**JRMO Comprehensive Risk Assessment Tool for Sponsored MHRA regulated studies**

**For use in conjunction with SOP 23 Risk Assessment**

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| --- | --- | --- | --- |
| **Study title (in full):** |  | | |
| **Short title:** |  | **Name of CI:** |  |
| **IRAS No** |  | **Name of CTU (if applicable):** |  |
| **ReDA No** |  | **Name of Trial co-ordinator:** |  |
| **Proposed Sponsor Organisation:** | Barts Health NHS Trust /  Queen Mary University of London | | |

**Review and revision record**

The Risk Assessment (RA) should be reviewed, and amended if necessary, whenever substantial amendments are made.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **RA date** | **Reason for review** | **Version of RA form reviewed** | **Protocol version & date** | **Outcome of review** | **Comment** |
|  | *Sponsorship with conditions application* | 2.0 |  |  |  |
|  | *change requested by Research Ethics Committee (REC); substantial amendment (amendment number); annual review; etc.* |  |  |  |  |

**Responsibilities:**

* It is the responsibility of the Good Clinical Practice (GCP) and Governance manager to ensure that the RA form is completed as part of provisional approval and study development.
* A RA form should be signed prior to submission of study documentation to the Medicines and Healthcare products Regulatory Agency (MHRA)/REC.
* The RA form should be reviewed, and amended if necessary, whenever substantial amendments are made to the protocol or other key study documents.
* An annual review of the RA should take place whether or not there have been any amendments. This will occur during annual Chief Investigator (CI) meeting. If no changes are needed this will be documented in the meeting notes.
* *Guidance notes are provided in blue italics. Guidance notes should not be copied and pasted into the RA form. The RA form should be made study specific.*

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Investigational Medicinal Product (IMP) or Device name** | **UK licencing status** | **EU licencing status** |
|  |  |  |  |
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| --- | --- |
| **IMP Risk Categorisation**  **(Applicable for Clinical Trial of an Investigational Medicinal Product (CTIMP) and Advanced therapy medicinal products (ATMPS) only)** | *(see appendix 1 for categorisation guidance)*  **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 risk of standard medical care  **Justification:** |

**Part 1- Applicable only for CTIMPS and ATMPS to be completed at protocol development stage (once risk type has been discussed with GCP manager and Sponsor Pharmacist and agreed delete non applicable columns and complete )**

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| --- | --- | --- | --- | --- | --- | --- |
| **Document** | **Type A** | | **Type B** | | **Type C** | |
| **Risk adaptation permitted?** | **Description or comment on Risk adaptation applied?** | **Risk adaptation permitted?** | **Description or Comment on Risk adaptation applied?** | **Risk adaptation permitted?** | **Description or Comment on Risk adaptation applied?** |
| Investigators Brochure (IB) | Yes |  | (Yes) |  | No |  |
| IB annual review or update | No |  | No |  | No |  |
| Template IMP label | Yes |  | (Yes) |  | No |  |
| Certificate(s) of analysis | Yes |  | (Yes) |  | No |  |
| IMP shipments | Yes |  | Yes |  | No |  |
| IMP handling instructions | Yes |  | (Yes) |  | No |  |
| Out of Pharmacy IMP storage |  |  |  |  |  |  |
| Master randomisation list | No |  | No |  | No |  |
| Unblinding procedures | No |  | No |  | No |  |
| Site IMP accountability | Yes |  | (Yes) |  | No |  |
| IMP return/destruction | Yes |  | (Yes) |  | No |  |
| IMP dossier | Yes |  | (Yes) |  | No |  |
| Manufacturer/Importer Authorisation (MIA) for IMP | Yes |  | (Yes) |  | No |  |
| Manufacturing authorisation (MA) | (Yes) |  | No |  | No |  |
| IMP importation authorisation | No |  | No |  | No |  |
| Qualified Person (QP) certification | N/a |  | (Yes) |  | No |  |
| Good manufacturing practices (GMP) compliance statement | Yes |  | (Yes) |  | No |  |
| 24 hour emergency medical out of hours cover | Yes |  | (Yes) |  | No |  |
| Adverse Event (AE)/Adverse Reaction (AR)recording | Yes |  | (Yes) |  | (Yes) |  |
| AE/AR reporting to  sponsor | Yes |  | (Yes) |  | (Yes) |  |
| Serious Adverse Event (SAE)/Serious Adverse Reaction (SAR) reporting tosponsor | (Yes) |  | (Yes) |  | (Yes) |  |
| Suspected Unexpected Serious Adverse Reaction (SUSAR) reporting to  MHRA/REC/investigators | No |  | No |  | No |  |
| Annual safety report (APR) | Yes | *(APR to be used)* | No |  | No |  |
| Study level IMP  Accountability | Yes |  | (Yes) |  | No |  |
| Subject level IMP  Accountability | Yes |  | (Yes) |  | No |  |
| Storage conditions  records | (Yes) |  | (Yes) |  | No |  |
| Document retention time | (Yes) |  | (Yes) |  | No |  |
| Reduced MHRA role for  approval | Yes |  | No |  | No |  |

**Part 2- To be completed at the Sponsorship assessment ( CI and Team to complete Columns marked in yellow)**

| **RISK/HAZARD** | **What is the risk in this area?**  **Low, moderate, high or unacceptable?** | **Considerations/Concerns Identified**  *Provide details of trial-specific considerations/risk concerns* | **Mitigation Strategies / Adaptations to minimise the hazard:**   * *Address all concerns identified*   *Provide details of any risk adaptations to conventional GCP management strategies employed*  *These are EXAMPLES and should be made study specific if they apply at all!* | **Additional comments on** impact on trial monitoring requirements |
| --- | --- | --- | --- | --- |
| ***Risks associated with trial IMP (CTIMPs and ATIMPs only)*** |  | * *Phase of development* * *Study population: healthy subjects or patients? Vulnerable populations?* * *If IMP is licensed, is it being used outside its licensed indication? Has the dosage/ regimen/ route 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)?* * *If unknown, what are the anticipated risks/other effects based on preclinical data or knowledge of class of drugs?* * *Is the duration of use compatible with previous experience?* * *Is there a potential risk for dosing errors?* * *May concomitant medications increase the risk, i.e. interactions.* * *Additional safety monitoring in comparison to standard care?* * *What are the arrangements for out of hours medical advice?* * *How will treatment compliance be monitored?* * *Are any other risk mitigation strategies necessary (restrictive eligibility criteria; treatment protocol (timing of dose, location of administration, availability of rescue medication); criteria for stopping or modifying study treatment; AE reporting strategy; duration of exposure and follow-up; Trial Oversight)?* | * *Where risks associated with the IMP / intervention are somewhat or markedly higher than the risk of standard care (i.e. Type B or C trials) details regarding specific risks to body systems and proposed methods for clinical monitoring of such risks should be described* * *Measures and controls where the risk of the intervention is considered to be comparable to standard care (i.e. Type A) need not be spelled out in detail. However basic assumptions about routine monitoring and consideration should be* *summarised as part of the justification provided* |  |
| ***Poor IMP management systems*** |  | * *Is its clear which drugs are classed as IMPs?* * *Is the supply of IMP from the drug company secure? Is the IMP manufactured by more than one company (for redundancy)?* * *Are IMP storage systems adequate?* * *Is there appropriate control of IMP release to Sites?* * *Are IMP handling instructions for sites clear (potential for dosing errors, temperature deviations, etc.)?* * *Is IMP management complex or subject to strict deadlines (e.g. unusual storage requirements, short expiry period)?* * *Is there potential for interruption to or change in standard of care?* * *Is standard of care likely to be different between sites?* * *Is there a need for/ will there be 24 hour emergency medical advice?* * *Is the process for dose escalation/reduction described in the protocol* |  |  |
| ***Risks associated with experimental medical device (Clinical Investigations only).*** |  | * *What is the class of the device?* * *Is the device CE-marked for another indication? Does the device have authorisation outside of the EU? Have there been any previous clinical studies using the device.* * *What safety information is currently available concerning the device? Are there any known safety issues with the device or its components? Are any of the materials or components used in the device novel? Are any of the materials allergenic?* * *Does the device administer or generate ionising or non-ionising radiation? What is the expected dose of radiation?* * *What “device deficiencies” could possibly occur?* * *What harm could be caused by misusing the device?* * *Are any activities, medications etc. prohibited while using the device?* * *What are the sterilisation and storage requirements of the device? How will device accountability be managed?* * *Does the device consist of or include software? If so, how has the software been validated? How will the integrity of recorded data be ensured? How will identifiable data collected by the device be kept confidential? How will software and security updates be managed?* * *Where is the manufacturer based? Are they experienced in acting as the manufacturer for Clinical Investigations within the UK or EU? Are they engaged with the development of the study?* * *Where will the device be produced? What quality management systems, accreditations and authorisations does the manufacturing facility have?* * *What impact could supply chain or manufacturing delays have of the treatment of participants?* * *Study population: healthy subjects or patients? Vulnerable populations?* * *What are the arrangements for out of hours medical advice?* * *How will treatment compliance be monitored?* | * *Are any other risk mitigation strategies necessary (restrictive eligibility criteria; location of administration, access to medical support; criteria for stopping or modifying study treatment; AE reporting strategy; duration of exposure and follow-up; Trial Oversight.* |  |
| ***Hazards of clinical procedures specified in protocol*** |  | * *Do the procedures differ from standard care (e.g. increased radiological exposure, additional biopsies, questionnaires involving ‘sensitive’ subject areas, contact with harmful chemicals, substances, equipment or organisms)?* * *Will all sites be performing all procedures, or will some only complete a sub-set of them?* | * *Data Monitoring and Ethics Committee* * *IRMER / ARSAC review* * *Adverse event reporting systems* * *Performed by trained staff*   *Provision for containment, shielding, monitoring, etc.* |  |
| ***Non-compliance with informed consent process*** |  | * *Does the study population involve vulnerable groups?* * *Will participants have capacity to give consent?* * *Is the consent process complex (e.g. multiple consent forms or stages)?* * *Will there be sufficient time to consider information (e.g. consent in an emergency setting)?* * *Is there a process for acting on patient request to withdraw from trial?* * *Is the trial capable of recruiting participants for whom English is not their first language?* | * *Training and awareness-raising* * *Supervision of consent process* * *100% source data verification of consents and eligibility* * *Re-consent throughout trial* * *Consent taken by treating clinician only* * *Assessment of capacity* * *Communication systems e.g. alerts stickers in patient notes, contact details on consent form* * *Confirmation of consent prior to randomisation* * *Audit of consent procedures including verification of signed consent forms in clinic records* * *Withdrawal procedure defined in protocol* * *Use of a withdrawal case report form* |  |
| ***Failure to protect participants’ privacy*** |  | * *Will health and social care data (sensitive data) be collected?* * *Will identifiable data be collected?* * *Are data collection methods secure (e.g. recording of qualitative interviews)?* * *Will data be transferred between organisations?* * *Will identifiable data be transferred to third parties?* * *Will data be sent outside UK?* * *Will transfer of data be secure?* | * *Anonymised or de-identified / linked data* * *Storage with IG toolkit approved location and systems* * *Minimise staff who have access to confidential information* * *Training and awareness-raising* * *Computer security systems* * *Fully auditable database* * *Use of encrypted media* * *Specific consent for data transfer, payment of travel expense, etc*   *.* |  |
| ***Study inadequately powered*** |  | * *Was a statistician involved with the power calculation?* * *Will the study have sufficient power to detect the anticipated treatment effect?* * *Is the recruitment target feasible (restricted access to patients, insufficient patient pool, adequate time scale, and competing trials)?* * *Might the inclusion/exclusion criteria be too restrictive?* * *Will there be sufficient statistical input and ongoing support?* | * *Statistical input to design and power* * *Recruitment assessment* * *Pilot or feasibility studies* * *External communication and trial promotion* * *Oversight of recruitment rates* * *Trial steering committee, data monitoring committee, and trial management group in place* |  |
| ***Major violation of eligibility criteria*** |  | * *Does the trial require very prescriptive or complex eligibility criteria (e.g. long list of prohibited previous or concomitant medications, requirement of presence/absence of previous or concomitant disease)?* * *Will confirmation of eligibility require special/complex assessments?* * *Will Inexperienced/untrained staff be carrying out eligibility assessments?* | * *Site initiation training covering eligibility criteria* * *Eligibility criteria detailed in protocol and protocol available at every research site* * *100% Source data verification of eligibility* * *Pilot study demonstrating suitability of eligibility criteria* * *Eligibility criteria verified prior to randomisation* * *Standard process for assessing eligibility queries* * *Use of well-designed CRFs* * *Monitoring of eligibility during site visits* |  |
| ***Lack of robust randomisation procedure*** |  | * *Is the person / organisation responsible for randomisation experienced?* * *How will site teams determine a participant’s randomisation allocation (e.g. telephone coordinator, web, interactive voice recognition)?* * *Is randomisation available / needed out of hours?* * *Is there a possibility of unbalanced/incorrect randomisation?* * *Is there a risk of prediction of treatment allocation when entering patients?* | * *Randomisation system tested before implementation* * *IDMC to review balance between trial arms at regular intervals* * *Independent central randomisation* * *Trial specific randomisation procedure* * *Trial specific unblinding procedures – refer to point 2.4* |  |
| ***Potential for loss of blinding*** |  | * *Will there be a robust emergency unblinding procedure?* * *Is the unblinding procedure complex?* * *Are the IMP and placebo distinguishable?* * *Could a clinical event effectively unblind the patient or group to which the patient was randomised?* * *Is there a robust unblinding procedure for reporting of SUSARs?* * *Will there be unblinded team members?* * *Will the randomisation allocations / keys be accessible to blinded individuals?* * *How will information that could lead to unblinding be kept secure?* | * *Independent randomisation* * *Access to randomisation schedule controlled (including for unblinding SUSARs, emergency unblinding, etc.)* * *Documented emergency unblinding procedure* * *Use of emergency code break envelopes* * *Detailed in protocol* * *Placebo formulated to match the IMP* |  |
| ***Unreliable outcome assessment*** |  | * *Are there key outcomes which require subjective or complex assessment?* * *Is there a risk of poor data quality?* * *Will source data be available for verification e.g. death certificate, laboratory investigation result?* * *Will equipment be calibrated?* * *Is there a risk to completeness of follow-up, i.e. is the follow up schedule difficult? Is there a risk of significant loss to follow up?* * *Have questionnaires been validated?* | * *Well defined objective end point* * *Standardised data collection forms* * *Training in CRF completion* * *Data Monitoring Committee* * *Trial Management Protocol* * *Central data monitoring* * *Statistical input to data monitoring and audit* * *Source Data Verification Detailed in protocol* * *Equipment calibration and maintenance contracts* |  |
| ***Data collection and management*** |  | * *Are Sites familiar with the data collection method?* * *Has the CRF been approved?* * *Has the eCRF been tested and approved?* * *Is there a risk of poor data quality?* * *Is there a risk of poor data quality?* * *Are unnecessary data points being collected?* * *Has the database been specified and tested?* * *Will the database be secure?* * *Is the data complex* | * *Standardised data collection forms* * *Training in CRF completion and data entry* * *Data Monitoring Committee* * *Central data monitoring* * *Source Data Verification* * *eCRFs with validation checks* * *Standardised data collection forms* * *Training in CRF completion and data entry* * *Trial specific Data Management SOP* * *Statistical input into central data monitoring* * *Statistical analysis in accordance Statistical Analysis Plan* * *Data encryption for all portable media* * *Specification document, system validation, and user acceptance testing all recorded* * *Database backup (use of centrally supported systems)* * *Restricted and role based access to database* * *Traceability for all data corrections* * *Detailed in protocol* * *Data Monitoring Committee* * *Data quality checks (inc SDV)* |  |
| ***CI experience*** |  | * *Has the CI acted as CI for a MHRA regulated study previously?* * *Has the CI been involved in an appropriate level of research prior to this study?* * *Is the CI’s speciality appropriate for this Trial? Can they perform the interventions listed?* * *Is the sponsor aware of non-compliance issues from past experience with the CI (this could be interaction with Sponsor, audit results, inspection outcomes, evidence of misconduct or local non-compliance with SOPs, or refusal to comply with sponsor requests)?* | * *Use if CI mentor or experienced trial chairman* * *Increase reporting* * *Set regular meetings with CI (e.g. monthly)* |  |
| ***Competence of partner organisations*** |  | * *Will the trial involve multiple sites?* * *Will key functions be performed by partner organisations (e.g. central laboratory, randomisation and unblinding, IMP management)?* * *Are responsibilities and liabilities of partner organisations clear?* | * *Site registration process (Inc. checking trial assurance processes)* * *Trial coordinator / manager* * *Site visits* * *Investigator initiation meetings* * *Site and collaborator agreements* * *Monitoring of collaborating sites* * *Delegated responsibilities clearly identified and agreed in site file / contracts (including supervision requirements)* * *Systems to ensure reporting obligations for medicinal trials (SUSARs, amendments, termination)* * *Partner competency assessment* |  |
| ***Inadequate trial management*** |  | * *Are key responsibilities defined?* * *Is the central trial management team sufficiently experienced?* * *Are there conflicts of interest for the central trial management team?* * *Is the sponsor aware of non-compliance issues from experience with the trial management team?* | * *Roles and responsibilities clearly outlined in conditions of sponsorship* * *SOPs in place* * *Trial Steering Committee* * *Regular GCP training (every 2 years) for trial management team* * *Regular trial management group meetings* * *Trial delegation log* * *Internal quality assurance audits* * *Use of a Clinical Trials Unit* |  |
| ***Appropriate resources not available*** |  | * *Have the research and treatment costs been fully costed?* * *Is the staffing level of the trial sufficient?* * *Consider the number of sites and countries involved.* * *Is there sufficient resource to conduct appropriate monitoring?* * *Is full recruitment possible within the current funding timelines?* * *Is there a risk of withdrawal of funding?* * *Has the cost of continuation of drugs or device provision after research has finished been considered?* * *Do all sites have the infrastructure to support the trial?* * *Has the funding source been secured?* | * *Trial costed via JRMO* * *Contract with funding body* * *Contact with service early in planning and throughout the trial* * *Trial uses routine clinics* * *NHS R&D approval* * *Multidisciplinary project teams* |  |
| ***Inadequate pharmacovigilance or Vigilance systems*** |  | * *Are SAEs and device deficiencies reported to the sponsor or the manufacturer?* * *Is the SAE reporting form/process complex?* * *Will there be an SAE monitoring and review process?* * *Are sites and trial management team familiar with SAE reporting requirements?* * *Are there systems to maintain awareness of and to act on new knowledge?* * *Will participants be able to report adverse events and study outcomes reliably?* * *Will adverse events be captured throughout the trial and appropriate follow up periods?* * *Is the CI familiar with the IMP/device and its potential side effects?* | * *Training in SAE reporting* * *Pharmacovigilance procedures detailed in protocol* * *Standardised SAE report form* * *SAE reporting / assessment checklist used by coordinating centre for each SAE* * *Reminder system to ensure Annual safety reports sent to MHRA and PIs* * *Additional Pharmacovigilance telephone calls to Sites* * *Data Monitoring and Ethics Committee* * *Dedicated Pharmacovigilance staff* |  |

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| ***Poor sample management*** |  | * *Are samples for the primary of secondary endpoints or outcomes being processed outside UKAS accredited laboratories?* * *Are the central laboratories known?* * *Are the central laboratories commercial or non-commercial?* * *Is the sample management process complex?* * *Are samples being sent to multiple laboratories?* * *Are sites familiar with sample collection and transfer requirements?* |  |  |
| ***Influence/ interference of private organisation upon trial governance*** |  | * *Have the CI and/or Collaborators declared any interests?* * *Is there a conflict of interest?( if yes please escalate)* * *Could there be a breach of patient confidentiality via inappropriate access to data / results?* * *Could external organisation misinterpret results?* * *Is ownership of data and Intellectual Property clear?* * *Are other organisations involved in trial design?* * *Will a manufacturer have used data from this trial for licensing or CE-marking purposes?* | * *Conflicts of interest declared* * *Non-disclosure agreements implemented* * *All organisations involved sign up to trial agreements* |  |
|  |  |  |  |  |
| ***RISKS TO THE ORGANISATION*** |  | * *If this study fails to complete what would be the risk to the sponsor?* * *Would ramifications be national or international?* * *Would any risk result in a lost revenue (actual or potential) or ability to perform core functions?* * *Is there any knock on costs of research projects being inaccurately costed at the outset?* * *Is there an Impact on clinical services?* * *Liability?* | * *Contact with service early in planning and throughout the trial* * *Multidisciplinary project teams* * *Clear identification of sponsor* * *Partnership agreements* * *Monitoring of collaborating sites* * *Delegated responsibilities clearly identified and agreed in site file (including supervision requirements)* * *Systems to ensure reporting obligations for medicinal trials (SUSARs, amendments, termination)* |  |
| ***Other*** *please give details:* |  | *E.g.*   * *Are the methods for advertising the study appropriate?* * *Will participants be paid travel expenses?* * *Is there a process for identifying and acting on potential serious breaches of GCP?* |  |  |

**Device section: To be completed for all Clinical Investigations**

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| --- | --- | --- | --- |
|  | **Device name** | **UK CE status** | **EU CE status** |
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| Has a Barts Health NHS Trust Clinical Physics assessment been performed? Yes / No | | | |
| If yes please insert a summary: | | | |

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| Summary of the main issues to be considered in the monitoring plan: |  |

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| **Level of risk** | | | | | |
| **Number of low risk areas** | |  | | | |
| **Number of moderate risk areas** | |  | | | |
| **Number of High risk areas** | |  | | | |
| **Risk category allocated** | |  | | | |
|  |  | |  |  |  |
| **Scoring guidance** | **All low risk**  **Or low apart from less than 5 moderate risk** | | **Up to 5 high risks identified but deemed in assessors view to be moderate risk due to mitigation strategies in place.** | **Over 5 High risk areas identified** | **At least one unacceptable risk identified** |
| **Low risk** | | **Moderate Risk** | **High risk** | **Unacceptable risk** |
| **The presence of certain risks classifies the trial as Unacceptable risk regardless of the number, as it is not possible to mitigate or minimize the hazard.**  **These include:**  **Insufficient funding,**  **Data to be used in Licencing application (i.e. a commercial study).** | | | | **Please document:** | |

**Authorisation: This section is to be signed once all risks and risk management strategies have been agreed. Signature indicates that the information is accurate, and agreement to comply with / complete mitigations.**

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| **CI** |  | **GCP and Governance Manager** |
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| Name of CI: |  | Name of sponsor representative: |
|  |  |  |
| Signature: |  | Signature: |
|  |  |  |
| Date: |  | Date: |

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| **Sponsor pharmacy representative** |  | **CTU ( if applicable)** |
|  |  |  |
| Name: |  | Name of CTU representative: |
|  |  |  |
| Signature: |  | Signature: |
|  |  |  |
| Date: |  | Date: |

**Additional authorisations e.g. CI mentor or trial chairman if applicable (please insert details):**

|  |  |  |
| --- | --- | --- |
| **[xxxx]** |  | **[xxxx]** |
|  |  |  |
| Name: |  | Name: |
|  |  |  |
| Signature: |  | Signature: |
|  |  |  |
| Date: |  | Date: |

**Acknowledgements**

This template is based on that developed by the Medicines and Healthcare products Regulatory Agency (MHRA), the University of Edinburgh Research Governance & QA Office (part of the Academic and Clinical Central Office for Research and Development (ACCORD- a collaboration between the University of Edinburgh, NHS Lothian and Edinburgh Research & Innovation).), and the South East Wales Trial Unit (SEWTU) on behalf of the Cardiff University. Available at: <http://forums.mhra.gov.uk/showthread.php?1678-Examples-of-risk-assessments> [Accessed 28 June 2016]

**Appendix 1 (TO BE DELETED UPON COMPLETION OF RA)**

*Guidance notes should not be ‘copied and pasted’ into the RA form. The RA form mitigation and management strategies should be made trial specific.*

**IMP Risk Categorisations:**

The following guidance has been taken from the MHRA's "Risk-Adapted Approaches to the Managerial of Clinical Trials of Investigational Medicinal Products", which can be read in detail here:

<https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/343677/Risk-adapted_approaches_to_the_management_of_clinical_trials_of_investigational_medicinal_products.pdf>

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| **Trial Categories based upon the potential risk associated with the IMP** | **Examples of types of clinical trials** |
| **Type A**: no higher than that of standard medical care | 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 (such as in paediatrics and in oncology etc) if this off-label use is established practice and supported by sufficient published evidence and/or guidelines |
| **Type B**: somewhat higher than that of standard medical care | Trials involving medicinal products licensed in any EU Member State if:  • such products are used for a new indication (different patient population/disease group) 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  (A grading of TYPE A may be justified if there is extensive clinical experience with the product and no reason to suspect a different safety profile in the trial population) |
| **Type C**: markedly higher than that of standard medical care | Trials involving a medicinal product not licensed in any EU Member State (A grading other than TYPE C may be justified if there is extensive class data or pre-clinical and clinical evidence) |

**Appendix 2 (TO BE DELETED UPON COMPLETION OF RA)**

*Guidance notes should not be ‘copied and pasted’ into the RA form. The RA form mitigation and management strategies should be made trial specific.*

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