# Sponsor Trial Risk Assessment

***<Trial Title>***

Version:

***<Risk Assessment version number and date>***

**EudraCT number: *<insert number or N/A for non-IMP trials>***

**Sponsor number: *<insert sponsor reference number >***

**This Risk Assessment should be completed for all studies indicated by Risk Assessment Decision Flowchart (see Appendix 4 to SOP- 1003).**

**Definitions**

***Hazard:*** anything that could cause harm

Likelihood: Taking account of the controls already in place, the probability of that hazard occurring.

Impact: Taking account of the controls in place and their adequacy, the severity of consequences should such a hazard occur.

**Risks should be scored and action taken in line the Risk Analysis Matrix at the end of this document.**

# 1. Trial Overview

The Risk Assessment Form must be completed by the Chief Investigator (Summary and Section 1 & 2 only) and Research Governance Manger (UoL) or their delegate when conducting Sponsor reviews on behalf of UoL. It is expected that queries or actions required are discussed with the Chief Investigator and research teams and plans for mitigation agreed as part of the sponsor review process.

Risk can be defined as the likelihood of a potential hazard occurring and resulting in harm to the participant and/or organisation, or to the reliability of the results.

A flowchart of the procedures required are detailed in the Sponsor Risk Assessment & Management of Research Sponsored by UOL – SOP S-1003.

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| --- | --- | --- | --- |
| **Full Title:** |  | | |
| **Name of Point of Contact (POC):** |  | **Name of CI:** |  |
| **Email/Phone of POC:** |  | **If multi-centre, how many sites?** |  |
| **Proposed number of patients (include in each arm if applicable):** |  | **Study Duration:** | Recruitment Period =  Intervention Period =  Follow-up Period =  Total Study Duration = |

|  |
| --- |
| Study Summary: |
| *Include a short summary of relevance and importance of this research and how this research will benefit UoL and/or it’s staff and patients* |

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| **Type of Study:** | | | | | |
| Clinical trial of an investigational medicinal product | | ☐ | Study involving qualitative methods only | | ☐ |
| Clinical investigation or other study of a medical device | | ☐ | Study limited to working with human tissue samples (or other human biological samples) and data (specific project only) | | ☐ |
| Combined trial of an investigational medicinal product and an investigational medical device | | ☐ | Study limited to working with data (specific project only) | | ☐ |
| Other clinical trial to study a novel intervention or randomised clinical trial to compare interventions in clinical practice | | ☐ | Research tissue bank | | ☐ |
| Basic science study involving procedures with human participants | | ☐ | Research database | | ☐ |
| Study administering questionnaires/interviews for quantitative analysis, or using mixed quantitative/qualitative methodology | | ☐ | Other study | | ☐ |
| **If IMP complete sections below** | | | | | |
| **Type of IMP:** | | | **Type of Research:** | | |
| Biological | ☐ | | Phase 1 | ☐ | |
| Chemical | ☐ | | Phase 2 | ☐ | |
| Advanced Therapy | ☐ | | Phase 3 | ☐ | |
| Other | ☐ | | Phase 4 | ☐ | |

# Document Control and Review Record

This Risk Assessment Form should be reviewed and amended if necessary whenever substantial amendments are made. An annual review of the RAF should be made whether or not there have been any amendments. It is recommended that this occurs at the same time as the submission of annual reports to REC or submission of the annual DSUR.

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| Risk Assessment Completion or Review Date | CompletedBy | State Initial Completion orReason for Review\* | Version of RAF Reviewed | Protocol Version & Date | Outcome of Review*(Revision Required/ no revision required)* | Summary of Revisions |
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**Add or delete rows as required.**

\*E.g. following:

Substantial amendment to the protocol or Patient Information Sheet

Significant changes in trial organisation (e.g. resource allocation, governance) and/or external funding

Any other changes that may alter risk, e.g. significant change in SPC/IB, serious breach, following DMC/interim analysis

# Risks to participant SAFETY associated with the intervention(s) being tested

|  |  |  |
| --- | --- | --- |
| **IMP trial** | **Non-IMP trial/research project** | **Device trial** |
|  |  |  |

**Risk category**

***Tick the appropriate box below to indicate trial type:***

|  |  |  |
| --- | --- | --- |
| **TYPE A** | **TYPE B** | **TYPE C** |
| Comparable to the risk of standard medical care | Higher than the risk of standard medical care | Markedly higher than the risk of standard medical care |
| **IMP trial examples**:  Trials involving medicinal products licensed in any EU Member State if:  they relate to the licensed range of indications, dosage and form  or,  they involve off-label use if this off-label use is established practice and supported by sufficient published evidence and/or guidelines | **IMP trial examples**:  Trials involving medicinal products licensed in any EU Member State if:   * such products are used for a new indication or * substantial dosage modifications are made for the licensed indication or * if they are used in combinations for which interactions are suspected * Trials involving medicinal products not licensed in any EU Member State if: * the active substance is part of a medicinal product licensed in the EU | **IMP trial examples**:  Trials involving a medicinal product not licensed in any EU Member State |
| **Non-IMP trial examples:**  Skin prick tests  Observational studies  Quality of Life studies | **Non-IMP trial examples**:  Radiotherapy dose modifications  New combinations of non-IMP treatment (e.g. surgery and radiotherapy) | **Non-IMP trial examples**:  New surgery technique  New radiotherapy technique  New diagnostic technique  Educational Study in vulnerable population |
| **Device trial examples:**  **CE marked device used within its intended purpose(s)** | **Device trial examples:**  **CE marked device which has been modified or will be used outside its intended purpose** | **Device trial examples:**  **Non –CE marked device** |
| **Justification for risk category:**  *List the intervention(s) and* ***briefly*** *justify the overall risk category selected (Type A, B or C).*  *Consider the following:*   1. *Phase of development* 2. *Study population – healthy subjects or patients?* 3. *Is the intervention licensed?* 4. *Is the intervention being used outside of its licensed indication?* 5. *Has the dosage regimen/route/surgical procedure/fractionation been modified? If so what are the implications of any modifications for participants?*   *Safety profile:*   * *What are the known/anticipated safety issues? Are they all addressed within normal clinical practice (standard care)?* * *Anticipated risks/other effects based on pre-clinical data or knowledge of class of intervention?* * *Is the duration of use compatible with previous experience? Is there a potential risk of dosing errors?* * *May concomitant medication increase the risk i.e. interactions?* * *Is there any published evidence – particularly for Type A trials intending to submit via the MHRA Notifications Scheme, or to support a risk category different to that indicated above?* | | |

*List below the key risks related to the intervention(s) and how these risks will be minimised. Consider all trial specific medically significant events.*

*Examples are provided in red italic text. Add or delete rows as required.*

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Risks related to the intervention/device | | | | | | |
| **Intervention/**  **Device** | **Body system/hazard** | **Mitigation/activity (including frequency)** | **Likelihood** | **Consequence** | **Residual Risk Score** | **Justification for tolerating risk where applicable and details of any checks required** |
| ***Pazopanib*** | ***Gastrointestinal disorders / Diarrhoea*** | ***Sites will be prompted to collect data on toxicity on day one of each cycle (except first cycle and at end of treatment visit) and assess if/when the patient will have to cease the drug.***  ***The protocol specifies that patients who experience severe diarrhoea will stop pazopanib until symptoms resolve to grade 1.***  ***Detailed supportive care guidelines for management of diarrhoea are also provided in the protocol.***  ***Patients are also advised in the Patient Information Sheet to notify the study doctor immediately if they experience severe diarrhoea.*** | *3* | *4* | *12* |  |
| ***Medroxyprogesterone acetate*** | ***Neurological disorders / Depression*** | ***Patient is advised to contact local site if experiencing depression.***  ***Patients will be seen at the local site at least every 4 weeks and can visit their GP/use the details on the patient card if depression occurs.*** |  |  |  | ***Depression is also monitored by the EORTC QLC-C30 at baseline and twice during therapy. However, this data is not looked at in real time.*** |
| ***Ch14.18/CHO Aldesleukin (IL-2)*** | ***Vascular disorders / Hypotension*** | ***Patient’s vital signs (including blood pressure) will be checked daily by site staff, while on treatment.*** |  |  |  |  |
| ***Walking Intervention*** | ***Vascular disorders / Muscular disorders*** | ***Participants will be asked to maintain a daily step count of 20,000 throughout the trial. Some participants may be unable to achieve this safety due to preexisting conditions that have not been identified during screening as consent is undertaken by non-medically qualified individuals.*** |  |  |  | ***Screening incudes PAR-Q questionnaire and all consenting trial team members will have undertaken study specific training to screen patients.*** |

**Other risk mitigation processes**

The table below documents other trial-specific risk mitigation associated with the intervention/device.

***Examples are provided in red italic text. Add/delete rows as required:***

|  |  |
| --- | --- |
| **Mitigation/activity** | **Comments** |
| ***Treatment protocol***  ***(e.g. timing/titration of doses, location of administration)*** | 1. ***As this is such a complex treatment schedule, the protocol will contain considerable detail via description and flow diagrams of the treatment route for each randomisation group. In addition checklists will also be provided and referenced in the protocol.*** 2. ***Participants will be enrolled onto the trial in a staged process whereby the first participant in each cohort will complete the vaccination schedule prior to the enrolment of further participants. The subsequent two participants will be treated in parallel, provided there has been no evidence of Dose Limiting Toxicity (DLT). If a DLT occurs, the subsequent participant will also complete the vaccination schedule before further participants are treated.*** |
| ***Trial-specific adverse event reporting strategy*** | 1. ***All Adverse Events will be collected for this trial which will be reviewed by an independent Data Monitoring Committee as defined by the protocol. Medically significant events as defined in the protocol will be captured on a Serious Adverse Event form.*** |
| ***Trial oversight committees (TSC and/or DMC), independent data review*** | 1. ***A Trial Steering Committee (TSC), Trial Management Group (TMG) and Data Monitoring Committee (DMC) are in place for this phase I trial. The DMC will meet after 2 patients have completed 1 cycle of treatment and will review the study data and advise on the continuation of the trial. They will continue to meet per 2 patients recruited until all patients are recruited. The TMG will meet every 2 months and the TSC will meet every 3 months during the treatment period. The DMC will then meet annually to discuss the progress of the trial.*** 2. ***The trial will have a safety review committee who will meet a minimum of every 3 months during the recruitment phase and review all Serious Adverse Events and evaluate the evolving safety profile of the trial. It will be formed of members from the Trial Management Group and an independent scientist and clinician.*** |
| ***Trial suspension between cohorts*** | 1. ***If any unexpected Serious Adverse Events (CTC grade 3, 4 only) are encountered in the second arm, consideration will be given to suspending the entry of new patients into this arm, pending clarification of a causal relationship.*** 2. ***Toxicity will be closely monitored and if necessary the study will be stopped in accordance with the early stopping rules, which include:***  * ***The occurrence of grade 3 mucositis in 2 patients at 90 days*** * ***>Grade 3 late radiotherapy induced complication in more than 2 patients at one year*** |

## Other risks associated with the design and methods of the trial

*Review the protocol to identify whether or not it contains any aspects that materially increase the risks in the areas outlined below. For each hazard identified, consider the appropriate mitigation, management and optimal quality assurance strategy.*

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| --- |
|  |

| **4. RISKS TO PARTICIPANTS**  ***Examples are provided in red italic text. Add/delete rows as required:*** | | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Risk area** | **Particular risk identified?**  **(No/Yes/N/A)** | **If yes, list specific concerns** | **If yes, can the risks be minimised?**  **(specify any mitigations)** | **Likelihood** | **Consequence** | **Residual Risk Score** | **Justification for tolerating risk where applicable and details of any checks required** |
| **Clinical procedures**  E.g.  Do they differ from standard care? If so, what is the likelihood of severity of harm to the participant? How will this harm be managed? | ***Yes*** | ***Blood sampling 5 times a day - increased skin trauma to areas already bruised, discomfort and pain to patient of regular sampling.*** | ***Blood sampling will be performed by skilled site staff. Where possible, samples will be taken when clinical blood samples are required.*** |  |  |  | ***N/A*** |
| ***Yes*** | ***Additional CT scan required - increased exposure to radiation from increased frequency of scans.*** | ***Additional scan is equivalent to about 8 years of average natural background radiation in the UK.***  ***The Radiological Protection Division of the Health Protection Agency describes ‘a few years’ average natural background radiation as ‘Low Risk’.***  ***The risks from these examinations would therefore be described as ‘Moderate Risk’ in normal healthy people. The risk of developing another cancer as a result of extra CT scans is considered very small.*** |  |  |  | ***N/A*** |
| **Consent**  E.g.  Is there any reason that the participants in the trial would not be able to give fully informed consent e.g. vulnerable groups, lack of capacity to consent, language difficulties?  How will this be managed? | ***Yes*** | ***The trial will involve patients aged from 12 – 25 years of age; <16 year olds are not legally able to consent for themselves.*** | ***Age specific Patient Information Sheets and a Parent Information Sheet will be produced. Informed consent will be obtained from parent(s)/legal guardian(s) for patients under the age of 16.*** |  |  |  | ***With explicit consent from parent/legal guardian (or patient where patient is under the age of 16) a copy of the Informed Consent Form will be sent to the Trial Manager for review. The Site Signature and Delegation Log will also be used to verify that the correct personnel are performing the consent procedures.***  ***The consent procedure will be reviewed during Quality Checks and Quality Assurance Audits.*** |
| ***Yes*** | ***This is an international trial involving 5 countries, with different language requirements.*** | ***The Patient Information Sheet and Informed Consent Form will be available in French, English, Spanish, Italian and Greek. Back translation of documents by a translation service will be performed.*** |  |  |  | ***N/A*** |
| **Data protection**  E.g.  Are particularly sensitive data being collected?  Are personal identifiers associated with the data?  Is there a need for data to be sent outside the country? Are data protection standards equivalent to those in the UK? | ***Yes*** | ***The patient’s full name and date of birth will be collected at randomisation (which is regarded as personal data in accordance with the Data Protection Act 1998). The patient’s full name is collected over the phone only and is entered directly into the trial database.***  ***In addition, copies of signed Informed Consent Forms will be collected and stored centrally by the Trial Manager with the patient’s explicit consent.*** | ***Personal data recorded on all documents will be regarded as confidential and will be handled and stored in a secure environment and in accordance with GCP and Data Protection Act 1998.***  ***Patients will be identified using only their unique trial number, on the Case Report Form and correspondence between the Trial Manager and the participating site.*** |  |  |  | ***Patient’s signed Informed Consent Forms will be checked in-house to verify that patient has given explicit consent for patient’s full name, date of birth and copy of the Informed Consent Form to be provided to the Trial Team*** |
| ***Yes*** | ***With the patient’s explicit consent GP data will be submitted directly to the Trial Team. The GP data displays the patient’s full name and address.*** | ***The Trial Team will ensure that identifiers will be replaced with trial number only.***  ***Personal data recorded on all documents will be regarded as confidential and will be handled and stored in a secure environment and in accordance with GCP and Data Protection Act 1998.*** |  |  |  | ***Patient’s signed Informed Consent Form will be checked in-house to verify that patient has given explicit consent for data to be collected from GP.*** |
| **Target population**  E.g.  Phase of the disease, age range of the group, co-morbidities, prognosis of group, susceptibility to infections/complications, risk carrying intervention | ***Yes*** | ***Critically ill patients with a poor prognosis will receive multiple concomitant medications, making both the effect of the IMP and the relatedness of the IMP to any SAEs difficult to assess.*** | ***All concomitant medications will be recorded on the CRFs and analysed by the Investigator for both their interaction with the IMP and relatedness to SAEs. Regular monitoring of SAE categories will also be performed.*** |  |  |  | ***N/A*** |
| ***Yes*** | ***This target population is at high risk of graft versus host disease and is at greater risk of infection associated with the transplantation procedure.*** | ***Vital signs and adverse events will be assessed whilst patient is on trial treatment and for up to 28 days following completion of treatment.*** |  |  |  | ***N/A*** |

| Risks to the reliability of the RESULTS *Examples are provided in red italic text. Add/delete rows as required:* | | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Category | Particular risk identified?  (No/Yes/N/A) | If yes, list specific concerns | If yes, how will risks be minimised?  (specify any mitigations) | Likelihood | Consequence | Residual Risk Score | Justification for tolerating risk where applicable and details of any checks required |
| Eligibility criteria  E.g.  Does the trial require very precise assessment of eligibility?  Are special tests/ assessments required? | **Yes** | **The trial has a restricted eligibility criterion, where patients need to be specifically assessed to be ECOG performance status 2 at the time of registration.** | **The eligibility form will contain tick boxes containing individual statements taken from ECOG performance status scales and criteria. The form will also contain yes/no eligibility questions relating to ECOG status. This will be double checked by confirming at registration.** |  |  |  | **Quality Checks and Quality Assurance Audits will include source data verification to ensure ECOG performance status recorded in the medical notes is consistent with the ECOG status recorded on the eligibility form and registration form.** |
| **Yes** | **Patients who are at an increased risk of pulmonary haemorrhage will be excluded from the trial.** | **Investigators have been made aware of the dangers to patients who fall into this category.** |  |  |  | **Quality Checks and Quality Assurance Audits will include checking patients meet eligibility criteria.** |
| **Yes** | **There is a risk of ineligible patients being enrolled as such a rare disease, symptoms may be misleading.** | **Only Investigators experienced in this disease site that have diagnosed and treated cases before will be able to randomise.** |  |  |  | **Quality Checks and Quality Assurance Audits will include checking patients meet eligibility criteria.** |
| Randomisation procedure  E.g.  Is there any possibility that the treatment allocation might be predicted prior to randomisation?  Is the system robust? | **Yes** | **The Investigator has provided their own web based randomisation service, concern with potential access issues/ system failure.** | **Investigator assures a back-up server system is in place and that usernames/passwords are registered for the LCTU trial management team. They also operate a 24 hour help line in the event of any access issues.** |  |  |  | **N/A** |
| **Yes** | **The Investigator is using block randomisation for the trial, which could lead to selection bias.** | **The block size will not be stated in the protocol and a varied block size will be used to limit bias.** |  |  |  | **N/A** |
| Intervention  E.g.  Is it a complex intervention/treatment regimen which might be applied incorrectly?  If applicable, can process of dose escalation be easily followed? | **Yes** | **The study involves the use of intensity modulated radiotherapy. The treatment is intensified i.e. radiotherapy dose delivered to the cancer is increased over 5 weeks.** | **Only Investigators with appropriate training will be treating patients within a single centre. In addition the site at which the trial will be run has experience in approximately 100 cases using this technique.**  **There will be strict adherence to the radiotherapy contouring protocol with a contouring review exercise prior to commencement according to the contouring protocol.** |  |  |  | **Quality Checks a will include checking that the contouring review exercise has been performed by Consultants prior to any treatment of patients by reviewing the date the exercise was performed and the date the patient received treatment.** |
| ***Yes*** | ***Complex treatment schedule requiring patients to attend 3 separate hospital departments on the first day of treatment with delivery of a highly potent drug in the 2nd department which must also be given at an exact measure. Timing of chemotherapy agents is precise and will need close monitoring.*** | ***Sites will be trained on the importance of treatment timing at site initiation. A checklist will be provided so that each department will be able to see each time the treatment was administered and each team will be required to sign off their treatment section (with start/finish times for the treatment given).*** |  |  |  | ***This checklist along with treatment CRFs will be requested immediately after treatment and will be checked in-house to ensure that not only has the correct dose been delivered but that the timing was exact. The prescription forms and accountability logs will also be collected and cross-checked.*** |
| **Yes** | **Patients required to take a total of 11 tablets per day. The patient population is elderly and may have other co-morbidities requiring medication, there is a risk the study instructions may not be followed correctly.** | **Eligibility criteria include assessment as to whether patient is able to comply with trial treatment.** |  |  |  | **Drug compliance will be actively monitored in-house by cross-checking CRFs, drug accountability logs and patient diaries.**  **Compliance will also be checked during on-site Quality Checks and Quality Assurance will review the prescription forms and CRFs.** |
| ***Yes*** | ***This trial uses a dose schedule finding algorithm with 7 potential dose schedules. A maximum of 4 of these will be tested during the study and clear communication between the sponsor and sites is essential to ensure correct dose.*** | ***Following patient registration, LCTU will inform sites of the assigned dose schedule for each individual patient which must be clearly documented and relayed to other members of the research team.*** |  |  |  | ***Quality Checks and Quality Assurance Audits* will include checking prescription that correct dose prescribed for cohort.** |
| Management of intervention  E.g. Consider any IMP supply, management, storage, QP release and dispensing requirements issues and impact/likelihood of non-adherence. | **Yes** | **One arm of the trial treatment uses an IMP supplied by Belgium who use a company in China for the mechanism to deliver the IMP. If there are any supply issues from either country the particular treatment arm of the trial will not be available and the arms will therefore be unbalanced.** | **Assurances have been sought from both suppliers that there is sufficient stock to supply for the duration of the trial.** |  |  |  | **Quality Checks and Quality Assurance Audits to ensure that usability of the stock is efficient and not wasteful to ensure demand for new supplies will not be required.** |
| **Yes** | **The IMP has to be temperature controlled and shipped at minus 10 degrees. It must also be at the site within 3 hours.** | **A specialist company that is already used by the supplier has been employed to transfer the IMP to sites.** |  |  |  | **Quality Checks and Quality Assurance Audits will include checking the shipment and delivery times to ensure that the protocol requirements are being adhered to.** |
| Blinding  E.g.  If it is required is there any risk that it could be ineffective?  Does the unblinding method provide 24-hour cover with the appropriate level backup and failover processes?  Is blinding to be performed by local pharmacies?  Could there be any unblinding during the course of the trial? | **Yes** | **As this is a small trial (recruiting 100 patients), unblinding procedures will be performed by local pharmacies. This could affect objectivity and result in inappropriate unblinding.** | **Local pharmacies have been assessed to ensure they can provide this service. The provision of this service is included within the site agreement.**  **Staff at sites will be trained that unblinding must only occur where knowledge of the treatment is essential for the correct clinical care of the patient or where a person other than the patient has taken trial medication**  **Site-specific instructions will be provided.** |  |  |  | **Quality checks on unblinding process will be performed.**  **Quality Checks and Quality Assurance Audits will include checking that all sites are conversant with the process and the reasons for unblinding.** |
| **Yes** | **This is a placebo controlled, double blinded trial. Unblinding will occur in the event of disease progression or SAE where knowledge of the trial treatment is essential for patient care. Disease progression is known to be high and therefore there is a risk that frequent unblinding may occur and could lead to the site becoming aware of which patients are receiving the placebo and active drug. Disease progression is also an end point and this could lead to results being available early and visible to sites.** | **A 24 hour unblinding service will be provided and controlled by the LCTU (office hours) and an external service provider outside of office hours. The caller will be asked to provide a brief reason for the unblinding requirement. Details of the unblinding procedures are located within the protocol, pharmacy file and on the patient card.** |  |  |  | **Reasons for unblinding will be monitored as will the number of patients unblinded.** |
| Outcome measures  E.g.  Are any key outcomes subjective, or require complex assessment?  Is there potential for standardised assessment or external verification (e.g. death certificate)? | **Yes** | **One of the outcome measures for the trial is complete pathological response.** | **An in-house review of all pathology reports will be performed by two independent assessors to conclude if complete Pathological Response has occurred. A standard form will be completed for each patient and compared. Where there is disagreement a third independent assessor will make the final decision.** |  |  |  | **Quality Checks and Quality Assurance Audits will include checking that each patient report has been reviewed by two assessors and any differences concluded.** |
| **Yes** | **One of the secondary outcome measures for this trial is complete resection. Local surgeons and radiologists will be asked to judge the resectability of the tumour based on imaging.** | **In order to assist sites in the decision making process, an Advisory Radiology Panel has been established which will review and provide a final opinion on a specific patient’s imaging for cases where it is difficult to ascertain if the tumour has been resected.** |  |  |  | **N/A** |
| Sub-studies/Sample Collection  E.g.  Are there any issues with sample collection, storage, transfer of materials?  Obtaining consent for the sub-study?  Sending data to patients? | **Yes** | **Sites will be asked to send different types of blood samples identifying the patient only by TNO via special delivery using Royal Mail containers. There is a risk that the samples may be lost in the postal system.** | **Sites will be asked to divide the samples equally across two boxes to minimise the risk of 1 box becoming lost.** |  |  |  | **Deliveries will be centrally monitored and alternative transportation methods identified and used if there is an issue with this system.** |
| **Yes** | **The trial examines the welfare of the patient by using booklets sent directly to them for 7 years. This is a long period in which patients may move address or cease to want to participate.** | **Patients have to provide explicit consent for their GP to be advised of their participation in the study, through which reminders will be sent if no response or “addressee unknown” post is returned to the LCTU.** |  |  |  | **N/A** |
| Follow-up  E.g.  Is the follow-up schedule difficult? (e.g. long and different from standard care)  What is the likelihood and impact on the trial results of non-adherence? | **e.g. Yes** | **This study has a 20 year follow up period. Patients may become lost to follow up or discharged to GP care. There is also the possibility that given the length of follow up, original research staff will leave and be replaced with staff members unfamiliar with the trial and its requirements, creating a danger of forms being incorrectly filled out or not completed.** | **In order to maintain follow-up compliance, a simple case report form will be used in addition to comprehensive guidelines for completion to ensure that new staff members have supporting information to work on the trial. Mail shots containing forms, reminders and queries will be sent along with ad hoc newsletters to ensure that trial awareness is maintained. The Informed Consent Form will request that patient data can be collected from the GP and Data Linkage Service. A GP letter will be produced to advise of the trial and request for their assistance in cases of patients discharged to GP care. Sites will be advised that they may also telephone the patient for follow-up.** |  |  |  | **The Trial Coordinator and Trial Statistician will monitor returns of data from sites, to identify any underperforming sites.** |
| IT Systems | **e.g. Yes** | **This study is using a bespoke Trial Management System that was created by the LCTU IT Team.**  **Due to the nature of the intervention, the system is required to send automated SMS text messages, there is a risk that these may not be received.** | **The LCTU IT team will put in place a manual process for checking the SMS logs to identify where text messages are not received and this will be communicated to the trial team.** |  |  |  | **The Trial Manager will review report from the IT team on a monthly basis.** |
| Statistical considerations  E.g.  Is there any concern that the trial may have insufficient power to detect the anticipated effect of the intervention?  Any other risks associated with trial design/outcome measures/analysis plans? | **Yes** | **There is a concern that there will be insufficient power to detect the anticipated effect of the intervention due to lower than anticipated patient numbers.** | **Research and feasibility questionnaires indicate that there should be sufficient numbers in this disease population to achieve recruitment targets. The scenario has been factored into the statistical analysis plan and alternate options are available if this occurs.** |  |  |  | **N/A** |
| Data collection  E.g.  Is there any particular cause for concern over the data collection (e.g. volume and complexity of the data)?  Potential for fraudulent data? Quality control checks? Data Management plan? | **Yes** | **This trial is not part of the NIHR Portfolio so research nurse time may be limited which may impact on data return/quality.** | **A modest payment is available to Trust R&Ds to cover nurse time. The Trials Team are aware that this may be an issue and will be proactive in ensuring data is returned in a timely fashion.** |  |  |  | **Sites will have on-site audit visits which will include source data verification to ensure quality is high and to encourage data return.** |
| **Yes** | ***The external CTU has provided the trial database which does not allow for tracking of data return.*** | ***Negotiations are ongoing with the CTU to provide sufficient reporting mechanisms. If required CRF return will be tracked internally.*** |  |  |  | **N/A** |

| **6. Other risks**  *Examples are provided in red italic text. Add/delete rows as required:* | | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Category** | **Particular risk identified?**  **(No/Yes/N/A)** | **If yes, list specific concerns** | **If yes, how will risks be minimised?**  **(specify any mitigations)** | **Likelihood** | **Consequence** | **Residual Risk Score** | **Justification for tolerating risk where applicable and details of any checks required** |
| **Finance**  E.g.  Availability of the appropriate resources. | ***Yes*** | ***Funding has been provided by XXX for 2 years. There are multiple targeted requirements that have to be met within this timeframe in order for finance to be renewed at the end of this period. One of the set criteria is that 50% of the recruitment target must be met within this period. Given the nature of the disease site, this is a challenging target which may require the initiation of additional sites to meet the target.*** | ***Recruitment will be monitored frequently with sites being encouraged by the Trial Coordinator to enter patients. Screening logs will also be collected and reviewed.***  ***Investigator meetings will be held to promote awareness of the disease site and the trial and to encourage referrals from non-participating centres.*** |  |  |  | ***N/A*** |
| **Investigator sites**  E.g.  Education and experience of study teams, location of sites, existence of quality systems | ***Yes*** | ***The investigator team have not undertaken CTIMP trials previously, although they will be receiving training from the LCTU, there is residual risk that they may fail to ensure that the trial is conducted in line with GCP*** | ***A Senior Trial Manager will be appointed centrally and additional money has been allocated within the budget for them to travel to site to undertake quality assurance audits, provide advice and guidance and have a higher level of oversight.*** |  |  |  | ***Increased Level 1 and 2 checks will be undertaken in line with LCTU SOPS to detect deviations and ensure that staff are fully supported.*** |
| **Sponsor/coordinating centre/partner organisations**  E.g.  Education and experience, existence of quality systems | ***Yes*** | ***This is an international trial. The trial will operate from National Coordinating Centres (NCC) in each country to manage the trial in accordance with the protocol and relevant laws.*** | ***The contract with the NCC specifies which aspects of trial management are to be taken on by the NCC.***  ***Each NCC will be assessed for its suitability.***  ***NCC will be consulted regarding any changes to trial documents in order to comply with local regulatory/ legislative requirements and translation of documents***  ***Trial Coordinator and Monitor will visit NCC to provide training.***  ***NCCs will perform site initiation and on-site monitoring of sites in their country.*** |  |  |  | ***Monitoring plan will detail level of checks to be performed at each site.*** |
| **Trial governance**  E.g. Influence upon/ interference with trial governance by a private organisation.  Consider requirements placed on sponsor by drug company if supply of drugs is provided free of charge. | ***Yes*** | ***The device used within the trial is only available through the current manufacturer. The device manufacturer also has interests in the results of the trial.*** | ***Responsibilities will be clearly defined in contracts between the Sponsor and the device manufacturer. This will include what trial data the device manufacturer has access to.*** |  |  |  | *N/A* |
| **Pharmacovigilance**  e.g. Consider any issues with AE/SAE SUSAR reporting, and any requirements for safety reporting to drug company as specified in any Safety Data Exchange Agreements. | ***Yes*** | ***Any SAE must also be reported to GSK with 24h and all AESI must be reported via line listings monthly.*** | ***Prompts put in CRF to remind study team to remember to report to third party vendor as well as sponsor.*** |  |  |  |  |
| **Insurance/Indemnity** |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |

**Appendix a – LIKELIHOOD**

The matrix below should be used to identify the frequency that each hazard may occur.

|  |  |  |
| --- | --- | --- |
|  | **Category** | **Description** |
| 5 | Almost certain | Likely to occur on many occasions / target or objective will definitely not be met |
| 4 | Likely | Will probably occur but not a persistent issue / almost certain that target or objective will not be met |
| 3 | Moderate | May occur occasionally / may not achieve target or objective on occasion |
| 2 | Unlikely | Do not expect it to happen but it is possible / achievement of target or objective almost certain |
| 1 | Rare | Can’t believe that incident will ever happen / achievement of target or objective certain |

**Appendix b – IMPACT**

The matrix below should be used to identify the consequences each hazard may have. Not all the columns will be relevant for each hazard.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Category/**  **Severity** | **Adverse Effect/Harm to Patient / Staff / Public** | **Service/**  **Environmental Impact** | **Reputation/Publicity/**  **Political Impact** | **Regulatory/**  **Legal Compliance** | **Patient Experience** | **Consequence** | **Financial Impact**  **£** |
| Catastrophic 5 | Death or major adverse effect/harm and permanent disability | The organisation would be rendered dysfunctional. Operational performance would be compromised to the extent that the organisation is unable to meet obligations and liabilities in core activity areas | Nationwide multi media coverage | Severe accountability likelihoods would result in the organisation being unable to meet key regulatory requirements | Totally unsatisfactory patient outcome | Detrimental effect  on use of people/ knowledge/  data | £1m+ |
| Major 4 | Major adverse effect/harm or long term disability | Operational performance of the function/activity areas would be severely affected with the organisation unable to meet a major proportion of its obligations and liabilities. The organisation's asset/ resource base may be significantly depleted | Extensive local coverage and widespread NHS coverage | Organisation would not be able to comply with the majority of its regulatory requirements effectively | Patient outcome or experience significantly below reasonable expectation across the board | Major effect  on use of people/ knowledge/  data | 50,000 - £1m |
| Moderate 3 | Significant adverse effect/harm – medical intervention necessary – some temporary incapacity | Operational performance of the organisation would be compromised to the extent that revised planning would be required to overcome difficulties experienced by function/activity area | Coverage throughout organisation and/or some public coverage | Organisation would experience difficulty in complying with key regulatory requirements, which would jeopardize some external interests | Patient outcome or experience below reasonable expectation in one or a number of areas | Moderate effect | 5,000 – 50,000 |
| Minor 2 | Minor adverse effect/harm – First aid or self treatment – No incapacity | Slight inconvenience/ difficulty in operational performance of function/activity | Coverage limited to elements within the organisation (e.g. trade unions) and /or some external stakeholders | Some accountability implications for the function/activity area, but would not affect the organisation’s ability to meet key regulatory/ compliance requirements | Patient experience temporarily unsatisfactory – rapidly resolved | Minor effect on use of people/ knowledge/  data | 500 – 5,000 |
| Insignificant 1 | Adverse effect/harm not requiring intervention | Operational performance of the function/activity would not be materially affected | Awareness limited to individuals within the organisation | Organisation would not encounter any significant accountability implications | Single resolvable problem in patient experience | No significant effect on use of people/ data knowledge | 0 – 500 |

**Appendix c – Risk Score and Action Matrix**

|  |  |  |
| --- | --- | --- |
| **Risk Score** | **Guidance** | **Action** |
| Low (1-6) | This level of residual risk can be tolerated | No further action required |
| Medium (7-14) | This level of residual risk can still be tolerated, but some additional mitigating action should be considered to reduce the risk | Document considered mitigating actions or rationale for accepting risk level.  An increased level of checks may be proportionate to ensure that where a risk is coming to fruition, this is identified early and addressed. |
| High (15-19) | This level of residual risk can only be tolerated if some additional mitigating action/checks are put into place. | Document mitigating actions and rationale for accepting risk level.  Refer to RSMOG and RSC for discussion and to confirm any mitigation decisions if necessary. |
| Critical (20-25) | This level of residual risk cannot be tolerated without further treatment. | Escalate this risk to RSMOG and RSC. Mitigation decisions and decision to sponsor study MUST be agreed by the RSMOG/RSC and documented. |