**Risk Management Tool for Research Studies - Study Level**

|  |  |  |  |
| --- | --- | --- | --- |
| **Full Study Title:** |  | | |
| **Study Number/Code:** |  | **Phase:** |  |
| **PI Name:** |  | **Investigational Product(s) (list all):** |  |
| **Study Coordinator:** |  | **Form Completed by:** |  |
| **Sites (list all):** |  | **Date Completed:** |  |
| **Sponsor Name:** |  |  |  |

**Purpose**

This tool is intended to be used by the sponsor in order to identify risks at the clinical trial level. This may involve the trial design, data collection, and the informed consent process. The sponsor should evaluate the likelihood of the risk occurring, the extent of which the risk can be detected, and the impact on participant’s safety and study data integrity.

Risk reduction strategies should be incorporated into the protocol design and contracts with parties involved in carrying out responsibilities, such as monitors. The monitoring plan should include strategies to monitor for and identify risk; working congruently with the clinical trial risk assessment tool.

The content of this entire tool is modifiable to meet the organization’s needs.

**Risk Management History**

As per ICH E6 (R2) 5.0.6, the sponsor should periodically review risk control measures to ascertain whether the implemented quality management activities remain effective and relevant, taking into account emerging knowledge and experience.

It is recommended to conduct a risk review annually, or in the event of a major protocol amendment.

| **Date of Risk Assessment** | **Parties Involved** | **Comments** |
| --- | --- | --- |
|  |  |  |
|  |  |  |

| **Date of Risk Management Planning** | **Parties Involved** | **Comments** |
| --- | --- | --- |
|  |  |  |
|  |  |  |

**Critical Processes and Data Identification**

During protocol development, the sponsor should identify those processes and data that are critical to ensure human participant protection and the reliability of trial results.1 This is an important prerequisite for identifying risks and determining risk tolerance.

For each of the critical data and processes listed below, describe in the ‘Rationale’ column how it relates to study endpoints (primary, secondary, exploratory), participant population, nature of the disease, type/complexity of the intervention, etc.

| **List critical data points (high level)** | **Rationale** | **Source of data (If applicable and known)** | **Visible only on site? (if applicable and known)** (Y/N/NA) |
| --- | --- | --- | --- |
|  |  |  |  |
|  |  |  |  |
|  |  |  |  |
|  |  |  |  |

| **List critical processes (high level)** | **Rationale** | **Source of data (If applicable and known)** | **Visible only on site? (if applicable and known)** (Y/N/NA) |
| --- | --- | --- | --- |
|  |  |  |  |
|  |  |  |  |
|  |  |  |  |
|  |  |  |  |

**Risk Scoring**

| **Risk Factors** | **Risk Scores (See Appendix 1)** | | | |
| --- | --- | --- | --- | --- |
| **Impact Score** | **Likelihood Score** | **Detectability Score** | **Total Score** |
| **Risk Category: Data Quality and Management** | | | | |
| Delays in data entry and/or query resolution |  |  |  |  |
| Database not signed off by PI according to contract |  |  |  |  |
| Data monitoring plan not available |  |  |  |  |
| Monitoring plan and timelines not followed |  |  |  |  |
| High volume of discrepancies between data and source |  |  |  |  |
| Critical data points not collected (safety outcomes, PKs, etc.) |  |  |  |  |
|  |  |  |  |  |
| **Risk Category: Delegation and Training** | | | | |
| Individual performed study task without being delegated |  |  |  |  |
| Individual performed study task without being trained |  |  |  |  |
| Major study tasks not specified / delegated |  |  |  |  |
| Initial training not done prior to start of the study |  |  |  |  |
| Amendment training not done prior to implementation |  |  |  |  |
| Inappropriately delegated task(s) (e.g. outside of individual’s qualification or scope of practice) |  |  |  |  |
|  |  |  |  |  |
| **Risk Category: Eligibility** | | | | |
| Participant enrolled without meeting all eligibility criteria |  |  |  |  |
| Eligibility waivers issued when waivers are not permitted by the protocol |  |  |  |  |
| Eligibility waiver not reported to the REB |  |  |  |  |
|  |  |  |  |  |
| **Risk Category: Informed Consent** | | | | |
| Incorrect version of the ICF used |  |  |  |  |
| Errors on the ICF document(s) (e.g. signatures, dates) |  |  |  |  |
| Not obtaining informed consent prior to performing study activities on the participant |  |  |  |  |
| Improperly obtained informed consent (e.g. not using a qualified interpreter or impartial witness, if required) |  |  |  |  |
| Lack of informed consent process documentation (including initial, re-consent, optional consent, consent withdrawal) |  |  |  |  |
| Not obtaining proper re-consent |  |  |  |  |
| Delay in obtaining proper re-consent |  |  |  |  |
|  |  |  |  |  |
| **Risk Category: Privacy** | | | | |
| Release of PHI outside of the institution |  |  |  |  |
| Study database captures participant identifier(s) that has not been approved by the REB/institution |  |  |  |  |
| Participant identifiers found in coded study files (e.g. names on questionnaires, source documents stored with coded information) |  |  |  |  |
|  |  |  |  |  |
| **Risk Category: Regulatory** | | | | |
| Lapse in REB renewal |  |  |  |  |
| REB renewals not by full board, where required |  |  |  |  |
| Delays in regulatory submissions and/or approvals (e.g. CTA-As or CTA-Ns) |  |  |  |  |
| Amendment(s) not submitted to REB |  |  |  |  |
| Amendment(s) implemented prior to REB approval |  |  |  |  |
| Delays in reporting unexpected serious adverse reactions to regulatory authority(ies) |  |  |  |  |
| Significant delays in processing major amendments |  |  |  |  |
| If applicable, biologics: Health Canada lot release fax back form not obtained from HC. |  |  |  |  |
| If applicable, QIU not completed (especially when there is a change of PI) |  |  |  |  |
| Trial not registered on publicly accessible registry (e.g. Clinicaltrials.gov) |  |  |  |  |
| Trial registered on publicly accessible registry (e.g. Clinicaltrials.gov) is not up to date |  |  |  |  |
|  |  |  |  |  |
| **Risk Category: Deviations** | | | | |
| Deviations not reported to the REB as per REB policy |  |  |  |  |
| Deviations not reported to the Sponsor |  |  |  |  |
| Deviations or deviation trends that affect the safety and integrity of the data are not reported or escalated accordingly |  |  |  |  |
| CAPAs for major deviations or deviation trends not in place or are ineffective. |  |  |  |  |
|  |  |  |  |  |
| **Risk Category: Randomization / Registration** | | | | |
| Randomization / registration procedures not followed |  |  |  |  |
| Randomization / registration not documented or insufficiently documented |  |  |  |  |
| Not achieving accrual target |  |  |  |  |
| Exceeding accrual target without REB approval |  |  |  |  |
|  |  |  |  |  |
| **Risk Category: Source Documentation** | | | | |
| Study events cannot be easily reconstructed (i.e. lack of documentation or disorganized documentation) |  |  |  |  |
| ALCOAC principle not followed (e.g. no audit trail) |  |  |  |  |
| Source documentation not signed off by investigators, where applicable |  |  |  |  |
| Delay in source documentation sign off by investigators |  |  |  |  |
| Inconsistent documentation practices |  |  |  |  |
| Double documentation, especially those leading to transcription errors |  |  |  |  |
|  |  |  |  |  |
| **Risk Category: Schedule of Events** | | | | |
| Protocol assessments / procedures done out of window |  |  |  |  |
| Protocol assessments / procedures not done at the right frequency / intervals |  |  |  |  |
| Protocol assessments / procedures not done |  |  |  |  |
| Extra assessments/procedures done (unexplained) |  |  |  |  |
| Critical processes affecting the end points or safety not completed |  |  |  |  |
|  |  |  |  |  |
| **Risk Category: Toxicity / Safety** | | | | |
| Missed communicating safety updates to team |  |  |  |  |
| SAE not reported to sponsor within 24 hours of discovery |  |  |  |  |
| Supporting source for SAE not complete / not obtained |  |  |  |  |
| Lack of investigator assessment of clinical significance for abnormal lab/test results |  |  |  |  |
| Action letter / DIL not reported to REB as per REB policy |  |  |  |  |
| Delay in reporting action letter / DIL to REB |  |  |  |  |
| Delay in implementing required actions indicated in the action letter / DIL (e.g. verbal re-consenting) |  |  |  |  |
| Signs, symptoms, and complaints from elsewhere in the participant’s medical record (e.g. drug administration record, inpatient record, dictation) not recorded on AE Log |  |  |  |  |
| Prohibited medications prescribed / administered to patient |  |  |  |  |
| Delay in reporting SAE to the REB as per REB policy |  |  |  |  |
| Delay in reporting SUADRs to regulatory authority(ies) |  |  |  |  |
| Not reporting SUADRs to regulatory authority(ies) |  |  |  |  |
|  |  |  |  |  |
| **Risk Category: Study Treatment / Intervention** | | | | |
| IP dose not modified according to protocol |  |  |  |  |
| Incorrect dose administered |  |  |  |  |
| IP order not signed off by an investigator prior to IP dispensation / administration |  |  |  |  |
| Protocol assessment(s) required for safety monitoring prior to IP administration not reviewed (and signed off) by investigator prior to IP administration |  |  |  |  |
| IP not administered as per protocol schedule |  |  |  |  |
| IP dosing time not documented |  |  |  |  |
| IP dosing time out of window |  |  |  |  |
| Pharmacy dispensing errors |  |  |  |  |
| Oral IP: discrepancy between participant pill diary and IP accountability records |  |  |  |  |
| IP compliance checks not performed |  |  |  |  |
| Blinded studies: unblinding / blinding procedures not followed |  |  |  |  |
| Improper storage of IP (e.g. not separate, not secure, not within temperature range) |  |  |  |  |
|  |  |  |  |  |
| **Risk Category: Correlatives / Sample Management** | | | | |
| Sample not collected at protocol required time points |  |  |  |  |
| Extra samples collected |  |  |  |  |
| Sample not stored as per protocol / lab manual |  |  |  |  |
| Improper documentation for sample collection |  |  |  |  |
| Laboratory specimen tracking form not completed (no control over sample storage and location or shipping, if applicable) |  |  |  |  |
| Improper processing of sample(s) |  |  |  |  |
|  |  |  |  |  |
| **Risk Category: General / Administrative** | | | | |
| Incorrect document (version) used |  |  |  |  |
| Electronic system downtime / errors / glitches |  |  |  |  |
|  |  |  |  |  |
| **Risk Category: Other Protocol Specific Risk Factors** | | | | |
|  |  |  |  |  |
|  |  |  |  |  |
|  |  |  |  |  |
|  |  |  |  |  |
|  |  |  |  |  |

**Risk Management**

The sponsor should decide which risks to reduce and/or which risks to accept.1 Using the table below, define risk tolerance limits and establish risk control priorities.

|  |  |
| --- | --- |
| **Risk Tolerance (3 point scale)** | |
| **Total Risk Score** | **Priority for Risk Controls** |
| 19-27 | High (risk controls required) |
| 10-18 | Medium (risk controls recommended) |
| 1-9 | Low (acceptable risk) |

Select those risk factors (from the Risk Scoring table) with a total risk score that is considered high (based on the risk tolerance limits), and list them in the Risk Control table below. Outline proposed risk controls, and any procedures / action items.

| **Risk Category** | **Risk Factor** | **Proposed Risk Control(s)** | **Risk Control Action Items** |
| --- | --- | --- | --- |
|  |  | *Risk control suggestions to consider:*   * *Create / revise monitoring plan* * *Modify database; build automatic queries* * *Training / retraining (list specific training sessions, tentative dates, and who should attend)* * *Create / revise written procedures or work instructions* * *Request internal audit / quality review* * *Create / modify communication plans; escalation procedures* * *Create / modify a study tool* |  |
|  |  |  |  |
|  |  |  |  |
|  |  |  |  |
|  |  |  |  |

Appendix 1. Risk Score Definitions

Total Score = Impact Score x Likelihood Score x Detectability Score

|  |  |  |  |
| --- | --- | --- | --- |
| **Score Definitions (3 point scale)** | | | |
|  | **1** | **2** | **3** |
| **Impact Score** | Low Impact | Medium Impact | High Impact |
| **Likelihood Score** | Unlikely | Possibly | Probably |
| **Detectability Score** | Difficult to Detect | Possible to Detect | Easy to Detect |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Score Definitions (Example of a 5 point scale)4** | | | | | |
|  | **1** | **2** | **3** | **4** | **5** |
| **Impact Score** | Negligible | Marginal | Moderate | Critical | Catastrophic |
| **Likelihood Score** | Rare | Unlikely | Possible | Likely | Almost certain |
| **Detectability Score** | Almost certain | Likely | Possible | Unlikely | Impossible |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Score Definitions (Example of a 10 point scale)2** | | | | | |
|  | **1** | **2** | **3** | **4** | **5** |
| **Impact Score** | Inconsequential | Barely perceptible | Very limited | Limited | Sensitive |
| **Likelihood Score** | Impossible | Extremely improbable | Very improbable | Improbable | Unlikely |
| **Detectability Score** | Certain | Extremely probable | Very probable | Probable | Possible |
|  | **6** | **7** | **8** | **9** | **10** |
| **Impact Score** | Significant | Very significant | Important | Very important | Disastrous |
| **Likelihood Score** | Possible | Probable | Very probable | Extremely probable | Certain |
| **Detectability Score** | Unlikely | Improbable | Very improbable | Extremely improbable | Impossible |

Factors to consider when assigning Impact Score:

* Impact on participant’s rights, safety, and well-being
* Impact on study data integrity

Factors to consider when assigning Likelihood Score:

* Experience of staff and PI
* Amount of trial transfers / staff turnover
* Automated procedures set in place to prevent error (e.g. auto queries in EDC)
* Rate and/or volume of accrual
* Audit/inspection history

Factors to consider when assigning Detectability Score:

* Experience of staff and PI
* Amount of trial transfers / staff turnover
* Automated procedures set in place to prevent error (e.g. auto queries in EDC)
* Rate and/or volume of accrual
* Audit/inspection history

Appendix 2. Definitions

|  |  |  |
| --- | --- | --- |
| **Terminology** | | |
| **Detectability** | The ability to discover or determine the existence, presence, or fact of a hazard | |
| **Impact** | A measure of the possible consequences of a non-compliance, with consideration of participant safety/rights and data integrity | |
| **Likelihood** | Chance of something occurring | |
| **Risk** | The combination of the probability of occurrence of harm and severity of that harm; the effect of uncertainty on objectives | |
| **Sponsor** | For the purpose of this tool, the term 'Sponsor' includes Sponsor-Investigators | |
| **Study** | For the purpose of this tool, the term 'Study' includes research studies, clinical studies, and clinical trials | |
|  |  |  |
| **Abbreviations / Acronyms** | | |
| **ALCOAC** | Attributable, Legible, Contemporaneous, Original, Accurate, Complete | |
| **CAPA** | Corrective Action and Preventive Action | |
| **CTA-A** | (Health Canada) Clinical Trial Application - Amendment | |
| **CTA-N** | (Health Canada) Clinical Trial Application - Notification | |
| **DIL** | Dear Investigator Letter | |
| **HC** | Health Canada | |
| **ICF** | Informed Consent Form | |
| **IP** | Investigational Product | |
| **PHI** | Personal Health Information | |
| **PI** | Principal Investigator | |
| **QI** | Qualified Investigator | |
| **QIU** | (Health Canada) Qualified Investigator Undertaking | |
| **REB** | Research Ethics Board | |
| **SAE** | Serious Adverse Event | |
| **SUADR** | Serious Unexpected Adverse Drug Reaction | |

Appendix 3. References

1. ICH E6(R2) Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice, <https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2__Step_4_2016_1109.pdf>
2. ECRIN-IA Guideline on Risk Management for Clinical Research, <https://ssl2.isped.u-bordeaux2.fr/OPTIMON/docs/citations/2015-02-16-Guideline%20on%20risk%20management%20for%20clinical%20research_1.0x.pdf>
3. ECRIN Risk-Based Monitoring Toolbox, <http://www.ecrin.org/tools/risk-based-monitoring-toolbox>
4. WHO Guidelines on Quality Risk Management, <http://www.who.int/medicines/areas/quality_safety/quality_assurance/Annex2TRS-981.pdf>
5. FDA Guidance for Industry - Q9 Quality Risk Management, <https://www.fda.gov/downloads/Drugs/Guidances/ucm073511.pdf>