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Standard Operating Procedures on monitoring

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1 Context

The SOP was developed by the WP5 on study monitoring, reviewed by the WP6 on standard operating procedures and validated by the WP5.
This SOP 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.

ECRIN-MO-SOPØØ1

Monitoring ECRIN studies

Monitoring ECRIN studies
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1. PURPOSE

This SOP is intended to provide guidance to the sponsor and ECRIN team for the development of a monitoring plan and to describe the minimum levels of monitoring required for all ECRIN studies.

2. SCOPE

All clinical trials selected by the ECRIN scientific board will require assessment using the risk assessment tool and a monitoring plan developed dependent on the risk level established
Monitoring requirements for studies that fall outside of EU Directives governing clinical trials and medical devices including 2001/20/EC, 2005/28/EC, 90/385/EEC, 93/42/EEC and 98/79/EC, shall be considered on a case by case basis in line with country specific requirements.
This procedure will cover all clinical trials selected by the ECRIN scientific board and that will be performed within the ECRIN network

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3. DEFINITIONS AND ABBREVIATIONS

CRF Case report/record form: A printed, optical, or electronic document designed to record all the protocol required information to be reported to the sponsor on each trial subject (ICH Harmonised Tripartite Guideline: Guideline for Good Clinical Practice E6)

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

***European Correspondent:** is the contact point and the local support to the sponsor in his/her country.*

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

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

Risk: ***In this paper, the term 'risk' refers exclusively to the risk of non-compliance with GCP objectives:***

1. ***(1) Protection of the safety, rights, well-being and confidentiality of identity of trial subjects;***
2. ***(2) Credibility of data and results.***

Risk may be divided in two primary components:- risk for study participants;
- risk for the validity of study results.

All other components of risk for studies follow from these primary risks:

- risk for sponsor or other study managing organisation;
- risk for study governance;
- risk for target population and public health.

Risk assessment tool:

Risk-assessment tool will be used to adapt monitoring intensity, but should be strongly related to primary risks. Therefore, validity of the risk-assessment tool should be assessed relatively to primary risks, not to monitoring intensity.
A good risk-assessment tool must respect the usual qualities of any good outcome: relevance, validity, and reliability.

SAE_ Serious adverse event: Definition to be assigned on a per protocol basis, as depends on intervention being studied.

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

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

Sponsor-Investigator: An individual who both initiates and conducts, alone or with others, a clinical trial, and under whose immediate direction the investigational product is administered to, dispensed to, or used by a subject. The term does not include any person other than an individual (e.g., it does not include a corporation or an agency). The obligations of a sponsor-investigator include both those of a sponsor and those of an investigator. (*ICH Harmonised Tripartite Guideline: Guideline For Good Clinical Practice E6*).
Source data: All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).

Study participant: an individual who participates in a clinical trial as either a recipient of the investigational medicinal product or a control (*Directive 2001/20/EC*) In addition individuals who participate in a clinical trial involving other interventions, can also be described as study participants.

4. RESPONSIBILITY

Common elements	Country specific elements
The sponsor (or delegated entity or person) is responsible for the development of the monitoring plan for each ECRIN study. They are also responsible for ensuring that adequate resource is assigned to the study as required to comply with the study specific monitoring plan and any additional requirements for national monitoring specific procedures	
Evaluation of risk by assessment tool and determination of whether study is low, medium or high risk must be done by the sponsor and a relevant monitoring plan will be developed according to the template provided in appendix 1.	
The sponsor is responsible for providing each ECRIN Member State, participating in the trial, with the validated version of the monitoring plan.	
The European Correspondent is the local contact point and is responsible for adding any additional national specific requirements to the ECRIN monitoring plan, for validating this document with the sponsor and then providing the	

national monitoring plan to all relevant parties	

5. DESCRIPTION

The extent and nature of monitoring will be based upon the risk involved as assessed by the risk assessment tool (RAT). The frequency and duration of visits is scheduled on a trial-specific basis and is dependent on the complexity of the trial, rate of recruitment at a site, and trial duration. The frequency of visits, suggested for each trial is to be understood as minimal and can be increased at the sponsors discretion.

Every protocol will be graded as high, medium or low risk and this will determine the minimum level of monitoring required. Irrespective of the minimum monitoring guidelines where there is any question over participant safety and/or data quality consideration to making a site visit must be made . It is the responsibility of the study sponsor to ensure all national requirements in relation to monitoring are also being observed.

All activities described can be conducted by an on-site visit or by remote central/monitoring by the sponsor.

5.1 Low risk

The minimum requirements for all ECRIN monitoring plans include:

A minimum of one on-site monitoring visit.

Verification of a proportion of SAE's, data query resolution, confirmation of consent and other monitoring procedures, can be conducted remotely, providing the study participants identity is not revealed.

Before study

Verify that appropriate ethical and regulatory approvals are in place prior to study commencement.
Ensure that investigators and their staff have received protocol specific training.

During study

Verify that all participants have properly conducted the process of informed consent and recorded it;
Verify eligibility of a sample of participants enrolled onto trial
Verify that a proportion of SAEs are reported within correct time frame (per protocol and national legislation)
Study end points: As part of the key data a percentage of the CRF's will be reviewed with respect to study end points. This will be specified in the study monitoring plan.

After study

Verify that all requirements with ethics and regulatory notification have been completed;
Verify that appropriate archiving of all essential documents has been completed by asking investigators to confirm this has been done.

All monitoring activities must be completed in writing with follow-up actions highlighted and tracked to completion

5.2 Medium risk

If the study is identified as medium risk the following must be monitored in addition to requirements above. This can be achieved through a combination of on-site and remote data monitoring, but a minimum of 2 on-site monitoring visits over the duration of the study must be performed.

During study

Key data as defined prospectively in the monitoring plan, to be reviewed for 50% of the participants at that trial site;
Drug/device and clinical supply accountability;
Ongoing acceptability and adequacy of staff and facilities.

5.3 High risk

If the study is classified as high risk the following must be monitored in addition to the requirements outlined for low and medium risk above.
This can be achieved through a combination of on-site and remote data monitoring, but a minimum of 3 on-site monitoring visits over the duration of the study must be performed.

During study

Key data as defined prospectively in the monitoring plan, to be reviewed for 75% of the participants at that trial site.

5.4 Monitoring Resource

It is the responsibility of the sponsor to ensure there is sufficient monitoring resource for each study.

6. Specific References

Risk-adapted monitoring in non-commercial clinical trials" draft paper supplied by the Adamon project group in Germany- Monitoring in IIT's project group (reference http://www.tmf-ev.de/site/DE/int/AG/MKS/Projekte/IIT-Monitoring/c_Monitoring.php)

7. ECRIN References

ECRIN-EC-SOP002 Interaction with Ethics Committees before the conduct of a multinational clinical trial on multinational products
ECRIN-EC-SOP003 Interaction with ethics committees duing the conduct of a multinational clinical trial on medicinal products
ECRIN-EC-SOP 004 Interaction with Ethics committees after the conduct of a multinational clinical trial on medicinal products
ECRIN-AE-SOP001 How to support adverse event reporting in multinational clinical studies

8. Appendices

Appendix 1: Monitoring template
Appendix 2: Overview of the proposed monitoring strategies

8 Appendix 1

Monitoring template, including mandatory elements. To be used as basis for monitoring plan to be developed for each protocol.

This must be generated by the sponsor for all ECRIN studies

Principles

- The monitoring activities focus on those trial data and information that are essential for an assessment of participant safety, well-being and rights, and to achieve the primary and secondary trial objectives (referred to in the following as 'key data')
- Each protocol should specify which montoring activities must be done by on-site monitoring and which can be achieved by remote/central monitoring.
- The extent of monitoring and the minimum frequency of site visits depends primarily on the level of risk established by the risk assessment tool and should also take other issues, including recruitment, visit schedule and trial duration into consideration..
- Timely central monitoring of the clinical trial's progress (by data management and other appropriate means) is warranted, with the option to trigger additional site visits if irregularities are noticed (referred to in the following as 'for-cause monitoring')
- In order to warrant an efficient supervision of the clinical trial's progress, CRFs have to be swiftly available at the data centres and have to be processed in a timely manner. This holds for trials using paper based documentation as well as for trials using remote data entry systems.
- The monitors are trained on all relevant aspects identified by the clinical trial risk analysis

Irrespective of the type of basic monitoring, an unscheduled visit should be made to the trial site if problems or irregularities are noticed by the central monitoring or if fraud is suspected. This for-cause monitoring is described in more detail below

Definition of the key data

The key data comprise the trial data and information that are essential to assess patient safety, well-being and rights, and to achieve the primary and secondary trial objectives.

Key data always include:

- **Existence** of the trial participant

A check is made to establish whether the trial participant is included in the patient identification list and whether a patient file exists in connection with any list entry.

- **Informed consent**

A check is made to establish whether a written inform consent form exists, and whether it was filled in correctly, completely and on time.

- **Serious adverse events (SAE)**

A check is made to establish whether all serious adverse events mentioned in the participant's file are correctly and completely documented and whether they correspond to the trial protocol specifications.

The following are also key data, though they have to be specified in the monitoring plan as per the trial protocol:

- **Inclusion and exclusion criteria**

In general, eligibility criteria in clinical trials should have been chosen due to their relevance for either safety or efficacy of the trial intervention or due to their relevance for the statistical power of the trial. Thus, all eligibility criteria should be considered as key data. In exceptional cases, it may happen that some inclusion and exclusion criteria do not match the description above – these criteria may be excluded from the key data.

- **Application and dosage** of the experimental intervention.
- **Primary endpoint**

The primary endpoint(s) for the clinical trial is/are subjected to a source data verification process. This applies if the parameter(s) was/were assessed at the trial site. If the assessment is done on a centralised basis by a reference panel or institution, the monitoring activity on site referring to the primary endpoint will consist in checking whether the necessary material or the necessary information has been passed on.

Further trial-specific data and information can be included in the key data. These are derived from the trial-specific risk analysis and include, for instance

- **Adverse events** (AEs): In clinical trials with **medicinal products** whose **safety profile (in the range of indications being investigated) is little known**, **AEs** should always be classified as key data.
- Essential **secondary endpoints** (if assessed locally in the trial sites)
- Possibly other aspects ensuing from the risk analysis of **patient-related indicators**

Planning monitoring activities

The planning phase involves the following:

- Clinical trial risk assessment as previously described
- Specification of the trial-specific key data
- Design of the monitoring plans specifying visit frequencies and durations. The following aspects have to be taken into consideration when estimating the duration of monitoring activities:
  - Parameters that can influence the duration of monitoring activities for an individual patient (e.g. extent of key data, number and type of inclusion and exclusion criteria and adverse events due to the underlying disease or co-morbidity)
  - Further tasks to be implemented at the trial site; these ensue from the analysis of trial site-related indicators
  - The type of data collection (data collection with remote data entry may simplify on-site monitoring).
- Definition of standard procedures for the reaction to and the follow-up of problems which are detected by the monitors during their on site visits and are described in the monitoring reports
- Trial-specific training for the assigned monitors

Low risk study monitoring

Pre-study visit	**Not made**
Initiation visit	**Can be replaced by an investigators' meeting (either face to face and/or teleconference)** and detailed written instructions, e.g. - in trials designed similarly to standard treatment and involving an established trial population if similar trials for the same range of indications have already been implemented in the trial sites - in trials with a very simple design
Visits	Each site is visited at least once during the duration of the trial. The order in which the trials are visited is randomly assigned by the central study office.
Verification of key data	- **Existence and informed consent for 100% of participants** - **Further key data** (if it is available at the time of the visit) **for at least 20% of the participants at the trial site**. (i.e. if there are 1-5 participants at the centre, 1 participant is selected. If there are 6-10 participants, 2 participants are selected etc.) The selection of participants to be monitored is made by the central study office.
Further contacts	Additional telephone and/or e-mail contacts **as required**.

Close-out visit	Not made

For-cause monitoring

It is necessary to ensure prompt intervention if problems become evident or are suspected at certain trial sites. This is only possible if the implementation and documentation of the trial are centrally monitored, which involves additional data management and central monitoring measures. The methods used to analyse possible problems or irregularities should, if possible, be statistical monitoring methods (e.g. multivariate analysis of possible outlier candidates, conspicuous data patterns, preferred numerical sequences, accumulation of values close to defined limits etc. Please refer to Al-Marzouki et al BMJ 2005, Buyse et al Stat Med 1999 in this connection). In clinical trials which use paper-based documentation, it is necessary to ensure that the CRFs are posted to the central study office in good time, and to operate a reminder system for outstanding documentation.

A structured interview in regular telephone calls can also be a source of information about potential problems at the site. The following questions are feasible:

- Investigator team member: Have any changes of personnel or task allocation taken place since the trial started? Do you have any training requirements? (Contact other trial team members if necessary)
- Current site status: participants who are taking part / have dropped out of the trial/ have concluded the trial
- Planned participants: get the centre to send screening lists if necessary and discuss them (including reasons for rejection)
- Problems: enquiry about current site-specific problems; specific questions about problems at other sites or general problems encountered in the course of the trial.
- Specific trial-related questions: requirements or questions about trial materials, incidence of (S)AEs, questions on trial documentation.

When problems or irregularities that exceed a trial-specific ???? are ascertained at a trial site a prompt unscheduled monitoring visit to the trial site is made. It is necessary to ensure that the criteria for a monitoring visit are quite specifically formulated so that not too many unscheduled visits are necessary.

Problems or irregularities can include:

- Relevant deviations from the scheduled intervention according to the trial protocol and/or diagnostic procedures without CRF-documented medical necessity, observed in several participants (e.g. dose too low / too high, therapy duration too short, unauthorised concomitant intervention, necessary diagnostic procedures not performed, components of the intervention omitted; criteria and number of participants to be defined in advance on a trial-specific basis)
- Conspicuously higher/lower incidence of SAEs compared with other trial sites, SAEs regularly reported too late or in too little detail
- Suspected fraud
- Suspected gross irregularities that cannot be clarified on the phone

monitoring visits are not made regularly to all trial sites, only on a random basis. That is why further criteria for an unscheduled monitoring visit should be considered, e.g.:

- Outstanding trial-specific documentation (>50% of documentation due) despite two reminders
- A high incidence of inconsistencies and/or implausible data compared with other trial sites
- If the inclusion/exclusion criteria define limits for certain laboratory values, and the trial site's values are often up to the limit at the time of inclusion
- Lack of response to data management queries

In for-cause monitoring visits, unresolved problems are clarified, up to 100% source document verification of all relevant trial-specific data for all participants (the proportion has to be specified in the monitoring manual) and personnel are trained in the use of the trial protocol and implementation methods.

Appendix 2

Overview of the proposed monitoring strategies

The following table provides an overview of the basic monitoring in each of the 3 risk assessment categories.

	High Risk	Medium risk		Low risk
Pre-study visit	Recommended	Recommended Can be substituted by telephone contact + request for qualification documents		Not made
Initiation	Recommended	Recommended (Exception: rare diseases – in this case, the initiation can take place when the first participant is recruited)		Can be replaced by an investigators' meeting and detailed written instructions
First visit	After inclusion of the first participant	After the recruitment of 1-2 participants		Not made
Further visits	The frequency and duration of visits is scheduled on a trial-specific basis. It depends on the list of tasks to be performed during the monitoring visits and takes the trial site's recruitment rate into account. The frequency of visits stated in the following is to be understood as minimal.			
		Trial site with noticeable problems	**Trial site without noticeable problems**	
Frequency	Depending on the site's recruitment and the catalogue of monitoring tasks (in general at least 6x year)	Depending on the site's recruitment and the catalogue of monitoring tasks (in general at least 3x year) Annual re-evaluation and, if applicable, change of status to 'without noticeable problems'	Depending on the site's recruitment and the catalogue of monitoring tasks (in general at least 1x year) Annual re-evaluation and, if necessary, change of status to 'with noticeable problems'	At least one visit at each trial site
Verification of key data	Existence, informed consent, SAE and all further key data for 100% of participants at the trial site	- Existence and informed consent for 100% of participants - SAE data for 100% participants - Further key data for at least 50% of the participants at the trial site	- Existence and informed consent for 100% of participants - SAE data for 100% participants - - Further key data for at least 20% of the participants at the trial site	Only at the trial sites visited: - Existence and informed consent for 100% of participants - SAE data for 100% participants - Further key data for at least 20% of the participants at the trial site

Verification of further data	Generally 10% of the trial site's participants, but at least one participant with 100% source data verification	A 100% SDV is made for one participant in the random sampled trial site (to ascertain any systematic errors)	None
Further contacts	As required	At least every 8 weeks, as a structured interview	As required
Close-out visit	Recommended	Only if there are still monitoring tasks to be performed or queries to be clarified	Not made