

**Clinical Trial Risk Assessment**

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| **Title of Research:** |  | **INSERT TRIAL LOGO** | |
| **Chief Investigator:** |  | **Name of Lead Centre:** |  |
| **REC Reference:** |  | **Lead Trust Reference:** |  |
| **ISRCTN Reference:** |  | **RSO Reference:** |  |
| **Funder Reference:** |  | **Sponsor Reference:** |  |
| **UKCRN Reference:** |  | **IRAS Reference:** |  |
| **EudraCT Reference:** |  | **Other References:** |  |
| **Start Date:** |  | **Proposed End Date:** |  |

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| **Date of Release** |  |
| **Version Number** |  |

**This template should be used in conjunction with SOP010 (Risk Assessment of Clinical Trials).**

**Blue text is provided as guidance and should be reviewed and deleted before finalisation of the document. This guidance is not exhaustive and should only be used as a guide.**

| **SECTION 1 – Sponsorship and Research Governance Risk Assessment** | | | |
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| **Risk/Hazard identified** | **Likelihood (Low, Medium or High)** | **Impact (Low, Medium or High)** | **Concerns and Recommendations for mitigation and management** |
| **Non-compliance with regulations** | **L** | **M** | The trial is of an investigational medicinal product. The sponsor(s) will need to assure compliance with the Clinical Trial Regulations 2004/1031 (as amended). |
| **Unclear accountability of organisations involved** | **M** | **L** | Contracts: Sponsorship is confirmed by XXX (add address).  This trial will be managed by XXX and a Subcontract/Sponsorship/Internal Delegation Plan will be put in place between xxx and the Sponsor  A Research Site Agreement (including a Material Transfer Agreement and any relevant data clauses) will be prepared and signed by each recruiting site and the Sponsor [and any other organisation required].  [Insert details of other agreements required]  Clear SOPs and plans describing trial procedures must in place as per Clinical Research Governance Team POL001 |
| **Inadequate/poorly documented delegation to recruiting sites** | **L** | **M** | A Research Site Agreement (including a Material Transfer Agreement and any relevant data clauses) will be prepared and signed by each recruiting site and the Sponsor [and any other organisation required].  Principal Investigators at recruiting sites will be take responsibility for the delegation of roles to the research team confirming each member ‘has been adequately trained on the current protocol for this trial’.  GCP certificates and curriculum vitae of team members will be held on the site trial file and the delegation log will be signed by both the PI and the team member specifying the roles they are delegated to do. |
| **Poor quality control and quality assurance** | **M** | **M** | There must be documented SOPs and plans describing trial procedures must in place as per Clinical Research Governance Team POL001  The Sponsor will undertake audits as per the annual audit programme.  The CTU will undertake regular internal audit of processes and procedures  At recruiting sites, the PI and research team will be GCP trained (as applicable) and familiar with the protocol thereby able to ensure SAEs and SUSARs are reported within the timeline stated in the protocol. |
| **Inadequate monitoring & auditing** | **M** | **M** | Monitoring by the CTU/research team will be undertaken according to a monitoring plan based on the outcome of the bespoke risk assessment. It is assumed that on site monitoring will/will not be required. This will include GCP, Research Governance, and source data validation, as well as monitoring of laboratory handling of samples and data reliability.  XXX is the greatest risk of this study and it will be important to develop necessary tools to prevent this risk occurring. |
| **Poor archiving of study related**  **information** | **L** | **L** | The party responsible for archiving the Trial Master File will follow Clinical Research Governance Team SOP020 or local SOP xxx  Recruiting sites will manage and archive patient data and the Investigator Site File in accordance with local practice, ICH GCP, the Caldecott Guardian /National Information Governance Board, the Data Protection Act and UK GDPR. |
| **Inadequate patient safety monitoring** | **L** | **M** | Necessary oversight committees must be in place prior to study opening.  The process for pharmacovigilance must be completed before recruitment opens.  The Chief Investigator will be required to report all relevant safety information to the relevant committees as outlined in the study protocol.  PIs at recruiting sites will report AEs and SAEs in accordance with the protocol and regulatory requirements. This is detailed in the Research Site Agreement which is signed prior to site opening. |
| **Study Design: inadequate study**  **powered recruitment** | **L** | **M** | XXX has contributed to the design of the study. The study has been reviewed by xxx. Feasibility will be undertaken at all identified trial sites prior to site set up. |
| **Inadequate costing of the study** | **M** | **H** | The trial has been costed by the Research Support Office (RSO) of the University of Liverpool and ongoing Post Award support is in place.  The xxx group will regularly review the finances throughout the study. |
| **Withdrawal of study funding** | **L** | **H** | The RSO will alert the Sponsor if this occurs. |
| **Insurance/indemnity** | **L** | **H** | Recruiting sites are provided indemnity by the NHS Litigation Authority.  The University of Liverpool will provide indemnity/insurance as appropriate for the protocol. |

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| **SECTION 1 Approvals:** (add/remove signatories as required) | | | | | |
| **Chief Investigator** |  | **Signature** |  | **Date** |  |
| **Sponsor representative** |  | **Signature** |  | **Date** |  |
| **Trial Statistician** |  | **Signature** |  | **Date** |  |
| **Trial Co-ordinator** |  | **Signature** |  | **Date** |  |

| **SECTION 2 – IMP Risk Assessment and Safety Monitoring**  ***IMP risk assessment based on SmPC/Investigator Brochure/protocol/relevant literature*** | | | | | |
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| **IMP Risk Assessment and Safety Monitoring Conducted by:** | | | | | |
| **IMP(s) to be used in trial:** | | | | | |
| **Risks associated with trial IMP(s)/intervention(s) for the IMP(s)/intervention(s) being investigated (single or in combination)**  CTIMP Type A = Comparable to the risk of standard medical care  CTIMP Type B = Somewhat higher than the risk of standard medical care  CTIMP Type C = Markedly higher than the risk of standard medical care  Non-CTIMP | | | **Justification for type of trial indicated:** | | |
| **IMP/Intervention** | **Hazard** | **Likelihood**  **(L=low; M= Medium; H=High)** | | **Mitigation** | **Comments** |
| ABC 123 | Hyperglycaemia | L | | Blood glucose monitoring | X Hourly |
| ABC 123 | Prolonged QT interval | M | | Digital ECG, Holter monitoring | X Hours |
| ABC 1234 | Concomitant administration of a drug interacts with the IMP | L | | Exclusion of individuals at particular risk of because of co-morbidities or taking certain drug which may react.  List of permitted and non permitted medications listed in the study protocol | Exclusion criteria review at randomisation |
| **Pharmacovigilance and processes that have been put in place to mitigate risks to participant safety (IDMC, independent data review etc.)** | | | | | |
| **Example text:**  IMP is considered a low/medium/high risk as the drug is given for standard clinical care and is therefore comparable to the risk of standard medical care/licensed for a different indication and is therefore somewhat higher than the risk of standard medical care/unlicensed and is therefore markedly higher than the risk of standard medical care.  The study population are a [vulnerable] group who are critically ill therefore many adverse events are anticipated due to the nature of critical illness triggered by 1) clinical condition 2) clinical interventions 3) supportive medication and therefore causality of Adverse Events (AE) is difficult to determine.  Due to the anticipated high number of Adverse events (AE) and Serious Adverse Events (SAEs) for reasons outlined above and the logistics of the trial, the protocol will outline which events need to be recorded by the investigator onto the CRF and which need to be reported immediately to the Sponsor (as per the Regulations). The Principal Investigator is required to record all AEs and SAEs as stated in the protocol in the Case Report Form (CRF). The investigator must report immediately to the Sponsor (or delegated other) all SAEs, except those stated in the protocol as ‘anticipated’ events.  The process for reporting SAEs (whether related to the IMP or not) to the Sponsor [name] will be defined in the protocol, pharmacovigilance plan and the research site agreement. The Sponsor [name] will monitor the incidence of reported SAEs. Any SUSARs will be reported to the MHRA and the Research Ethics Committee (REC) within the required timelines. All SAEs whether related to the IMP or not will be recorded in the case report form and a summary provided for the Sponsor [name] and the Independent Data Monitoring Committee (IDMC). | | | | | |

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| **SECTION 2 Approvals:** (add/remove signatories as required) | | | | | |
| **Chief Investigator** |  | **Signature** |  | **Date** |  |
| **Sponsor representative** |  | **Signature** |  | **Date** |  |
| **Trial Statistician** |  | **Signature** |  | **Date** |  |
| **Trial Co-ordinator** |  | **Signature** |  | **Date** |  |

| **SECTION 3 – Bespoke Trial Risk Assessment**  **(participant safety relating to the IMP, study design, methods, safety and rights and reliability of results)** | | | | |
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| **Bespoke Trial Risk Assessment Conducted by:** | | | | |
| 1. **Investigational Medicinal Products** | | | | |
| **General Risk Identified** | **Potential Risks** | **Likelihood (Low, Medium or High)** | **Mitigation or Adaption** | **Monitoring methods to address** |
| **IMP administered off label** | IMP dose has low efficacy | M | Dose specified in protocol has been chosen according to the appropriate literature and has been peer reviewed by experts within the relevant field  Case Report Forms will systematically collect data on patient status | A TSC and/or IDMC will be established for ongoing IMP safety monitoring.  An interim analysis takes place as planned in the protocol. |
| **Storage** | IMP stored inappropriately |  | Reference safety information is provided to site together with the Pharmacy Operating Manual prior to site activation  Feasibility questionnaires will be sent out at the beginning of the study to assess any anticipated problems with IMP storage  Sites that have experience with working on clinical trials will be selected to take part in the study. | Checks required on storage areas by on site monitoring. |
| 1. **Subject safety, consent, rights and well being** | | | | |
| **General Risk Identified** | **Potential Risks** | **Likelihood (Low, Medium or High)** | **Mitigation or Adaption** | **Monitoring methods to address** |
| **Breach of Data Protection/confidentiality** | Patient identifiable information sent to the trial team in error | M | Site initiation visit to include training about sending anonymised data to the trial’s unit at site initiation  On receipt of any patient identifiers, site will be reminded not to send any unauthorised patient identifiers | CVs, GCP training and delegation logs are reviewed by the trial team to ensure that site staff are trained in data protection which should be covered within their GCP training |
| **Lack of Informed Consent** | No consent  Patient consented on incorrect version of the PIS and ICF  Incorrect information provided to participant |  | PI and RN to have ICH  GCP and protocol training  highlighting consent  process  Copy of signed consent  form must be received by trial team before randomisation  process can begin  Trial team to check at randomisation that correct version of PIS has been provided to the participant.    Only REC approved PIS/ICF to be used to consent a patient | TC to verify ALL trial  participants have valid  fully informed written  consent  TC/DM to record any issue with consent at randomisation into the randomisation audit section of the MACRO database. This audit is reviewed as part of central monitoring |
| **Lack of Insurance cover/indemnity** | Patients are in the exclusion criteria for automatic insurance cover;   * pregnant women * children under five years of age   people with special needs or reduced capacity to consent. |  | UoL Legal and Governance department to review the insurance cover prior to the start of the study to ensure that there are no conflicts between the insurance cover and the protocol requirements  UoL Legal and Governance department to review of the cover on an annual basis  UoL to send the study protocol and any amendment to the insurance broker to be revised if changes that could affect the cover has taken place |  |
| **Apart from the intervention, protocol requires investigations that carry significant risks/or are over and above those expected from standard care** | Non-standard biopsy required for protocol inclusion  e.g. additional MRI scans/blood test |  | PI and RN to have ICH  GCP and protocol training    Trial team to ensure specialist facilities/equipment is available at site | Feasibility is completed prior to site set up to ensure adequate facilities and resource are available |
| **Lack of a robust system for the review and expedite reporting of SAEs and SUSARs** | SAEs are not reviewed properly and SUSARs may be missed  SUSARs are not reported in a in the required time to regulatory authorities |  | A robust pharmacovigilance plan is developed that includes arrangements for cover for review and submission of all adverse events |  |
| 1. **Trial Results** | | | | |
| **General Risk Identified** | **Potential Risks** | **Likelihood (Low, Medium or High)** | **Mitigation or Adaption** | **Monitoring methods to address** |
| **Slow recruitment - Lack of target population** | Overestimation of recruitment target  Strict eligibility criteria e.g. age range is narrow 25 – 45 years old affecting recruitment |  | Peer review of study design  Site feasibility  Collaboration with experienced colleagues  Early statistical input into study design | Trial Oversight Committees to review and monitor recruitment |
| **Organisational Complexity (Multi-centre sites)** | Multi-centre study  which can lead to   * Inclusion of sites with inadequate trial experience * Necessary approvals not in place   Issues with communication to all sites |  | Appropriate site feasibility  Tracking of approvals obtained  Robust communication plan |  |
| **Complexity of trial related procedures** | Large number of protocol deviations  Serious Breaches  Required assessments not completed |  | Feasibility questionnaires  Site initiation visit for training in study procedures  Confirmation that the site has an appropriate serious breach procedure in place  Appropriate reporting of serious breaches. | Review of protocol deviations and serious breaches |
| **CRF data** | CRF not fit for purpose e.g. CRF does not collect tumour lesion at baseline  Inaccurate data collected  Follow-up is too infrequent to capture key data items  Poorly design case report form  No procedures in place to ensure a timely flow of data from sites  Site non-adherence to the protocol  No database backup plan  Large amount of complex data required |  | CRF designed with appropriate expertise  Monitoring of CRFs to ensure adequate data collection |  |
| **Lack of statistical considerations or poor statistical design** | The data collection process if not documented in the study protocol  Data collection is unrelated to the primary research question  Insufficient/unrealistic sample size  Inappropriate design selected  No formal analysis plan in place  Poorly defined patient population (potential for section bias) |  | The protocol includes details of data collection process |  |
| **Lack of previsions for efficacy and safety analyses** | No unbinding procedure  No formal pre-specified analyses |  |  |  |
| **Inadequate process for the preparation for the clinical study report** | The report is compilation of sections prepared by various departments and there are inconsistencies |  |  |  |
| **Poor quality data** | Un-validated database  No audit trail  Fraudulent data |  |  |  |
| **Inadequate medical record keeping (e.g. archiving)** |  |  |  |  |
| 1. **Facilities, equipment and resources** | | | | |
| **General Risk Identified** | **Potential Risks** | **Likelihood (Low, Medium or High)** | **Mitigation or Adaption** | **Monitoring methods to address** |
| **Insufficient Investigator facilities/resource** | No local lab that can run all of the required biochemistry parameters |  | Feasibility is completed prior to site set up to ensure adequate facilities and resource are available  Research Site Agreement must be signed off by all parties prior to site opening  Pharmacy local practice forms are completed during site set up and prior to site green light |  |
| **Inexperienced Clinical team** | Personnel other than the PI and pharmacist have never been involved in a clinical trial  Incorrect advice to  patients about taking/administration of IMP |  | Trial team to obtain current CVs and GCP training records to assess suitability of staff qualifications, training and experience prior to site opening  Site delegation log to be completed for PI to formally authorise delegation of tasks to appropriate site personnel  SPC available at  participating sites  Site research staff trained  on the use of the drug and the trial procedures at the site initiation visit  Only PIs/sites with  experience of administering  chemotherapy selected to  participate  Dispensing label attached  to the container to give  clear instructions  Site staff delegation log with  clearly defined delegation of responsibility ensures site  research staff are aware of  their responsibilities | Independent oversight of  safety reporting by  IDSMC |
| 1. **Documentation, Governance and GCP compliance** | | | | |
| **General Risk Identified** | **Potential Risks** | **Likelihood (Low, Medium or High)** | **Mitigation or Adaption** | **Monitoring methods to address** |
| **Trial Master File (TMF)** | Lack of documentation  to reconstruct trial and  confirm compliance with  CT regulations, the protection of subject’s rights/wellbeing/safety and the reliability of the trial results. | L | SOPs are in place to cover the maintenance of the trial master file  The research site agreements state that all site and patient documentation must be kept by the participating site |  |
| **Inadequate Monitoring** | Non-compliance with regulations  Lack of source data  Data reliability |  | Appropriate Trial Oversight Committees must be in place  Monitoring plan must be in place prior to study opening |  |
| **Insufficient Sponsor Overview of study** | Sponsor are unaware of protocol amendments/trial progress/serious breaches/SUSARs |  | Responsibilities clearly documented in the internal delegation plan and/or the Sponsor communication plan  Sponsor representative to attend Trial Steering Committee  All study amendments must be reviewed by the Sponsor |  |
| **Lack of qualifications or training in research team to carry out assigned duties** | Data Manager has not received training on MACRO databases before entering study data  Research team member has not received ICH GCP, data protection training |  | Regular ICH GCP and study specific training is required for trial team |  |
| **Long term absence or vacancy of research team member post** | Trial Co-ordinator absent on long-term sickness leave |  |  |  |
| **Lack of adequate SOPs or plans** | No process documented for pharmacovigilance, randomisation or registration procedures |  | Clear SOPs/plans describing trial procedures must in place |  |
| **Lack of QC and QA systems implemented and maintained** | MACRO database not validated prior to entry of patient data |  |  |  |

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| **SECTION 3 Approvals:** (add/remove signatories as required) | | | | | |
| **Chief Investigator** |  | **Signature** |  | **Date** |  |
| **Sponsor representative** |  | **Signature** |  | **Date** |  |
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