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| **TGHN-256x151px**  **Standard Operating Procedure** | | | **SOP No:**  **Version: 1**  **Effective Date:** | |
| **Title: Risk Assessment** | | | | |
|  | NAME | **SIGNATURE** | | **DATE** |
| **PREPARED BY** |  |  | |  |
| **REVIEWED BY** |  |  | |  |
| **QA UNIT**  **AUTHORITY** |  |  | |  |
| **APPROVAL**  **AUTHORITY** |  |  | |  |

1. **Purpose/scope**

To describe the procedure for assessing the risk of the [institution/group] conducting a trial. The procedure is as per the MRC/DH/MHRA Joint Project: Risk-adapted approaches to the management of clinical trials of investigational medicinal products (10th October 2011), subsequently adapted by T Symons Associates Pty Ltd (with kind permission).

1. **Templates/forms**

QA04.1 Risk assessment form

1. **Glossary/definitions**

**Trial risk assessment**

A process of identifying the potential hazards associated with a trial, and assessing the likelihood of those hazards occurring and resulting in harm. This risk assessment will include: the risks to participant safety in relation to the investigational medicinal product (IMP); all other risks related to the design and methods of the trial (including risks to participant safety and rights, as well as reliability of results.

**Investigational medicinal product**

A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorisation when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.

1. **Responsibilities and procedure**
   1. This risk assessment should be conducted as early as possible, before a trial is submitted to an ethics committee/Medicines Control Council for review and/or before a trial agreement is finalised with the sponsor.

**Defining the risk category**

* 1. The risks to participants associated with the drug(s)/device(s) under investigation are assessed in relation to standard care.

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| **Type of clinical trial** | **Risk category** |
| Trials involving medicinal products licensed by the South African Medicines Control Council if:   * They relate to the licensed range of indications, dosages and forms, or * Involve off-label use, if this off-label use is established practice and supported by sufficient published evidence and/or guidelines (for example in paediatrics or oncology) | **Type A**  Risk comparable to standard medical care |
| Trials involving medicinal products licensed by the South African Medicines Control Council if:   * Such products are used for a new indication (different patient population/disease group) or * Substantial dosage modifications are made or * They are used in combinations for which interactions are suspected   Trials involving medicinal products not licensed by the South African Medicines Control Council if the active substance is part of a medicinal product licensed by the South African Medicines Control Council.  NB A ‘Type A’ grading may be justified if there is extensive clinical experience with the product and no reason to suspect a different safety profile in the trial population. | **Type B**  Risk somewhat higher than standard medical care |
| Trials involving a medicinal product not licensed by the South African Medicines Control Council.  N.B. A grading other than ‘Type C’ may be justified if there is extensive class data or pre-clinical and clinical evidence. | **Type C**  Risk markedly higher than standard medical care |

**Defining additional risks when comparing with standard of care**

* 1. The risk category assigned will guide the nature and extent of patient safety monitoring that will be required. In general, a Type A trial will involve a low intensity of safety monitoring, Type B, a moderate intensity and Type C, a high intensity.
  2. The points to consider when developing a safety monitoring plan include:
* The nature of the medicinal product(s)/device(s)
* The potential for known or anticipated toxicities/adverse consequences
* Which body systems may be affected
  1. Some other issues to consider:
* Phase of development
* Study population: healthy volunteers or patients?
* What are the known/anticipated safety issues and are they all addressed within the normal clinical practice?
* If unknown, what are the anticipated risks/other effects based on preclinical data or knowledge of class of drugs?
* Is the duration of use compatible with previous experience?
* Is there a potential risk of dosing errors?
* Might concomitant medications increase the risk (i.e. drug interactions)?

Example Form

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| **PART 2: DEFINE THE ADDITIONAL RISKS ASSOCIATED WITH THE TRIAL MEDICINAL PRODUCT(S) WHEN COMPARED TO STANDARD CARE** | | | | | |
| IMP | Body system | Hazard | Likelihood  (L [low], M[medium], H[high]) | Mitigation | Comments |
| ABC 123 | Metabolic | Hyperglycaemia | L | Additional blood glucose monitoring | X hourly |
| GIT | Raised transaminases | H | LFTs | weekly |
| CVS | Prolonged QT interval | M | Digital ECG, holter monitoring | X hourly |

* 1. Is a Data Monitoring Committee (DMC)/Data & Safety Monitoring Board (DMSB) required? A fundamental reason to establish a DMC is to enhance the safety of trial participants in situations in which safety concerns may be unusually high, in order that regular interim analyses of the accumulating data are performed. Trials should consider using a DMC when:
* The study endpoint is such that a highly favourable or unfavourable result, or even a finding of futility, at an interim analysis might ethically require termination of the study before its planned completion;
* There are *a priori* reasons for a particular safety concern, as, for example, if the procedure for administering the treatment is particularly invasive;
* There is prior information suggesting the possibility of serious toxicity with the study treatment;
* The study is being performed in a potentially fragile population such as children, pregnant women or the very elderly, or other vulnerable populations, such as those who are terminally ill or of diminished mental capacity;
* The study is being performed in a population at elevated risk of death or other serious outcomes, even when the study objective addresses a lesser endpoint;
* The study is large, of long duration, and multi-centre.

In studies with one or more of these characteristics, the additional oversight provided by a DMC can further protect study participants. In other studies, such as short-term studies for relief of symptoms as noted above, such committees are generally not warranted[[1]](#endnote-1).

Other trial oversight measures that may be appropriate: a specifically convened Study Safety Group and/or the appointment of a Medical Monitor to look at single cases and aggregate safety data for identification and verification of safety signals, stopping rules and rules for modifying study treatment: E.g. Local clinical review and decision making with a pre-specified decision making algorithm. In order to perform this role effectively, the reviewing body would require access to the complete safety dataset for the trial. Review procedures should be defined in the protocol or other documentation.

**Defining additional risks associated with the design and methods of the trial**

* 1. Areas where additional risks may be identified:
     1. *Risks to participant safety from clinical procedures specified by the protocol.* Just as for the risks associated with the trial medicinal product(s), these should be assessed relative to standard investigations and procedures for the clinical condition of the participants in the trial. For example, if an invasive procedure (such as a biopsy) is normal practice for good quality care, then its inclusion in the study protocol would not be an additional risk to participants. Some issues to be considered in the assessment (this list is not comprehensive):
* Does the protocol require additional procedures over and above those which would be expected from standard care for the participant’s clinical condition – e.g. blood tests, biopsies, x-rays, lumbar puncture, contrast media scans?If so, what is the likelihood and severity of the harm that might be caused to the participant?
* What measures might reduce either the likelihood or severity of harm to the study participants? For example: qualifications, experience and training of clinical staff at site; special facilities or equipment; additional training.
  + 1. *Risks to participant rights from failure to obtain appropriate consent.* The ability of trial participants to give fully informed consent depends on: (i) the vulnerability and mental capacity of the study population, and (ii) the consent process. For example, participants may lack the capacity to give fully informed consent or the trial intervention may need to be administered in the emergency setting. In such cases there should be careful consideration to ensure that the optimal consent process is identified (e.g. numbers of stages or timing). The risks should be judged relative to the ability of a fully competent adult with a chronic, non-life-threatening condition to give consent. Some issues to be considered in the assessment (this list is not comprehensive):
    - Does the study population include particularly vulnerable groups (e.g. children, elderly, and patients with mental health problems)?
    - Are the participants likely to lack capacity to give fully informed consent (e.g. severe pain, cognitive impairment, language difficulties)?
    - Who will decide whether or not a participant is capable of giving consent?
    - Does the consent process allow sufficient time for the participants to consider their decision and discuss it with a third party (e.g. non-emergency treatment)?
    - What measures might reduce the likelihood that participants might be included in the study without the appropriate level of consent? For example: **e**xperience and training of clinical staff at site; assent guidance; additional training.
    1. *Risks to participant rights from failure to protect their personal data.*It is essential that personal data collected in the course of any clinical study, even if collected with the consent of the individual, are held securely and are only accessed by authorised staff. Some issues to be considered in the assessment (this list is not comprehensive):
    - Are particularly sensitive data being collected?
    - Are personal identifiers associated with the data?
    - Are data being transferred between organisations?
    - Will consent to access and use the data been obtained?
    - Are data to be sent outside the South Africa? Are data protection laws equivalent?
    - Has consent been given to share the data with third parties (if relevant)?
    - Are the data security measures appropriate?
    1. *Risks to the reliability of results.* Features of a robust design include:
* Simple, relevant eligibility criteria,
* Outcome measures which are objective and simple to assess accurately
* If objective outcome measures cannot be used, then effective masking of the intervention when assessing the outcome.
* A properly generated randomization schedule and a randomization method that prevents the prediction of treatment allocation when entering patients into the trial.
* A simple intervention that is difficult to apply incorrectly.
* Sufficient power to detect realistic effects of the intervention.

Example Form

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| **Risks to participant safety from clinical procedures specified by the protocol (e.g. additional tests, invasive procedures, increased radiological exposure compared with standard care)** | | | | | |
| Risk | | Specify concerns | | Can the risk be minimised?  Specify | Could monitoring methods help to address concerns? |
| Right heart catheterisation | | Risk of complication:  Excessive e.g. bleeding, pneumothorax | | Trial sites experienced with the procedure  Contact details of a clinical advisor in protocol | Data Safety Monitoring Committee convened  On-site adverse event monitoring checks |
| **Risks to participant rights from failure to obtain appropriate consent** | | | | | |
| Risk | | Specify concerns | | Can the risk be minimised? | Could monitoring methods help to address concerns? |
| Consent Procedure:  Vulnerable population | | Children between 4 and 10 years)  Failure to obtain fully informed parental consent | | Study team with paediatric expertise  Specific training on the consent/assent process  Age appropriate information leaflets reviewed by a patient group for levels of clarity and understanding | Central monitoring of consent forms by trial centre (with statement in the information leaflet to ensure explicit consent for this activity) |
| **Risks to participant rights from failure to protect their personal data** | | | | | |
| Risk | Specify concerns | | Can the risk be minimised? | | Could monitoring methods help to address concerns? |
| Breach of confidentiality | Identifiable data transferred out of South Africa | | Confidentiality agreement in place between the hospital and the institution undertaking the analysis  Computer security systems assessed | | Patient consent sought - An explicit statement that data processing will take place is added in the Patient Information Leaflet |
| **Risk to the reliability of results** | | | | | |
| Risk | Specify concerns | | Can the risk be minimised? | | Could monitoring methods help to address concerns? |
| Strict eligibility criteria and complex study requirements | Increased risk of ineligible patients being entered/ protocol violations | | Central review of eligibility prior to randomisation by  faxed form  with key de-identified data  Protocol-specific training delivered at start-up meeting | | Annual monitoring visit to include checks of clinical records of eligibility/endpoint data  Annual investigator meeting with issue resolution session and top-up training |

1. **Document history:**

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| **Version No.** | **Date** | **Reviewer** | **Details of changes** |
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1. <http://www.fda.gov/RegulatoryInformation/Guidances/ucm127069.htm> [↑](#endnote-ref-1)