SCTO PLATFORMS

Guidelines for Risk-Based Monitoring

Version 3.0

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Acronyms

ADAMON	ADApted MONitoring
CDM	Central Data Monitoring
ClinO	Ordinance on Clinical Trials with the exception of Clinical Trials of Medical Devices (Clinical Trials Ordinance)
ClinO-MD	Ordinance on Clinical Trials with Medical Devices
COV	Close-Out Visit
(e)CRF	(electronic) Case Report Form
ECRIN	European Clinical Research Infrastructure Network
EDC	Electronic Data Capture
EMA	European Medicines Agency
FDA	U.S. Food and Drug Administration
FOPH	Federal Office of Public Health
GCP	Good Clinical Practice
GGOP	Guidelines for Good Operational Practice
HRO	Ordinance on Human Research with the Exception of Clinical Trials (Human Research Ordinance)
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IMD	Investigational Medical Device
IMP	Investigational Medicinal Product
ISF	Investigator Site File
ISO	International Organization for Standardization
IIT	Investigator-Initiated Trial
kofam	Coordination Office for Human Research (Koordinationsstelle Forschung am Menschen)
OPTIMON	OPTimisation of MONitoring
PI	Principal Investigator
RBM	Risk-Based Monitoring
RMV	Routine Monitoring Visit
SAE	Serious Adverse Event
SAKK	Swiss Group for Clinical Cancer Research (Schweizerische Arbeitsgemeinschaft für Klinische Krebsforschung)
SCTO	Swiss Clinical Trial Organisation
SDV	Source Data Verification
SIV	Site Initiation Visit
SOP	Standard Operating Procedure
SQV	Site Qualification Visit
TMF	Trial Master File

1. Introduction

1.1. Background

Monitoring is an essential part of quality management in clinical trials. The purposes of monitoring and the responsibilities of the monitor are specified in the Good Clinical Practice (GCP) guidelines for:

- Drug studies: the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) in its *Guideline for Good Clinical Practice*[1]. In the version of the guideline published in 2016, the concepts of risk management and especially risk-based monitoring were further developed and specified.
- Medical Device studies: the ISO 14155 guidelines, namely the *Clinical investigation of medical devices for human subjects — Good clinical practice*. A risk-based approach to monitoring is also recommended in the version published in 2020.

According to GCP and the latest developments in the regulatory environment, risk-based approaches in clinical trials are internationally encouraged, e.g. by the European Medicines Agency (EMA[2]), as well as by the U.S. Food and Drug Administration (FDA[3,4]). Especially in non-commercial Investigator-Initiated Trials (IITs), the implementation of risk-based procedures is essential in order to use limited resources efficiently. A risk-based approach to monitoring does not suggest a reduced vigilance regarding the oversight of clinical investigations. Rather, it focuses sponsor oversight activities on preventing or mitigating important and likely risks to data quality and on processes which are critical for human participant protection and trial integrity.

On a worldwide level, several helpful, well documented, and widely used academic or industry-driven initiatives provide risk-based monitoring tools: ADApted MONitoring (ADAMON[5]), OPTimisation of MONitoring (OPTIMON[6]), European Clinical Research Infrastructure Network (ECRIN[7]), and TransCelerate[8].

Swiss regulations require the categorisation of clinical trials and research projects according to the risks of the study (see the *Ordinance on Clinical Trials with the exception of Clinical Trials of Medical Devices* (ClinO[9]), the *Ordinance on Clinical Trials with Medical Devices* (ClinO-MD[10]), and the *Ordinance on Human Research with the Exception of Clinical Trials* (HRO[11])). The Federal Office of Public Health (FOPH) provides, via its kofam portal, a standardised electronic risk-categorisation tool[12]. This categorisation may feed into the risk-based monitoring strategy that is chosen for the study.

The first version of this guideline was developed based on a guideline for risk-based monitoring by the Swiss Group for Clinical Cancer Research (SAKK) and risk-adapted monitoring strategies proposed by ADAMON. This first version was developed further by representatives of the Clinical Trial Unit (CTU) Network and the SAKK as a joint project in the context of an initiative to strengthen academic clinical research in Switzerland, led by the Swiss Clinical Trial Organisation (SCTO).

1.2. Objectives and scope

This guideline describes recommended risk-based monitoring procedures, more specifically for interventional clinical trials running under the ClinO and ClinO-MD. This guideline can, however, also be used to develop monitoring strategies for projects running under the HRO. It is strongly recommended that

[1] ICH GCP
[2] Reflection paper on risk based quality management in clinical trials, EMA, November 2013
[3] Guidance for Industry: Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring, FDA, August 2013
[4] Draft Guidance for Industry: A Risk-Based Approach to Monitoring of Clinical Investigations Questions and Answers, FDA, September 2019
[5] ADAMON
[6] OPTIMON
[7] ECRIN
[8] TransCelerate BIOPHARMA Inc.
[9] ClinO art. 19, 20, 40, 61
[10] ClinO-MD art.6
[11] HRO art. 7
[12] kofam categoriser

all full and associated members of the SCTO apply it in all trials within their scope. However, the final decision regarding its implementation lies with each clinical trial unit.

1.3. Components

The guideline for risk-based monitoring consists of three components:

- A seven-category **risk-based monitoring score calculator**
- A **decision tree** for determining risk categories
- Risk-based **monitoring strategies** for each risk category

1.4. Definitions of monitoring activities

The monitoring strategies developed below will detail the scope of the following activities:

- **Informed Consent Form (ICF) and process review**: Check that the participants are informed according to ethical standards, that approved ICFs are correctly used and signed prior to any study-related procedures by both parties, and that theparticipant's participation in the study as well as the informed consent process is documented in the source data.
- **Source Data Verification (SDV)**: Process by which data within the Case Report Form (CRF) or other data collection systems are compared to the original source of information (and vice versa).
- **Investigational Medicinal Product (IMP) / Investigational Medical Device (IMD) accountability**: A check of the different logs allowing to trace the route of IMP/IMD reception, storage, dosing, randomisation, dispensation, return, destruction, reconciliation, etc.
- **Trial Master File (TMF) / Investigator Site File (ISF) review**: Verification that essential documents (according to ICH GCP, or ISO 14155) are complete, up-to-date, and well-kept at research sites.
- **Query**: Request generated when a discrepancy is detected either automatically by the Electronic Data Capture System (EDC) or manually during the SDV process or remote data checks.
- **On-site monitoring**: The monitoring activities described above are performed at the sites at which the clinical trial is being conducted.
- **Off-site Monitoring:** Allows monitors to perform remote verifications (e.g. check of study documentation, protocol and regulatory compliance).
- **Central Data Monitoring (CDM)**: Central review of the accumulating data in the study database. Usually performed on the data collected in eCRFs via EDC; allows the identification of missing, incomplete or inconsistent data, outliers, evaluation of site performance or identifying trends that may need attention from the sponsor or monitoring institution mitigate problems with the trial.

2. Procedures

According to ICH GCP and ISO 14155, the investigator is responsible for ensuring that the data reported to the sponsor in the CRF is complete and accurate. The sponsor is responsible for implementing and maintaining a quality assurance and quality control system, and for developing a systematic, prioritised, risk-based approach to monitoring clinical trials.

A risk-based monitoring strategy should be part of an entire quality risk management approach, including but not limited to the following preventive aspects:

- Well-designed protocol and study documentation
- Appropriate training of trial personnel
- Qualification of (sponsor-)investigators (according to education, experience, and training)
- Validation of eCRF and statistical analysis plan
- SOPs, at least for safety reporting
- Risk-based audit strategy

2.1. Risk-Based Monitoring Score Calculator

The RBM Score Calculator is available on the SCTO Platforms' website in the tools section: www.sctoplatforms.ch/rbmscorecalculator.

The monitoring strategy to be applied for a particular clinical trial will be determined by completing a questionnaire.

Seven risk categories have been identified:

1. Participants
2. Design
3. Safety
4. Intervention
5. Management
6. Data
7. Other

For each risk category, several risk factors are evaluated on a three-point scale for their *impact*, *(likelihood of) occurrence*, and *detectability*. They are then automatically classified according to low-, medium- and high-risk factors.

At the end of the assessment, the composition of the amount of medium and high-risk factors classifies the clinical trial in one of three categories of monitoring strategies (see decision tree, below):

- low-risk monitoring strategy
- medium-risk monitoring strategy
- high-risk monitoring strategy

2.2. Decision tree

The recommended monitoring strategy for a clinical trial should be defined according to the table below and determined by the following criteria:

- Study risk category, according to the Swiss laws ClinO and ClinO-MD
- Number of medium and high-risk factors

Table 1: Determining a suitable monitoring strategy, according to the results of risk analysis

Number of risks	Swiss categorisation A	Swiss categorisation B	Swiss categorisation C
Less than 6 medium risks No high risks	low-risk	low-risk	medium-risk
6 to 12 medium risks or 1 high risk	low-risk	medium-risk	high-risk
More than 12 medium risks or more than 1 high risk	medium-risk	high-risk	high-risk

Note: For medical devices, the sub-categories A1, A2, C1, C2 and C3 are not further distinguished in this guideline. Please refer to the main categories A and C to determine the monitoring strategy.

2.3. Monitoring strategies

According to the results of the Risk-Based Monitoring Score Calculator and the decision tree, the clinical trial is then classified in one of the monitoring strategies, described below. The selected strategy will be adapted to meet the requirements of the specific trial and details described in the trial-specific monitoring plan. Special requirements for specific trial sites can also be incorporated as needed.

In general, SDV will focus on critical data, which is defined as follows:

- Existence of the trial participant
- Informed consent documentation and process
- Eligibility criteria
- Administration and dosage of the IMP / IMD or therapy
- Primary outcome
- Serious Adverse Events (SAEs)
- Further key data related to the safety analysis (e.g. adverse events for products for which the safety profile is not well known or device deficiencies for medical devices)

The monitoring extent and all checks that has to be performed should be described in detail in the Monitoring Plan, which has to be developed and agreed upon before the study start according to the sponsor.

Ideally, Central Data Monitoring should be performed for each trial, particularly in case of multicentre trials. The various consistency checks performed either by the monitor or the system should be defined in the trial-specific CDM plan.

Should substantial amendments to a clinical trial be required, the risk analysis should also be re-evaluated. The monitoring extent could be adapted during the study according to the site performance.
For further details, consult Table 2.

Table 1: Overview of recommended monitoring strategies

		low-risk	medium-risk	high-risk
Site qualification visit (SQV)		Site qualification visits are recommended, especially if the sites involved are to date unknown. The visit may be conducted on site or remotely.		
Site initiation visit (SIV)		The initiation visit may be conducted on site or remotely. The Principal Investigator (PI) and his / her team should be present. In the case of a remote initiation, the TMF / ISF will be checked at the first monitoring visit.	This visit will be done on site, in presence of the Principal Investigator (PI) and his / her team.	This visit will be done on site. The entire trial team at the site should be present (the PI, his / her team, pharmacists, and specialists, as applicable).
Routine monitoring visit (RMV)	Monitoring frequency for on-site visits	**1st visit** At least one routine monitoring visit as soon as possible after the inclusion of the 1st few trial participants (depending on the sample size). **Additional visits**	**1st visit** As soon as possible after the inclusion of the first few trial participants (approximately 5–10%, depending on the sample size) **Additional visits**	**1st visit** As soon as possible after the inclusion of the 1st trial participant **Additional visits**
		In case of major or critical findings, further visits will be conducted. The timing will depend on the findings. The timing and frequency of additional visits depends on the following factors: site recruitment, extent of monitoring tasks, findings at the site, visit schedule of participants within the trial, safety issues. Criteria for conducting unplanned monitoring visits and / or additional measures have to be defined in the monitoring plan.		
	ICF	**Check of existence of the participant + informed consent** All trial participants included at the time of the visit	**Check of existence of the participant + informed consent** 100% trial participants	
	SDV	**Full SDV** none **Partial SDV (key data)** For 1st trial participant and up to 20% of trial participants included *at the time of the visit*, as far as available	**Full SDV** 1st trial participant + up to 5% randomly selected trial participants **Partial SDV (key data)** For 20 to 50% of trial participants	**Full SDV** 1st trial participant + up to 10% randomly selected trial participants **Partial SDV (key data)** For 100% participants
		Example of key data: Eligibility, primary outcome, IMP / IMD administration (if applicable), SAEs, additional protocol-specific safety parameters		
	Accountability of the IMP or IMD (if applicable)	**Drug / medical device accountability** At least 1 trial participant, depending on the sample size and the number of included participants at the time of the visit.	**Drug / medical device accountability** At least 10% of trial participants.	**Drug / medical device accountability** At least 50% of trial participants.

		low-risk	medium-risk	high-risk
Routine monitoring visit (RMV)	TMF / ISF	**Full review of the TMF / ISF** □ At least one review will be performed, at the beginning of the study. **Updates** Whenever necessary (amendments, etc.) if further visits are programmed	**Full review of the TMF / ISF** □ At least two reviews will be performed, at the beginning and the end of the study. **Updates** □ Whenever necessary (amendments, etc.)	**Full review of the TMF / ISF** □ At the beginning and the end of the study. **Updates** □ At each visit. The monitor should check the completeness of the authorisation list and of the screening, identification, and enrolment list, as well as the training documentation on a regular basis.
Off-site activities		Depending on the trial recruitment, site contacts (e.g. email, phone call, teleconference ...) should be conducted at least once a year.	Depending on the trial recruitment, regular site contacts (e.g. email, phone call, teleconference, ...) should be performed (e.g. every 4 months, except if the interval between 2 on-site visits is shorter than 4 months)	Depending on the trial recruitment regular site contacts (e.g. email, phone call, teleconference ...) should be performed (e.g. every 2 months, except if the interval between 2 on-site visits is shorter than 2 months)
Central data monitoring		Depending on the study recruitment and the amount of data collected, CDM should start as soon as possible and be performed on a regular basis (e.g. every tree months or each time 30% of new participants are enrolled).	Depending on the study recruitment and the amount of data collected, CDM should start as soon as possible and be performed on a regular basis (e.g. every two months or each time 20% of new participants are enrolled).	Depending on the study recruitment and the amount of data collected, CDM should start as soon as possible and be performed on a regular basis (e.g. every month or each time 10% of new participants are enrolled).
		The frequency can be adapted depending on site performance / data quality.		
Close-out visit (COV)		Optional but recommended. May be conducted remotely.	A COV is recommended, but in some cases it could be combined with the last on-site monitoring visit.	An on-site COV is strongly recommended.