy of the manufacturer/importer authorisation (referred to in Article 13.1of the Directive stating the scope of the authorisation).	**Sweden**: 6 copies of all the required documents are needed.
Fees	
Trial registration will incur a fee. The payment of the fee is a prerequisite to any submission. Amount of fee and practical information are detailed in Instruction "ECRIN-EC-QCD ØØ2" for each country.	
Specific competent authorities	
For some categories of research an authorisation from an additional competent authority or board has to be obtained.	**Denmark:** for clinical trials using gene therapy or genetically modified organisms the Danish Working Environment Authority and the Danish Forest and Nature Agency need to give permission, (http://www.at.dk/sw7737.asp or tel. +45 3915 2000) All clinical trials need permission from the Danish Data Protection Agency, (http://www.datatilsynet.dk/eng/index.html) **France:** for gene therapy clinical trials, an approval should be obtained from Ministries of Research and Agriculture **Germany:** before conducting a clinical trial on medicinal products, the competent authority responsible under "Landesrecht" (in most cases it is the local "Regierungspräsidium", see: http://www.zlg.de) and the competent authority (BfArM or PEI) pursuant to section 67 AMG have to be notified of the activity. For clinical trials with radiological evaluation a permission from the Radiation Committee is required http://www.bfs.de/de/bfs/dienstleitungen/med_forschung/strlschv/Hinweise_StrlSchV.html For clinical trials involving the use of X-Rays permission is required according to section 28 of the Röntgenverordnung (X-Ray Ordinance) www.bfs.de/bfs/dienstleitungen/med_forschung/roev/Hinweise_Roentgenverordnung.doc **Sweden:** for clinical trials with radiological evaluation a permission from the local Radiation Committee is required. For clinical trials with genetic testing the Data Inspection Board needs to give permission prior to ethics committee submission (http://www.datainspektionen.se/in_english/start.shtml) **UK:** Trials which use genetically modified organisms (contained use activities) will need to obtain approval from the Health and Safety Executive: http://www.hse.gov.uk/biosafety/gmo/index.htm The Department for Environment, Food and Rural Affairs (Defra) regulate the deliberate release activities, further information can be obtained from: http://www.defra.gov.uk/

	Trials using radioactive substances will need to gain approval from The Administration of Radioactive Substances Advisory Committee (ARSAC), further information can be obtained from: http://www.arsac.org.uk/

6 SPECIFIC REFERENCES

Common elements	Country specific elements
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*) Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products (*Official Journal L 91, 9/4/2005 p. 13 - 19*) Commission Directive 2003/94/EC of 8 October 2003 laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use (*Official Journal L 262, 14/10/2003 p. 22 - 26*). 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 October 2005 Revision 2 Detailed guidance on the application format and documentation to be submitted in an application for an Ethics Committee opinion on the clinical trial on medicinal products for human use February 2006 Revision 1 Detailed guidance on the European clinical trials database (EUDRACT Database) Good manufacturing practices ANNEX 13 : Manufacture of investigational medicinal products ICH-GCP. International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use. Guideline for Good Clinical Practice. E6 (R1). ICH Harmonised Tripartite Guideline 1996.	**Denmark:** Danish Medicines Act http://lms-lw.lovportaler.dk/ShowDoc.aspx?docId=lov20051180uk-full **Finland:** Ihmiseen kohdistuvat kliiniset lääketutkimukset, Lääkelaitoksen määräys 1/2007 http://www.nam.fi/instancedata/prime_product_julkaisu/laakelaitos/embeds/maaraykset_M_2007-1.pdf (in Finnish) **Germany:** Arzneimittelgesetz (AMG), German Drug Law http://www.gesetze-im-internet.de/bundesrecht/amg_1976/gesamt.pdf GCP-Verordnung (GCP-V), GCP ordinance, http://www.gesetze-im-internet.de/bundesrecht/gcp-v/gesamt.pdf Bekanntmachung (which is a Guideline of the BfArM and the PEI regarding clinical trials on medicinal products for human use) http://www2.bfarm.de/bekanntmachungen/3bk_kp.pdf **Ireland:** http://www.dohc.ie/legislation/statutory_instruments/pdf/si20040190.pdf http://www.dohc.ie/legislation/statutory_instruments/pdf/si20040878.pdf http://www.dohc.ie/legislation/statutory_instruments/pdf/si20060374.pdf http://www.imb.ie/images/uploaded/documents/9294939_GuideCTApp1.pdf **Spain:** Real Decreto 223/2004, de 6 de febrero, por el que se regulan los ensayos clínicos con medicamentos. **UK:** Statutory Instrument 2004 No. 1031 The Medicines for Human Use (Clinical Trials) Regulations 2004 http://www.opsi.gov.uk/si/si2004/20041031.htm Statutory Instrument 2006 No. 1928 The Medicines for Human Use (Clinical Trials) Amendment Regulations 2006 http://www.opsi.gov.uk/si/si2006/20061928.htm

	Statutory Instrument 2006 No. 2984 The Medicines for Human Use (Clinical Trials) Amendment (No. 2) Regulations 2006 http://www.opsi.gov.uk/si/si2006/20062984.htm

7 ECRIN references

- ECRIN-EC-QCDØØ1 "EudraCT: obtaining a clinical trial number and management of the authorisation request form"
- ECRIN-EC-SOPØØ2 "Interaction with ethics committees before the conduct of a multinational clinical trial on medicinal products"
- ECRIN-EC-SOPØØ3 "Submission of amendments to ethics committees during the conduct of a multinational clinical trial on medicinal products"
- ECRIN-EC-SOPØØ4 "Interaction with ethics committees after the conduct of a multinational clinical trial on medicinal products"
- ECRIN-CA-SOPØØ2 "Submission of amendments to competent authorities during the conduct of a multinational clinical trial on medicinal products"
- ECRIN-CA-SOPØØ3 "Interaction with competent authorities after the conduct of a multinational clinical trial on medicinal products"
- ECRIN-EC-QCDØØ2 "Practical aspects of interacting with authorities (ethics committee and competent authority) throughout the conduct of a multinational clinical trial on medicinal products"
- ECRIN-CA-SOPØØ4 "Archiving in ECRIN studies"
- ECRIN-AE-SOPØØ1 "How to support adverse events reporting in multinational clinical studies"

ECRIN-CA-SOPØØ2

Submission of amendments to competent authorities during the conduct of a multinational clinical trial on medicinal products

Submission of amendments to competent authorities during the conduct of a multinational clinical trial on medicinal products

Reference: ECRIN-CA-SOPØØ2-VØ.4
Version number: VØ.4

APPROVAL	
Author(s): Kate Whitfield, Christine Kubiak	
Validated by working group leader: Jacques Demotes-Mainard/ Christian Gluud Date:	Signature:
Validated by QA Unit representative: Date:	Signature:
Effective date:	
Supersedes version number (if applicable):	
REVISION	
Version number: not applicable	
Date: not applicable	
Modifications: not applicable	
COUNTRIES	
Valid in: Denmark, Finland, France, Germany, Hungary, Ireland, Italy, Spain, Sweden, United-Kingdom	

1 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 submission of substantial amendments to the competent authorities for an authorised multinational clinical trial on a medicinal product.

Additional or specific requirements of an individual member state are described in the section 'Country specific elements' of this SOP and in the instructions "Practical aspects of interacting with authorities (ethics committee and competent authority) throughout the conduct of a multinational clinical trial on medicinal products"

2 SCOPE

This procedure covers all clinical trials on medicinal products involving (chemical entities, biotechnology products, cell therapy products, gene therapy products, plasma derived products, other extractive products, immunological medicinal products, herbal medicinal products, radiopharmaceutical products, homeopathic products) selected by ECRIN scientific board and performed within the network and applies to all clinical trials involving human participants.

After the clinical trial has started, the sponsor may make amendments to the initial clinical trial application documentation or protocol. An amendment may be urgent, substantial, or minor (see Definitions and abbreviations).

It is for the sponsor to decide whether or not an amendment is substantial. If the amendment is substantial then it cannot be implemented without approval from the competent authorities. The sponsor shall notify the competent authorities of the Member States concerned of the reasons for, and content of, the substantial amendments and shall inform the ethics committees concerned. Only those specific documents affected by the substantial amendments have to be re-submitted to the competent authority and/or the ethics committee.

The substantial amendments may affect documentation and information submitted to both the competent authority and the ethics committee; in these cases the sponsor should make the notifications in parallel. For substantial amendments to information that only the competent authority assess (e.g. quality data in most member states) the sponsor should submit the amendment to the competent authority and also inform the ethics committee. Similarly, substantial amendments to information that only the ethics committee assess (e.g. changes in an advertisement for subjects to participate in the trial or changes in facilities for the trial) the sponsor should submit the amendment to the ethics committee and also inform the competent authority.

This SOP is only concerned with the notification of substantial amendments to the competent authorities, the notification of substantial amendments to the ethics committees is described in the SOP ECRIN-EC-SOPØØ3.

3 DEFINITIONS AND ABBREVIATIONS

Common elements	Country specific elements
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).* **Minor amendment:** an amendment that does not fulfil the criteria for a substantial amendment. **Substantial amendment:** an amendment that is likely to have an impact on the safety of the trial participants, to change the interpretation of the scientific documents in support of the conduct of the trial, or it may be otherwise significant. **Urgent amendment:** an amendment that is made in order to protect the trial participants against any immediate hazard. The sponsor and investigator must take the appropriate urgent safety measures, then the sponsor shall inform the competent authority and ethics committee.	***Denmark:*** LMS: Lægemiddelstyrelsen (DMA: Danish Medicines Agency) ***Finland:*** LL: Lääkelaitos (NAM: National Agency for Medicines) ***France:*** AFSSAPS: Agence française de Sécurité Sanitaire des Produits de Santé ***Germany:*** BfArM: Bundesinstitut für Arzneimittel und Medizinprodukte PEI: Paul Ehrlich Institute ***Hungary*:** OGYI: (NIP: national Institute of Pharmacy) ***Ireland:*** IMB: Irish Medicines Board ***Spain:*** AEMPS: Agencia Española de Medicamentos y Productos Sanitarios ***Sweden:*** Läkemedelsverket (MPA: Medical Products Agency) ***UK:*** MHRA: Medicines and Healthcare Products Regulatory Agency

4 RESPONSIBILITY

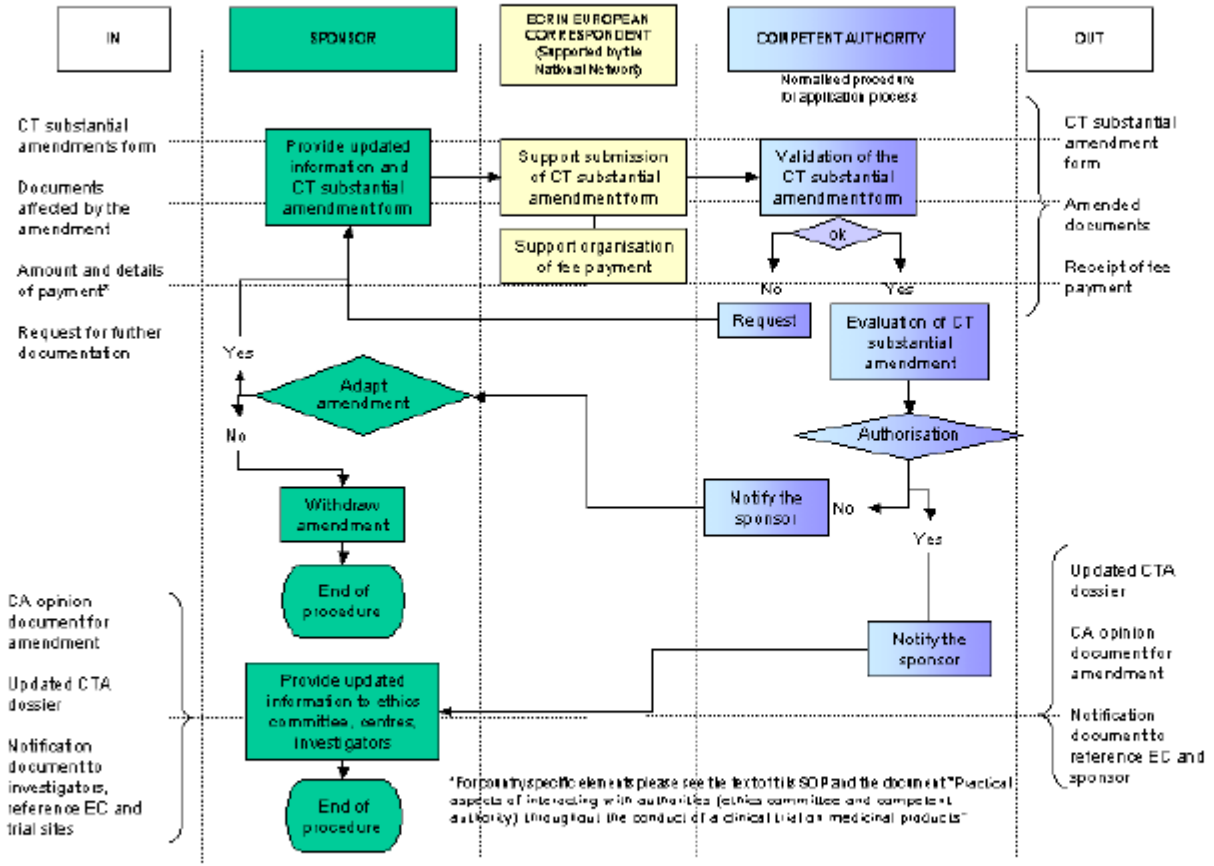
Common elements	Country specific elements
Sponsor (or delegated entity or person): is responsible for writing the amendments, for assessing whether or not an amendment is substantial and provide and prepare any necessary documents. **European Correspondent**: is the contact point and the local support to the sponsor in her/his country and is responsible for facilitating the interaction between the sponsor and the national competent authority.	

5 DESCRIPTION

5.1 Process Flow chart

The following flow chart describes a common framework for submitting a substantial amendment of the initial clinical trial application authorisation documents to a competent authority for a clinical trial on a medicinal product.

Procedure Chart: **APPLICATION OF SUBSTANTIAL AMENDMENTS TO COMPETENT AUTHORITY**



5.1 Notification of amendments to competent authorities

Submitting a substantial amendment to the ethics committees is also necessary, and is described in the ECRIN-EC-SOPØØ3 "Submission of amendments to ethics committees during the conduct of a multinational clinical trial on medicinal products".

Common elements	Country specific elements
Completing the application form for a clinical trial amendment declaration	
The application form for a clinical trial amendment and guidance documents can be obtained through the website of EMEA (https://eudract.emea.europa.eu/eudract/index.do) or from each national competent authority (list of websites in instructions ECRIN-EC-QCDØØ2 "Practical aspects of interacting with authorities (ethics committee and competent authority) throughout the conduct of a clinical trial on medicinal products") Once completed in English, the application form for a substantial amendment to a clinical trial should be saved as an .xml file and sent electronically to the competent authorities.	
Content of the application	
The request for a substantial amendment in a clinical trial with a medicinal product requires a number of documents, including: • Covering letter (should contain the EudraCT number, the title of the trial with the sponsor protocol number and justification of the amendment) • Substantial amendment notification form (clinical trial amendment form in .xml file) • List of modified documents and new version of documents (if applicable) • Supporting information including summaries of data, possible consequences for participants already included in the trial, possible consequences for the evaluation of the results of the clinical trial (if applicable).	**Sweden:** If substantial amendments are made a new CTA is required, updated pages of the CTA-application (the latter as XML-on CD or disc). Submission of amendments should take place after primary assessment of the first CTA-application, See: http://www.lakemedelsverket.se/Tpl/NormalPage____4120.aspx

5.2 Other information to competent authorities

During the clinical trial the sponsor has to send reports to the competent authorities regarding adverse events, SUSARs, other safety issues and an annual safety report. These processes are not described in this SOP, please see "How to support adverse events reporting in multinational clinical trials" ECRIN SOP-AE-SOPØØ1.

6 SPECIFIC REFERENCES

Common elements	Country specific elements
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*) Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products (*Official Journal L 91, 9/4/2005 p. 13 - 19*) Commission Directive 2003/94/EC of 8 October 2003 laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use (*Official Journal L 262, 14/10/2003 p. 22 - 26*). 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 October 2005 Revision 2 Detailed guidance on the European clinical trials database (EUDRACT Database) http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-10/13_cp_and_guidance_eudract_april_04.pdf Good manufacturing practices ANNEX 13: Manufacture of investigational medicinal products ICH-GCP. International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use. Guideline for Good Clinical Practice. E6 (R1). ICH Harmonised Tripartite Guideline 1996.	***Denmark*:** Danish Medicines Act http://lms-lw.lovportaler.dk/ShowDoc.aspx?docId=lov20051180uk-full ***Finland:*** Ihmiseen kohdistuvat kliiniset lääketutkimukset, Lääkelaitoksen määräys 1/2007 http://www.nam.fi/instancedata/prime_product_julkaisu/laakelaitos/embeds/maarayksset_M_2007-1.pdf (in Finnish) ***Germany:*** Arzneimittelgesetz (AMG), German Drug Law, http://www.gesetze-im-internet.de/bundesrecht/amg_1976/gesamt.pdf GCP-Verordnung (GCP-V), GCP ordinance, http://www.gesetze-im-internet.de/bundesrecht/gcp-v/gesamt.pdf Bekanntmachung (which is a Guideline of the BfArM and the PEI regarding clinical trials on medicinal products for human use) http://www2.bfarm.de/bekanntmachungen/3bk_kp.pdf ***Ireland:*** http://www.dohc.ie/legislation/statutory_instruments/pdf/si20040190.pdf http://www.dohc.ie/legislation/statutory_instruments/pdf/si20040878.pdf http://www.dohc.ie/legislation/statutory_instruments/pdf/si20060374.pdf http://www.imb.ie/images/uploaded/documents/9294939_GuideCTApp1.pdf ***Spain:*** Real Decreto 223/2004, de 6 de febrero, por el que se regulan los ensayos clínicos con medicamentos. ***Sweden:*** http://www.lakemedelsverket.se/upload/Foretag/Humanläkemedel/Klinisk%20prövning/Provisions%20and%20guidelines%20on%20clinical%20trials%202003-11.pdf (clinical trials started after May 1, 2004) ***UK:*** Statutory Instrument 2004 No. 1031 The Medicines for Human Use (Clinical Trials) Regulations 2004 http://www.opsi.gov.uk/si/si2004/20041031

	.htm Statutory Instrument 2006 No. 1928 The Medicines for Human Use (Clinical rials) Amendment Regulations 2006 http://www.opsi.gov.uk/si/si2006/20061928 .htm Statutory Instrument 2006 No. 2984 The Medicines for Human Use (Clinical Trials) Amendment (No. 2) Regulations 2006 http://www.opsi.gov.uk/si/si2006/20062984 .htm

7 ECRIN References

- ECRIN-EC-SOPØØ3 "Submission of amendments to ethics committees during the conduct of a multinational clinical trial on medicinal products"
- ECRIN-CA-SOP ØØ1 "Interaction with competent authorities before the conduct of a multinational clinical trial on medicinal products"
- ECRIN-CA-SOP ØØ3 "Interaction with competent authorities after the conduct of a multinational clinical trial on medicinal products"
- ECRIN-EC-QCDØØ2 "Practical aspects of interacting with authorities (ethics committee and competent authority) throughout the conduct of a clinical trial on medicinal products"
- ECRIN-CA-SOPØØ4 "Archiving in ECRIN studies"
- ECRIN-AE-SOPØØ1 "How to support adverse events reporting in multinational clinical trials"

ECRIN-CA-SOPØØ3

Interaction with competent authorities after the conduct of a multinational clinical trial on medicinal products

Interaction with competent authorities after the conduct of a multinational clinical trial on medicinal products

Reference: ECRIN-CA-SOPØØ3-VØ.4
Version number: draft VØ.4

APPROVAL
Author(s): Kate Whitfield, Christine Kubiak
Validated by working group leader: Jacques Demotes-Mainard/ Christian Gluud Date: Signature:
Validated by QA Unit representative: Date: Signature:
Effective date:
Supersedes version number (if applicable):
REVISION
Version number: not applicable
Date: not applicable
Modifications: not applicable
COUNTRIES
Valid in: Denmark, Finland, France, Germany, Hungary, Ireland, Italy, Spain, Sweden, United-Kingdom

1 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 declaration of the end of a multinational clinical trial on medicinal products to a competent authority.

Additional or specific requirements are described in the section 'Country specific elements' of this SOP and in the instructions "Practical aspects of interacting with authorities (ethics committee and competent authority) throughout the conduct of a multinational clinical trial on medicinal products".

2 SCOPE

This procedure covers all clinical trials performed within the network and applies to all clinical trials on medicinal products (chemical entities, biotechnology products, cell therapy products, gene therapy products, plasma derived products, other extractive products, immunological medicinal products, herbal medicinal products, radiopharmaceutical products, homeopathic products) selected by ECRIN scientific board and applies to all clinical trials involving human participants.

The end of a clinical trial should be notified to both the competent authorities and ethics committees. The notification should be done when the trial ends in the member state concerned and when the complete trial has ended in all the centres in all the member states concerned.

The sponsor must notify the competent authorities of the end of the trial, whether it ends earlier than planned or according to the protocol. The notification should also be made if the trial was not performed.

This SOP is only concerned with the notification of the end of the trial to the competent authorities, the notification to the ethics committees is described in the SOP ECRIN-EC-SOPØØ4.

Within one year after the completion of the trial, a summary of the trial report should be provided to the competent authorities and ethics committees of the member states concerned.

3 DEFINITIONS AND ABBREVIATIONS

Common elements	Country specific elements
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*). **End of a clinical trial**: the date of the last visit of the last trial participant.	***Denmark :*** LMS : Lægemiddelstyrelsen (DMA : Danish Medicines Agency) ***Finland:*** LL: Lääkelaitos (NAM: National Agency for Medicines) ***France:*** AFSSAPS : Agence française de Sécurité Sanitaire des Produits de Santé ***Germany*** : BfArM :Bundesinstitut für Arzneimittel und Medizinprodukte PEI : Paul Ehrlich Institute ***Hungary*** : OGYI = (NIP= national Institute of Pharmacy) ***Ireland*** : IMB: Irish Medicines Board

	Spain: Agencia Española de Medicamentos y Productos Sanitarios (AEMPS) www.agemed.es ***Sweden:*** Läkemedelsverket (MPA : Medical Products) Agency ***UK:*** Medicines and Healthcare Products Regulatory Agency (MHRA)

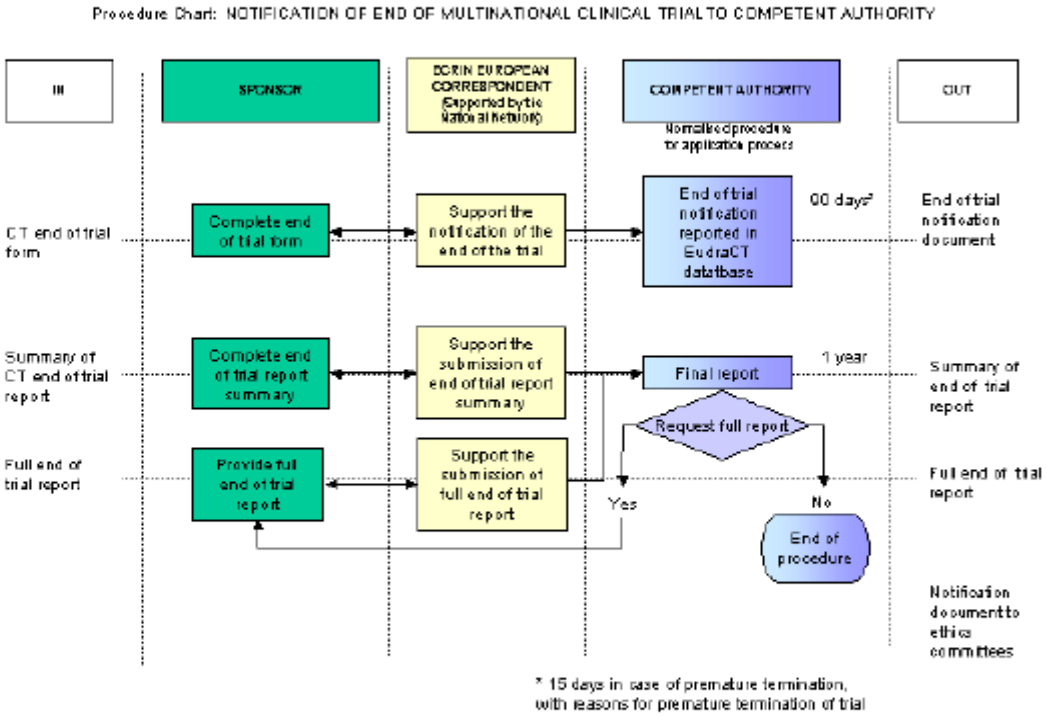
4 RESPONSIBILITY

Common elements	Country specific elements
Sponsor: (or delegated entity or person): is responsible for the declaration of the end of a clinical trial to the competent authority and to provide the necessary documents **European Correspondent**: is the contact point and the local support to the sponsor in her/his country and is responsible for facilitating the interaction between the sponsor and the national competent authority.	

5 DESCRIPTION

5.1 Process Flow chart

The following flow chart describes a common framework for notifying the end of a clinical trial on medicinal products to the competent authority.



5.2 Declaration of the end of clinical trial to Competent Authorities

Common elements	Country specific elements
Completing the declaration of the end of trial form	
1) The declaration of the end of trial form can be obtained through the website of EMEA (https://eudract.emea.europa.eu/eudract/index.do) or from each national Competent Authority (list of websites in the document ECRIN-EC-QCDØØ2 "Practical aspects of interacting with authorities (ethics committee and competent authority) throughout the conduct of a multinational clinical trial on medicinal products") 2) Once completed in English, the declaration of the end of trial form should be saved as an .xml file and sent electronically to the competent authorities.	
Timelines	
The end of a clinical trial should be notified within 90 days of completion. This notification should be made when the - trial ends in the territory of the Member State concerned - complete trial has ended in all the centres of all the Member States concerned In case of early termination the notification should be made within 15 days.	
Clinical trial report	
Within one year after the completion of the trial (completion in all the centres), a summary of the clinical trial report should be provided to the competent authorities of all the Member States concerned.	

6 SPECIFIC REFERENCES

Common elements	Country specific elements
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*) Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products (*Official Journal L 91, 9/4/2005 p. 13 - 19*) Commission Directive 2003/94/EC of 8 October 2003 laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use (*Official Journal L 262, 14/10/2003 p. 22 - 26*). 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. October 2005 Revision 2 Detailed guidance on the European clinical trials database (EUDRACT Database) Good manufacturing practices ANNEX 13: Manufacture of investigational medicinal products ICH-GCP. International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use. Guideline for Good Clinical Practice. E6 (R1). ICH Harmonised Tripartite Guideline 1996.	***Denmark:*** Danish Medicines Act http://lms-lw.lovportaler.dk/ShowDoc.aspx?docId=lov20051180uk-full ***Finland:*** Ihmiseen kohdistuvat kliiniset lääketutkimukset, Lääkelaitoksen määräys 1/2007 http://www.nam.fi/instancedata/prime_product_julkaisu/laakelaitos/embeds/maaraykset_M_2007-1.pdf (in Finnish) ***Germany:*** Arzneimittelgesetz (AMG), German Drug Law, http://www.gesetze-im-internet.de/bundesrecht/amg_1976/gesamt.pdf GCP-Verordnung (GCP-V), GCP ordinance, http://www.gesetze-im-internet.de/bundesrecht/gcp-v/gesamt.pdf 3. Bekanntmachung (which is a Guideline of the BfArM and the PEI regarding clinical trials on medicinal products for human use) http://www2.bfarm.de/bekanntmachungen/3bk_kp.pdf ***Ireland:*** http://www.dohc.ie/legislation/statutory_instruments/pdf/si20040190.pdf http://www.dohc.ie/legislation/statutory_instruments/pdf/si20040878.pdf http://www.dohc.ie/legislation/statutory_instruments/pdf/si20060374.pdf http://www.imb.ie/images/uploaded/documents/9294939_GuideCTApp1.pdf ***Spain:*** Real Decreto 223/2004, de 6 de febrero, por el que se regulan los ensayos clínicos con medicamentos. ***Sweden:*** http://www.lakemedelsverket.se/upload/Foretag/Humanläkemedel/Klinisk%20prövning/Provisions%20and%20guidelines%20on%20clinical%20trials%202003-11.pdf (clinical trials started after May 1, 2004) ***UK***: Statutory Instrument 2004 No. 1031 The Medicines for Human Use (Clinical Trials) Regulations 2004 http://www.opsi.gov.uk/si/si2004/20041031.htm

	Statutory Instrument 2006 No. 1928 The Medicines for Human Use (Clinical Trials) Amendment Regulations 2006 http://www.opsi.gov.uk/si/si2006/20061928.htm Statutory Instrument 2006 No. 2984 The Medicines for Human Use (Clinical Trials) Amendment (No. 2) Regulations 2006 http://www.opsi.gov.uk/si/si2006/20062984.htm

7 ECRIN References

- ECRIN-EC-SOPØØ4 "Interaction with ethics committees after the conduct of a multinational clinical trial on medicinal products"
- ECRIN-EC-QCDØØ2 "Practical aspects of interacting with authorities (ethics committee and competent authority) throughout the conduct of a multinational clinical trial on medicinal products"
- ECRIN-CA-SOPØØ4 "Archiving in ECRIN studies"
- ECRIN-AE-SOPØØ1 "How to support adverse events reporting in multinational clinical studies"

ECRIN-CA-SOPØØ4

Archiving in ECRIN studies

Archiving in ECRIN studies
Reference: ECRIN-CA- SOPØØ4-VØ.9
Version number: draft VØ.9

APPROVAL
Author: Wolfgang Kuchinke and Kate Whitfield
Validated by working group leader: Date: Signature:
Validated by QA representative: 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, Switzerland, UK

1. PURPOSE

The purpose of this SOP is to describe the standard level of archiving required for all ECRIN studies at the beginning, during and after their termination, including: minimal documents required; responsibilities; and the process for archiving.

2. SCOPE

The ECRIN process of archiving described here follows the standards for clinical trials with an investigational medicinal product (Directive 2005/28/EC, ICH-GCP 1996). In principle it applies to all types of multinational clinical study, on all categories of research selected by the ECRIN Scientific Board and performed within the network. ECRIN has identified eight categories of clinical research: 1. clinical trials on medicinal products, 2. clinical research on medical devices, 3. other therapeutic trials (radiotherapy trials, surgery trials, physical therapy trials,...), 4. diagnostic studies, 5. clinical research on nutrition, 6. other clinical research (complementary and alternative medicine, biobanking, psychology studies,...), 7. epidemiologic studies, 8. miscellaneous studies (usual care,...). Each category implies in principle different requirements for documentation and archiving, which can be described by using three different groups of archiving (Fig. 1). In general only for interventional trials on medicinal products the requirements for GCP compliant documentation and archiving, including the keeping of an ISF and TMF applies Europe wide and are legally binding. For epidemiological studies the GEP guideline gives recommendations for archiving. For all other categories the trial protocol defines documents needed for archiving according to the requirements of ethics committee, competent authorities, additional local authorities and different guidelines and medical codes of conducts. For different categories of clinical research ECRIN recommends a minimal set of documents ("relevant documents") to be archived (see appendix).

The following regulations apply to archiving:

- For GCP compliant archiving essential clinical study documents have to be archived by the sponsor and the investigator over an adequate time period to be readily available at a reasonable time for audits and inspections.
- The investigator and the sponsor are responsible for archiving ECRIN recommended documents for at least five years (Directive 2005/28/EC), or longer according to country-specific requirements.
- All ECRIN recommended documents shall be recorded, handled, and stored in such a way that they can be accurately reported, interpreted, and verified, while the confidentiality of records of study participants remains protected (Directive 2005/28/EC).
- Additional study documents or archiving requirements may apply according to national or site-specific regulations, e.g., archiving of patient records or radiation protection regulation, x-rays.

There are three levels of archiving in ECRIN GCP-compliant studies:

1. Sponsor level. The trial master file (TMF) shall, at all times contain the GCP essential documents relating to that clinical study and must be archived at the sponsor site. The clinical database is sent to the sponsor by the Clinical Data Centre (CDC) for archiving. The sponsor may delegate archiving of the TMF to an external organisation or third party.

2. Investigator level. The investigator site file (ISF) contains all GCP essential documents necessary for the investigator to carry out the study, and is archived at all individual clini-

cal centres (study sites). If there is no separate or defined sponsor, then the coordinating investigator assumes all responsibilities of the sponsor and must also archive the trial master file (TMF) either at the investigator site or the corresponding national coordinating centre (NCC).

3. ECRIN level. Contracts between ECRIN and the sponsor including the archiving contract and task delegation forms are archived at the national coordinating centre (NCC). ECRIN SOPs are archived at the ECRIN Quality Assurance unit at the ECRIN Coordination Office.

For archiving of non-GCP compliant studies requirements are defined by the corresponding study protocols. Nonetheless, ECRIN recommends to establish a similar three level structure for filing and archiving of essential study documents in non-GCP compliant studies. A list of ECRIN recommended essential documents that should be archived in non-GCP compliant studies is given in the Annex. In non-GCP compliant studies too, contracts between ECRIN and the sponsor including the archiving contract and task delegation forms are archived at the national coordinating centre (NCC). ECRIN SOPs are archived at the ECRIN Quality Assurance unit at the ECRIN Coordination Office

3. DEFINITIONS AND ABBREVIATIONS

Archiving: the action of storing the essential study documents, this can be according to the study category GCP essential documents or ECRIN recommended documents after the study has been terminated.

Archiving confirmation document: contract about the content of the complete archive of a trial.

Archiving log: document that lists all access to the archive and all incoming and outgoing documents.

Archiving representative: set up by the sponsor the archiving representative keeps the archiving log and controls access to the archive, supervises the archiving duration and the input of documents.

Clinical Data Centre (CDC): conducts the electronic data management of the study. It is audited by ECRIN. After termination of the study it sends the study database to the sponsor to complete the trial master file (TMF).

ECRIN individual clinical centre: specific site where clinical study is conducted, signed copies of SOPs and the investigator site file (ISF) are archived here.

ECRIN recommended documents: suggested essential documents for non-GCP studies. They allow the design, conduct and analysis of non-GCP clinical studies to be assessed and demonstrate participant safety and data quality during trial conduct. The recommended ECRIN documents are based on the 'essential documents' for clinical trials with an investigational medicinal product (ICH-GCP 1996), and the recommendations of good epidemiology practice (GEP 1997).

Essential documents: documents that individually and collectively permit evaluation of the conduct of a study and the quality of the data produced. (ICH-GCP E6 Glossary).

Filing: the action of collecting either the GCP essential documents or the ECRIN recommended documents. Filing should start before the study begins and continue throughout the study.

GEP: good epidemiological practice, a guideline written by the International Epidemiological Association for proper conduct in epidemiological research.

Investigator site file (ISF): shall, at all times, contain all GCP essential documents that are necessary for the investigator to carry out the study (and ICH-GCP 1996 and EuraLex Vol 10, Chapter 5, 2006). Any or all of the documents in the ISF may be subject to, and should be available for audit and inspection by the regulatory authorities (ICH-GCP 1996).

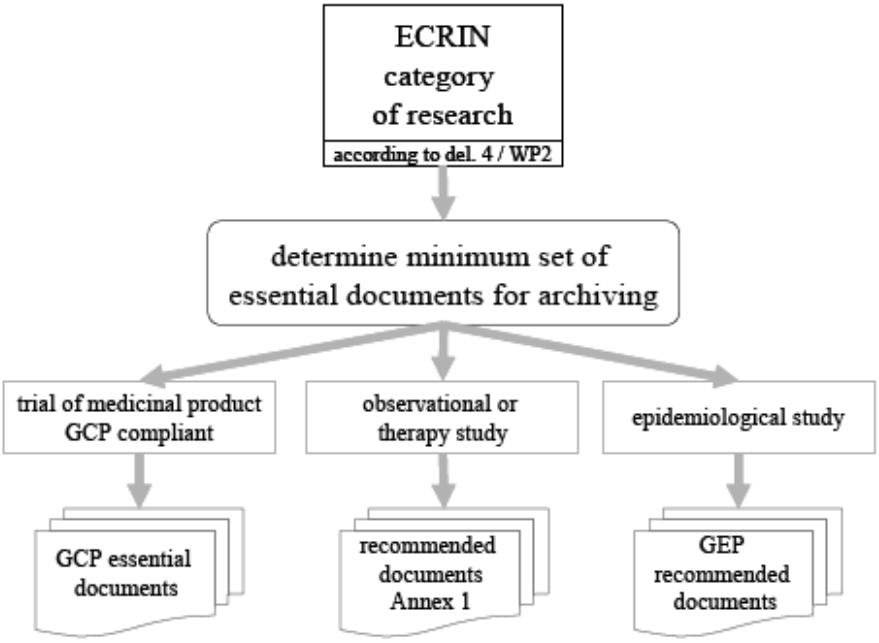
Sponsor-investigator: An individual who both initiates and conducts, alone or with others, a clinical trial, and under whose immediate direction the investigational product is administered to, dispensed to, or used by a subject. The term does not include any person other than an individual (e.g., it 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-GCP 1996).

Trial master file (TMF): the trial master file shall, at all times, consist of GCP essential documents relevant for the sponsor. The documents shall show whether the investigator and the sponsor have complied with the principles and guidelines of good clinical practice and with applicable requirements (Directive 2001/20/EC, Directive 2005/28/EC, ICH-GCP 1996, and EuraLex Vol 10, Chapter 5, 2006). Any or all of the documents in the TMF may be subject to, and should be available for audit by the sponsor's auditor and inspection by the regulatory authorities (ICH-GCP 1996).

4. RESPONSIBILITY

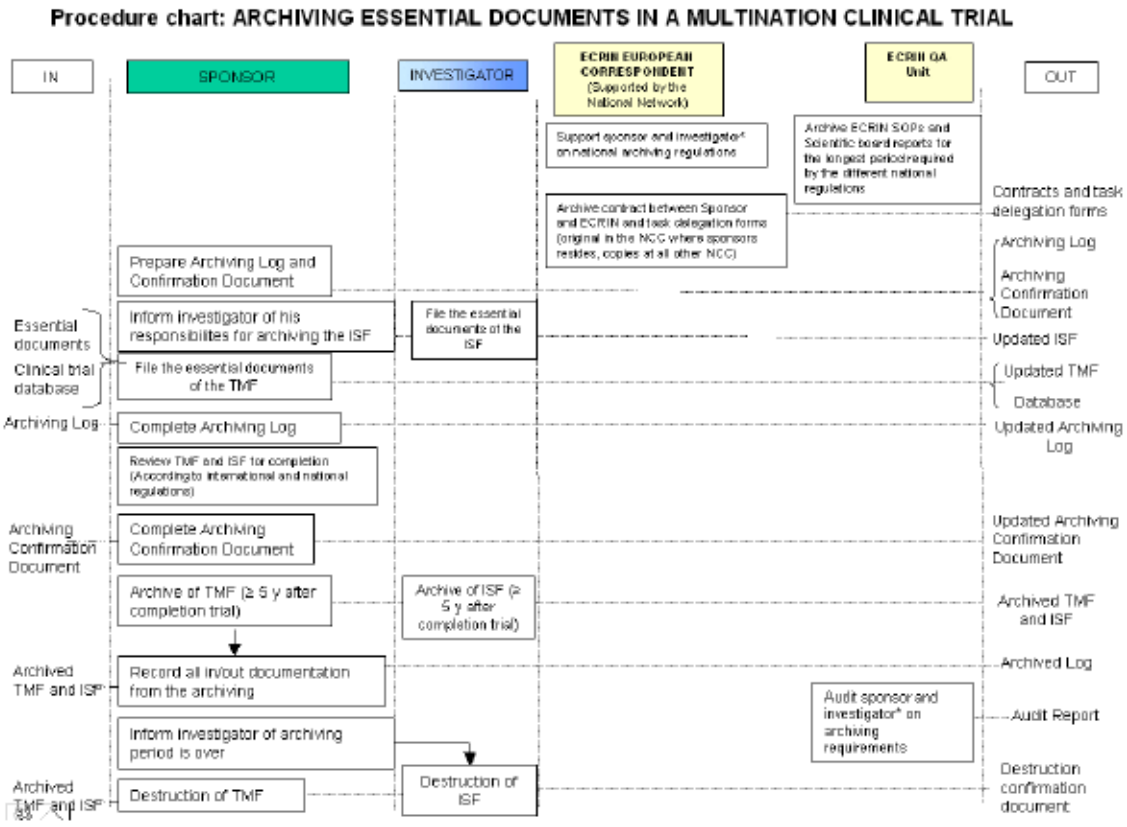
Common elements	Country specific elements
Sponsor (or delegated entity) is responsible for filling and archiving the GCP essential or the ECRIN recommended documents in the trial master file (TMF) (Fig. 2) and other relevant documents in the ECRIN quality assurance (QA) unit, as well as any further documents in accordance with country-specific requirements, before, during and after a study (Fig. 3 and 4). The sponsor is also responsible for informing the investigator of his responsibilities for archiving the investigator site file (ISF) and of the time when the records are no longer needed (Directive 2005/28/EC). The sponsor may delegate archiving to a third party, e.g. an archiving representative, but responsibility always remains with the sponsor. **Investigator** is responsible for filling and archiving the GCP essential or ECRIN recommended documents, and any further documents in accordance with country-specific requirements, in the investigator site file (ISF), before, during and after a study (Fig. 2). **Sponsor-investigator** is responsible for filling and archiving the GCP essential or ECRIN recommended documents in both the investigator site file (ISF), trial master file (TMF), and ECRIN quality assurance (QA) unit. **European correspondent** is the local support to the sponsor in his/her country and is responsible for providing relevant national information and coordination. **ECRIN Quality Assurance Unit** is responsible for the quality concerns of the ECRIN network and the archiving of high-ranking documents (contracts, service level agreements, etc.). It resides at the ECRIN Coordination Office. The QA unit will be directed by the ECRIN Coordination Office. Here we note its archiving-related responsibilities. **Monitor** may advise the investigator and/or sponsor with respect to filling and archiving obligations before, during and after a study, in order to comply with GCP. Final close-out of a study should be done when the monitor has reviewed both investigator site file (ISF) and sponsor's trial master file (TMF) and confirmed that all necessary documents are in the appropriate files (ICH-GCP 1996).	***UK :*** *The sponsor shall keep a TMF for a clinical study. The sponsor shall ensure that any alteration to a document contained, or which has been contained, in the TMF shall be traceable.*

Fig. 1: *Decision process about what GCP essential or ECRIN recommended documents to archive*



ECRIN SOP

Fig.: 2: *Overview of filing and archiving of GCP essential documents.*



5. DESCRIPTION

Please see 'Procedure chart archiving documents in a multinational clinical study' for common elements (Fig.2).

5.1. DOCUMENTS, REQUIREMENTS OF THE ARCHIVE AND ARCHIVING DURATIONS

Please see 'Decision process about what essential or recommended documents to archive' (Fig. 1).

<table>
<tr><th>Common elements</th><th>Country specific elements</th></tr>
<tr><td>The sponsor (or delegated entity) and investigator shall retain the ECRIN relevant documents relating to a clinical study for at least five years after its completion (Directive 2005/28/EC).</td><td rowspan="3">Austria:
According to the Austrian drug act (Arzneimittelgesetz) the following requirements are needed for trials with medicinal products (§46):
-The Sponsor is responsible to archive all study related documents for 15 years after the end of the trial or 5 years after end of approval of the medicinal product.
-The investigator is responsible to archive all documents regarding treatment allocation of study participants for 15 years after the end of the trial.

Denmark:
No specific requirements.

Finland:
Original research documents should be archived for at least 15 years after the termination of the trial.
This only applies to clinical trials with a medicinal product.

France:
According to law 2004-806 of 9 August 2004 and the decree of the 8 November 2006 "Arrêté du 8 novembre 2006 fixant la durée de conservation par le promoteur et l'investigateur des documents et données relatifs à une recherché biomédicale portant sur un médicament à usage humain" essential documents relating to a clinical trial must</td></tr>
<tr><td>The sponsor and investigator shall retain the ECRIN relevant documents for a longer period, where required by other applicable requirements (Directive 2005/28/EC).</td></tr>
<tr><td>ECRIN relevant documents shall be archived in a way that ensures that they are readily available, upon request, to the competent authorities, and are complete and legible. The media used to store ECRIN relevant documents shall be such that those documents remain complete and legible throughout the required period of retention and can be made available to the competent authorities upon request (Directive 2005/28/EC).</td></tr>
</table>

Any transfer of ownership of the data or of documents shall be documented. The new owner shall assume responsibility for data retention and archiving (Directive 2005/28/EC).	*be archived for 15 years following the end of the trial. The documents can be archived for a longer period if agreed by the sponsor and the investigator.* *This applies only to clinical trials with a medicinal product.* ***Germany:*** German Drug Law (AMG) according to 12th amendment (GCP regulation §42): 10 years after end or termination of CT, for all relevant clinical trial documents including case report forms. This applies only to clinical trials with medicinal product clinical studies. Regulations for Radiation Protection and X-ray trials apply for corresponding studies. MBO-Ä and the joint recommendation of BfArM and PEI apply for other types of studies. *Arzneimittelprüfrichtlinie (CT using drugs which results are used for application for marketing authorization):* - *Patient's records and source: hospital regulations* - *Patient identification list: 15 years after termination* - *TMF: as long as the drug is approved* - *Protocol: 5 years after end of approval of the drug* *Radiation Protection Regulation (StrlSchV), §87: 30 years* X-ray Regulation (RöV), §28c: 30 years *Medical Device Law (Medizinproduktegesetz MPG), §12:* - *documentation according to number 3.2 of appendix 6 of 90/385/EWG at least for 10 years,* - *and documentation according to number 3.2 of appendix VIII of 93/42/EWG at least for 5 years after end of trial.* *§20:* - *archiving of documents according to number 2.2 of appendix 6 of 90/385/EWG for trials with active implanted medical devices is at least for 10 years.* *BfArM and PEI: joint recommendation of BfArM and PEI for planning, conduct and analysis of observational studies ("Anwendungsbeobachtungen"), version May 9, 2007: Archiving of results, documents and final report of observational studies for minimum of 10 years*
Patient records and clinical source data have to be archived for the longest time that the local hospital or institute of the site requires, according to national laws.	

In case documents exist in electronic form and/or documents and data have to be transferred into a different medium for archiving, the archiving and transfer system (e.g. scanning) should be validated to ensure that no information is altered or lost. Transaction control protocols should be generated. A written detailed description of the system should exist and be kept up to date. Stored data should be checked for accessibility, durability and accuracy (Annex 11)[1]. For electronic archiving documents and data should be stored in an open format (preferable XML, ASCII, PDF) and be archived on durable data media. The electronically archived data should be readily accessible on the storage medium for inspection or audit without the need for special software. The readability of data should be guaranteed for the entire archiving duration. This applies for all electronic essential documents (ISF and TMF). The corresponding SOP of the Clinical Data Centre will provide details of archiving of electronic study data. For electronic archiving over longer periods of time, data migration strategies may be necessary, to maintain an accessible electronic format.	*MBO-Ä: Medicinal Association's professional code of conduct (Muster-Berufsordnung für die deutschen Ärztinnen und Ärzte, 2006): §10(3): archiving of medical records for 10 years after treatment, in case a longer retention time is not required* ***Hungary:*** *No specific requirements.* ***Ireland :*** *No specific requirements* ***Italy:*** *According to Legislative Decree of November 6, 2007 n.200, all documents should be archived for at least 7 years after the termination of the trial, or more if other requirements are to be observed, or there is a specific agreement between sponsor and investigator* ***Sweden**:* *The documentation of a clinical trial should be archived and retrievable for at least 10 years after end of trial/report if the trial was initiated after 1 May, 2004 and 15 years if the trial was initiated before this date. http://www.lakemedelsverket.se/upload/lvfs/LVFS_2003-6.pdf, LVFS 1996:17, 19 kap, LVFS 2003:6, 8 kap, AR. Registries This applies to all clinical studies.* ***Switzerland:*** *The sponsor must archive all the data relating to the clinical trial until the expiry date of the last batch delivered of the preparation tested or the last medical device manufactured, but at least for ten years after the date upon which the clinical trial is completed or halted. The investigator in charge must archive all the documents necessary for the identification and medical monitoring of the trial participants as well as all other original data for ten years after the date upon which the clinical trial is completed or halted Verordnung über klinische Versuche mit Heilmitteln (VKlin), 17. Oktober 2001 (Stand am 1. Januar 2008)* ***UK:*** *No specific requirements.*
Access to archives shall be restricted to the named individuals responsible for archives (Directive 2005/28/EC).	

[1] The new Draft Annex 11, Computerised Systems, February 2008 requires that the archived data should be secured by physical and/or electronic means against wilful and/or accidental damage. Backup, archiving, retrieval and restoration (recovery) practices need to be defined, tested and established in accordance with the manufacturing authorisation holder's QMS, ISMS and risk management requirements.

Requirements of the archive	
An archive for clinical study documents must: - be lockable. - have an arrangement for access authorisation. Access to the archive is only allowed for authorised persons. - have appropriate measures to protect documents against water, fire, and unauthorised access. - have an index for archived documents to allow quick retrieval.	
Multinational processes	
To prepare for archiving of multinational studies the sponsor will liaise with the national coordinating centre (NCC) of each country taking part in the study and with each individual study centre in order to complete the trial master file (TMF), ensure filing of essential or recommended documents, ensure the correct archiving of the investigator site files (ISFs), observe the national archiving time spans of different documents and consider national archiving regulations (Fig. 3 and 4). The EU correspondents will support the sponsor by providing information about national archiving durations for different sort of documents. In each country the national rules apply for archiving, even if the sponsor is in a foreign country. The EU correspondent will communicate the national requirements and the archiving time line to the sponsor. The data base may be transferred from the country of the Clinical Data Centre to the country of the sponsor.	

5.2. Processes

Common elements	Country specific elements
Preconditions for archiving of study documents	
ECRIN may audit the sponsor in order to ensure that s/he is able to observe archiving requirements. The sponsor may have an archive representative, who is responsible for archiving study documentation and who supervises access to the trail master file (TMF). For archiving the trial master file (TMF) an archiving confirmation document is prepared by the sponsor (or the archive representative) containing an index, the archived documents and the corresponding archiving duration. An archiving log is run for the entire archiving duration.	
Archiving sites	
The sponsor must archive the trial master file (TMF) (Fig. 2) he sponsor may chose to archive the TMF outside the sponsor's premises e.g. the national coordinating centre (NCC), but responsibility always remains with the sponsor. The investigator must archive the investigator site file (ISF), the archiving site for the ISF is the ECRIN individual clinical centre (study site).	

5.3. Archiving ECRIN-specific documents

Common elements	Country specific elements
Archiving of clinical database	
The Clinical Data Centre (CDC) sends the complete database in a durable, secure and readable format to the sponsor for archiving with the trial master file (TMF).	
Archiving at ECRIN coordination office/ quality assurance unit	
Relevant ECRIN SOPs and scientific board reports are archived for the maximal duration at the ECRIN coordination office.	

Archiving at leading study national coordination centre (NCC)	
Contracts between ECRIN and sponsor (or coordinating investigator if no sponsor exists) and task delegation forms are archived for the maximal duration at national coordination centre in which country the sponsor or coordinating investigator resides.	
Archiving at national coordination centre (NCC)	
Copies of contract and task delegation are archived for the maximal duration at all national coordination centres (NCCs) involved in the study.	
End of archiving	
After the end of archiving duration is reached the contents of the archive can be destroyed. In this case the archiving representative has to produce a receipt to document the destruction of the archive.	

6. SPECIFIC REFERENCES

Common elements	Country specific elements
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*) Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products (*Official Journal L 91, 9/4/2005 p. 13 - 19*) International Conference on Harmonisation Guideline for Good Clinical Practice E6 (ICH/135/95 – adopted 1996) EudraLex Volume 10, Clinical Trials, Chapter 5: Recommendation on the content of the trial master file and archiving (July 2006). ANNEX 11 - COMPUTERISED SYSTEMS. Eudralex Vol 4, ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-4/pdfs-en/anx11en.pdf Good Epidemiological Practice – International Epidemiological Association Guidelines for proper conduct of epidemiological research, updated 2007, http://www.dundee.ac.uk/iea/download/GEPNov07.pdf	***Austria***: *Austrian drug act - Arzneimittelgesetz (AMG) (www.ris.bka.gv.at)* ***Denmark:*** *executive order, no. 744 of 29 June 2006 (only in Danish) http://lms-lw.lovportaler.dk/showdoc.aspx?docId=bek20060744-full* ***Finland:*** *Ihmiseen kohdistuvat kliiniset lääketutkimukset, Lääkelaitoksen määräys 1/2007 http://www.nam.fi/instancedata/prime_product_julkaisu/laakelaitos/embeds/maaraykset_M_2007-1.pdf (in Finnish)* ***France***: *law 2004-806 of 9 August 2004* ***Germany***: *German Drug Law (AMG), 12th amendment; Guideline for drug studies (Arzneimittelprüfrichtlinie); Radiation Protection Regulation (StrlSchV), X-ray Regulation (RöV), Medical Device Law (Medizinproduktegesetz, MPG)* ***Hungary:*** *35/2005 Decree of Ministry of Health* ***Ireland:*** *SI 190 & 878 of 2004 and SI 374 of 2006 European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations 2004 to 2006.* ***Italy:*** *Legislative Decree n. 200 of 6 November 2007, Legislative Decree n.211 of 24 June 2003, Ministerial Decree 21 Dicembre 2007, Ministerial Decree 12 Maggio 2006, Ministerial Decree 17 Dicembre 2004, Ministerial Decree 18 Marz 1998* ***Warning**: the above are the most recent and relevant regulatory reference for experimental studies. However the number of Legislative Decrees and Minesterial Decrees includes other items, that are available at the OssC https://oss-sper-clin.agenziafarmaco.it/normativa.htm There is also a limited number of items also available in English at https://oss-sper-clin.agenziafarmaco.it/normativa_ing.htm* ***Spain:*** *Real Decreto 223/2004, de 6 de febrero, por el que se regulan los ensayos clínicos con medicamentos. LEY 14/2007, de 3 de julio, de Investigación biomédica.* ***Sweden:*** *The Medical Product Agency's provisions and guidelines on clinical trials of medicinal products for human use (LVFS 2003:6), Archives Act (Arkivlagen 1990:782), Archives Ordinance (Arkivförodningen 1991:446).* ***Switzerland:** Verordnung über klinische Versuche mit Hielmitteln (VKlin), vom 17. Oktober 2001 (Stand*

	am 1. Januar 2008) ***UK:*** *The following Codes of Practice are a guide to the standards of practice required in the management of NHS records, based on current legal requirements and professional best practice. The guidance applies to all NHS records and contains details of the recommended minimum retention period for each record type. This includes all clinical research conducted in the NHS or involving NHS patients.* *Department of Health (England). Records management: NHS code of practice, Department of Health Policy, 5 April 2006* *http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4131747* *NHS Scotland. Records Management: NHS Code of Practice (Scotland) Version 1.0, July 04, 2008* *http://www.scotland.gov.uk/Publications/2008/07/01082955/0* *National Assembly for Wales. Managing Records in Trusts* *and Health Authorities. WHC(2000)71.* *www.wales.gov.uk/* *Health and Social Care Services in Northern Ireland: Good Management, Good Records,* www.dhsspsni.gov.uk/dhs-goodmanagement.pdf

7. ECRIN REFERENCES

ECRIN-GE-SOPØØ1 'Development, review, approval and management of standard operating procedures'
ECRIN-MO-SOPØØ1 'Monitoring ECRIN studies'

8. APPENDIX

(Checklists were adapted from GCP (good clinical practice) guideline EudraLex, Vol 10, Chapter 5: Recommendation on the content of the trial master file and archiving, July 2006 and GEP (good epidemiological practice) guideline from the International Epidemiological Association). For non-GCP trials ECRIN recommends to keep an file ("archive") corresponding to the TMF.

8.1 GCP compliant trials

Following essential documents have to be filed in the trial master file of the sponsor and the investigator site file for all ECRIN studies.

Before the start of the study: ECRIN relevant document	Location
Protocol, amendments and synopsis	File of the investigator (ISF) and sponsor (TMF)
Ethics committee (EC) and regulatory authority's (CA) approval. Composition of ethics committee	File of the investigator (ISF) and sponsor (TMF)
Documentation of relevant and scientific information regarding the intervention, where applicable	File of the investigator (ISF) and sponsor (TMF)
Information given to study participants including informed consent form (including translations), advertisement	File of the investigator (ISF) and sponsor (TMF)
Investigators brochure	File of the investigator (ISF) and sponsor (TMF)
Signed agreements between involved parties	File of the investigator (ISF) and sponsor (TMF)
Contracts, financial agreements, legal documents, insurance statements	File of the investigator (ISF), sponsor (TMF), and ECRIN quality assurance (QA) unit
Normal values or ranges for clinical, laboratory procedure, and statistical tests, where applicable	File of the investigator (ISF) and sponsor (TMF)
Interim analysis charter, including stopping rules, planned statistical analysis and thresholds, independent adjudicator, and decoding procedures for blinded trials, where applicable	File of the investigator (ISF) and sponsor (TMF)
Documentation of randomisation method, decoding procedure, where applicable	File of the sponsor (TMF) (third party if applicable)
Monitoring reports: trial initiation monitoring report, pre-trial monitoring	File of the investigator (ISF) and

report, where applicable	sponsor (TMF)
CV and other relevant documents about investigator qualification	File of the investigator (ISF) and sponsor (TMF)
Instructions for handling IMP, label samples, distribution records	File of the investigator (ISF) and sponsor (TMF)

During the conduct of the study: ECRIN relevant document	**Location**
Signed informed consent forms	File of the investigator (ISF) and sponsor (TMF)
Relevant ethics committee (ECX) and regulatory authorities (CA) approval of amendments	File of the investigator (ISF) and sponsor (TMF)
Revisions of protocol, CRFs, informed consent. Documentation of up-dated relevant and scientific information regarding the intervention, where applicable	File of the investigator (ISF) and sponsor (TMF)
Notification of CA and EC about SUSARs and safety information	File of the investigator (ISF) and sponsor (TMF)
Documentation of adverse events and SUSARs, and their appropriate reporting, where applicable	File of the investigator (ISF) and sponsor (TMF)
Subject screening / enrolment, subject identification list, where applicable	File of the investigator (ISF) and sponsor (TMF)
Signed case report forms (CRFs), CRF corrections, where applicable	File of the investigator (ISF) and sponsor (TMF)
Signature sheet	File of the investigator (ISF) and sponsor (TMF)
Source documents (original documents related to the study, intervention, and history of participant)	File of the investigator (ISF)
Raw data and documentation relating to its collection, where applicable	File of the investigator (ISF)
Updates to normal values or ranges, laboratory procedures, and statistical tests, where applicable	File of the investigator (ISF) and sponsor (TMF)
Documentation of transport and distribution of intervention, and study-related materials, where applicable	File of the investigator (ISF) and sponsor (TMF)
Monitoring reports, where applicable	File of the sponsor (TMF)

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Planned interim analysis and report, where applicable	File of the investigator (ISF) and sponsor (TMF) (third party if applicable)
Record of human biological samples retained (retention according to informed consent), where applicable	File of the investigator (ISF) and sponsor (TMF)
Annual safety report to ethics committee and competent authority, where applicable	File of the investigator (ISF) and sponsor (TMF)

After completion or termination of the study: ECRIN relevant document	**Location**
Documentation detailing ethics committee and regulatory authorities notification of the end of the study	File of the investigator (ISF) and sponsor (TMF)
Final safety report to the ethics committee and regulatory authorities, where applicable	File of the investigator (ISF) and sponsor (TMF)
Monitoring report, trial close-out monitoring, where applicable	File of the investigator (ISF) and sponsor (TMF)
All signed case report forms (CRFs), where applicable	File of the investigator (ISF) and sponsor (TMF)
All source documents (original documents related to the study, intervention, and history of participant), where applicable	File of the investigator (ISF) and sponsor (TMF)
All raw data and final analysis sufficiently documented to allow third party to repeat the data analysis	File of the sponsor (TMF), and an open-access data repository
Completed participant identification code list (archived according to informed consent), where applicable	File of the sponsor (TMF)
Intervention allocation decoding documentation, where applicable	File of the sponsor (TMF)
Investigational product accountability / destruction record	File of the investigator (ISF) and sponsor (TMF)
Clinical study report. Final report to ECRIN Scientific Board	File of the ECRIN quality assurance (QA) unit

For requirements of monitoring the ECRIN study, and thereby archiving the resulting documents, please see ECRIN-MO-SOPØØ1 'Monitoring ECRIN studies'

8.2 GEP compliant trials

Documents	Location
Correspondence pertaining to the study	archive
Copies of all quality assurance reports and audits	archive
Copies of signed institutional review board and other external reviewer reports	archive
Standard operating procedures	archive
Final report by investigator to ethics committees (where required) and where applicable, to the regulatory authority(ies)	archive
A final report of the study	archive
Information on relevant measurement instruments, calibration information and procedures	archive
Documentation relating to the collection and processing of study data, including laboratory / research notebooks, training and reference documents for abstracts, interviews, and coders	archive
Clinical study report	archive
Study protocol and copies of all approved modifications	archive
All source data and, where feasible, specimens. Master computer data file(s)	archive
Documentation to identify and locate all computer programs and statistical procedures used	archive
Copies of computer printouts, including relevant execution code, that form the basis of any tables, graphs, discussions, or interpretations in the final report	archive
Informed consent releases	archive
Data base	archive
Final report to ECRIN Scientific Board	archive

8.3 Recommended documents to archive in all categories of medical research with the exception of interventional medicinal product trials, devises and therapeutic trials

Documents	Location
Ethics committee composition /authorisation / approval / notification of protocol, where applicable	archive
Signed protocol and amendments, if any, and sample case report form, where applicable	archive
Informed consent form (including all translations), where applicable	archive
Any other written information or documents given to participants	archive
Advertisement for participant recruitment and details of participant compensation, where applicable	archive
Financial agreements between the investigator / institution and the sponsor for the study, where applicable	archive
Insurance police, where applicable	archive
Signed agreements between involved parties: e.g.: investigator / institution and sponsor; investigator / institution and contract research organisation and other involved parties; sponsor and contract research organisation and other involved parties, investigator/institution and authority(ies)	archive
Curriculum vitae and / or other relevant documents evidencing qualifications of investigator(s) and / or supporting study staff	archive
Normal value(s) / range(s) for medical / laboratory / technical procedure(s) and / or test(s) included in the protocol, where applicable	archive
Medical / laboratory / technical procedures / tests, where applicable	archive
Decoding procedures for blinded trials, e.g. for blind data analysis, where applicable	archive
Curriculum vitae for new investigator(s) and / or supporting study staff to whom investigator tasks are delegated	archive
Updates to normal value(s) / range(s) for medical / laboratory / technical procedure(s) / test(s) included in the protocol	archive

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Updates of medical / laboratory / technical procedures / tests.	archive
Monitoring visit reports, where applicable	archive
Signed informed consent forms, where applicable	archive
Source data and documents (original documents related to the study, to medical treatment, and history of participant)	archive
Signed, dated and completed case report forms, or other collection forms, where applicable	archive
Participant identification code list, where applicable. Participant pseu-donymisation list, where applicable	archive
Participant enrolment log (enrolment of participants by study number), where applicable	archive
Record of retained body fluids/ tissue samples, where applicable	archive
Final report by investigator to ethics committees where applicable	archive
Clinical study report	archive
Final report to ECRIN Scientific Board	archive

8.4 Process overview of archiving in different forms of international ECRIN clinical studies

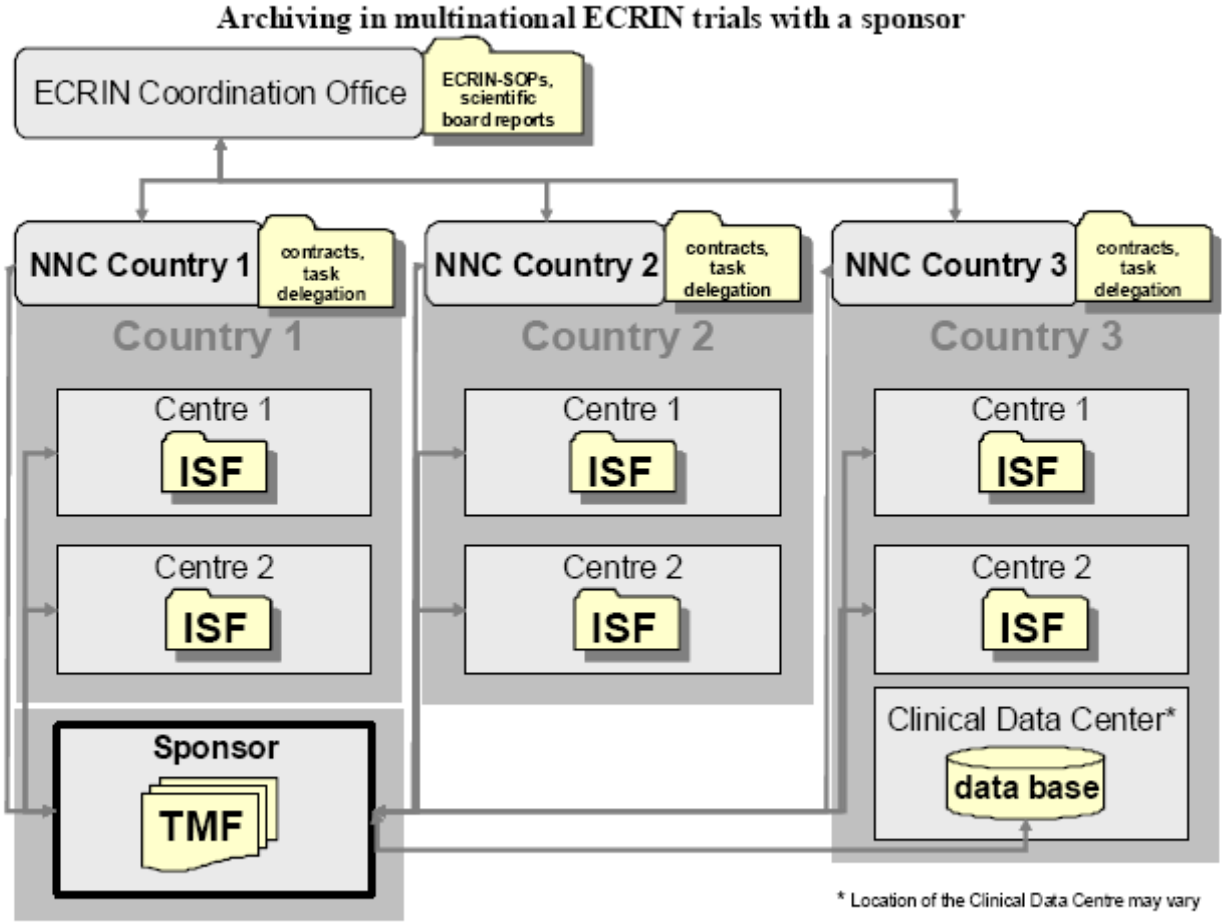


Fig. 3: *Process of archiving in international ECRIN studies with a separate sponsor*

ECRIN SOPs

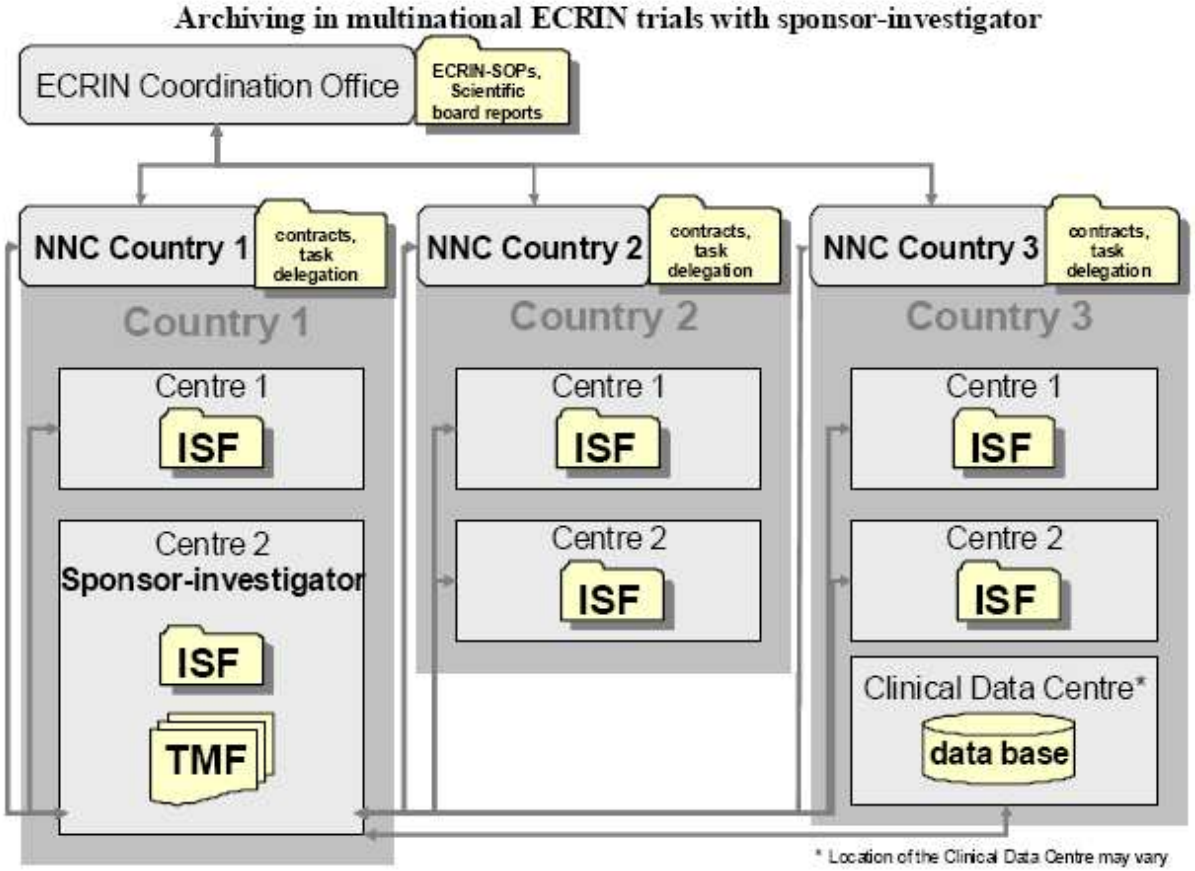


Fig. 4: *Process of archiving in international ECRIN studies with a sponsor-investigator*

ECRIN- CA- SOPØØ5

Insurance in multinational clinical trials on medicinal products

Insurance in multinational clinical trials on medicinal products
Reference: ECRIN-CA- SOPØØ 5
Version number: final draft

APPROVAL	
Author: Christine Kubiak	
Validated by WP Leader: Date:	Signature:
Validated by QA Representative: 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, Switzerland, United-Kingdom	

1 PURPOSE

The purpose of this SOP is to describe the general procedure for obtaining insurance in multinational clinical trials on medicinal product.

2 SCOPE

According to the EU Directive 2001/20/EC a clinical trial may be undertaken only if "provision has been made for insurance or indemnity to cover the liability of the investigator and sponsor".

The SOP intends to cover the clinical trials liability coverage in addition to the general liability and product liability coverage. It covers all multinational clinical trials on medicinal product selected by the ECRIN scientific board and performed within the network.

The policies can be of two types: liability and no-fault. The liability policies cover the sponsor against legal liability claims (ie, where the sponsor is at fault). The no-fault policy provides compensation to the participants, regardless of liability, in the event of their suffering a significant and enduring injury which is attributable to their involvement in the trial.

As no European coverage is available, an insurance certificate must be obtained from each country participating in the clinical trial.

In addition, investigators are under legal obligation to take out a personal insurance policy covering their research activities, if they are not automatically covered by their national insurance system.

3 DEFINITIONS AND ABBREVIATIONS

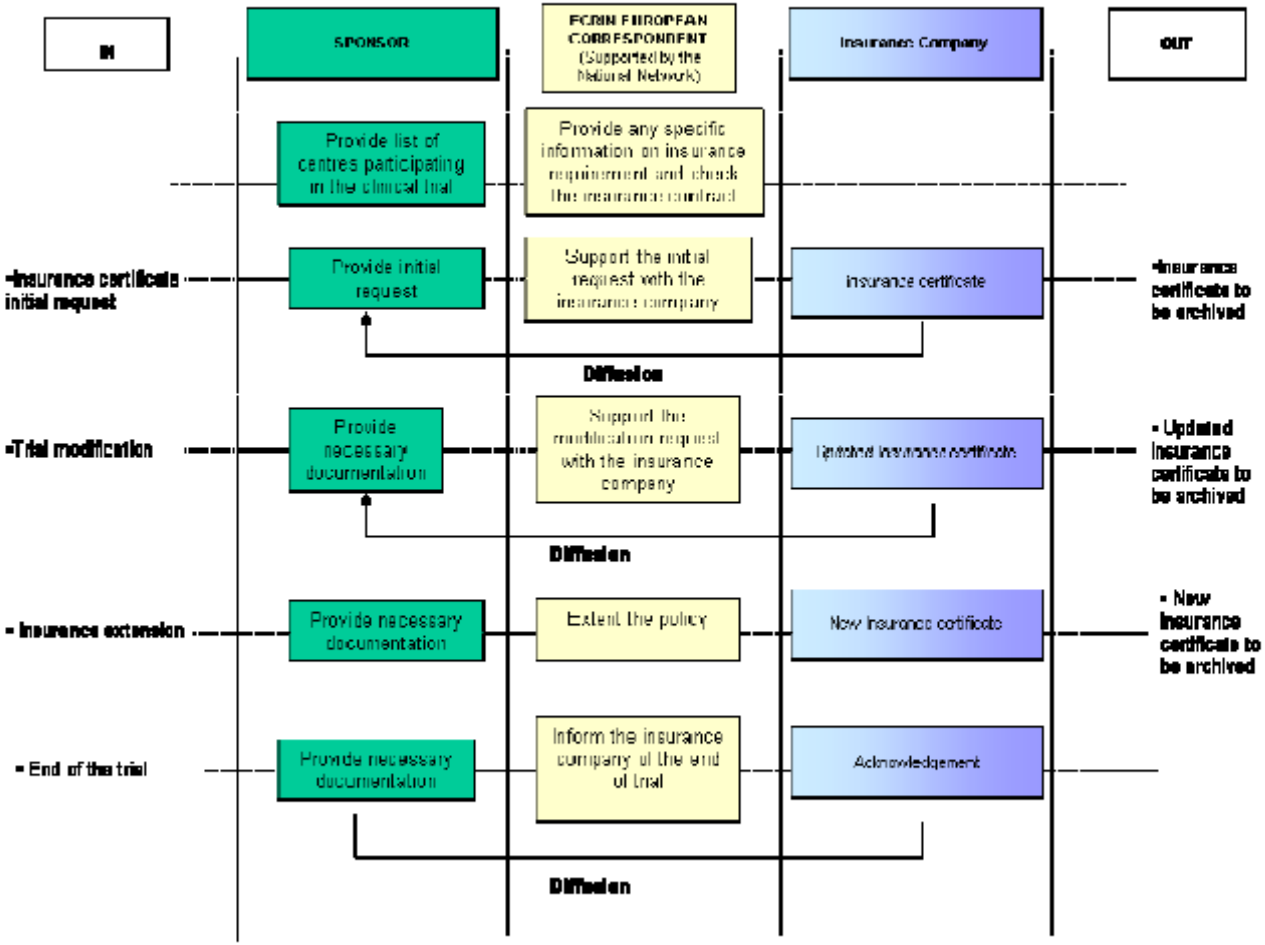
Common elements	Country specific elements

4 RESPONSIBILITY

Common elements	Country specific elements
Sponsor (or delegated entity or person): is responsible for the selection of investigators centres. He informs as soon as possible, the European correspondents of the countries in which he intends to perform the clinical trial, so they can contact the insurance companies. He provides all the necessary documents for the insurance certificate request and is responsible for obtaining the appropriate cover for the clinical trial. European Correspondent: - is the contact point and the local support to the sponsor in his country - is in charge of the interaction with insurance company and sponsor. - is in charge of securing the insurance process based on the information provided by the sponsor and with the support of existing resources at the national network.	**Germany**: In the case of clinical studies with xenogenic cell therapeutics the conclusion of an insurance must be proven also to the competent authority in the framework of the authorization procedure.

5 DESCRIPTION

5.1 Process Flow chart



5.2 Request and issue of insurance certificates

Common elements	Country specific elements
General information	
	Finland: Voluntary insurance for medicine-related injuries is taken out by the Finnish Cooperative for the Indemnification of Medicine-Related Injuries. More information: www.laakevahinkovakuutus.fi/en/ and www.laakevahinkovakuutuspooli.fi. Other than medicine-related injuries in the clinical trial are covered by the national Patient Insurance. More information: www.pvk.fi. **Ireland:** clinical negligence for investigators and their staff in non-industry trials in covered under National Clinical Indemnity Scheme. All studies must be notified to this body in order to confirm inclusion in the scheme. **UK:** Clinical negligence (known as 'NHS indemnity) scheme for NHS Trusts (cover for negligent harm via Clinical Negligence Scheme for Trust (CNST)) for all healthy volunteer or NHS patient trials that are conducted by a NHS Trust employee and the study has been granted NHS R&D Management approval for the study from the NHS Trust employer. The Risk Management Team at the NHS Trust research site should evaluate the level of risk the study poses, considering the types of patients recruited to the trial and assessing the financial robustness of the organisation sponsoring the trial, to determine the Sponsor's ability to meet and set the claims for compensation for which it is liable. Non negligent harm cover should be arranged by the Sponsor (or commercial company) of a trial, the NHS indemnity scheme does not offer no fault compensation. However, in the independent sector or publicly funded bodies may make arrangements to indemnify research subjects from non negligent harm. In the UK GPs working in general practice routinely obtain indemnity cover from a medical defence organisation (MDO) when undertaking standard clinical care procedures because Primary Care Trusts do not indemnity independent practitioners. However, the MDOs do not routinely provide cover for research related activity, but need to be informed that GPs may be involved in such activity to ensure that appropriate cover is in place. GPs who are employed by a PCT will be covered by the indemnity arrangements of their employer i.e. the PCT. It should be noted that if the research study is sponsored by a Commercial company or a Higher Education Institution they may provide cover for general practice staff for clinical negligence and non negligent harm. It may be useful to review the Department of Health's guidance document on research governance in health and social care: notes for primary and community care, July 2002. The following guidance document issues by Department of Health (England) - Research

	governance in health and social care: notes for primary and community care, July 2002. http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4122566
Before the beginning of the clinical trial	
1) The Sponsor must provide as soon as possible the European Correspondents of the countries where the trial will be conducted with: - the trial protocol - the information and consent form (in local language and with the information regarding the insurance) 2) Each country (through the European Correspondent) will discuss the cost of the insurance, as soon as possible with their insurance company 2) The European Correspondent will with the help of their national network (and any specific department in place in their national coordination) submit the insurance certificate request form with the following documents: - protocol and amendment if applicable - copy of the information and consent form for each centre 3) When the certificates are obtained, the European correspondent transmits the certificate to the sponsor.	**Requested information on the insurance certificate** **Austria:**per centre, guarantee amount, duration of the study, number of participants **Denmark:** **Finland:** A photocopy of the membership of the local pharmaceutical Cooperatives (see above) and a copy of the General Terms and Conditions of the insurance in force (only if separately required). **France**: per country (but asking a certificate per centre allow to verify that all centres are taken into account), guarantee amount, duration of the study (provisional end date), provisional number of participants **Germany**: per centre, guarantee amount, investigator **Hungary**: per country, guarantee amount, duration of the study **Ireland**: Medical liability insurance covered by national insurance (Clinical Indemnity scheme) **Italy**: per centre, guarantee amount, duration of the study **Spain:** per centre, guarantee amount, duration of the study (provisional end date), provisional number of participants, investigator **Sweden**: No specific requirement. For CRO's the trial identification no is stated. **Switzerland**: per centre, guarantee amount, duration of the study **United-Kingdom**: Details of any insurance or indemnity to cover the liability of the Sponsor and Investigator.

4) The insurance statement is an essential document for archiving in the Investigator Site File (ISF) and the Trial Master File (TMF) (ICH-GCP) (see ECRIN-CA-SOPØØ4)	
Modification	
Each significant modification (duration of the study, increase of the number of participants, modification of the investigator) must be sent to the insurer with a copy of the amendment.	
Renewal	
When the trial is prolonged after the provisional end date, a new certificate must be requested according to the national rules.	Austria: Without tacit renewal Finland: With tacit renewal (if at all) France: With tacit renewal Germany: With tacit renewal Hungary: without tacit renewal Ireland: With tacit renewal Italy: With tacit renewal Spain: Without tacit renewal Sweden: With tacit renewal Switzerland: Without tacit renewal United-Kingdom: With tacit renewal
End of the trial	
When the trial is completed (last follow-up of last participant) the European correspondent notifies the insurer of the end of the study.	

6 SPECIFIC REFERENCES

Common elements	Country specific elements
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*) ICH-GCP. International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use. Guideline for Good Clinical Practice. E6 (R1). ICH Harmonised Tripartite Guideline 1996.	**Denmark:** -Patient Insurance Act (Patientforsikringloven) - Liability for Drug Incurred Injury Act (Lægemiddelskadeerstatningsloven) - Damages liability Act (Erstatningsansvarsloven) - Liability for Defective Products Act (Produktansvarsloven) **Finland:** - Patient Insurance Act (585/1986) - Medical Research Act (488/1999) - Medicine Act (395/1987) **France:** Law 2004-806 of 9 August 2004 on Public Health (art L 1121-10 and art L1142-3) **Germany:** German Drug Law (AMG; „Arzneimittelgesetz"), http://www.gesetze-im-internet.de/bundesrecht/amg_1976/gesamt.pdf GCP-Decree (GCP-Verordnung; Verordnung über die Anwendung der guten klinischen Praxis bei der Durchführung von klinischen Prüfungen), http://www.gesetze-im-internet.de/bundesrecht/gcp-v/gesamt.pdf **Sweden:**

	Pharmaceutical Insurance (Läkemedelsförsäkringen) obtained by membership to the Swedish Pharmaceutical Insurance Association, covers 99.9% of all trials. http://www.lakemedelsforsakringen.se/default.asp?id=12821&ptid= Public Patient Insurance (Patientskadeförsäkringen), regulated by the Patient Injury Act Product Liability Act (for Medical Device, Produktansvarslagen) UK: Statutory Instrument 2004 No. 1031 **The Medicines for Human Use (Clinical Trials) Regulations 2004** http://www.opsi.gov.uk/si/si2004/20041031.htm Statutory Instrument 2006 No. 1928 **The Medicines for Human Use (Clinical Trials) mendment Regulations 2006** http://www.opsi.gov.uk/si/si2006/20061928.htm Statutory Instrument 2006 No. 2984 **The Medicines for Human Use (Clinical Trials) Amendment (No. 2) Regulations 2006** http://www.opsi.gov.uk/si/si2006/20062984.htm Section 21 National Health Service & Community Care Act 1990 (England and Wales) http://www.opsi.gov.uk/ACTS/acts1990/ukpga_19900019_en_1 Schedule 1 National Health Service Reform (Scotland) Act 2004 http://www.opsi.gov.uk/legislation/scotland/acts2004/asp_20040007_en_1 Article 24 Health and Personal Social Service (NI) Order 1991 http://www.opsi.gov.uk/si/si1991/uksi_19910194_en_1

7 ECRIN REFERENCES

- ECRIN-EC-SOP ØØ2'Interaction with Ethics Committees before the conduct of a multinational clinical trial on medicinal products'.
- ECRIN-CA- SOP ØØ1 'Interaction with competent authorities before the conduct of a multinational clinical trial on medicinal products'
- ECRIN-CA-SOP ØØ4 "Archiving in ECRIN studies"

ECRIN-EC-QCDØØ2

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

See deliverable 18.

Guidance document

Logistics of the investigational Medicinal Products within ECRIN multinational clinical trials

Guidance document regarding the « The logistic of the Investigational Medicinal Products within ECRIN multinational clinical trials».

PURPOSE:
The purpose of this document is to describe the logistic of the IMP within ECRIN. This includes the responsibilities of each actor at each stage of the process, and the complete availability of the required official documents for the traceability of the investigational medicinal products.

The main steps are:
- The shipment
- The reception & storage,
- The dispensation & accountability
- The return or destruction of unused products
- The management of eventually expired IMP

SCOPE:
This guidance document applies to all multinational clinical trials performed within the ECRIN network.

The proposed guidance must ensure that:
- The transport is made in appropriate conditions, by an authorised structure
- The IMPs are received by the authorised person (hospital pharmacist or investigator in case the clinical trial is carried out outside the hospital) and are handled and stored as planned
- The investigational medicinal products are delivered according to the protocol. The accountability performed during the trial will allow the reconciliation of the delivered and undelivered investigational medicinal products.
- The return and/or destruction of unused IMP and the management of any eventually expired IMP will be done according to the procedure defined in the protocol.

All the official documents regarding these stages listed above shall be available and archived by the Sponsor.

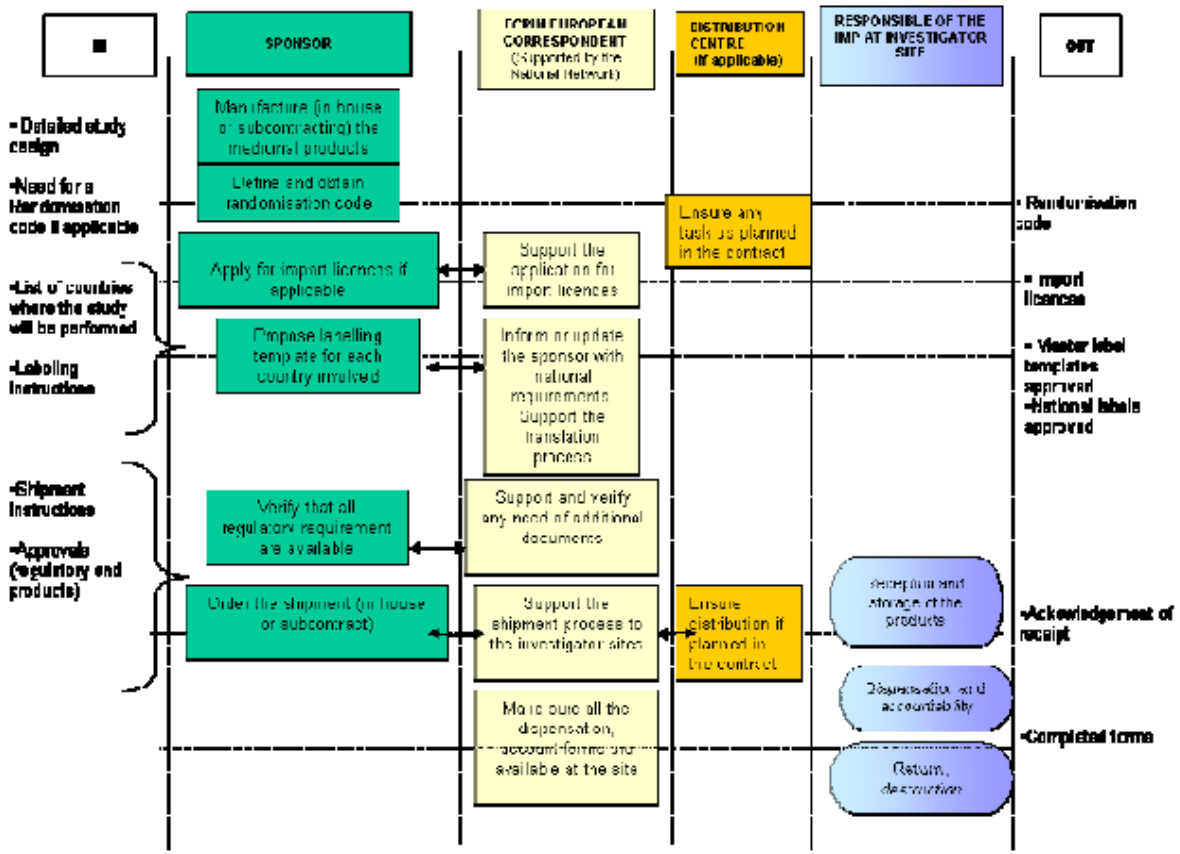
DEFINITIONS AND ABBREVIATIONS

Common elements	Country specific elements
See ECRIN Glossary for common definitions and abbreviations Investigational medicinal product: **IMP** 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*)	

RESPONSIBILITY

Common elements	Country specific elements
Sponsor (or delegated entity or person): - ensure that medicinal product: - is characterised as appropriate to the stage of development - is manufactured and released in accordance with requirements of the EU guide to Good Manufacturing Practice - is coded and labelled to comply with legal requirements and in a way that protects the blinding, if applicable. - ensure timely delivery of medicinal product (s) to the investigators' sites - maintain a system for handling complaints in connection with IMP and retrieving IMP 'in case of recall, claim or expired products). **European Correspondent**: -is the contact point and the local support to the sponsor in her/his country - is in charge of facilitating the interaction between the Sponsor, the national authorities and ethics committees and the investigators' sites with regards to the legal requirements and circuit organisation of investigational medicinal products **Distributing centre:** -must be a structure authorised for preparation, importation and distribution of IMP -ensure the tasks as planned in the contract with the sponsor **Responsible of the IMP at the investigator site**: *Depending on the specificity of the trials or of the countries, this responsibility can be assigned to the pharmacist at the hospital or to the investigator himself. Any way, the main responsibility regarding the IMP will be to :* - maintain a system for the reception, the storage and dispensation of IMP - ensure dispensation according to the protocol -manage the return/destruction of unused IMP at the end of the trial -could be involved in the management of expired IMP - maintain all the documentation detailed records of the reception, dispensation, accountability and return/or destruction of IMP during the whole duration of the clinical trial	

DESCRIPTION
Proposed Flow chart



RESPONSIBILITES AND ESSENTIAL OFFICIAL DOCUMENTS AT THE DIFFERENT STEPS

1/ Shipment
Before the shipment, it is the responsibility of the sponsor (or delegated entity) to ensure that all the documents required by the EU directive regarding the IMP are present. These main documents are:

- GMP certificate
-Certificate of analysis, batch release certificate
-Import/Export authorisations and licences
- Shipment order

Also some more specific local documents and certificate could be required by the country in addition of this common list. That shall be clarified and adapted according to local requirements.

In case the sponsor decided to delegate the set-up shipment instructions to a sub-contractor (distributing centre), the structure must mandatory be authorised by the local authorities for the storage and shipment of medicinal products. The sub-contractor will be responsible to ensure the traceability of the IMP during the shipment and perform the tasks as planned in the contract with the sponsor.

2/ Reception of the IMP at the Investigator' site

The responsible of the reception of the products (hospital pharmacist or investigator) verifies the conformity of the shipment and returns the acknowledgement of receipt to the appropriate person.

3/ Storage
- All IMPs should be managed by the Pharmacy (or investigator), and stored in a separate area from normal outpatient supplies.
- Medicines that require storage below room temperature should be stored in a medicines refrigerator and monitored regularly throughout the day. A document attesting of a continuous power supply of the refrigerator will be requested during the whole study.

4/ Dispensation & Accountability
- The IMP should be dispensed against a specific prescription form according to the clinical trial.
- The information about the accountability will be collected into an appropriate form to be used in ECRIN studies containing main items as the Name of the study, the Name of the Investigator site, Name of the IMP, N and date of the delivered IMP, expiry date of the IMP, signature of the delivery person, etc...

5/ Return and/or destruction of the unused IMP

The pharmacy (or investigator) is responsible for the reconciliation of used and unused IMP.
Depending on the procedure planned, the pharmacy will return to the sponsor the medicinal products or will ensure the destruction is performed in accordance with the protocol. The European correspondent will make sure that the documentation relating to the process of destruction will be completed, signed and kept a copy with the essential study documentation.

6/ Management of the eventual expired IMP

In case of expired IMP, the situation should be managed and adapted according to each protocol. In some cases the IMP could be destroyed or returned with the unused IMP. If the expiry date is extended, specific procedures must be in place to manage this extension.

SPECIFIC REFERENCES

Common elements	Country specific elements
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*) Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products (*Official Journal L 91, 9/4/2005 p. 13 - 19*) Commission Directive 2003/94/EC of 8 October 2003 laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use (*Official Journal L 262, 14/10/2003 p. 22 - 26*). European Commission Enterprise Directorate-General – Volume 4: Good manufacturing practices, Annex 13: Manufacture of investigational medicinal products, July 2003	. UK – Management issues for clinical trials of medicines in NHS Hospitals with particular reference to the Pharmacy http://www.ct-toolkit.ac.uk/_db/_documents/Hospitals.pdf Practice guidance on Pharmacy services, June 2005 http://www.rpsgb.org.uk/pdfs/clinicaltrialsguid.pdf Royal Pharmaceutical Society of Great Britain. Revised Duthie Report: Safe and Secure Handling of Medicines: A team approach, March 2005. http://www.rpsgb.org.uk/societyfunctions/peopleandstructures/membershipandspecialinterestgroups/hospitalpharmacistsgroup.html#safe

ECRIN References

ECRIN-MO-SOPØØ1 « Monitoring ECRIN studies»

Guidance document

Blood and tissue samples: collection, circulation, storage

How to manage human biological samples in multinational clinical trials	
Reference:	
Valid in:	

APPROVAL	
Author: C Libersa	
Validated by: (working group leader)	Signature:
Validated by : (QA representative)	Signature:
Effective date:	
Supersedes version number (if applicable):	
REVISION	
Version number:	
Date: 11 11 2008	
Reason for change:	
Main modifications:	

1. PURPOSE

The purpose of this SOP is to describe the specific requirements, responsibilities, and the process to manage human biological samples during a multinational clinical trial conducted by ECRIN in a GCP compliant way.

2. SCOPE

This SOP covers all clinical trials selected by the ECRIN scientific board and performed within the network. This includes trials for medicinal products according to phase I, phase II, phase III, phase IV, as well as trials for specific interventions, like biotherapy trials, trials for biopharmaceuticals and vaccines, fixed combination of medicinal products, multimodal trials, medical device, psychotherapy, diagnostic studies, and complementary and alternative medicine trials.

All documents generating in the trial must be managed according to the ECRIN SOP relative to document management.
Management of human biological samples during a clinical trial can be divided into several steps: sampling, identification of the sample, conditioning, transfer, storage, and destruction.

3. DEFINITIONS AND ABBREVIATIONS

CT: Clinical trial

ECRIN: European Clinical Research Infrastructures Network

ECRIN central lab:

ECRIN individual clinical centre: specific site where clinical trial is conducted.

Investigator: a medical doctor or a competent 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). If the trial is a multi-centre trial (al all multinational ECRIN trials will be) then the investigator in charge of the trial is called the coordinating investigator (ICH-GCP 1996).

Monitor: person entrusted with overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, SOPs, GCP, and the applicable regulatory requirements (ICH-GCP 1996).

NCC: national coordinating centre. The function of NCC is the coordination of networks in the corresponding countries. The NCC doesn't need to be localised at a single centre.

ECRIN SOPs

Standard operating procedure (SOP): Detailed, written instructions to achieve uniformity of the performance of a specific function (ICH-GCP 1996).

Sponsor: An individual, company, institution, or organisation, 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 (eg, 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-GCP 1996).

4. RESPONSIBILITIES

See "Procedure Chart for managing human biological samples in a multinational clinical" for common elements (Figs. 1).

Common elements	Country specific elements
Sponsor (or delegated entity) is responsible for is responsible for the overall management and traceability of samples. **Investigator** is responsible for the information of the participant about the sampling and the aim of the research and for obtaining from him informed consent. The investigator is responsible for the collection, testing, labeling, transfer and the future uses of samples **European correspondent** is the local support to the sponsor in his/her country and is responsible for providing relevant national information and coordination. **ECRIN individual clinical centres (trial sites)** the clinical sites where samples are collected, labeled and transferred to the central laboratory (ECRIN central laboratory?). **ECRIN Central laboratory** could be the designated laboratory for a specific trial where sample testing and storage will take place. The ECRIN Central laboratory can order sample disposal in-house and at the individual clinical centres.	

5. DOCUMENTS, REQUIREMENTS

Common elements	Country specific elements
Sampling The sampling should be done only when the participant has signed an informed consent For the sampling, investigators must pay attention to the primary containers used for sampling, the type of additives according to the scheduled analysis. The investigators should respect the amount of sample needed for the analysis the time between sampling and initial processing, and should take into account the factors that could affect the stability of the biological samples according to the specific procedures of the clinical trial. When the flow chart is designed, investigators must pay attention to the possibility of a local back up of samples in order to counter-balance transfer or central storage accidents.	***- Austria :*** **Circulation**: access to personal information of individuals participating in trials is protected by law (Datenschutzgesetz= data protection act) with restriction to trial related investigators and regulatory authorities. Data have to be anonymised before access is granted to the sponsor. Biobank regulations are stated in the biobank act (Gewebebankenverordnung).handling and storage of blood are regulated in the blood safety act (Blutsicherheitsgesetz - BSG), handling and storage of other tissue samples in the tissue safety act (Gewebesicherheitsgesetz – GSG). ***Genetic:*** all genetic studies within clinical trials have to be performed in accordance with the genetic engineering act. If genotyping is included within a clinical trial, a separate informed consent form should be provided to allow for a separate decision whether to also take part in or step back from the genotyping part. **- Denmark :** **Circulation**: there are no specific requirements regarding the competent authority. **Biobank**: permission must be sought from the Danish Data Protection Agency for storage of biological material in a biobank. Storage of biological material in a biobank must adhere to specific Danish Data Protection Agency terms and conditions. If a clinical trial involves removal of biological samples that will be stored in a biobank then participants need to give informed consent and the regional ethics committee and Danish Data Protection Agency must give permission. Any research that involves sensitive **personal information** must receive permission from the Danish Data Protection Agency, this would include any health-related data, according to the Danish Act on Processing of Personal Data.[1] The Danish Data Protection Agency stipulates specific terms and conditions relating to clinical research. The application can be made at the same time as that to the ethics committee and the Danish Medicines Agency. **Genetic**: there are no specific requirements for these types of trials

Identification and labelling Effective labelling and inventory management systems are essential. In a multinational clinical trial, biological samples must be tracked from the collecting site to a Central Lab "or Ecrin Lab". An appropriate system of management should be established. Such systems include the use of labels that identify samples according to the European regulation relative to GCP and GLP. The use of a unique barcode system given to each sample and printed on the label pasted on the container is recommended in order to reduce human intervention during tracking process. The labels used must be adapted to the storage conditions of the samples (freezing and humidity) and have to tightly adhere under all of these storage conditions. The identification of the samples must appear on the shipping log. To facilitate interactions between different sites, and to increase the efficiency of sample's tracking, use of standardization systems should be applied. Labelling of containers (primary and subsequent) must be done at the time of the sampling or aliquoting by the technician who realizes the sampling or its processing. The label must be made in order to avoid mistake on the identification of the sample. The label should include both barecode format and human readable form giving indications as to what is stored in the container : The label minimum data set must include the identification of the sample type, the patient's ID, the date of sampling and visit identification. When anonymity is needed, a procedure must be established in order to link the patient and the biological sample. During the process generating subsequent samples or aliquots, secondary containers must be labeled according to rigorous procedures in order to identify without any ambiguity the sample at every technical step and storage. **Processing and/or conditioning the samples:** Biological samples may need various processing	**- France :** **Circulation:** Importation and exportation of blood and tissue samples have to be notified to the Research Ministry (law 2004-800 of 6 august, 2004 article L. 1235-1 , L. 1245-5 and article R.1235-7, R.1235-8 of the French public health code). **Biobank**: if biobanking is part of a interventional biomedical research, the legal requirements relating to biomedical research have to be followed. If the biobanking is set up outside a biomedical research, the positive opinion of a CPP should be obtained, the consent of the person must be obtained prior to the sampling and the collection must be notified to the Research Ministry and the Regional Health Care Agency (ARS) (if conducted in a Health organisation). Data protection boards (CNIL and CCTIRS) should also give permission. Researches on **embryos** and other products from abortion need to be notified to the Research Ministry and Agence de Biomédecine (law 2004-800 of 6 august, 2004 article L. 1245-5). **Genetic**: samples for genetic studies follow the biobanking regulation. In case of genetic research, the consent form is mandatory and it is not possible to start new genetic researches without a new consent. The CCTIRS examines the scientific relevance for collection of genetic and family data. These studies are regulated by the 'loi de Bioethique'[2] and by the national ethics committee and a specific informed consent is necessary. samples for genetic studies follow the biobanking regulation. The **privacy** of individuals is protected by Law 2004-801 relating to the protection of individuals with regard to the processing of personal data that modify the Act 78-17 of 6 January 1978 on Data Processing, Data Files, and Individual Liberties. This law includes provisions concerning health data collecting within clinical research including collection of blood or tissue samples. The study must be submitted to committees for data protection (Commission Nationale de l'Informatique et

prior to storage.
Sample processing is a key step for samples' validity, quality and scientific value and must be done according to the Good Laboratory Practices.
The methods used for sample processing must be chosen according to the storage and analysis requirements.
The choice of the types of subsequent containers in the process is mandatory because it may affect the sample quality.
Each step of the sample treatment or conditioning must be described in standard operating procedures linked to the research protocol and the laboratory reference manual. Each centre treating or conditioning samples must have a copy of the laboratory reference manual.
The biological samples not meeting the validation criteria can not be included in the collection except in specific cases which must be thoroughly described. Each validation of such samples must be signalled to the "Ecrin Central Lab". The "Ecrin Central Lab" is the only instance able to take the final decision to keep or throw away these samples.

Transfer between Ecrin Centres , traceability

Traceability of samples is a process which must be applied during the whole clinical trial duration

des Libertés (CNIL)) assessing the storage and Comité Consultatif sur le Traitement de l'Information en Matière de Recherche dans le Domaine de la Santé (CCTIRS) assessing the content of information collected.

- Germany :

Circulation:
biobanking law doesn't yet exist, but several regulations apply to the circulation of blood and tissue samples. Sampling and analysis is covered by a treatment contract with the patients. Different country-specific hospital laws regulate and limit the sort of informed consent, the use of samples in special research projects (in context of the care treatment), the use of samples by third parties. In addition, one has to take into consideration: transfusion law (Transfusionsgesetz), guidelines for hemotherapy (Richtlinien zur Hämotherapie), blood guideline (Blutrichtlinie) and the Ordinance of GMP and good practices during production of products from humans (Verordnung über die Anwendung der guten Herstellungspraxis bei der Herstellung von Arzneimitteln und Wirkstoffen und über die Anwendung der Guten fachlichen Praxis bei der Herstellung von Produkten menschlicher Herkunft (Arzneimittel und Wirkstoffherstellungsverordnung – AMWHV-Verordnung). The Human Tissue Act (Gewebegesetz 2007) deals with the handling of human cells and tissues. This Act amended the Arzneimittelgesetz (German Medicinal Products Act) and Transplantationsgesetz (German Transplantation Law). Blood and Tissue samples are medicinal products according to the Drug law (Arzneimittelgesetz).

Biobank:
it doesn't yet exist a special biobanking law. Important regulations e.g. regarding manufacturing and explantation of cells and tissues can be found in the Arzneimittelgesetz (German Medicinal Products Act) and the Transplantationsgesetz (German Transplantation Law). Due to the fact that Biobanks partly deal with personal and health data the German Data Protection Act (Bundesdatenschutzgesetz, BDSG) also has to be regarded. Several other regulations that may apply are: transfusion law (Transfusionsgesetz), guidelines for hemotherapy (Richtlinien zur Hämotherapie) and blood guideline (Blutrichtlinie)). For data acquired and recorded in connection with taking the samples the physician has to consider duties according to the professional code for physicians (MBO-Ä). Personal data stored in a biobank for the purpose of research are subject to the security mechanisms of data protection law (eg. §40 BDSG). In most cases the ownership of samples in a biobank are with the donator and not with the biobank; and the donor has the right to utilize his samples. Sample collection is only allowed to take place after an consent by the donor is available. For an exclusive use for research the donor has to be informed about and agree to the duration of utilization of his samples. In addition §40 BDSG prescribes the pseudonymisation / anonymisation of personalized data for research purposes.

Genetic:

from the initiation visit to the end of analyses. The traceability of the samples must be managed by a Central Laboratory Core (e.g.: the Central Ecrin Lab)
All steps must be clearly identified (who makes what and when) and all documentation needed for this purpose must be thought and established. All documents must be transmitted as fast as possible to the Central Ecrin Lab in charge of the samples' traceability.

Depending on the location of the centres, the transfer of samples to the Ecrin labs must be done according to the enforced regulation concerning diagnostic specimen and depending on the infectious status of the samples. If samples are transferred by plane, the applicable regulation is the International Air Transport Association one. If the samples are transferred by road, the European legislation relative to dangerous goods transport by road (ADR) must be applied.

Sample shipping must be realized as quickly as possible taking into account possible delay at custom. All the precautions must be taken in order to avoid contamination or damage to the sample during transfer.
The current procedure and the associated documents establish the specific conditions of time allowed for carriage, temperature of preservation and integrity of packaging.

Each transfer of a biological sample is done following the reception of a transfer order. The transfer order to users could be initially defined in the research protocol. The frequency and kind of transfer are also mentioned in the protocol. In the other case, the Biological Resource Center (BRC) can receive the transfer order by mail or facsimile.

As biological samples are considered as potentially dangerous material they should be conditioned according to the rule of the triple packaging, especially when there is a risk of producing infectious disease : the labeled biological samples (primary receptacle) are introduced in a leak-proof bag (secondary container) containing enough absorbent material to absorb all of the liquid in case the primary receptacle breaks. The all is put in outer container.
The shipping can be done at a room temperature or can need regular ice, dry ice or liquid nitrogen. The frozen samples .need for the shipping special procedures and containers.

The strength of the packaging must respect the regulations concerning the carriage of dangerous

there are no specific legal requirements for genetic studies. If medicinal products are not used - the only requirement is a submission of the study to the local ethics committee.
the privacy of individuals is protected by the law (clinical trials on medicinal products according AMG§40(2a) - other studies according to general regulations (Datenschutzgesetze - German Data Protection Act and the Data Protection Acts of the regions (Länder)).[3]

- Hungary :

Circulation:
there is no specific regulation at present, except the recent law (2008/XXI) about biobanks which describes human-genetic research

Biobank:
there is a recent law about biobanks (2008/XXI) but the implementation of it is still missing.

Genetic:
a specific informed consent is necessary when collecting DNA samples. The samples can be stored for a maximum of 15 years, discharged at any time upon participant's request and the studies planned need to be described in the protocol. If new studies are to be performed on those samples a new informed consent must first be obtained.
, There is a specific law for Data Protection and the protection of privacy needs to be part of the protocol. Hungary has an ombudsman for data protection as well.

- Ireland :

Circulation:
The Irish Council for Bioethics details recommendations for use.[4] The Irish Medicines Board has also detailed guidance in Pharmacogenetic Research.[5]

Biobank:
there is a recent law about biobanks (2008/XXI) but the implementation of it is still missing.

Genetic:
the Irish Council for Bioethics details recommendations for use.[6] The Irish Medicine Board has also detailed guidance in pharmacogenetic research.[7]

the research must adhere to the Data Protection Act of 1988 and 2003 with respect to data handling and transfer.[8] The transfer of **personal data** to a country or territory outside the European Economic Area may not take place unless that country or territory ensures an adequate level of protection for the privacy and the fundamental rights and freedom of data participants in relation to the processing of personal data having regard to all the circumstances surrounding the transfer.

goods.

To assure the preservation of the samples, the time allowed for the carriage must be as short as possible.

The biological samples needing a controlled preservation temperature must be closely monitored during carriage. That is why temperature indicators or recorders are put inside the packaging.

Samples preservation conditions during carriage must fit the kind of samples and carriage duration. The carriage method must be chosen according to these criteria.

Sample identity must be checked before the transfer is prepared. Sample transfer must be in accordance with the transfer order.

The data associated to the samples must be transferred according to the local regulation relative to data transfer. In case of electronic personal data, the transfer will be in accordance with the Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data.

STORAGE:

Preservation conditions of samples must be in accordance with the Hygiene and security rules in order to avoid staff contamination and

- Italy:

Circulation: circulation and storage of blood and tissue samples is regulated by a rule of the Ministry of Health July 20, 1996 n.16 which established safety norms. Biological samples for specific studies, in particular for DNA studies should be collected after a specific informed consent is given by the patient.

Biobank: collection of biological material is subjected to the same requirements as for other studies, and a request to ethical committee is required. Particular attention is to be paid to the aspects concerning the informed consent and the safeguard of the principles of personal data protection.

Genetic:
the privacy of individuals is protected by a Statute n°675 of 31 December 1996 that includes provision concerning health data. The legislative decree on clinical trials of June 24, 2003 mentions the Statute as a safeguard for people involved in clinical trial. The authority responsible is called the 'Garante della Privacy'.[9]

- Spain:

Circulation:
The circulation of blood and tissue samples must follow the biomedical law[10] and the specific requisites to import and export are described in the Royal Decree 65/2006.[11] There are also several regulations on imports/exports of human biological samples: One for those used for diagnostic purposes (Royal Decree 65/2006, other one referring to imports and exports of human cells and tissues (Royal Decree 1301/2006, of 10th November), other on imports and exports of biological samples used for research purposes (Law 14/2007 on biomedical research)

Biobank:
Law 14/2007, of 3 July on Biomedical research contains specific provisions with respect to investigations related to genetic analysis, human biological samples and biobanks. This Law establishes the requirements for biobank authorisation by the corresponding Regional Health Authority. Details about their organisation, data protection requirements, management etc. are given. All biobanks should be registered in a national database on biobanks for biomedical research.
Genetic: these studies are regulated by the 'LEY 14/2007, de 3 de Julio, de Investigación biomedica'. A specific informed consent is necessary. The samples can be stored in an anonymous manner.
the **privacy** of individuals is protected by law.[12,13] In general, this law states that study data are confidential. For that reason, data will be dissociated resulting in the avoidance of linking study data with study participants. Providing access to personal data is voluntary. Therefore, participants should give their consent. Participants have the right to access or rectify their personal data or revoke their consent at any time. However, the participant must consent to the scrutiny of personal information during inspection by competent

samples' damage.
Samples must be stored carefully in the storage conditions mentioned by users. Samples and aliquots must be stored in conditions allowing their best preservation and scientific value.

Identification conditions, containers closure, and preservation temperature must be rigorously tracked in order to avoid risk of mistakes, qualitative or quantitative modifications and at last contamination of the sample.

The storage area must be adapted to the sample preservation. Preservation containers must be adapted to the kind of samples and to specific storage conditions. These conditions are established in the research protocol.

The sample storage temperature is a key parameter during the storage process. A lack in the temperature control at this step can result in an unacceptable risk of quality failure of the samples.

A temperature recording system of the storage containers must be used. This system must permit a continuous recording of the temperatures. In case of failure, an alarm must be coupled to the temperature recording system. In case of container failure, a corrective action must be taken in order to preserve sample integrity.

In order to ensure containers functioning, a preventive maintenance must be done to avoid curative intervention on preservation containers. A recording of all maintenances must be done.

Physical safety of the samples and associated data must be realised during all sample storage period. The access to the storage areas must be restricted to authorized staff.

A recording system of the entries and exits must be installed in order to verify all movements in the storage areas' perimeter and to avoid malevolence. A security system must trigger an alarm when unauthorized personnel enters inside the restricted perimeter.

The data associated to the samples must be protected using dedicated data management software. The access to these data must be as restricted as possible to authorized staff using personal ID and password. The role of each member of the staff must be as partitioned as possible. Personal ID and password must have a definite period of validity.
The preservation period and the limit date of storage must be established before the

authorities and properly authorised persons, provided that such personal information is treated as strictly confidential and is not made publicly available) and for prersonnal data protection (organic law 15/1999 of data protection) [14].

- Sweden:

Circulation:
circulation and storage must abide to the biobank legislation (SOFS 2002:11 (M)). This will be replaced by the European directive on cell and tissue when it has been implemented in the Swedish legislation.

Biobank:
the collection of tissue, blood or other biological samples, is regulated by the Swedish biobank law (Lag om biobanker I hälso- och sjukvården m.m. 2002:297). Consent must be obtained by the participant whether it is in the health care setting or in a clinical trial prior to sampling. If samples are sent outside of Sweden for analysis, special permission is required and the samples must be destroyed or returned Special requirements may be imposed in the future for specimens taken for genetic testing, by the National Board of Health and Welfare.
Genetic:
genetic studies are regulated in the ethics regulation, the Biobank law, the Data protection law, and is currently being reviewed for a new provision suggested by the National Board of Health and Welfare where additional regulation may be imposed on investigators.
In Sweden, all handling of genetic data requires permission from the competent authority 'Datainspektionen' and permission must be granted before application to the Ethical Review Board.
There are specific requirements regarding personal data protection.[15]
From July 1 2008, all research on sensitive personal data must be assessed by the EC, including observational studies which do not involve personal consent (lagen om etikprövning 2003:460).

- UK:

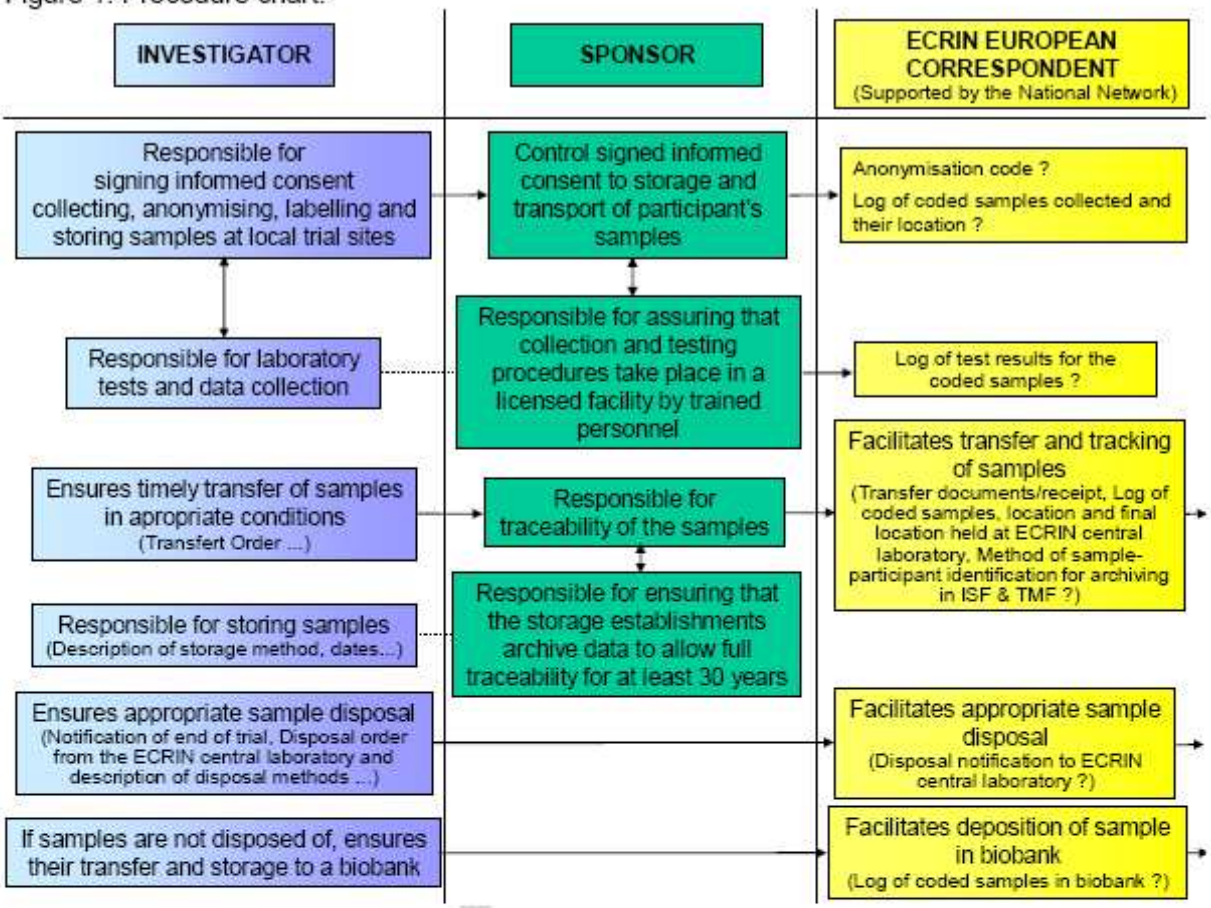
Circulation:
in England, Wales & Northern Ireland research involving human blood & tissue must comply with the Human Tissue Act 2004 which sets out a legal framework for regulating the storage and use of human organs, tissue and cells from the living, and the removal, storage and use of human organs, tissues and cells from the deceased. The Human Tissue Act 2004 is regulated by the Human Tissue Authority who provides a code of practice on the import and export of tissue in relation to research.

In Scotland researchers are required to comply with the Human Tissue (Scotland) Act 2006 and Section 45 of the Human Tissue Act 2004, which regards the use of tissue for DNA analysis.

beginning of the study. There is no regulatory concerning the storage duration. The validity period of samples must be respected and the storage duration is establish by the Ecrin Study Group and mentioned in the research protocol and associated SOPs. In case of long term storage, investigators have to set quality controls adapted to the final use of samples in order to ensure their good preservation. The quality controls permit to maintain the scientific value of the collection.	In the whole of the UK, R&D Management permission is required for any study taking place within the National Health Service (NHS) or with NHS patients. **Biobank:** biobanks require approval from an NRES (National Research Ethics Service) Committee. Biobanks that store samples that are classed as 'relevant material' under the Human Tissue Act 2004 require a licence from the Human Tissue Authority (HTA). Where the Biobank stores embryos a licence must be sought from the Human Fertilisation and Embryology Authority who regulate the use of gametes and embryos in fertility treatment and research. Where a study involves NHS participants or resources a sponsor is required if under Research Governance Framework. Co-sponsorship is permitted. Regarding the insurance, the sponsor must have in place arrangements for compensation for participants. Research Governance Management permission is also required for any study taking place within the NHS or with NHS patients. **Genetic:** these types of studies are regulated by the provisions under 'Human Tissue Act 2004 for genetic analysis', regulated by Human Tissue Authority and if applicable authorised by the Gene Therapy Advisory Committee (GTAC). there are specific requirements regarding the use of **personal data** in clinical research. Personal data, in the context of the 1998 Data Protection Act (Section 3.2, and Annex 3), comprise information about living people who can be identified from the data, or from combinations of the data and other information which the person in control of the data has, or is likely to have in future. There must be consent in place which allows access to, and the use of the research participant's personal data for specific aspects of the trial and when the data is shared with the sponsor it should be in an anonymised format.
Sample destruction: In case of samples needing to be destroyed, e.g: because they can not be qualified for research analyses, have been exposed to unsafe conditions leading to their unuseability, or because the destruction was planned at the end of the trial (The protocol should also specify when and wether the samples and data might be destroyed or anonymised (EMEA/CPMP/3070/01 21 Nov 2002)) or if the participant does no more want to participate to the research. The Ecrin Central lab could be the only structure qualified to order sample destruction. Samples'	

destruction can not be made before the official closure of the trial. Samples could be destroyed in local labs in order to reduce transport fees. In all cases, a destruction certificate must be established mentioning the reason leading to sample destruction, the samples ID, the date of destruction, the way of destruction, the name and signature of the technician and the name and signature of a witness accredited by the Central Ecrin Lab. Technician and witness must follow the specific procedures according to the local regulation on infectious material treatment. When the destruction procedure is completed, the certificate is transmitted to the Central Ecrin Lab in charge of the traceability of the samples.	

Figure 1: Procedure chart:



6. REFERENCES

Common elements	Country specific elements
- DIRECTIVE 99/9/EC of the European Parliament and of the Council of 11 March 1996 *on the legal protection of data base* - 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 - DIRECTIVE 2004/23/EC on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissue and cells - DIRECTIVE 2006/86/EC implementing Directive 2004/23/EC of the European Parliament and of the Council as regards traceability requirements, notification of serious adverse reactions and events and certain technical requirements for the coding, processing, preservation, storage and distribution of human tissues and cells - DIRECTIVE 95/46/EC of the European parliament and of the council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movements of such data - DIRECTIVE 2004/66/EC adapting Directives 1999/45/EC, 2002/83/EC, 2003/37/EC and 2003/59/EC of the European Parliament and of the Council and Council Directives 77/388/EEC, 91/414/EEC, 96/26/EC, 2003/48/EC and 2003/49/EC, in the fields of free movement of goods, freedom to provide services,agriculture, transport policy and taxation, by reason of the accession of the Czech Republic,Estonia, Cyprus, Latvia, Lithuania, Hungary, Malta, Poland, Slovenia and Slovakia - ICH E6: *Guidelines for Good Clinical Practices, step 5, consolited guidelines, 1-5-96*	**- Austria:** Blood safety act (Blutsicherheitsgesetz - BSG), handling and storage of other tissue samples in the tissue safety act (Gewebesicherheitsgesetz – GSG). Biobank act (Gewebebankenverordnung). Datenschutzgesetz= data protection act **- Denmark:** Danish Act on Processing of Personal Data. http://www.datatilsynet.dk/english/the-act-on-processing-of-personal-data/ http://www.cvk.im.dk/cvk/site.aspx?p=150 **- France:** JORF n°150 du 30 juin 2001 texte n°26, Arrêté du 1 er juin 2001 relatif au transport des marchandises dangereuses par route (dit « arrêté ADR »). Law 2004-800 of 6 august, 2004 article L. 1235-1 , L. 1245-5 and article R.1235-7, R.1235-8 of the French public health code Arrêté du 9 novembre 2004 définissant les critères de classification et les conditions d'étiquetage et d'emballage des préparations dangereuses et transposant la directive 1999/45/CE du Parlement européen et du Conseil du 31 mai 1999 Decree n°2007-1220 10 August 2007 (JORF n°187 du 14 Aout 2007 page 13591 texte n°23) relatif au prélèvement, à la conservation et à la préparation à des fins scientifiques d'éléments du corps humain et modifiant le code de la santé publique Arrêté du 16 août 2007 fixant le modèle de dossier incluant le protocole relatif aux prélèvements à des fins scientifiques d'organes, de tissus ou de cellules issus du corps humain Decree n°2008-891 2 september 2008 (JOFR n°du 4 Septembre 2008 texte n°19) relatif à l'importation et à l'exportation des produits du corps humain http://www.agencebiomedecine.fr/fr/doc/revision_loi060804.pdf

European Convention on Human Rights: 1950 - World Medical Association Declaration of Helsinki: 59th WMA General Assembly, October 2008, *Ethical Principles for Medical Research Involving Human Subjects* - Council of Europe Treaty Series - no 195: *additional protocol to the convention of human rights and biomedicine concerning biomedical research (2005)* - Council for international Organizations of Medical Sciences (CIOMS): . *International Ethical Guidelines for Biomedical Research Involving Human Subjects* . *International guidelines for ethical review of epidemiological studies 2008* - OECD Best Practice Guidelines for Biological Resource Centres https://www.oecd.org/dataoecd/7/13/38777417.pdf Draft Guidelines For Human Biobanks And Genetic Research Databases (2008) - *Best Practices For Repositories, Collection, Storage, Retrieval and Distribution of Biological Materials for Research.* International Society for Biological and Environmental Repositories (ISBER): *Cell Preservation Technology (CPT), March 2008* - Recommendations Rec (2006) 4 of the committee of ministers to members stes on research on biological materials of human origin https://wcd.coe.int/viewdoc.jsp?id=977859&sitecoe - International Network of Biological Resource Centres for Cancer Research (IARC): *Recommendations on Minimum Technical Standards*: IARC Working Group Report, No2 (2007) - Guidance on regulations for theTransport of Infectious Substance 2007– 2008 WHO_CDS_EPR_2007.2_eng.pdf - International Civil Aviation Organization 2005-2006 Technical Instructions Addendum Document *http://www.wfcc.info/new/Documents/icaoAddendum.pdf* - International Air Transport Association (IATA) Dangerous Goods Information *http://www.iata.org/whatwedo/dangerous_goods* - IATA Dangerous Goods Regulations 49th Edition (English) Effective 1 January 2008	**- Germany :** Datenschutzgesetze - German Data Protection Act and the Data Protection Acts of the regions (Länder)): Federal data protection law : "Bundesdatenschutzgesetz in der Fassung der Bekanntmachung vom 14. Januar 2003 (BGBl. IS. 66), zuletzt geändert durch Artikel 1 des Gesetzes vom 22. August 2006 (BGBl. I S. 1970) http://www.gesetze-im-internet.de/bundesrecht/bdsg_1990/gesamt.pdf http://www.gesetze-iminternet.de/bundesrecht/bdsg_1990/gesamt.pdf **- Hungary:** law 2008/XXI **- Ireland:** Data Protection Act of 1988 and 2003 with respect to data hand and transfer http://www.bioethics.ie/pdfs/BioEthics_fin.pdf http://www.imb.ie/EN/Publications/Medicines/Clinical-Trials/Guidlines-for-Pharmacogenetic-research.aspx?categorypageid=0&categorytypeid=-1 http://www.imb.ie/EN/Publications/Medicines/Clinical-Trials/Guidlines-for-Pharmacogenetic-research.aspx?categorypageid=0&categorytypeid=-1 http://www.dataprotection.ie/documents/legal/act2003.pdf http://www.irishstatutebook.ie/1988/en/act/pub/0025/index.html http://www.irishstatutebook.ie/1988/en/act/pub/0025/index.html **- Italy:** www.garanteprivacy.it rule of the Ministry of Health July 20, 1996 n.16 Presidential Decree of September 21, 2001, n. 439, Ministry of Health Decree March 18, 1998. Gazzetta Ufficiale – May 28 1998, n. 122. **- Spain :** LEY 14/2007, de 3 de julio, de Investigación biomedical REAL DECRETO 65/2006, de 30 de enero, por el que se establecen requisitos para la importación y exportación de muestras biológicas Ley Orgánica 15/1999 de 13 de diciembre de Protección de

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7. REFERENCED GUIDES/ SOP

SOP How to prepare an information and Informed Consent form for a multinational trial on medicinal products

8. APPENDIX