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*EUROPEAN CLINICAL RESEARCH INFRASTRUCTURES NETWORK - TRANSNATIONAL WORKING GROUPS*

## **ECRIN-TWG**



**FP6-2005-Life Sciences and Health LSH-2005-3-4  
Contract # 037199**

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### **Deliverable D15**

# **Specification of quality based Standard Operating Procedures design to address the issues and needs of transnational projects**

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**Date of preparation:** 29 October 2007, final version

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

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## Summary

Quality management (QM) in multinational studies is a major challenge for academic research. ECRIN must guaranty that the clinical studies are conducted in compliance with the legal and ethical requirements, and respect international guidelines of Good Clinical Practice (GCP).

In a first (ECRIN-RKP) FP6-funded step (2004-2005), the status of quality systems in clinical trials was assessed in each country participating in the ECRIN-project, and a comparative analysis between the countries was performed. The analysis demonstrated that there is a major diversity between countries. Although most of the individual centres have implemented a quality system and have developed their own set of Standard Operating Procedures in order to guaranty the quality of the clinical studies performed at their sites, and in order to comply with the regulatory and Good Clinical Practices (GCP) requirements, the development of harmonised SOPs at a national level is not done in all the countries. Yet, the need to harmonise and make the systems compatible within the network is a prerequisite to perform multinational clinical research.

In the current ECRIN-TWG project, the objective of the transnational working group 6 on Standard Operating Procedures (SOPs) is to propose a frame for the development of ECRIN SOPs describing the tasks and responsibilities in the conduct of multinational studies.

The SOPs will provide information on the multinational aspects of the study but will not to enter in the conduct of the study at the level of each national centre.

The set of procedures to be developed will cover all the activities proposed by ECRIN i.e. interaction with Ethics Committees, interaction with Competent Authorities and regulatory affairs, adverse event reporting, data and study management, management of Investigational Medicinal Products and management of blood and tissue samples.

In order to promote as much as possible shared, harmonised tools within the network, the SOPs will consist of a common core part containing the elements applicable to the whole ECRIN, and a variable part containing what differs from that standard part in some countries.

The development of this first set of procedures will allow ECRIN to perform pilot studies as planned in the third step of the programme (ECRIN-PPI).

At the same time the conduct of those pilot projects will also help a continuous assessment of the system implemented and help refine if necessary this set of SOPs, in line with the objective of quality improvement of the system.

## 1 Background

**ECRIN** (European Clinical Research Infrastructures Network) is designed to bridge the fragmentation of clinical research in Europe through the interconnection of national networks of clinical research centres (CRC) and clinical trial units (CTU) and to develop services to provide support for multicentre clinical studies in Europe.

Quality management (QM) in multinational studies is a major challenge for academic research. Although the objective of academic research is to develop knowledge on diseases and to establish state of the art treatment rather than to register new medicinal products or medical devices, there is a need to guaranty that the clinical studies are conducted in compliance with the legal and ethical requirements and respects the international guidelines of Good Clinical Practice (GCP).

The need to harmonise and make the systems compatible within the network is a prerequisite to perform multinational clinical research, and this is the task devoted to the Working group 6 on Standard Operating Procedures (SOPs) in the current project.

In a first (ECRIN-RKP) FP6-funded step (2004-2005), the status of quality systems in clinical trials was assessed in each country participating in the ECRIN-project, and a comparative analysis between the countries was performed. The analysis demonstrated that there is a major diversity between countries.

Although most of the individual centres have implemented a quality system and have developed their own set of Standard Operating Procedures in order to guaranty the quality of the clinical studies performed at their sites, and in order to comply with the regulatory and Good Clinical Practices (GCP) requirements, only two countries (Denmark and Germany) have developed harmonised SOPs within their national network. From the time of the survey some other countries such as France entered this process.

However, these procedures are rarely developed to support multinational studies.

Regarding audits, only two countries (France for the Clinical Investigations Centres' network and Germany) underwent system audit evaluating the whole organisation of clinical research within the centres. For the other countries the audits performed by sponsors or authorities only concern conduct of clinical studies.

Accreditation of the clinical centres is not really a topical question although some of the centres investigate the ISO 9001 process.

These results led to consider the following points as a first step to develop the quality system within ECRIN:

- What could be the common procedures
- Identify the procedures that require harmonisation
- How to assess the procedures in translational projects.

Based on the outcome of this first project, the quality management activity in the current programme (ECRIN-TWG, 2006-2008) is limited to the EU component of ECRIN, through the development of a set of Standard Operating Procedures (SOPs) designed to provide support to multinational studies.

The objective of the Working group 6 on Standard Operating Procedures is to propose a frame for the development of the ECRIN SOPs for multinational studies, leading to shared and harmonised tools to be used within the network.

This first set of SOPs will cover all the activities developed by ECRIN i.e. Ethics and interaction with Ethics Committees, regulatory affairs and interaction with competent authorities, adverse events reporting, data management, monitoring, management of Investigational Medicinal Products and management of blood and tissue samples.

The quality management requirements at the level of national networks and centres will be defined and implemented in the next project (ECRIN PPI, 2008 – 2010, FP7-funded). This next project will consist in the preparation phase for the construction and operation of an infrastructure for EU wide clinical studies and bioterapy (ECRIN-PPI) that will provide 'one-stop shop' services to investigators and sponsors in multinational studies.

During this preparation phase, a quality assurance (QA) unit will be set up to ensure the updating of the SOPs developed during the current project, to develop new procedures when required, to upgrade the process in order to permanently improve the quality assurance and quality control systems, and to adapt them to the needs and expectations of the users.

In addition the QA unit will address, with the contribution of the European Forum for Good Clinical Practice (EFCGP), the issue of how to cost-effectively perform GCP audits of individual centres – this is already implemented in some national networks, namely the German KKS network and the French CIC network, the cost of audits being supported by national funding. In the long term, this could become one of the criteria for connection of new networks.

During this preparatory phase, pilot clinical studies will be conducted allowing a continuous assessment of the QA system implemented. This system will then be adapted if necessary.

These quality management activities will also be reinforced during the third step with the collaboration with the other biomedical infrastructures funded by the Framework Programme 7 (FP7) such as the EATRIS (European Advanced Translational Research Infrastructure in Medicine) project.

## **2 Quality system requirements within ECRIN**

According to GCP, quality management covers

- the quality assurance that is all those planned and systematic actions that are established to ensure that the trial is performed and the data are generated, documented (recorded) and reported in compliance with CGP and applicable regulatory requirements;
- the quality control, represented by the operational techniques and activities undertaken within the system to verify that the requirements for quality of the trial-related activities have been fulfilled.

For ECRIN, the first step will be the implementation of a set of standard operating procedures to help professionals involved in multinational clinical research to work with high quality standards and to ensure harmonised conduct of clinical studies within the network.

This can be considered as a first step, and quality improvement should become prevalent within the network.

The Working group 6 will focus on SOPs, but the quality assurance system will also be developed through the activity of the other working groups; for example the WG 5 on study monitoring that will define monitoring (quality control) strategies based on the risk assessment and WG 8 on Education that will build an educational programme including training to SOPs developed within this project.

## **3 Proposed system to be developed in ECRIN**

The working group 6 is composed of at least one representative from each national network. All the representatives are experienced in Quality Management and most of them are involved in the quality network of their country.

During the first half of the year 2007, the group had 5 teleconferences allowing in depth discussion regarding ECRIN needs and existing experiences in the different networks.

In addition, a face to face meeting was organised in May 2007 in Paris in order to further discuss the architecture of the quality system, present the

first outcomes to the other working groups, and reach an agreement regarding the SOPs to be developed in collaboration with the relevant working groups.

### 3.1 General considerations to the development of the ECRIN quality system

The first activity of the working group, as defined in the description of work is to identify and harmonise the required elements that must be controlled and documented in SOPs in all the network's institutions, in order to assure the quality of the conduct of transnational clinical studies. The objective is to build a centralised system, efficient, effective and supportive, that will guaranty the quality of multinational clinical trials and help understand the national specificities. This will be achieved through the development of a comprehensive set of standard operating procedures to provide support to multinational studies i.e. to allow studies (academic studies, investigators-initiated studies, or SME-driven) to cross the borders between the EU countries. Therefore, the group will focus only on what is specific for supporting multinational studies and will not describe the requirements at the level of each individual centre.

One of the major issues raised when developing standard operating procedures is the increase in the paperwork. This is one of the pitfalls that the WP6 would like to avoid. The objective of the group is to develop the "minimal necessary" number of standard operating procedures in order to facilitate the conduct of multinational studies, but without increasing the bureaucratic burden.

As stated in the current project, the detailed approach where every working instruction goes into a SOP was not accepted and the working group recommended a pragmatic approach with the development of checklists and all-encompassing standard operating procedures.

The general framework was given by the survey on regulatory requirements that was performed by the working group 2 "regulatory affairs and interaction with competent authorities".

One of the aims of the survey was to delineate the relevant categories of clinical research as defined by the national laws and to identify what is required in each country for each type of clinical research.

According to the results of this survey, seven categories of research will be considered and will require the development of a set of standard operating procedures:

- clinical trials on medicinal products
- clinical trials on medical devices
- other therapeutic clinical trials (radiotherapy, surgery, transplantation, transfusion, physical therapy, psychotherapy)



- 
- diagnostic studies
  - nutrition studies
  - other clinical research (physiology, pathophysiology, psychology, biobanks, complementary and alternative medicine)
  - epidemiology

Some categories may be later pooled if requirements appear to be similar in all the countries.

Based on the experience of the participants, different proposals were discussed regarding the way to develop the SOPs:

- development of SOPs at the national level, meaning different SOPs per country.
- development of general SOPs applicable to every category of clinical research and then development of specific SOPs for each category
- development of SOPs with a common or core element containing the elements that can apply to the whole ECRIN, and a variable part containing the country specifications, meaning what is different from the standard elements

As ECRIN is designed to bridge the fragmentation of clinical research in Europe, and to promote and share harmonised tools and practices, the third proposal will probably better fit with the ECRIN mission.

This approach will provide a better multinational vision and will have a stronger harmonising effect.

This approach will also avoid duplication of efforts by writing only one SOP for the network instead of 13 SOPs.

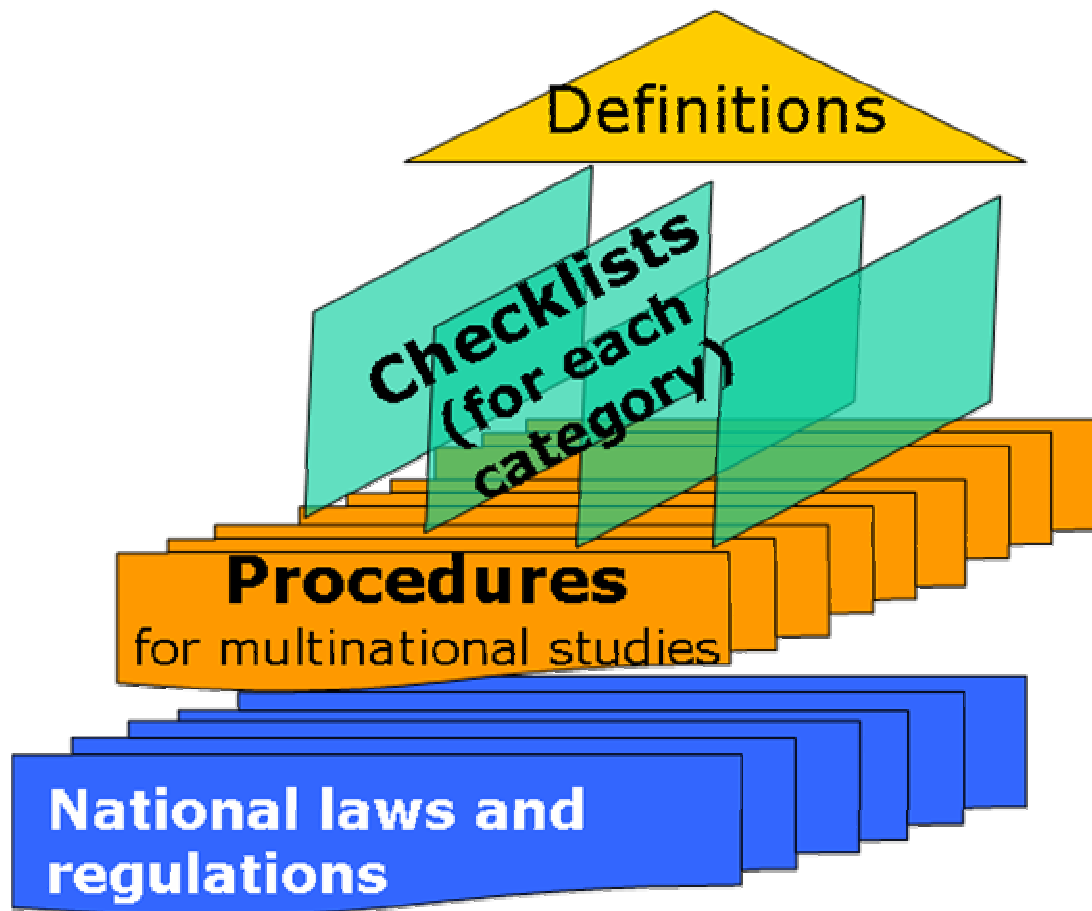
However, one drawback of this approach can be the implementation. This can be more difficult for some categories of research where the regulatory and ethical requirements are very different from one country to another one.

The EC Directive 2001/20/EC resulted in partial harmonisation in the conduct of clinical trials on medicinal products, thus the first set of SOPs will be developed for the trials on medicinal products. The extension to the other categories of research will then be discussed.

### 3.2 General architecture of the system

The decision regarding the SOP architecture is a keystone of the ECRIN-TWG project.

The system proposed is based on the international and national regulations and requirements and will be composed of three levels of documentation (fig 1).



**Figure 1: ECRIN SOPs Architecture**

The first level will include the definition of the different categories of research and will help users to identify the specific requirements regarding a specific project.

The information to be included in this document will be provided by the survey on regulatory requirements performed by the working group 2.

The second level of the documentation of the quality system will be based on check-lists. Those check-lists will be developed by the working group 6 and will give a rapid overview of the requirements for each category of

research covering the different steps of the clinical trials and will help the different actors (sponsors and investigators) to fulfil their requirements.

Then the third level will consist of procedures for multinational studies. These procedures, written in English, will be stratified by task and will provide detailed description of the requirement to perform that task taking into account the common elements to the whole network and the specific elements different from one country to another one. As the network plans progressive extension, and as some countries may lack a specific regulation for a given category of research, each procedure will list the countries where it is validated and applicable.

All the system will be based on European and national laws and regulations.

### 3.3 Proposed plan to develop, approve and review Standard Operating Procedures

The first standard operating procedure on how to develop, approve and review the Standard Operating Procedures was under the responsibility of the working group and was validated by the ECRIN network committee on the 28 august 2007 (appendix 1).

This procedure describes the responsibilities of the different working groups, of the Network Committee, of the coordination and of the ECRIN representatives, and provides a template to be used for the development of the ECRIN procedures.

### 3.4 List of Standard Operating Procedures

The SOPs to be developed will cover the different steps in the management of a clinical study and will be taken in charge by one of the working group.

This list proposed by the working group 6 was discussed with the other working groups and approved by the Network Committee, and consists of the following procedures:

- informed consent (WP1)
- interaction with ethics committees (WP1 with contribution of WP2)
- detection and handling on suspected fraud (WP1 with contribution of WP4 and WP5)
- protocol and protocol amendment (WP1 with contribution of WP2)
- personal data protection (WP1 with contribution of WP2)
- study registration (WP1)
- interaction with competent authority (WP2 with contribution of WP1)
- archiving (WP2)

- insurance (WP2)
- management of IMP, devices etc.. under study (WP2)
- site requirements (WP2)
- blood and tissue samples: collection, circulation, storage (WP2 with contribution of WP1 and biobanks)
- adverse event reporting (WP3)
- randomisation (WP4)
- unblinding (WP4 with contribution of WP3)
- CRF design (WP4)
- CRF fill-in (WP4)
- clinical data management (WP4)
- final study report (WP4)
- management of data and source documents (WP5 with contribution of WP4)
- monitoring, study visits (selection, initiation, follow-up, closure) (WP5)
- Participant recruitment (information visit, screening visit, etc...) (WP5)
- SOP management (WP6)
- development, approval and review of SOPs (WP6)
- research team: role definition, responsibilities, task delegation (WP6)
- contracting (WP6)

The working group 6 will be responsible to review all the procedures in order to ensure comprehensiveness and consistency and avoid overlap between the different working groups.

This first list may evolve depending on the development of the SOPs and cannot be considered as the final list of SOPs.

## **4 References**

Directive 2001/20/EC of the European Parliament and Council

Directive 2005/85/EC of the European Parliament and Council

ICH Topic E6, Guide for Good Clinical Practice  
Consolidated Guideline

## 5 Abbreviations

|           |  |
|-----------|--|
| CRC       | Clinical Research Centre   |
| CTU       | Clinical Trial Unit  |
| CIC       | Centre d'Investigation Clinique (Clinical Investigation Centre)  |
| ECRIN     | European Clinical Research Infrastructures Network   |
| ECRIN-PPI | European Clinical Research Infrastructures Network and Biotherapy Facilities: preparation phase for the infrastructure |
| ECRIN-RKP | European Clinical Research Infrastructure Network – Reciprocal Knowledge   |
| ECRIN-TWG | European Clinical Research Infrastructures Network-Transnational Working Groups  |
| EU        | European Union   |
| EFCGP     | European Forum for Good Clinical Practice  |
| FP        | Framework Programme  |
| GCP       | Good Clinical Practice   |
| KKS       | Koordinierungszentrum für Klinische Studien  |
| QA        | Quality Assurance  |
| QM        | Quality Management   |
| SOP       | Standard Operating Procedure   |

## 6 Appendix



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**Appendix 1:** SOP “Development, Approval and review of Standard Operating Procedures”



|  |
|--|
| <b>Development, Approval and review of Standard Operating Procedures</b> |
| Reference: ECRIN SOP 01  |
| Version number: V01  |

|  |
|--|
| <b>APPROVAL</b>                                  |
| Author: Working group 6                          |
| Validated by: _____ Date: _____                  |
| Effective Date: _____                            |
| Supersedes version number (if applicable): _____ |
| <b>REVISION</b>                                  |
| Version number: _____                            |
| Date: _____                                      |
| Reason for change: _____                         |
| Main modifications: _____                        |

**ECRIN SOPs**

**1. PURPOSE**

Describe the preparation, review, approval and revision of ECRIN Standard Operating Procedures (SOPs).

**2. SCOPE**

The SOPs produced by ECRIN will cover the requirements for multinational studies, particularly interaction with ethics committees, interaction with competent authorities and regulatory affairs, adverse event reporting, monitoring, data management. This will be achieved for any category of clinical research, in any medical field and in any patient population.

The SOPs must be used in conjunction with national laws and regulation.

**3. DEFINITIONS AND ABBREVIATIONS**

ECRIN: European Clinical Research Infrastructures Network

SOP: Standard Operating Procedure

**4. RESPONSIBILITY**

| Responsibility                                  | Activity   |
|---|--|
| Working group 6 (Standard Operating Procedures) | -Establish the listing of required SOPs<br>-Name and number the SOPs<br>-Supervise the consistency of the set of SOPs<br>-Write the checklists for each category of research |
| Working groups 1-8                              | -Write the SOPs related to their activity area<br>-Submit SOP to Working group 6<br>-Review the final version of the SOPs  |
| Network committee                               | Final validation of the SOPs ensuring that national particularities are taken into account   |
| Any ECRIN representative                        | Suggest to Working group 6 new SOP or revision of existing SOPs  |
| ECRIN coordination                              | Maintenance on the website of a consistent and up-to-date set of procedures, and archiving<br>Dissemination of SOPs  |



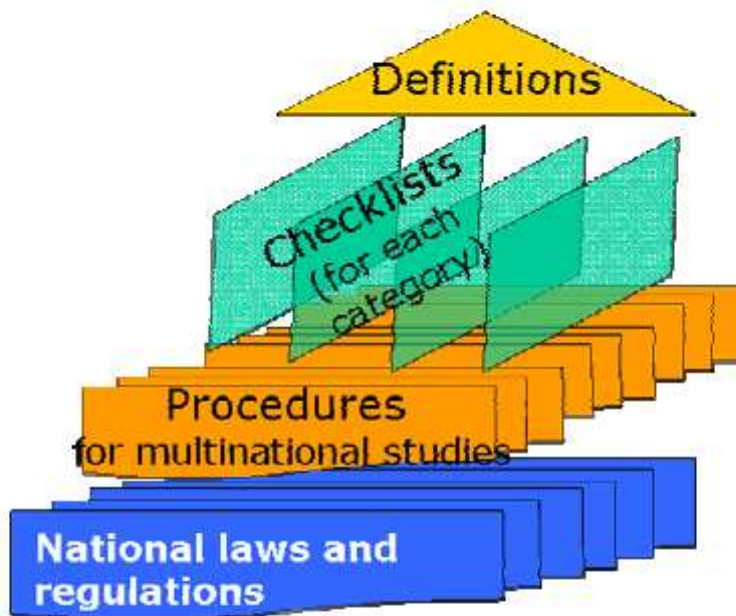
## 5. DESCRIPTION

### 5.1. Background

The Standard Operating Procedures are detailed written instructions that describe policy and procedures for ECRIN. They focus on a stepwise description of each task, and are designed to reach uniform performance and best practice.

They must clearly define "who does what". They should be clear, concise, using pictures and diagrams as far as possible.

The documentation is organised as follows:



The definitions allow to determine which is the relevant category of research.

The checklists summarise the requirements for multinational support to sponsors and investigators, stratified by category of research.

The ECRIN SOPs, stratified by task, provide detailed description of the specific requirements for each category of research. They are based on a core element valid throughout the EU, with adaptation to the particularities of each country.

All documents are based on the national laws and regulations.

**ECRIN SOPs**

**5.2. Preparation**

The SOP will adhere to the standard format as defined in appendix 2.

The content of the SOP will be as follow:

- SOP: identification number provided by the working group 6 according the rules in appendix 1.
- Title
- Version N°: the first version will be numbered as 01. Any further change will be altered accordingly ie 02, 03 etc.
- Effective date: date of implementation following validation
- Purpose:
- Scope:
- Definitions and abbreviations
- Responsibility: specify responsibilities for each task/action
- Description
- References: list all references related to SOP
- Referenced SOP /guidelines: list all referenced SOP or guidelines
- Appendices

When a section is not needed it will be noted as "not applicable".  
When necessary, additional sections can be added.

**5.3. Review/approval**

The network committee will review and approve all the SOPs produced by ECRIN. The approved SOP (pdf version) will be uploaded on the website. The website version is the version into force.  
Information on the implementation of a SOP will be disseminated by the coordination, via email, to the European Correspondent in each country. The European correspondent will be in charge of the dissemination within the country.

**5.4. Revision**

The SOPs will be reviewed every two years, and revised when necessary. In the meantime, if a new SOP needs to be created or if a SOP requires a change (regulatory update, participation of a new country with particularities not covered in the SOP), any ECRIN representative should send a note to the leader of working group 6 who will be in charge of initiating the creation or the revision, in collaboration with the relevant working groups.

**6. REFERENCES**

| ECRIN references   | Specific references |
|--|---------------------|
| International Conference on Harmonisation -ICH E6 Good Clinical Practices (1996) |                     |

ECRIN SOPs

**7. REFERENCED GUIDE /SOP**

Not applicable

**8. APPENDICES**

Appendix 1: Rules for numbering the SOPs

Appendix 2: SOPs Standard format

## ECRIN SOPs

### **Appendix 1: Rules for numbering the SOPs**

Each SOP will be issued with a unique SOP number eg ECRIN- SOP 01-V01  
This number identifies firstly the origin of the document [ECRIN], the SOP number [S01] and the version number [V01].

The draft versions will be numbered draft 01 and altered accordingly draft 02, draft 03.

The first approved version will have the number V01. Any further version change will be altered accordingly ie 02, 03, 04.

ECRIN SOPs

**Appendix 2: SOPs Standard Format**

ECRIN SOPs



|                      |
|----------------------|
| <b>TITLE</b>         |
| Reference: ECRIN SOP |
| Version number:      |

|  |
|--|
| <b>APPROVAL</b>  |
| Author:  |
| Validated by: <span style="float: right;">Date:</span> |
| Effective Date:  |
| Supersedes version number (if applicable):             |
| <b>REVISION</b>  |
| Version number:  |
| Date:  |
| Reason for change:                                     |
| Main modifications:                                    |

**ECRIN SOPs**

**1. PURPOSE**

**2. SCOPE**

**3. DEFINITIONS AND ABBREVIATIONS**

| Common elements | Country specific elements |
|-----------------|---------------------------|
|                 |                           |

**4. RESPONSIBILITY**

| Common elements | Country specific elements |
|-----------------|---------------------------|
|                 |                           |

**5. DESCRIPTION**

| Common elements | Country specific elements |
|-----------------|---------------------------|
|                 |                           |

**6. REFERENCES**

| Common elements | Country specific elements |
|-----------------|---------------------------|
|                 |                           |

**7. REFERENCED GUIDES/ SOP**

**8. APPENDICES**