Clinical Risk Assessment and Management Plan

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| **Study Acronym / Short Title** | Click or tap here to enter text. | **R&D Number** | Click or tap here to enter text. |
| **Protocol Version** | Click or tap here to enter text. | **Date** | Click or tap to enter a date. |
| **IB / SPC Version & Date** | Click or tap here to enter text. | **CRAMP version number** | Click or tap here to enter text. |
| **Phase:**  ***If phase 1, page 5-9 must be completed*** | Choose an item.  First in human? Choose an item.  Dose Escalation? Choose an item. | **Is this study blinded?** | Choose an item. |
| **Is this a GMO study, or study with a CBC risk assessment?** | Choose an item. |

* Do not delete any rows - mark as “not applicable” if there are genuinely no risks / actions identifiable in that area.
* For GMO studies also complete a GM Risk Assessment for activities Involving Gene Therapy and Genetically Modified Micro-organisms.

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| **(1) IMP, Device, Schedule:** *This section to be completed in all cases.*  *Be brief: Provide only enough background to set the risks and mitigations in context.* ***Do not exceed one page for this section or CRAMP will be returned******for shortening*** | |
| (a) Summarise the investigational medicinal product / intervention  *e.g. small molecule, antibody, biologic, vaccine, cytotoxic etc* | Click or tap here to enter text. |
| (b) For Dose escalation studies, describe dose intervals between participants and any particular considerations | Click or tap here to enter text. |
| (c) Highlight special issues regarding IMP administration (e.g. PPE needs, cytotoxicity, route or rate etc). | Click or tap here to enter text. |

*There is no limit on text length for the following sections*

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| **(2) Pharmacovigilance** | | | | | | | | |
| (a) Describe SAE reporting system | | Choose an item. | Provide details if other: Click or tap here to enter text. | | | | | |
| **(3) Medication** | | | | | | | | |
| (a) Specify who will be preparing IMP | | Choose an item. | | | | If other, specify: Click or tap here to enter text. | | |
| (b) Where will IMP be prepared? | | Choose an item. | | | | If other, specify: Click or tap here to enter text. | | |
| (c) Describe IMP storage requirements | | Choose an item. | | | | Comments: Click or tap here to enter text. | | |
| (d) Describe Prescribing procedure | | Choose an item. | | Details: Click or tap here to enter text. | | | | |
| (e) Is there a need for pre-medication? | | Choose an item. | | | | | | |
| (f) Summarise the unblinding process, or state N/A | | Click or tap here to enter text. | | | | | | |
| **(4) Staff** | | | | | | | | |
| (a) Is there any specific qualification / certificate or training required, beyond normal study specific training? If so, describe: | | Choose an item.  Click or tap here to enter text. | | | | | | |
| (b) **Study team and ICRF staffing required for IMP administration or other interventions**  \* *Describe staff requirements, specifying if staff are supplied by ICRF or study team.* | | **Dosing preparation**\*  Enter details of staff required: Click or tap here to enter text.  **During dosing**\*  Enter name and contact details of medical cover: Click or tap here to enter text.  Where will medical cover be located? Choose an item. Click or tap here to enter text.  What level of life support training is required for medical cover? Choose an item.  **Post dose observation**\*:  Enter name and contact details of medical staff and for how long the post-dose monitoring is in place: Click or tap here to enter text.  Where will staff be located? Choose an item. Click or tap here to enter text.  For how long after dosing will ICRF staff monitor patient? Click or tap here to enter text.  Is a medical review required before patient discharge? Choose an item. If yes, who will do this? Choose an item.  **Non-dosing visits\***:  Enter name and contact details of staff: Click or tap here to enter text.  Where will staff be located? Choose an item. Click or tap here to enter text.  **Note that medical cover is the responsibility of the PI. ICRF staff may provide pre-agreed support with emergency medical cover during normal working hours (Monday-Friday, 9-5pm).** | | | | | | |
| **(5) ICRF Facilities** | | | | | | | | |
| ICRF Facilities: specify rooms and/or other requirements | | Choose an item.  *(If more than one required, select other and describe in comments)* | | | Comments: Click or tap here to enter text. | | | |
| **(6) Characteristics Of Study Participants** | | | | | | | | |
| List any particular risks to / from participants, infection control, special requirements, GP medical history, TOPS etc. | | Click or tap here to enter text. | | | | | | |
| **(7) Emergency admission / unfit for discharge pathway, on call speciality contacts** | | | | | | | | |
| *The ICRF closes at 8 PM Mon-Thu, 6PM Friday. Pre -arranged overnight stays are staffed according to the agreed CRAMP risk assessment, and any deterioration from this will be managed according to our Emergency Procedures SOP. The default is for ICRF staff to arrange immediate transfer by emergency ambulance to the ED. Please describe anyagreed pathway to admit patients to another serviceas required.* | | | | | | | | |
| Click or tap here to enter text. | | | | | | | | |
| **(8) Potential study specific Adverse Reactions (IMPs, NIMPs, controls) Adverse Complications (procedures / devices)**  *List most serious / frequent ARs individually, and group infrequent / low risk ARs together. Give a Consequence, Likelihood and multiplication Risk score for each row.* ***See Risk matrix overleaf for Scoring.*** *Examples given below – delete these rows when completing the form. Estimate the risk AFTER all the mitigations you will put in place. Mitigation may reduce the consequence (by monitoring & intervention) or likelihood (by reducing chance of it happening).* ***Add extra rows if needed*** | | | | | | | | |
| AR Name / description | Describe risk mitigation / prevention strategy, monitoring, etc. | | | | | | Risk Scores After Mitigation | |
| *e.g. anaphylaxis* | *This has a risk of < 1:million and is idiosyncratic. Staff are trained in anaphylaxis management; resuscitation equipment is at hand. Onset is most likely within 60 minutes when subjects are resident in ICRF, and reversible.* | | | | | | *Consequence: 3 Likelihood: 1* ***Risk score: 3 x 1 = 3*** | |
| 1. Click or tap here to enter text. | Click or tap here to enter text. | | | | | | Consequence: n. Likelihood: n. **Risk score:** n. | |
| 2. Click or tap here to enter text. | Click or tap here to enter text. | | | | | | Consequence: n. Likelihood: n. **Risk score:** n. | |
| 3. Click or tap here to enter text. | Click or tap here to enter text. | | | | | | Consequence: n. Likelihood: n. **Risk score:** n. | |
| 4. Click or tap here to enter text. | Click or tap here to enter text. | | | | | | Consequence: n. Likelihood: n. **Risk score:** n. | |
| 5. Click or tap here to enter text. | Click or tap here to enter text. | | | | | | Consequence: n. Likelihood: n. **Risk score:** n. | |
| **(9) Other study specific Clinical Risks That Are Not Adverse Reactions** (e.g. chemical risks, carcinogens, devices, etc.)*List most serious / frequent events individually, and group infrequent / low risk events together. Give a multiplication score for each row.* ***Add extra rows if needed*** | | | | | | | | |
| *e.g. Transmission of herpes virus gene therapy vector via sharps or mucosal splash* | *May cause a viral lesion of no consequence to immune competent persons. GM Risk Assessment / COSSH assessments describe PPE and procedures to limit risk and occupational health follow-up. Immunodeficient staff should not undertake risk-prone procedures on this trial.* | | | | | | *Consequence: 2 Likelihood: 1* ***Risk score: 2 x 1 = 2*** | |
| 1. Click or tap here to enter text. | Click or tap here to enter text. | | | | | | Consequence: n. Likelihood: n. **Risk score:** n. | |
| 2. Click or tap here to enter text. | Click or tap here to enter text. | | | | | | Consequence: n. Likelihood: n. **Risk score:** n. | |
| 3. Click or tap here to enter text. | Click or tap here to enter text. | | | | | | Consequence: n. Likelihood: n. **Risk score:** n. | |
| 4. Click or tap here to enter text. | Click or tap here to enter text. | | | | | | Consequence: n. Likelihood: n. **Risk score:** n. | |
| **(10) Highest Mitigated Risk Score Calculated Pick the highest Mitigated Risk Score from rows above (do not add-up the scores)** | | | | | | | | n. |

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| **(11) ITU notification** | |
| Describe the process if notification has to be given to ITU in advance of patient dosing/treatment. | Click or tap here to enter text. |

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|  | **Completed by** | **Principal Investigator** | **ICRF sign off** |
| **Name (in capitals)** | Click or tap here to enter text. | Click or tap here to enter text. | Click or tap here to enter text. |
| **Date** | Click or tap to enter a date. | Click or tap to enter a date. | Click or tap to enter a date. |
| **Signature** |  |  |  |

**Please ensure all parties are happy with the content before signing.**

## Risk Matrix

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| 1. Insignificant – expect no obvious harm 2. Minor - expect non-permanent harm 3. Moderate – expect semi-permanent harm 4. Major – expect major permanent harm or death 5. Extreme – expect multiple deaths / population | 1. Rare- Not expected to occur for years 2. Unlikely- Expected to occur approx. annually 3. Possible- Expected to occur approx. monthly 4. Likely- Expected to occur approx. weekly 5. Almost certain- Expected to occur approx. daily | **Risk score**  Consequence Score x Likelihood score  e.g.  MINOR consequence that is LIKELY = 2 x 4 = 8 RISK SCORE  EXTREME consequence that is RARE = 5 x 1 = 5 RISK SCORE |

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| **Likelihood** | **Consequence** | | | | |
| 1 Insignificant | 2 Minor | 3 Moderate | 4 Major | 5 Extreme |
| 5 (Almost Certain) | **5 (M)** | **10 (H)** | **15 (E)** | **20 (E)** | **25 (E)** |
| 4 (Likely) | **4 (M)** | **8 (H)** | **12 (H)** | **16 (E)** | **20 (E)** |
| 3 (Possible) | **3 (L)** | **6 (M)** | **9 (H)** | **12 (H)** | **15 (E)** |
| 2 (Unlikely) | **2 (L)** | **4 (M)** | **6 (M)** | **8 (H)** | **10 (H)** |
| 1 (Rare) | **1 (L)** | **2 (L)** | **3 (L)** | **4 (M)** | **5 (M)** |

Overall RISK SCORE: LOW (L score 1-3), MODERATE (M score 4-6), HIGH (H score 8-12) and EXTREME (E score 15-25)

This score is based on “NPSA A risk matrix for risk managers Jan 2008”.

**Phase 1 Studies ONLY: Risk Stratification Matrix and Contingency Plans**

The Risk Matrix has been developed as a tool to risk assess a Phase I classified study and allow pragmatic and risk-adapted approach to manage hazards associated with the trial. The risk outcome is a combination of the score from the status of the intervention and the trial design, and additional factors (i.e. study team experience) including the score from the risk assessment above.

It is the responsibility of the PI to make these assessment, and where necessary, peer reviewed to ensure the outcome is a reflection of the study conducted at their site.

For studies with a Low or Medium risk outcome, the corresponding pre-set contingency plan will be used. For studies with a high risk, addition risk assessment will be required to identify the risk and the mitigation plan. The patient risks should be balanced against the level of risk that a trial subject would be exposed to outside the trial as follows:

* Type A = no higher than the risk of standard medical care
* Type B = somewhat higher than the risk of standard medical care
* Type C = markedly higher than the risk of standard medical care

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| **Intervention Status** | | | | | | | | | | | | |
| **Study Design** | | | Used as per licence / off-label use is established practice and supported by published evidence and/or guideline | Licensed and used in new formulation/ new delivery | | Licensed, but used in new age group/ disease | Unlicensed, used in healthy volunteers but first in patient group | | | | Unlicensed and never been used in humans (Healthy Volunteers or Patient group) | |
| Dose escalation - multiple/ complex cohorts, SAD/MAD, dose leaders, to establish recommended dose Double-blinded Randomised | | | Moderate | Moderate | | High | High | | | | High | |
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| Dose escalation - single dose Single-blinded | | | Moderate | Moderate | | Moderate | High | | | | High | |
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| Dose expansion / dose escalation with known/ tested doses Open-label | | | Low | Moderate | | Moderate | Moderate | | | | Moderate | |
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| Dosage used as per authorisation | | | Low | Low | | Moderate | Not applicable | | | | Not applicable | |
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| **Additional Risk** | | |  |  |  |  | |  | |  | |  | |
| Study team experience | | | **Research experienced** |  | |  | | | No/lack of experience | | | |
| Experience with type of intervention | | | **Experienced** |  | |  | | | Unfamiliar/not used before | | | |
| Number of intervention | | | **Single intervention** |  | |  | | | Multiple interventions | | | |

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| **Phase 1 Studies: The following plan must be followed to mitigate the identified risk of the study** | | |
| **Item** | **Required?** | **Responsibility / comments** |
| **Staffing and training** | | |
| Emergency scenario training required for ICRF staff | Choose an item. | Click or tap here to enter text. |
| Medic cover per dosing visit | Choose an item. | Click or tap here to enter text. |
| Minimum nursing staff level requested per subject per dosing visit | 2 nurses | Click or tap here to enter text. |
| Level of Resuscitation training for medic required | Choose an item. | Click or tap here to enter text. |
| Level of Resuscitation training for nurses required | ILS | Click or tap here to enter text. |
| **Facility and Equipment** | | |
| Proposed room allocation or specific requirements for participant observation for the duration of the CRF visit. | Choose an item. | Click or tap here to enter text. |
| Specialist equipment required for dosing visit. | Choose an item. | Click or tap here to enter text. |
| **Subject Identification and medical history** | | |
| Photographic identification of subjects utilised for this study? | Choose an item. | Click or tap here to enter text. |
| **Healthy Volunteers only**: The Over Volunteering Prevention System (TOPS) registration required? | Choose an item. | Click or tap here to enter text. |
| Verification of subject’s medical history required? (e.g. GP contact or Summary Care Record) | Choose an item. | Click or tap here to enter text. |
| **Dosing** | | |
| PRB review following first dose? | Choose an item. | Click or tap here to enter text. |
| Dose Setting Committee / Safety Review Committee / DSMC etc. minutes to be provided to PRB? | Choose an item. | Click or tap here to enter text. |
| Data and safety submitted for PRB review prior to subsequent subject recruitment? | Choose an item. | Click or tap here to enter text. |
| Maximum number of subjects on any given day (after review of initial dosing studies)? | Click or tap here to enter text. | Click or tap here to enter text. |
| **AE management** | | |
| 24/7 Emergency contact test | Choose an item. | Click or tap here to enter text. |
| Un-blinding system review | Choose an item. | Click or tap here to enter text. |
| ICU Notification required | Choose an item. | Click or tap here to enter text. |
| Specific antidote / supportive medication required | Choose an item. | Click or tap here to enter text. |
| Specialist required to be available to support emergencies and adverse event management? | Choose an item. | Click or tap here to enter text. |

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| **Additional Comments / Special Considerations** |
| Click or tap here to enter text. |

**Guidance Notes for CRAMP**

When completing the form please avoid copy and pasting from the protocol.

These notes are to act as a guide to help improve completion and consistency.

It is impossible to identify every possible risk, the aim of the CRAMP is to identify the most likely to occur and highest risks applicable to the particular research project. Below are some areas to consider. This is not intended to be definitive.

* IMP Details: Pre clinical toxicology data – did it identify any particular concerns? Any downstream cascade affects from the molecule? Is this a novel compound or has this been used and developed before in previous trials?
* IMP Dosing: Is there a clear process and reason for dose selection based on pre-clinical or subject safety data? IDMC and/or steering group over seeing dose escalation decisions. Is the drug administered IV or aerosol? Will there be a staged dosing to allow for identification of any untoward reaction? The number & skill of staff required should there be a reaction.
* Pharmacy: Temperature storage monitoring? Reconstitution process is this simple? Aseptic preparation required? Dose the dose need to be calculated before admin or simple dosing instructions?
* Safety General: Any specific safety reporting processes – is there a medical monitor? If blinded – who, where and how accessible are the un-blinding codes? Are un-blinding procedures tested?
* Study Team: Any experience working in early phase? Experience of being a Principal Investigator? Number of studies conducted. Have received training on the protocol? Have received training on ICRF SOP’s or study specific procedures?
* CRF Facilities: Is there a need for a specific room/nurse etc which could prevent bookings if not available? Any equipment that if broken could delay procedure?
* Participants: How will past medical history be confirmed – from GP? Could participants have been part or are part of another clinical trial? Is this a particular high risk group with respect to mobility, capacity, vulnerability, cross infection?
* Adverse Reactions/ Invasive Procedures: Anaphylaxis will be the most common and obvious, but are there any specific areas of caution from previous safety data or pre-clinical data such as liver, kidney or cardiac reactions? Venepuncture, cannulation are the most common – are there any study specific procedures like central line insertion?

**Risk Mitigation**: Risks will vary across each project and it is impossible to remove risk entirely. Mitigations can take the form of adhering to SOPs for procedures, to detailing specific staffing requirements or training that will be undertaken before carrying out particular study procedure. The score quoted shoud assume the mitigations have been implemented and so will probably be lower than worst case scenario.