**Risk Assessment Form of Papworth Sponsored Clinical Trials of Investigational Medicinal Products**

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| **Study Title (in full)** |  |
| **Short Title** |  |
| **EudraCT Number** |  |
| **Chief Investigator** |  |
| **Sponsor’s Project Reference** |  |

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| **Risks Associated with the IMP** (please tick either A, B or C below and complete the justification box |
| [ ]  **Type A = Comparable to the risk of standard medical care****[ ]  Type B = Somewhat higher than the risk of standard medical care****[ ]  Type C = Markedly higher than the risks of standard care** |
| **Justification for the risk selected above** | ***Consider in this section:**** *Phase of development: healthy subjects or patients; being used outside licensed indication; modification of dose / route of administration*
* *Safety profile: known / anticipated issues; anticipated risks; duration of use; risk of dosing errors, route of administration.*
* *Do concomitant medications or disease states increase the risk*
* *Risk mitigation strategies: restrictive eligibility criteria; DMC oversight; duration of exposure; AE reporting strategy. Staff training?*
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**Chief Investigator Signature ………………………………………………. Date: …………………………………………**

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| **Risk factor** | **Identification of Risks***Provide details of trial specific considerations / risk concerns* | **Likelihood** *(Low / medium / high)* | **Mitigation*** *Address all risks / concerns identified*
* *Provide details of any risk-adaptations to conventional GCP management strategies employed*
* *Detail who is responsible for managing the mitigation and frequency of review*
* *Discuss any impact on trial monitoring requirements*
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| **Risks to participants** |  |  |  |
| Risk to participant safety from study investigations specified in the protocol | For Example:* *Does the protocol require any investigations or other clinical procedures that carry significant risk. These could be IMP or non-IMP related.*
* *Does the protocol require additional procedures over and above those that would be expected from standard care (and what is the likelihood and severity of harm)*
 |  | *Measures that may reduce the likelihood of risks could be:** *Experience and training of personnel + additional training if required*
* *Monitoring to identify problems and take measures to protect current & future patients*
* *Are any special facilities or equipment required*
* *Additional SOPs to cover complex procedures*
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| Failure to obtain informed consent process*The risks should be judged relative to the ability of a fully competent adult with a chronic, non-life-threatening condition to give consent.* | For Example:* *Vulnerable patient population*
* *Are participants likely to lack capacity to give fully informed consent (eg severe pain, cognitive impairment, language difficulties)*
* *Who makes decision if participant is capable of giving consent*
* *Where, when and how + length of time to consider giving consent.*
 |  | *Measures that may reduce the likelihood of risks could be:** *Experience and training of personnel + additional training if required*
* *Nomination of a professional legal representative*
* *Assent guidance*
* *Monitoring to identify problems and take measures to protect current & future participants*
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| Failure to protect participants’ privacy - Information and personal information, data protection. | For Example: * *Data or samples to be sent outside the EU where data privacy laws may not be as rigorous*
* *Is potentially sensitive data being collected*
* *Are personal identifiers associated with the data (especially important for rarer conditions)*
* *Has consent been given to share the data with third parties*
 |  | *Measures that may reduce the likelihood of risks could be:** *Experience and training of personnel + additional training if required*
* *Ensure Patient information sheet and consent form details any data / tissue going outside the EU*
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| Patient well being*The risks should be judged based on the risk/benefit balance; burden of study visits; lifestyle requirements* | For Example:* *Does the protocol require patients to attend for a large number of follow-up visits. Are these required clinically.*
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| **Investigational Medicinal Product risks** |  |  |  |
| Hazards of the IMP*Where risks associated with the IMP are somewhat or markedly higher than the risk of standard care (eg Type B or Type C trials), details regarding specific risks to body systems and proposed methods for clinical monitoring of such risks should be described* | For Example* *IMP with additional cardiovascular risks:Body system: cardiovascularRisk: prolonged QT intervalClinical Monitoring 12 lead ECG at 6, 12 and 24 hours post dose*
* *If a licensed drug is being used out of indication*
* *Potential for side-effects*
* *Interaction with concomitant medications*
* *Congenital abnormalities*
* *Is the IMP blinded? Any risks associated with comparator product*
 |  | MitigationDetail here what mitigation factors have been put into place in the protocol to ensure that these hazards are being carefully monitored. |
| IMP handling and administration risks  | For example:* Contact/inhalation risk resulting from contact with IMP
* Risks associated with repeated exposure to IMP
* Risks to both patient and staff associated with errors in IMP preparation and administration
* Consider route of administration and inherent risks i.e IV administration
 |  | Mitigation:* Consider completion of trial/IMP specific IMP handling guidelines that will clearly document all processes to be followed in the handling of the relevant IMP
* Calculation worksheets, incorporating second checks
* All staff appropriately trained to administer IMP and covered by professional registration.
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| Pharmacovigilence*AE reporting**SUSAR Reporting**Safety Monitoring Committee / plan* | For Example* *For medicines where there is already a significant amount of safety data available, such as many marketed medicines, it may be possible to state in the protocol that certain adverse events do not need to be reported to the sponsor in the normal way.*
* *The nature and extent of patient safety monitoring should be based on the assessment of the risks of the trial intervention relative to standard care and the extent of the knowledge about the IMPS being tested.*
 |  | Mitigation* Ensure the protocol clearly states the expected adverse events and which ones need to be reported to the sponsor
* A safety monitoring plan needs to be developed for each study regardless of the risk rating. Eg Type A &B studies – central monitoring +/- additional monitoring to address specific vulnerabilities within the trial designType C studies – more intense monitoring to ensure confidence in the study data
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| IMP Management*Tracking & accountability processes**Storage* | For Example* *The further away from standard practice the trial is the greater the record keeping requirements.Is this a product with no marketing authorisationIs the trial design markedly different from standard care*
* *Does the trial involve blinded IMP?*
* *If this is a pragmatic trial where local provision of the IMP may be hampered by complex record keeping requirements, thought needs to be given to what information is required to confirm the results and end-points of the trial.*
 |  | Refer to the MHRA guide to GCP for advice on how these can be reduced from a pragmatic risk assessment approach |
| **Reliability of results** |  |  |  |
| Study Design*The design of a study has a major impact on the robustness of the results.* | For Example (these are expanded in more detail below):* *Objectives of study may limit design options*
* *Complex eligibility criteria may be required in early phase studies*
* *Subjective outcome measure may be required for trial endpoint / masking may be difficult*
* *Large sample size required or may be difficulties in recruiting sufficient patients*
* *Study insufficiently powered*
* *Potential of loss to follow-up leading to insufficient data available at key milestones*
 |  | * *Simple relevant eligibility criteria*
* *Objective outcome measures which are simple to assess accurately*
* *Properly generated randomisation sequence that prevents prediction of treatment allocation*
* *Sufficient power / sample size*
* *Experienced statistician involved in study design and sample size calculations*
* *Reliable estimates of potential number of suitable participants for the study*
* *Protocol design that minimises risk of missing key data items e.g. short follow-up or similar to standard care*
* *Sample size accounts for potential withdrawals, loss to follow-up, missed data points*
* *Site selection and recruitment targets to be based on known activity data*
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| Data Collection | For Example* *Ambiguous data collection forms*
* *Large volume of data required*
* *Complex database*
* *Does the database allow an audit trail*
 |  | * *Well-designed case report forms*
* *Piloting of CRFs*
* *Use of user-friendly database*
* *Database validation and testing*
* *Data verification checks*
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| Randomisation | For Example* *Access to 24hr randomisation required*
* *Unbalanced /incorrect randomisation*
* *Randomisation of ineligible patients*
* *Blinding required to treatment allocation*
* *Risk of participant being randomised incorrectly*
 |  | * *Robust method used to generate and check the randomisation schedule*
* *Does method of allocation prevent prediction before a pt is entered into the trial eg central allocation; allocation by pharmacy rather than envelopes in clinic; avoidance of known block sizes*
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| Masking of intervention | For Example* *Is this essential*
* *Who needs to be blinded*
* *Is it effective*
* *Is there a potential for unblinding to be required*
 |  | * *Detail who (patients/ research staff) will be blinded to the study intervention*
* *Distinct roles for research staff to maintain blinding*
* *Monitoring of randomisation activities and staff roles*
* *Is emergency code breaking procedure robust and tested?*
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| Eligibility criteria | For Example* *Complex inclusion / exclusion criteria*
* *Special tests / assessments required*
 |  | * *Simple, relevant eligibility criteria*
* *Training of staff*
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| Intervention | For Example* *Complex intervention with potential for error eg dose escalation study/ complex chemotherapy regimen/ multiple drugs, risk of toxicity*
* *Impact and likelihood of non-adherence*
 |  | * *Intervention as close as possible to standard care*
* *Fully trained research team*
* *Training of participants with regard to adhering to protocol*
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| Outcome measures | For Example* *Inexperienced research staff*
* *Non-standardised outcome measures or unvalidated methods*
* *Impartiality of researchers*
 |  | * *Clearly defined empirical endpoints*
* *Independent assessor of study outcomes*
* *Potential for simple external verification e.g. death certificate*
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| Statistical analysis | For Example* *Complex objectives and endpoint measurements*
* *Valid analysis requires complex statistical techniques*
* *Data transfer from primary database to final analysis file*
 |  | * *Adequate sample size*
* *Clear and appropriate analysis plan*
* *Appropriate trial design*
* *Clear objectives and endpoint measurements*
* *Development of a statistical analysis plan*
* *Quality control checks of statistical outputs*
* *Testing of output methods and validation of output files*
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| Data management system | For Example* Inadequate management of trial data
* Poor data quality and integrity
 |  | * *Training of research staff on use of data management system*
* *Monitoring frequency and intensity*
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| Archiving of Data for Primary or secondary outcomes | For Example* Inadequate storing on differing formats for future data retrieval
* Environmental factors damaging electronic media
 |  | * *Storing Primary/secondary outcomes on differing formats*
* *Use an environmentally controlled archive facility*
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| **Trial Management** |  |  |  |
| Trial Staff | For Example* *Inexperience research staff*
* *Inexperienced Principal Investigator*
 |  | * *Training of research staff in GCP and research procedures*
* *Monitoring of training logs / CVs as part of site initiation and monitoring visits*
* *PI GCP trained and actively involved in protocol development and trail set-up*
* *Support provided for inexperienced staff*
* *Appropriate level of experience with managing and administering drugs*
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| Management at site | For Example* *Potential ambiguity between roles and responsibilities between CI and Sponsor and site*
* *Complex arrangements for drug stocking, dispensing, re-labelling etc (potential for using ward stock rather than IMP or vice versa)*
* *Complex dose calculation*
* *Contracts between departments*
 |  | * *CI / sponsor delegation log completed*
* *Delegation log completed and kept up-to-date at each site to define duties for individual research staff*
* *Technical agreements in place as required*
* *Clear labelling of IMP / NIMPs*
* *Clear arrangements for dose calculation*
* *Clear arrangements in place for study drug management including temperature monitoring*
* *Regular training and updates for non-research staff who may be involved ad-hoc*
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| Trial Resources | For Example* Potential for insufficient funding for completion of trial
* Potential for sites withdrawing from study
* Insufficient research staff at each site to perform trial duties
* Facilities available at each site to perform protocol requirements
 |  | * *Detailed costing undertaken by sponsor*
* *Contracts in place between sponsor and each site involved in study*
* *Funding available to cover all additional research duties*
* *Site selection visit to assess resources*
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| **Monitoring Procedure** | For Example – justify which you are going to you and frequency of meetings / visits.* *Trial oversight structure eg Steering Committee/ independent Data Monitoring Group*
* *Central Monitoring*
* *On-site monitoring visits*
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