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Appendix 3

GUIDELINES FOR RISK-BASED MONITORING

Version

2.0

Guidelines for Risk-Based Monitoring
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ACRONYMS

ADAMON	ADApted Monitoring (ADAptiertes MONitoring)
ClinO	*Ordinance on Clinical Trials in Human Research*
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*
HRA	*Human Research Act*
HRO	*Ordinance on Human Research with the Exception of Clinical Trials*
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (commonly referred to as International Council for Harmonisation)
IIT	Investigator-Initiated Trial
IMD	Investigational Medical Device
IMP	Investigational Medicinal Product
ISF	Investigator Site File
kofam	Coordination Office for Human Research (Koordinationsstelle Forschung am Menschen)
NORM	Nordic Monitoring Network
OPTIMON	OPTimisation of MONitoring (OPTimisation du MONitorage)
PI	Principal Investigator
RF	Risk Factor
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
SoC	Standard of Care
SOP	Standard Operating Procedure
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 were specified in the Good Clinical Practice (GCP) guidelines of the International Council for Harmonisation, namely in its *Guideline for Good Clinical Practice E6(R2)*, (see item 5.18[1]). In this new version of the guideline published in 2016, the concepts of risk management and especially risk-based monitoring were further developed and well defined.

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]). Especially for non-commercial Investigator-Initiated Trials (IITs), risk-based procedures are essential in order to use limited resources efficiently. A risk-based approach to monitoring does not suggest any less vigilance in 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 to human subject 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[4]), OPTimisation of MONitoring (OPTIMON[5]), European Clinical Research Infrastructure Network (ECRIN[6]), TransCelerate[7], and Nordic Monitoring Network (NORM[8]).

Both ADAMON and OPTIMON strategies investigate prospectively whether the proposed trial-specific, risk-based, reduced on-site monitoring strategy is indeed as effective as an intensive monitoring strategy. While the OPTIMON evaluation is still ongoing,[9] the ADAMON team published a comparison of non-inferiority of risk-based monitoring versus extensive on-site monitoring.[10] These two strategies serve as different, but complementary resources.

Although it does not address the issue of monitoring and therefore does not directly affect the extent of monitoring activities, the *Human Research Act* (HRA) of Switzerland allows for a risk-based approach in research in humans, according to Art. 45. The *Ordinance on Clinical Trials in Human Research* (ClinO) and the *Ordinance on Human Research with the Exception of Clinical Trials* (HRO) both require a risk assessment (ClinO Arts. 19, 20, 49, and 61, and HRO Art. 7) including evaluating the risks associated with an intervention, prior to its submission to the competent authorities. The Federal Office of Public Health (FOPH) provides, via its kofam registry, a standardised electronic risk-categorisation tool[11] intended for sponsors and/sponsor-investigators.

When the authors drew up the first version of this Appendix 3 for the *Guidelines for Good Operational Practice* (GGOP) in May 2014, they were inspired by and drew substantially upon a guideline (not in public circulation), developed by the Swiss Group for Clinical Cancer Research (SAKK), as well as from risk-adapted monitoring strategies proposed by ADAMON.

The authors of this second version are experts from the Monitoring Platform of the Swiss Clinical Trial Organisation (SCTO). They leveraged several years of collaboration and sharing of experiences among those who contribute to the platform, serving thus to revise and improve the guidelines. The result of this endeavour is the publication of this second version in June 2019, with the support of SAKK.

1 ICH E6(R2), November 2016
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 ADAMON
5 OPTIMON
6 ECRIN Risk-Based Monitoring Toolbox
7 TransCelerate Risk Based Monitoring
8 NORM
9 OPTIMON: First results of the French trial on optimisation of monitoring
10 Risk-adapted monitoring is not inferior to extensive on-site monitoring: Results of the ADAMON cluster-randomised study, Brosteanu et al. Clin Trials Dec 2017; 6: 584-596
11 kofam categoriser

1.2 Objectives and scope

This guideline describes the risk-based monitoring procedures for non-commercial clinical trials, and its scope covers clinical trials as defined by the HRA.[12] Even though this Appendix does not focus on research projects as covered by the HRO, the content is nonetheless applicable. Although the Appendix was first developed by the Quality Assurance Working Group and subsequently revised by the Monitoring Platform of the SCTO, so as to facilitate and harmonise the conduct of multicentre trials, it is applicable to local single-centre trials. It is strongly recommended that 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

- **Informed Consent Form (ICF) and process review:** check that the subjects are informed according to ethical standards, that approved ICFs are correctly used and signed, and that the subjects' participation in the study 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, dispensation, return, destruction, etc.
- **Trial Master File (TMF) / Investigator Site File (ISF) review:** verification that essential documents (according to ICH E6(R2), s. 8) 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 during the SDV process
- **On-site monitoring:** the monitoring activities described above are performed at the sites at which the clinical trial is being conducted
- **Off-site/Remote Monitoring:** allows monitors to remotely conduct monitoring activities that were previously conducted on site
- **Central/Centralised Monitoring:** usually performed from the data collected via CRFs via EDC; allows the identification of missing data, outliers, or trends that may need attention from the sponsor or monitoring institution to identify and mitigate problems with the trial

2 PROCEDURES

According to ICH E6(R2), item 4.9.1, 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 (ICH E6(R2), item 5.1), and for developing a systematic, prioritised, risk-based approach to monitoring clinical trials (ICH E6(R2), item 5.18.3).

A risk-based monitoring strategy can only be implemented if on-site monitoring with SDV is part of an entire quality management programme, including but not limited to:

- training of trial personnel, pre-trial and initiation visit/teleconference
- review of protocol and related trial documents (e.g. CRF, ICF, etc.) according to Standard Operating Procedures (SOP)
- qualification of sponsors/sponsor-investigators/investigators (according to education, experience, and training)
- validation of database/eCRF and statistical analysis
- central monitoring with resolution of queries
- real-time validation and plausibility checks for trials using an EDC system
- audit trail of all changes to the data
- safety reporting procedures
- risk-based audit strategy

12 HRA, Art. 3, letter l: "Clinical trial means a research project in which persons are prospectively assigned to a health-related intervention in order to investigate its effects on health or on the structure and function of the human body."

Monitoring is usually the best method of quality control to influence whether these objectives are met, unless other quality management measures are determined to be more efficient. The efficiency of monitoring can be optimised by focusing on those aspects of a clinical trial that are critical, i.e. that influence subjects' rights and their well-being, as well as the quality of the data.

2.1 Risk-Based Monitoring Score Calculator

The monitoring strategy will be assessed by completing a questionnaire for a particular clinical trial.

Seven risk categories have been identified:

I. **Subject**
II. **Design**
III. **Safety**
IV. **Intervention**
V. **Management**
VI. **Data**
VII. **Other**

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

At the end of the assessment, the composition of the amount of low-, 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**

To view the instructions on how to fill in and complete the Risk-Based Monitoring Score Calculator, please visit: www.stco.ch/monitoring

2.2 Decision tree

The monitoring strategy for a clinical trial should be defined according to Table 1 below and determined by the following criteria:

- **study risk category**, according to ClinO, Arts. 19, 20, 49, and 61[13]
- **number of low-, medium- and high-risk factors**

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 sites can also be incorporated as needed.

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

- existence of the trial subject
- informed consent documentation and process
- eligibility criteria
- administration and dosage of the IMP/IMD or therapy
- primary endpoint
- Serious Adverse Events (SAEs)
- further key data derived from the safety analysis (e.g. adverse events for products for which the safety profile is not well known)

In this guideline, no recommendation is made regarding the extent of central monitoring, since trial requirements and electronic data capture system options are very different. In general, the EDC system should be used to identify missing data, outliers, or trends that need attention from the monitor during the following on-site visit. The various consistency checks performed by the monitor should be defined in the monitoring plan, and those checks to be performed by the system should be defined in the trial- specific data management plan.

Should substantial amendments to a clinical trial be required, the risk analysis should also be reconsidered. For further details, consult Table 2.

13 ClinO Arts. 19, 20, 49, and 61

Table 1: Decision tree for determining a suitable monitoring strategy, according to the results of risk analysis

Recommended monitoring strategy			
No. of RFs / **STUDY**	**ClinO A**	**ClinO B**	**ClinO C**
0 ≤ low RF ≤ max and 0 ≤ medium RF ≤ **5** **and** high RF ≤ 0	**low-risk**	**low-risk**	**medium-risk**
0 ≤ low RF ≤ max and **6** ≤ medium RF ≤ **12** **or** 0 < high RF ≤ **1**	**low-risk**	**medium-risk**	**high-risk**
0 ≤ low RF ≤ max and **13** ≤ medium RF ≤ **max** **or** **2** ≤ high RF ≤ max	**medium-risk**	**high-risk**	**high-risk**

Notes: ClinO: Ordinance on Clinical Trials in Human Research; No.: number; RF: risk factor

Table 2: Overview of recommended monitoring strategies

		low-risk	**medium-risk**	**high-risk**
Pre-trial visit		Pre-trial 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 their team should be present. In the case of a remote initiation, the TMF / ISF will be checked at the 1st routine monitoring visit.		This visit will be done **on site.** The entire trial team at the site should be present (the PI, their team, pharmacists, and specialists, as applicable).
Routine monitoring visit	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 subjects** (depending on the sample size). **Additional, subsidiary visits**	**1st visit** **As soon as possible after the inclusion of the first trial subjects** (approximately 5–10%, depending on the sample size) **Additional visits** 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 subjects within the trial	**1st visit** **As soon as possible after the inclusion of the 1st trial subject** **Additional visits** 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 subjects within the trial
		In case of major or critical findings, further visits will be conducted. The timing will depend on the findings. Criteria for conducting unplanned monitoring visits and / or additional measures have to be defined in the monitoring plan.		

		low-risk	medium-risk	high-risk
Routine monitoring visit	ICF	**Check of existence of the subject + informed consent** **All trial subjects included at the time of the visit**	**Check of existence of the subject + informed consent** **100% trial subjects**	
	SDV	**Partial SDV (key data)** **For 1st trial subject and up to 20%** of trial subjects included **at the time of the visit**, as far as available: – eligibility – primary endpoint – IMP administration (if applicable) – SAEs – additional protocol-specific safety parameters	**100% SDV** **1st trial subject + up to 5% randomly selected trial subjects** **Partial SDV (key data)** **For 20 to 50% of trial subjects (depending on findings):** – eligibility – primary endpoint – IMP administration (if applicable) – SAEs – additional protocol-specific safety parameters	**100% SDV** **1st trial subject + up to 10% randomly selected trial subjects** **Partial SDV (key data)** **For 100% subjects:** – eligibility – primary endpoint – IMP administration (if applicable) – SAEs – additional protocol-specific safety parameters
	Accountability of the IMP or IMD (if applicable)	**Drug / Medical Device accountability** **1 trial subject or more, depending on the sample size** (as far as available, at the time of the last monitoring visit).	**Drug / Medical Device accountability** **At least 10%** of trial subjects (as far as available, at the time of the last monitoring visit).	**Drug / Medical Device accountability** **At least 50%** of trial subjects.
	TMF / ISF	**Full review of the TMF / ISF** **At least one** review will be performed	**Full review of the TMF / ISF** 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.
Close-Out Visit (COV)		**Optional** **May be conducted remotely**	A COV is **recommended**, but may be **combined** with the last on-site monitoring visit.	A COV is **strongly recommended** but may be combined with the last on-site monitoring.

Notes: COV: Close-Out Visit; ICF: Informed Consent Form; ISF: Investigator Site File; IMP: Investigational Medicinal Product; PI: Principal Investigator; SAE: Serious Adverse Event; SDV: Source Data Verification: SIV: Site initiation visit; TMF: Trial Master File