APPENDIX 3

Guidelines for Risk-Adapted Monitoring

Introduction

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 guideline [ICH GCP 5.18]; the necessary scope involved, however, is not clear enough[1]. While it is generally agreed that quality management measures are indispensable, their extent and effective implementation is still a matter of debate.

According to GCP and the latest developments in the regulatory environment, risk-adapted procedures in clinical trials are internationally encouraged, e.g. by the EMA[2] as well as by the FDA[3]. Especially for non-commercial investigator initiated trials, risk-adapted procedures are essential in order to use limited resources in an efficient way. A risk-based approach to monitoring does not suggest any less vigilance in the oversight of clinical investigations. Rather, it steers sponsor oversight activities on preventing or mitigating important and likely risks to data quality and to processes which are critical to human protection and trial integrity.

On a European level, there are several helpful, well-documented and widely used initiatives running which recommend and evaluate risk-adapted monitoring strategies (the ADAMON[4] Project, the OPTIMON[5] Project, the UK MRC/DH/MHRA Joint Project[6]). The ADAMON and OPTIMON strategies are already partly in use at several CTUs. They both prospectively investigate whether the proposed trial-specific, risk-adapted, reduced on-site monitoring strategy is indeed as effective as an intensive monitoring strategy.

Although it does not address the issue of monitoring and therefore does not directly affect the extent of monitoring activities, the Swiss Human Research Act (HRA) allows for a risk-adapted approach in research in humans according to Art. 65. The Ordinance on Clinical Trials in Human Research (ClinO) and the Ordinance on Human Research with the Exception of Clinical Trials (HRO) even require a risk assessment by evaluating the risks associated with an intervention prior to submission to the competent authorities [ClinO Art. 19, 20, 49, 61, and HRO Art. 7]. The Federal Office of Public Health (FOPH) provides a standardised electronic categorisation tool[7] for sponsors/sponsor-investigators.

In view of these developments and the limited resources within the network, it was decided to adopt the concept of risk-adapted monitoring strategies of the SAKK, which is based on the risk-adapted monitoring strategies proposed by the ADAMON Project. The SAKK concept was adapted to the needs of sponsor-investigators and Swiss legal requirements as of January 2014.

Objectives and Scope

These guidelines describe the risk-adapted monitoring procedures for non-commercial clinical trials, and their scope covers clinical trials as defined by the HRA[8]. Even though this document does not focus on research projects as covered by the HRO, the content may also be applicable. This document was developed by the Quality Assurance Working Group of the Swiss Clinical Trial Organisation (SCTO) to facilitate and harmonise the conduct of multicentre trials, but may also be applied to local mono-centre trials. It is strongly recommended for application to all trials within their scope by all full and associated members of the SCTO. However, the final decision on its implementation lies within the responsibility of each CTU.

1 Refer to ICH GCP 5.18.3

2 Reflection paper on risk based quality management in clinical trials EMA/INS/GCP/394194/2011

3 Guidance for Industry: Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring, FDA, August 2013

4 www.adamon.de/ADAMON_EN/Home.aspx
Risk analysis and risk adapted on-site monitoring in noncommercial clinical trials, Brosteanu et al. Clin Trials December 2009; 6: 585–596, first published on November 6, 2009

5 https://ssl2.isped.u-bordeaux2.fr/OPTIMON/default.aspx
Liénard JL, Quinaux E, Fabre-Guillevin E, Piedbois P, Jouhaud A, Decoster G, Buyse M; European Association for Research in Oncology. Impact of on-site initiation visits on study subject recruitment and data quality in a randomized trial of adjuvant chemotherapy for breast cancer. Clin Trials. 2006; 3(5): 486–92

6 www.mhra.gov.uk/home/groups/l-ctu/documents/websiteresources/con111784.pdf
MRC/DH/MHRA Joint Project: Risk-adapted Approaches to the Management of Clinical Trials of Investigational Medicinal Products, October 2011

7 http://snctp.begasoft.ch/snctp/pages/public/wizard.jsf?lang=en

8 HRA Art. 3 lit. 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.

Structure

The guidelines for risk-adapted monitoring consist of:

- a categorisation scheme for clinical trials
- a questionnaire for risk analysis with respect to required on-site monitoring
- risk-adapted monitoring strategies for each monitoring category

The templates for monitoring plans for each defined monitoring strategy will follow once experience has been gained with this new procedure.

Review, Updates, Release

The guidelines will be reviewed and updated by the SCTO in collaboration with the CTUs and associated networks if there is any major regulatory change or new evidence as to which monitoring approaches are useful, such as results of the ADAMON Project with quantitative data on the impact of the different monitoring strategies, which are expected in 2015. The relevance and accuracy of the guidelines will be reviewed every two years.

1 Procedures

According to ICH GCP 4.9.1, the investigator is responsible for ensuring that the data reported to the sponsor in the Case Report Form (CRF) are complete and accurate. The sponsor is responsible for implementing and maintaining a quality assurance and quality control system [ICH GCP 5.1].

The best way to control the risks of participating in a clinical trial is to identify and to minimise them with appropriate measures. A risk-adapted monitoring strategy can only be implemented if on-site monitoring with Source Data Verification (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 (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 electronic data capturing system
- audit trail of all changes to the data
- safety reporting procedures
- risk-adapted audit strategy

Adherence to GCP guidelines ensures the protection of the three following objectives:

- safety of trial participants
- rights, integrity and confidentiality of trial participants
- data quality (data accuracy and protocol compliance)

Monitoring is the best method of quality control if it has an impact on these objectives, and if other quality management measures are not determined to be more efficient. The efficiency of monitoring can be optimised by focusing on the aspects of a clinical trial that are critical, i.e. that influence participants' rights and well-being and the quality of the data.

1.1 Risk Analysis

The risk of a clinical trial can be assessed by completing a questionnaire (see Figure 1) adapted from the ADAMON Project[9]. Trials are categorised into:

- high risk
- intermediate risk
- low risk

9 Risk analysis and risk adapted on-site monitoring in noncommercial clinical trials. Brosteanu O, Houben P, Ihrig K, Ohmann C, Paulus U, Pfistner B, Schwarz G, Strenge-Hesse A, Zettelmeyer U. Clin Trials. 2009 Dec;6(6):585-96.

Figure 1: Risk Analysis for Risk-adapted Monitoring. (* Copy only: please refer to the excel-tool.)

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Insert your Logo here

Risk Analysis for Risk-Adapted Monitoring

Title of Protocol: _____ Sponsor's Name: _____

Principal Investigator: _____ Date: _____

Ethics Committee No.: _____ Signature: _____

Trial Site(s): _____

Project No.: _____ Completed by: _____

Function: _____

Monitoring Class (resulting from the risk analysis below; if no risk analysis has been conducted, a high risk will be assumed) **High Risk**

To complete the questionnaire please use "Tab" for navigation.

Please type **"1"** in the corresponding field.

Potential risk of therapeutic intervention in comparison to standard of medical care

Type of clinical trial	**Comparable** (see also ClinO Art. 19, 20, 61, category A)	
	Higher (see also ClinO Art. 19, 61, category B)	
	Markedly higher (see also ClinO Art. 19, 20, category C)	

Please type **"1"** for Yes and **"0"** for No.

Potential trial participant-related critical indicator

Participant-related indicators (P)	Yes / No	If Yes, specify its nature. Participant safety	Participant rights	Data validity	If Yes, which QA measure can control the risk?	If no QA measure, can monitoring control the risk?
P1 Will a vulnerable population be included?						
P2 Will adult participants who are temporarily unable to provide informed consent be included into the trial?						
P3 Will trial participants be recruited within the scope of emergency medical treatment?						
P4 Are there any critical eligibility criteria?						
P5 Is there a lack of previous experience on the (combination of) medications and/or therapies being studied?						
P6 Is it likely that participants receive additional medication for concomitant diseases/symptoms?						
P7 Is there only very limited knowledge about at least one of the investigational drugs?						
P8 Are there any additional risks of the therapies being tested not yet taken into account?						
P9 Are there any additional risks associated with trial-related procedures (other than the therapy being tested)?						
P10 Are trial procedures (therapy and/or diagnostics) clinically unusual and complex?						
P11 Are there any risks of coincidental or deliberate unblinding?						
P12 Are there any risks of (informative) withdrawals or drop-outs?						
P13 Are there any sources of bias or variance with regard to the primary endpoint?						
P14 Are there any potential trial protocol deviations that could have a negative impact on participant safety and/or the validity of the trial?						
P15 Are there any further risks that could have a negative impact that haven't been answered adequately in questions P1-P14?						
Summary of participant-related indicators						**0**

Robustness-related indicators (R)	Yes / No
R1 Is a "hard" primary endpoint being investigated?	
R2 Are the clinical trial procedures (design) very simple?	
Summary of robustness-related indicators	**0**

Site-related indicators (S) (No influence on risk category.)	Yes / No	If Yes, specify its nature. Participant safety	Participant rights	Data validity	If Yes, which QA measure can control the risk?	If no QA measure, can monitoring control the risk?
S1 Are there any technical requirements for the trial sites?						
S2 Are there any essential personnel requirements for the trial sites?						
S3 Are there any essential storage requirements for the investigated product?						
S4 Are there any essential documentation requirements for the investigated product?						
S5 Are there any essential transport and/or storage requirements for material samples?						
S6 If the trial is randomised but not blinded, is randomisation performed locally at the trial sites (e.g. by envelopes)?						
Summary of site-related indicators						**0**

1.2 Risk-Based Categorisation

The category of a clinical trial is defined according to Table 1 below and determined by the following criteria[10]:

- potential risk of the therapeutic intervention in comparison to standard therapy (critical evaluation of the standard of care has to be performed) and according to ClinO
- trial participant-related indicators that are identified in the risk analysis as critical and that can be controlled by monitoring
- indicators of robustness with respect to protocol compliance or to assessment of the primary endpoint

Site-related indicators evaluated in the risk analysis are not relevant for the definition of the monitoring strategy but can be used to determine whether additional individual site-specific measures or special training are necessary.

10 For details please refer to the Risk Analysis for Risk-Adapted Monitoring, Figure 1.

Table 1: Determination of the monitoring strategy according to the results of the risk analysis

		Potential risk of therapeutic intervention in comparison to standard of medical care		
		comparable [11]	higher [12]	markedly higher [13]
Potential trial participant-related critical indicator	absent	at least one indicator of robustness ↓ **low risk**	independent of the indicators of robustness ↓ **intermediate risk**	at least one indicator of robustness ↓ **intermediate risk**
		no indicator of robustness ↓ **intermediate risk**		no indicator of robustness ↓ **high risk**
	present	independent of the indicators of robustness ↓ **intermediate risk**	independent of the indicators of robustness ↓ **high risk**	independent of the indicators of robustness ↓ **high risk**

11 See also ClinO Art. 19, 20, and 61, category A.
12 See also ClinO Art. 19 and 61, category B.
13 See also ClinO Art. 19 and 20, category C.

1.3 Monitoring Strategies

According to the results of the above-mentioned risk analysis and its categorisation, one of the monitoring strategies described below must be chosen. The selected strategy is 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 focus on critical data, which are defined as follows:
- existence of the trial participants
- Informed Consent documentation
- eligibility criteria
- application and dosage of the investigated product or therapy
- primary endpoint(s)
- Serious Adverse Events (SAEs)
- further key data derived from the safety analysis (e.g. Adverse Events for products where the safety profile is not well known)

In case of substantial amendments to a clinical trial, a reconsideration of the risk analysis is necessary.

Table 2: Overview of monitoring strategies

		High risk trial	Intermediate risk trial	Low risk trial
Pre-trial visit		Pre-trial visits are recommended, especially if unknown sites are involved. The visit may be conducted on site or remotely.		
Site initiation visit		The site initiation visit will be done on site. All trial team members should be present at the site (principal investigator, his team, pharmacist, specialist, as applicable).	The site initiation visit may be conducted on site or remotely. The principal investigator and his team should be present. In case of a remote initiation, the TMF/ISF should be checked at the first monitoring visit.	
Regular monitoring visit	**Monitoring frequency**	The first regular monitoring visit will generally take place within 1–4 months[14], at the latest after the inclusion of the first trial participant. The next visits will take place according to trial participant recruitment, but generally every 2–8 months.	The first regular monitoring visit should be conducted after the inclusion of the first or second trial participant. The timing and frequency of additional visits depend on the following factors: – site recruitment – extent of monitoring tasks – findings at the site – visit schedule of the participants within the trial In general, visits take place 1–3 times per year.	One regular monitoring visit will take place within one year after the inclusion of the first trial participant.

14 In case of phase 1 trials or first-in-man trials, a more intensive schedule is required.

		High risk trial	Intermediate risk trial	Low risk trial
Regular monitoring visit	**Monitoring frequency**	In case of major or critical findings [15], further visits should be conducted. The timing depends on the findings. Criteria for conducting unplanned monitoring visits and/or additional measures have to be defined in the monitoring plan.		
	Source Data Verification	First trial participant and in addition 10% of all remaining trial participants: – 100% SDV All trial participants: Key data 100%: – existence – Informed Consent – SAEs – eligibility – drug administration – primary endpoint – additional protocol-specific safety parameters	First trial participant: – 100% SDV All trial participants: – existence – Informed Consent Further key data for at least 20 – 50% of trial participants, depending on findings: – SAEs – eligibility – drug administration – primary endpoint – additional protocol-specific safety parameters	All trial participants included at the time of the visit: – existence – Informed Consent First trial participant and at least 20% of trial participants recruited at the time of the visit, as far as available: – SAEs – eligibility – drug administration – primary endpoint – additional protocol-specific safety parameters
	Central monitoring	Some of the consistency checks are performed by the system at the time of data entry. The system should then be used as far as possible by the monitor (or the central data monitor) during the visit to perform further checks and he/she will evaluate if a query has to be issued. The different consistency checks to be performed by the monitor should be defined in the monitoring plan, and the checks to be performed by the system should be defined in the trial-specific Data Management Plan.		Some of the consistency checks are performed by the system at the time of data entry. The different consistency checks to be performed by the monitor should be defined in the monitoring plan, and the checks to be performed by the system should be defined in the trial-specific Data Management Plan.
	Accountability of the Investigational Medicinal Product (if applicable)	Drug accountability will be verified for 100% of all trial participants.	Drug accountability will be verified for 10% of all trial participants (as far as available at the time of the last monitoring visit).	
	Trial Master File (TMF), Investigator Site Files (ISF)	At least once a year a full review of the TMF/ISF should be performed. 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		A close-out visit is mandatory.	A close-out visit is mandatory, but may be combined with the last regular monitoring visit.	A last visit should take place after closure for accrual and/or end of trial treatment/intervention of the last trial participant at the site.

15 Definition of the findings:

- **Minor**: a GCP, protocol and/or SOP deviation that would not be expected to adversely affect the rights, safety or well-being of participants and/or the quality and integrity of data. However, they are deviations from sponsor or regulatory requirements. Many minor observations may indicate a bad quality and the sum with its consequences might be equal to a major finding. There must be a commitment to take corrective/preventive actions.
- **Major**: a GCP, protocol and/or SOP deviation that might adversely affect the rights, safety or well-being of participants and/or the quality and integrity of data. Major observations are serious deficiencies and high priority items for correction/prevention. Observations classified as major may include those situations where there is a pattern of deviations and/or numerous minor observations.
- **Critical**: a GCP, protocol and/or SOP deviation that adversely affects the rights, safety or well-being of participants and/or the quality and integrity of data. Critical observations are considered totally unacceptable. Fraud belongs to this group. They require immediate attention.