Clinical Risk Assessment and Management Plan

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| **Study Acronym / Short Title** |  | **R&D Number** |  |
| **Protocol Version** |  | **Date** |  |
| **IB / SPC Version & Date** |  | **CRAMP version number** |  |

* 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) Briefly describe pre-clinical, clinical data, class/type-related risks, novelty, etc. |  |
| (b) Justify starting dose / treatment selection |  |
| (c) Describe drug /device administration: route and rate, any special issues, etc. |  |
| (d) Describe & justify intervals between subjects / cohorts / repeat doses |  |

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

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| **(2) Pharmacovigilance** | | | | | | | | |
| (a) Describe AE/SAE reporting system | |  | | | | | | |
| (b) Describe dose / treatment escalation plan | |  | | | | | | |
| (c) Describe DSMB / IDMC arrangements | |  | | | | | | |
| **(3) Pharmacy** | | | | | | | | |
| (a) Specify who will be preparing IMP | | Choose an item. | | If other, specify: | | | | |
| (b) Where will IMP be prepared? | | Choose an item. | | If other, specify: | | | | |
| (c) Describe IMP storage requirements | | Choose an item. | | Comments: | | | | |
| (d) Describe Pharmacy handling / dispensing | |  | | | | | | |
| (e) Describe Prescribing procedure | |  | | | | | | |
| (f) Describe Unblinding procedures | |  | | | | | | |
| **(4) Staff** | | | | | | | | |
| (a) Describe experience of **PI** and **Study Team** | |  | | | | | | |
| (b) Describe training/supervision of **Study Team** | |  | | | | | | |
| (c) Describe **ICRF Staff required**: grade, training/supervision and experienced required.  Describe each staff group’s role in project.  *ICRF staff cover many trials and availability on any specific day cannot be guaranteed, especially medical staff. Medical staff are generally non-specialist ST2s, and all specialist duties (e.g. checking bloods) are ultimately the responsibility of the Study Team.* | |  | | | | | | |
| (d) **Study team and ICRF staffing required for specific dosing / treatments**: *During/after dosing / treatment & other visits. Requirement for 1st and subsequent doses / treatments. Describe the staff necessary (e.g. name, bleep number – vague description not enough).* ***Describe how long named staff should be (i) in CRF (ii) contactable in HH (iii) contactable elsewhere****. Describe level and number of ALS / ILS / BLS staff required for each event. Specify if a doctor is required.* | |  | | | | | | |
| (e) **Doctor, ILS or ALS Cover Duration: Log** | | **If doctor/ALS/ILS cover in (d):** *(tick one box)* | **Specified Duration Is For Guidance** Clinical judgement may be applied | |  | **Specified Duration Is Mandatory** Sign-in/sign-out logs and check telephone calls recorded | |  |
| **(5) ICRF Facilities** | | | | | | | | |
| ICRF Facilities: specify rooms or other requirements | |  | | | | | | |
| **(6) Characteristics Of Study Participants** | | | | | | | | |
| Risks to / from participants, infection control, special requirements, GP medical history, TOPS etc. | |  | | | | | | |
| **(7) Emergency admission / unfit for discharge pathway, on call speciality contacts** | | | | | | | | |
| *No provision can be made to investigate or nurse patients who deteriorate while in the CRF, which 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 at St Mary’s. Clearly describe below any pathway to admit day attenders who become unfit for discharge by 6 PM, or participants whose condition deteriorates during an admission. Precisely describe the agreed pathway to admit patients to another service* ***before 8 PM*** *Mon-Thu, 6PM Friday.* *Proposing that the Study Team nurse sick patients in the CRF is unlikely to be agreed by PRB as the ICRF is a Day Unit not included in HH overnight Bed State. Clearly identify any emergency on-call doctors / practitioners who may be contacted to assess participants if Study Team not available. Provide accurate names / telephone / bleep numbers.* | | | | | | | | |
| Click or tap here to enter text. | | | | | | | | |
| **(8) Potential 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 matrix below for Risk 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*** | | |
| *e.g. fever, rashes, injection site reactions, myalgias, mild liver and WBC abnormalities* | *mild/moderate systemic reactions common after immunisation; last <72 hours. Diary cards reviewed at study visit, 24 hr contact number; receive telephone calls day 3. Mild NCS fluctuations in haem / biochem associated with immune response. Regular review of diary cards and bloods. Sponsor has remote monitoring in place.* | | | | | *Consequence: 1 Likelihood: 4* ***Risk score: 1 x 4 = 4*** | | |
| *e.g. neutropaenic sepsis* | *Severe neutropaenia has been observed with drugs in this class < 1 : 100 doses, within first 3 weeks. Modest falls in neutrophil count of no clinical significance occur more frequently. Participants excluded if neutrophils <20,000; regular counts on days 0, 1, 3, 5, 7, 14 and 21 reviewed within 24 hours by study team. Dose delay and stopping rules for neutropaenia described in protocol and staff trained on this specifically.* | | | | | *Consequence: 4 Likelihood: 2* ***Risk score: 4 x 2 = 8***  ***(this score of 8 would be the highest – enter 8 in the Highest Risk Score Calculated b***  ***ox below)*** | | |
| 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 Clinical Risks That Are Not Adverse Reactions** (e.g. cross infection, chemical risks, carcinogens, sharps, devices, staff injury, 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*** | | |
| *e.g. the immunisation device delivers an electric shock which could be applied to staff or observer* | *The device has a safety guard that must be deactivated. Staff are trained on the correct use of device and tested on this to avoid risk to themselves / third parties.* | | | | | *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. | | |
| **(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 any notifications that have to be given to ITU in advance of patient dosing/treatment; procedures to manage ITU unavailability; lines of communication and acknowledgement; and lines of responsibility. |  |

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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** |  |  |  |

## 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 establised practice and supported by publised evidence and/or guideline | licenced 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 ecalation with known/ tested doses Open-label | | | Low | Moderate | | Moderate | Moderate | | | | Moderate | |
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| Dosage used as per authorisation | | | Low | Low | | Moderate | Moderate | | | | Moderate | |
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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.