AUDITING
PLATFORM

User Instructions for the Risk Assessment Form for Clinical Trials according to the Clinical Trial Ordinance (ClinO)

General instructions

The **Risk Assessment Form for Optimising Clinical Trials and Research Projects** was developed by the Auditing Platform of the Swiss Clinical Trial Organisation (SCTO), in consultation and collaboration with other platforms of the SCTO and staff of its Clinical Trial Unit (CTU) network. The first version was released in December 2019. While the **User Instructions** below pertain to clinical trials, they can be adapted for filling in the form to conduct risk assessment on research projects run according to the Ordinance on Human Research (HRO).
These **User Instructions** refer to a Word document, the **Risk Assessment Form**, hosted separately at www.scto.ch/auditing. You are welcome to adapt it to your needs and brand it with your institution's logo. Please send your user feedback to us at auditing@scto.ch, as we hope to continue improving this resource.

Components of these User Instructions

These **User Instructions** are intended to help you fill in the **Risk Assessment Form** and contain three components with explanations and examples, to illustrate the use of the tool:

- Introduction: a step-by-step approach
- Part A: assessing potential risks at system level, and
- Part B: addressing specific risks at project level

Introduction

To make best use of this form, you need to tackle these key questions: **why, who, when, how,** and **what**.

Why do you need to use this form?

According to the International Council for Harmonisation, namely its Guideline for Good Clinical Practice (referred to as ICH-GCP E6(R2)), it is the *sponsor's responsibility* to assure that an adequate Quality Management System (QMS) is in place. This QMS is necessary for overseeing the clinical project and addressing potential risks of the clinical trial, i.e. to the well-being and safety of trial participants, to the validity of trial results, and to regulatory compliance.

Who should complete this form?

The **Risk Assessment Form** should be filled in by the Sponsor-Investigator, together with other key team members involved in the clinical trial (e.g. Investigators, Study Nurses/Coordinators, Statisticians, and Monitors) and with a CTU or Clinical Trial Centre (CTC) representative.

Whether the involved stakeholders take over a decision-making role or act as advisors, the ultimate responsibility for risk management of the clinical trial lies with the Sponsor-Investigator.

Part A can be used as a higher-level document, for overseeing the entire trial site or research site. Accordingly, Part A should then be signed off by or agreed upon with the Head of the Trial Site/Research Site. However, Part A must be (re)evaluated for each project, to ensure it is in accordance with the research focus for that specific project.

When in the course of your study should you fill it in?

The form should be completed *prior* to the conduct of the clinical trial or when a substantial amendment occurs. Risk assessment at project level should be based on the trial protocol and, if available, on the participant information and informed consent in their most current version. Therefore, risk assessment should start as soon as an advanced version of the protocol is available. This will allow you to address detected risks in the protocol, to manage them with written Standard Operating Procedures (SOPs) and/or a with risk-adapted monitoring plan. We

suggest that you consult the **Risk-Based Monitoring Score Calculator** and its instructions, first published by the Monitoring Platform in June 2019.

During the course of a clinical trial, new risks might arise or become obvious, whereas other risks might become less relevant. Assessing and reviewing risks, as well as adapting risk control measures throughout the whole trial, must be a continuous process. To this end, the risk assessment form should be considered a dynamic document, which should be updated regularly. At least once a year is recommended.

How should you fill in the form, column by column?

Work through the columns from left to right, noting: a **description** of the risks, a **rating** (high vs low), a **rationale** for your rating and other related comments, **risk-minimising measures** you can use, a **deadline** for action, and a person who will be **responsible**.

Description

In this first column, critical processes of the clinical trial should be identified and evaluated according to GCP, ch. 5.0.2 and 5.0.3.
In general, you should address the following three fundamental questions:

1. What might go wrong?
2. What is the likelihood (probability) it will go wrong?
3. What are the consequences (impact or effects) if it goes wrong? Can the risk be detected (i.e. what is its detectability)?

Rating

Rate the risk as “high”, if the

- potential event results in non-compliance with GCP or legal provisions (e.g. having no QMS in place)
- error is likely to occur
- extent to which such an error would be detected is low
- impact of such an error on human subject protection (i.e. protection of the study participant) is severe or
- impact on the reliability of trial results is substantial.

Rate the risk as “low”, if the

- error is highly unlikely to occur (e.g. no causal relationship to the treatment is expected)
- detection of such an error is very likely

- impact of such an error on human subject protection is negligible (e.g. the event is transient, mild, or does not require further treatment) or
- impact on the reliability of trial results is marginal.

Rationale for Rating/Comments: Give a short explanation for your risk rating.

Predefine your study's quality tolerance limits, as they will help you both identify systematic issues that can impact on safety of participants or on the reliability of trial results, and determine if action is needed (see GCP 5.0.4).

What action must you take?

Risk-minimising measures: Define measures for risk mitigation (including how, when, and who).

Risks identified as "high" should be addressed immediately. Risks rated as "low" can be addressed at any given time or it should explain why no measure is needed. Actions can include, for example:

- Training
- A detailed explanation, guidance, or process description e.g. in form of SOPs or Working Instructions (WIs)
- Continuous support by CTU/CTC or other key players, e.g. project manager/coordinator
- Controlling/supporting functionality implemented in the (electronic) case report form (eCRF) or
- Performing additional tasks such as double-data entry, source data verification, or independent outcome assessment.

Explanations and examples for completing the Risk Assessment Form, Parts A and B

Non-exhaustive examples and guidance notes within tables appear in grey, in italics.

Insert your institution's logo here

Part A: Potential risks at sponsor's clinical trial site and/or general at system level

Sponsor's name, phone, and mailing address: (*or if applicable:* Head of Site, phone and mailing address)	*Example:* *Sam Muster* *Institute of Clinical Research* *Max.muster@inst_clin_research.ch* *+01 79 111 111 11*
Investigator's name, phone, and mailing address:	*(if different to Sponsor)*

Risks at systems level					
Description	**Rating**	**Rationale for rating / Comments**	**Risk-minimising measures**	**Action deadline**	**Person responsible**
A1 QMS / Processes					
e.g. • *no QMS / SOPs in place*	☐ low ☐ high	*e.g.* *"high" because vulnerable*	*e.g.* • *develop system-/ project-/ or site-specific SOPs*	*e.g.* *01-Apr-2019*	*e.g.* *Principal Investigator*

• *new work processes not described and trained* • *SOPs do not describe current work processes* • *no training records for SOPs available*	*Sections answered with "high" should have suggested actions under "action". Note: Whenever a GCP-requirement is not fulfilled, the risk for the clinical trial or project is considered to be "high".*	*subjects are included*	• *train staff on SOPs*		
A2 Infrastructure / Systems					

e.g.
• *poor data management system e.g. not suitable for the purpose*
  ○ *complex data management process*
  ○ *complex data*
  ○ *new database in use*
  ○ *several databases needed*
  ○ *import/ export from/to other databases*
  ○ *risk of unauthorised deletion, alteration or exchange of data*
  ○ *data sharing does not comply with data protection policies*
	☐ low
	☐ high
			e.g.
			• *contact data management experts*
			• *create specification document*
			• *perform system validation and testing*
			• *record all activities*
			• *implement database back-up (use of centrally supported systems)*
			• *restrict access to database*		

○ *data not reproducible* • *no system description available* • *no audit trail available* • *not validated* • *no access control (e.g. limiting system access to authorised individuals)* • *inadequate use of (pharmaco-) vigilance systems* ○ *no process/system in place to assess safety issues* ○ *complex serious adverse events (SAE) reporting process (e.g. multicentre projects)* ○ *project management team not experienced with SAE reporting requirements (e.g. Principal Investigator shall notify the ethics committee of a SAE within 7 days)* ○ *no system in place to maintain awareness of new safety information* • *no (protocol) deviation documentation and reporting process* • *inadequate material, equipment or facility resources* ○ *no freezers for biobanks* ○ *no lab space* ○ *no centrifuges* • *inadequate insurances coverage of institution*			• *Implement traceability for all data corrections* • *validate import/export of data* • *verify that statistical analysis is in accordance with statistical analysis plan (SAP)* • *implement data encryption for all portable media* • *perform training and documentation* • *purchase missing equipment*		

A3 Resources / Personnel					
e.g. • *inexperienced, untrained or non-dedicated staff or Investigators* • *appropriate resources not available* • *no experts involved (e.g. disease specialists, statisticians, data manager, logistical support)* • *staff changes frequently* • *funding is not secure (risk of withdrawal)* • *staff time is highly limited*	☐ low ☐ high		*e.g.* • *perform/complete adequate Principal Investigator/staff training and document training* • *periodically update site delegation logs, CVs and GCP and file in the TMF/ISF* • *perform regular team meetings to review procedures* • *assure that funding is in place for the duration of the project* • *define what resources are needed to run the project and if applicable hire relevant staff* • *set up contract with funding body* • *submit cost extensions to funding bodies in a timely manner to ensure there is no disruption to the conduct of the project*		

A4 Others *e.g. Logistics*					
e.g. • *temperature-sensitive samples need to be transported over long distance and time* • *patients have to go to several departments/ locations to complete a trial visit*	☐ low ☐ high		*e.g.* • *organise specialised courier service* • *organise validated transport system* • *include temperature logger* • *generate a visit agenda for the patients* • *rent additional rooms* • *work together with local CTU/CTC*		

Sponsor / Sponsor-Investigator / Head of Site	*Full name*
Date and signature	*dd.mm.yyyy and signature*

Non-exhaustive examples and guidance notes within tables appear in grey, in italics.

Insert your institution's logo here

Part B: Specific risks at clinical trial level/research project level

Trial title	*Short title of the clinical trial*
Trial number	*BASEC-no. / Swissmedic-no / WHO-register-no. including indication*
Site contact	*name of contact person with e-mail address, tel. no.*

Risks at project level					
Description	**Rating**	**Rationale for rating / Comments**	**Risk-minimising measures**	**Action deadline**	**Person responsible**
B1 Project Design					
e.g. • *processes and data critical to assure human subject protection and reliability of study results were poorly considered during protocol development (GCP, 5.0.1)* • *no quality tolerance limits were predefined (GCP, 5.0.4)* • *international, multi-centre* • *Inadequate recruitment to reach required sample size* • *subject/patient population not available* • *many competing studies* • *restricted access to patients or data*	☐ low ☐ high *Sections answered with "high" should have suggested actions under "action". Note: Whenever a*	*e.g. "high" because multi-centred*	*e.g.* • *organise Investigator meetings/ trainings, newsletters* ○ *perform protocol training covering eligibility criteria* ○ *ensure that eligibility is adequately documented in the CRF* ○ *implement process that any eligibility violation is reported to the Principal*		

• *lack of robust randomisation procedure* • *loss of blinding* • *expected low patient compliance* • *complex trial schedule with frequent visits and narrow time windows* • *long trial with many follow-up visits bare the risk of losing patients (drop-outs)* • *risk of losing participants due to side effects* • *risk of unbalanced distribution of participants* • *risk of predicting treatment groups* • *potential for unintentional unblinding* • *no emergency unblinding in place* • *risk of missing primary endpoint, due to poor patient compliance* *risk of frequent protocol deviations due to patient visit time constrains* • *risk of wrong sample size calculation that results in an underpowered study with no conclusion* • *risk of erroneous statistical analysis*	*GCP-requirement is not fulfilled, the risk for the clinical trial or project is considered to be "high"*		*Investigator, Sponsor-Investigator* • *support recruitment* ○ *define recruitment targets* ○ *regularly compare recruitment rates against recruitment targets to assess achievability* ○ *consider opening additional sites* ○ *replace drop-outs, if applicable* • *define handling of missing data (trial protocol or statistical plan)* • *give detailed guidance for special/complex assessments (SOPs, WIs, etc.)* • *Meeting with statistician to discuss different scenarios, the assumptions for the study and the consequences* • *SOP on data preparation and programming, which is checked by a second statistician*		
B2 Data Collection / Project-specific Procedures					
e.g. • *numerous source systems* • *electronic and paper source systems*	☐ low ☐ high		*e.g.* • *provide detailed descriptions of planned data acquisition*		

• *different data collected in CRF as described in trial protocol* • *primary endpoint outcomes require subjective or complex assessment* • *many questionnaires, diaries, patient reported outcomes (PROs) required* • *several 3rd-party labs involved*			• *ensure that sufficient resources (financial, personnel, infrastructure) are available* • *define and ensure that regular meetings of data committees are organised according to contracts* • *plan audits for quality assurance* • *Implement risk-adapted monitoring* • *train trial teams* • *prepare CRF completion guideline* • *implement double-data-entry* • *ensure security of database* • *test and validate database* • *ensure restricted access to database* • *establish training records for database entries and use*		
B3 Informed Consent Process / Project Participants					
e.g. • *risk of non-compliance with informed consent process* • *failure to protect participants privacy (data protection)* • *complex process with e.g. vulnerable participants (children, emergency…)*	☐ low ☐ high		*e.g.* • *identify who will be taking participant consent, including training and delegation* • *ensure that optional consent clauses are clearly labelled*		

○ *multiple consent forms* ○ *will participants have capacity to give consent?* ○ *short time to consider information (e.g. emergency setting)* ○ *special risks due to increased radiological exposure, additional biopsies, questionnaires involving 'sensitive' subject areas, contact with harmful chemicals, substances, equipment, or organisms* • *risk due to new/insecure data collection methods (e.g. recording of qualitative interviews)*			*and tracked in an appropriate system* • *ensure that protocol is detailed enough. If not: complete with specific guidelines.* • *in case of emergency situation: need to obtain a proxy and post hoc consent* • *define withdrawal process* • *document the consent process in the source documents and file original ICF in the ISF* • *re-consent participants throughout the duration when procedures change and ICFs are updated* • *make sure that process is in place for participant request to withdraw* • *ensure that access to computer systems is controlled* • *implement computer security systems including the use of encrypted media* • *implement specific consent for data transfer including patient samples etc.* • *ensure that ICFs, lists and other documents containing patient data are filed appropriately in the ISF* • *make sure that transfer of sensitive data is secure*		

B4 Participants' safety					
e.g. • *inadequate/no use of (pharmaco-) vigilance systems* • *many adverse events anticipated due to the nature of the illness/ interventions/ drug interactions* • *complex SAE reporting process* • *sites and project management team are not experienced with SAE reporting requirements* • *participants are actively involved in reporting of adverse events* • *potential risk of compromising patient safety, rights, well-being, and dignity during trial conduct* • *protocol foresees data safety monitoring board (DSMB) but no charter available to describe work processes* • *vulnerable study-population* • *participant recruitment in emergency situations or of patients that are temporarily not able to consent* • *special inclusion/exclusion criteria* • *limited IMP safety knowledge*	☐ low ☐ high		*e.g.* • *update the protocol with any new relevant safety information as and when available* • *create "Dear Investigator letters", providing Investigator alerts* • *give detailed guidance for safety recording and (SOPs, WIs, etc.)* • *complete line listing of SAEs in an on-going manner* • *perform periodic review of Reference Safety Information for updates* • *update ICF following significant updates Reference Safety Information* • *assure that there are SAE monitoring and review processes in place* • *generate specific SAE and pregnancy reporting forms* • *provide full safety recording and reporting training to the team & document* • *generate a DSMB charter*		

B5 IMP and / or Sample Management					

e.g.
• *poor IMP management system*
• *complex IMP shipping process*
  ○ *supply of IMP is at risk*
  ○ *IMP stored at sites*
  ○ *IMP handling/ preparation/ administration has potential for dosing errors, temperature deviations*
  ○ *potential for interruption to or change in standard of care*
  ○ *dosing volume is small, leading to risk of in-built volume errors*
  ○ *IMP is handed out to patients for self-administration*
• *poor sample management system*
  ○ *samples are stored at site*
• *complex sample storage and/ or shipping process*
• *a biobank is needed*
• *samples need to be sent to external laboratories*
	☐ low
	☐ high
			e.g.
			• *finalise contract with IMP supplier including provisions for ensuring constant supply*
			• *give detailed guidance for IMP handling and supply (SOPs, WIs)*
			• *create IMP tracking documents, accountability logs, pharmacy manual, prescriptions, drug inventory log*
			• *create participant diaries to check participant IMP compliance, if applicable*
			• *ensure that all IMP orders processed via coordinating centre*
			• *maintain a central accountability log*
			• *ensure that dosage modifications are implemented in accordance with the protocol and pharmacy manual (where applicable)*
			• *give detailed guidance for sample handling and biobanks*
			• *make sure that sites have equipment and capabilities to perform sample handling*		

			• *make sure that sites are familiar with sample collection and transfer requirements* • *ensure that labs are aware of which participant samples should be collected and at which time points* • *ensure correct labelling of samples* • *validate/qualify/monitor the labs where the samples are processed and stored* • *check set up und procedures about biobank*		
B6 Trial site(s)					
e.g. • *trial site team not experienced (e.g. first project at trial site)* • *trial site-team not qualified* • *frequent changes in staff* • *insufficient resources and inadequate facilities* • *roles and responsibilities not clearly assigned*	☐ low ☐ high		*e.g.* • *perform adequate staff training and keep delegation logs updated* • *perform protocol/ procedures training at participating sites* • *perform regular team meetings to review procedures* • *periodically update site delegation logs, CVs, and GCP certificates and file in TMF*		

B7 Monitoring **(**See also the **Risk-Based Monitoring Score Calculator** available at scto.ch/monitoring)					
e.g. • *insufficient or no monitoring planned*	☐ low ☐ high		*e.g.* • *generate and implement monitoring plan according to project type and category* • *consider risk-based monitoring* • *establish external and independent monitoring* • *consider risk-based monitoring approach*		
B8 Others					
e.g. • *insufficient funds* • *incompetence of partner institutions* • *influence/ interference of private organisations upon governance* • *data will be shared with several third (international) parties* • *unclear data transfer* • *risk of breach of participant confidentiality*	☐ low ☐ high		*e.g.* • *apply for grants* • *perform feasibility check of potential partners/collaborators* • *train partner institutions* • *define tasks and responsibilities in project agreements and collaboration agreements* • *ask for (legal) support to review contracts with third parties* • *define detailed procedures for data transfer to third countries (SOPs)*		

Completed by	*Full name*
Role	*Role at trial site or within clinical trial*
Date and signature	*dd.mm.yyyy and signature*

Sponsor / Sponsor-Investigator	*Full name*
Date and signature	*dd.mm.yyyy and signature*

Please note: Add signatures of other relevant staff if needed, e.g. Principal Investigator, Head of Site

Acronyms

The following acronyms appear in this document.

CRF	Case Report Form
eCRF	(electronic) Case Report Form
CTU	Clinical Trial Unit
CTC	Clinical Trial Centre
CV	Curriculum Vitae
DSMB	Data Safety Monitoring Board
GCP	Good Clinical Practice
ClinO	ClinO Ordinance on Clinical Trials in Human Research
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (commonly referred to as International Council for Harmonisation)
ISF	Investigator Site File
IMP	Investigational Medicinal Product
QMS	Quality Management System
SAE	serious adverse event
SAP	Statistical Analysis Plan
TMF	Trial Master File
SOP	Standard Operating Procedure
WIs	Working Instructions

The Swiss Clinical Trial Organisation (SCTO), together with partner organisations, hosts thematic platforms to promote excellence in clinical research in Switzerland. **www.scto.ch**

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