DIRECTORATE OF RESEARCH AND INNOVATION

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Title: Reporting and Escalation for Clinical Research Studies	
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	Name	Position
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1. Scope

This SOP is applicable to

- All Great Ormond Street Hospital for Children (GOSH) or UCL Great Ormond Street Institute of Child Health (GOS-ICH) staff working on the delivery or oversight of clinical research.

Further to the requirements listed in this SOP, personnel must also comply with:

- Any additional study-specific requirements mandated by the CI, PI, Sponsor or R&I.

2. Purpose

This SOP details the reporting and escalation requirements and procedures that must be followed during the conduct of a research study; including:

- Reporting changes to a study (section 5.1)
- Safety reporting (section 5.2)
- Reporting progress, end of study and study outcomes (section 5.3 and 5.4)
- Support and escalation (section 5.5)

3. Definitions/Abbreviations

Advanced Therapy Investigational Medicinal Product (ATIMP) – Investigational medicine for human use that is based on genes, tissues or cells.

Amendment – A change made to a study after approval from a review body. It can be substantial (significant impact on the safety, or physical or mental integrity of participants, or the scientific value of the study) or non-substantial. It is the Sponsor's responsibility to decide whether an amendment is substantial or non-substantial.

Deviation Terms

Deviation – a non-compliance with study and/or research procedures resulting from error or fraud/misconduct that has been identified retrospectively.

Serious Breach – A breach to the protocol or of Good Clinical Practice (GCP) which is likely to affect to a significant degree the safety, or physical or mental integrity of the participants of the study or the scientific value of the research.

Fraud – The intent to create a gain or cause a loss to another through false representation, failing to disclose information or abuse of position.

Misconduct – Behaviour or actions that fall short of the standards of ethics, research and scholarship required to ensure that the integrity of research is upheld; includes fabrication, falsification, plagiarism and failure to meet ethical, legal or professional obligations.

EDGE – A database used to track study progress and recruitment.

EPR – Electronic Patient Record

EudraCT – European Union Drug Regulating Authorities Clinical Trials Database

GCP – Good Clinical Practice

HRA – Health Research Authority

IB – Investigator's Brochure

MHRA – Medicines and Healthcare Products Regulatory Agency

PI – Principal Investigator

REC – Research Ethics Committee

SmPC – Summary of Product Characteristics

Safety Terms and Abbreviations

AE – Adverse Event
ADE – Adverse Device Effect
AR or ADR – Adverse (Drug) Reaction
DSUR – Development Safety Update Report
IME – Important Medical Event
RSI – Reference Safety Information
SADE – Serious Adverse Device Effect
SAE or SAR – Serious Adverse Event or Reaction
SUSAR – Suspected Unexpected Serious Adverse Reaction
USADE – Unanticipated Serious Adverse Device Effect

Adverse Event (AE) - Any untoward medical occurrence, (including an abnormal laboratory finding) in a participant which does not necessarily have a causal

relationship with the study. For device studies, this definition includes events that occur in users or other persons if they are related to the investigational device.

Device deficiency – Inadequacy of an investigational medical device related to its identity, quality, durability, reliability, safety or performance. May include use error, malfunctions, or inadequacy in the information supplied by the manufacturer.

Related (e.g. AR or ADE) – a causal relationship between an intervention and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out. For device studies this includes any AEs resulting from insufficiencies/inadequacies in use instructions, deployment, implantation, installation, the operation, or from device malfunction, use error or intentional abnormal use.

Serious – A medical occurrence or effect that:

a) results in death;
b) is life-threatening (at the time; not an event which hypothetically might have caused death if it were more severe);
c) requires hospitalisation or prolongation of existing hospitalisation;
d) results in persistent or significant disability or incapacity;
e) consists of a congenital anomaly or birth defect; or
f) is otherwise considered medically significant by the investigator e.g. an IME (an Important Medical Event that may jeopardise the participant or may require an intervention to prevent the above consequences).

Unexpected – the nature and/or severity of the related adverse event is not consistent with the applicable RSI (e.g. as set out in the Summary of Product Characteristics (SmPC), Investigator's Brochure (IB), Protocol or risk analysis report).

4. Responsibilities

Duties may be delegated but the responsibility always remains with those listed.

4.1 The study Sponsor is responsible for:

- Reporting relevant safety information to CI and PI(s) in a timely manner.
- Reporting to MHRA (UK regulatory authority) and HRA/REC (UK ethical authorities) within the applicable timeframes. The Sponsor may delegate the HRA/REC reporting to the CI in the Sponsor-CI agreement.

4.2 The study Chief Investigator (CI) is responsible for:

- Reporting to the HRA/REC within the applicable timeframes, if delegated by the Sponsor in the Sponsor-CI agreement.

4.3 The study Principal Investigator (PI) is responsible for:

- Ensuring that the reporting and escalation process is followed at site.
- Ensuring their own and study team compliance with this SOP, the protocol, GCP and any applicable legislation, policies, procedures or guidelines.
- Evaluating seriousness, causality and expectedness of adverse events, in collaboration with the study team, study medic, CI, Sponsor, data safety monitoring board and/or trial steering committee as appropriate.
- Reporting to the Sponsor and R&D Office within the applicable timeframes.

4.4 All study staff are responsible for

- Ensuring their practice meets the requirements of this SOP, the protocol, GCP and any applicable legislation, policies, procedures or guidelines.

5. Procedure

Once all approvals have been granted for the study, regular reporting needs to occur to ensure that all relevant parties are kept informed about the study and have suitable oversight. Such reporting is an essential part of study conduct and management and is a condition of the study approval. Sections 8.2 and 8.4 provide a summary of the reporting requirements which are listed in more detail below.

As a safety measure, all GOSH patients that take part in research must be linked to the study on EPR.

The Trust Incident Reporting and Management Policy must also be followed, with incidents reported via Datix where appropriate.

R&D Office contact is: Research.Governance@gosh.nhs.uk. The R&D Office will acknowledge receipt of reports within 3 working days. If you do not receive an acknowledgement, contact the R&D Office.

5.1 Reporting changes to the study (contact: Research.Governance@gosh.nhs.uk)

5.1.1 Amendments

The PI must ensure the R&D Office is informed of any amendments.

If there is an amendment planned for a research study, the Sponsor will need to determine whether the review bodies which have approved the study need to be notified. With the exception of urgent safety measures (see Section 5.1.2); an amendment that requires approval(s) cannot be implemented until all the relevant approvals are in place (~35 days), this includes any training on the amendment. If local R&D approval hasn't been received within 35 days, contact the R&D Office prior to implementation.

Information on the submission processes can be found on the MHRA and HRA websites.

Once the R&D office have received the amendment documentation they will send this out to the study team for capacity and capability review. The study team and PI are responsible for completing the review (including contacting any relevant support departments) and communicating the outcome to the R&D Office in a timely manner. The R&D Office will not issue approval for the amendment until all responses have been received and any issues have been resolved (e.g. if new contract or costing arrangements are needed). The PI/study team can check the status of the amendment by using the EDGE amendment workflow.

Once the amendment has received all approvals, the PI must ensure that study staff are suitably aware of the amendment and trained on new processes. Depending on the complexity of the amendment this might be

by done by email, update in a team meeting (ensure this is minuted) or a specific training session. The study team must inform the R&D Office once an amendment has been implemented by updating the EDGE workflow.

The study team must track the study amendments using the amendment tracker TMP/R/013 (see Section 6 Related Documents) or equivalent Sponsor or Host documentation (e.g. EDGE workflow).

5.1.2 Urgent Safety Measures

A Sponsor or Investigator can take appropriate urgent safety measures in order to protect research participants against any immediate hazard to their health or safety, without prior authorisation from a regulatory body.

The R&D Office and the REC (and the MHRA for CTIMPs) must be notified immediately and in any event within 3 days, in the form of a substantial amendment, that such measures have been taken and the reasons why.

Information on the submission processes can be found on the MHRA and HRA websites.

5.1.3 Deviations and Serious Breaches

The deviation reporting requirements for each study should be specified in the study protocol. If they are not, the requirements must be clarified with the Sponsor and documented. All deviations must be reported to the PI.

Deviations must be documented in the Investigator Site File (ISF) using the Deviation Log TMP/R/012 (see Section 6 Related Documents), or equivalent Sponsor document, and appropriate corrective and preventative actions (CAPA) taken.

Significant deviations (e.g. those that are likely to have a significant impact on participant safety, confidentiality, or the scientific value of the study and/or are likely to impact the risk-benefit ratio of the study) must be reported to the Sponsor and R&D Office using the appropriate form (see Section 6 Related Documents). The Sponsor must assess if the deviation constitutes a serious breach; if so the Sponsor must notify the approving bodies within 7 days of becoming aware of the breach. If the PI has concerns on the Sponsor's assessment and/or reporting they should contact the R&D Office.

Information on the submission processes to approving bodies can be found on the MHRA and HRA websites.

The Sponsor is responsible for ensuring that significant deviations are included and considered when the clinical study report is produced, as they may have an impact on the analysis.

With the exception of urgent safety measures (see Section 5.1.2); planned, prospective deviations to the protocol or GCP (e.g. protocol waivers) are not acceptable as they constitute a deliberate breach of the requirement to conduct the study in accordance with the protocol and GCP.

5.1.4 Research Misconduct, Staff Performance/Conduct and Fraud

Suspected research misconduct must be reported to the R&D Office who will decide the appropriate action (e.g. reporting to individual's manager, the study Sponsor and/or approving bodies).

GOSH staff performance or conduct issues are to be handled under the Trust Performance Management Policy, Trust Disciplinary Policy or Trust Conduct Capability, III Health and Appeals Policies and Procedures for Medical Practitioners (MHPS) as appropriate.

If fraud is suspected; the Trust Countering Fraud, Bribery and Corruption Policy must be followed. Confirmed research fraud must be reported to the R&D Office and Sponsor and will usually be considered a serious breach.

5.2 Safety Reporting (See Section 8.3 and Section 8.4)

5.2.1 Individual Reports (contact: CTIMP.safety@gosh.nhs.uk)

The safety reporting requirements for each study should be specified in the study protocol. If they are not, the requirements must be clarified with the Sponsor and documented.

Recording and reporting requirements are dependent on seriousness, causality (or relatedness) and expectedness assessments (see Section 3 and Section 8.3). Seriousness and causality should (must for CTIMPs) be assessed by a medically qualified doctor. Expectedness is then assessed by the Sponsor (but may be delegated to the PI or CI). If a safety report is amended after it has been signed off; changes should (must for CTIMPs) be endorsed by a medically qualified doctor.

Unless otherwise specified by the Sponsor, all adverse events must be recorded in the participant's medical notes, and all serious events and pregnancies (in study participant or partner) must be reported to R&D and the Sponsor/manufacturer within 24hrs of study team awareness using the specified forms (see Section 6 Related Documents). The Sponsor/device manufacturer is responsible for reporting the required serious events to the approving bodies and all relevant investigators. The initial report must be submitted within the specified timeframe, even if this means the report is incomplete (e.g. missing investigator signature or outcome). Follow-up reports must be provided if relevant information was not provided in the initial report. This guidance and timelines are summarised in Section 8.4.

A Sponsor cannot 'downgrade' the PIs reported event; if the Sponsor disagrees with the PI, the opinion of both the PI and the Sponsor must be provided within the report.

Information on the reporting processes to the Sponsor should be provided in the study protocol. If it is not, the process must be clarified with the Sponsor and documented. The Sponsor is responsible for providing any necessary training on the reporting process.

Participant confidentiality must be respected when reporting to Sponsors. Participant study identifiers must be used instead of participant names or hospital numbers. If copies of medical records must be provided, these must be appropriately redacted and there must be a robust quality control check of the redaction, preferably by someone other than the person who did the redaction, to ensure it is complete. The Sponsor is required to keep a detailed record of all reported AEs.

Information on the submission processes to approving bodies can be found on the MHRA and HRA websites.

Adverse events that are related to medicinal products, procedures or devices that are **not** investigational/comparators are to be reported under the usual Trust and national processes (e.g. Yellow Card).

5.2.2 Reporting to R&D

A copy of the report form should be sent to CTIMP.safety@gosh.nhs.uk. This includes when the report is completed on an electronic system. The study team must ensure that the SAE reporting for the study allows that a copy can be shared with the R&D Office. The R&D Office will acknowledge receipt of the report within 3 working days. If you do not receive an acknowledgement contact CTIMP.safety@gosh.nhs.uk immediately.

5.2.3 Additional Considerations for ATIMPs

The Sponsor should provide information and, as appropriate, training on any additional protocol and/or product specific requirements for the recording or reporting of adverse events.

If appropriate, the Sponsor is responsible for ensuring the safety reporting forms and data capture systems allow a causality assessment that differentiates between each component of the ATIMP, the application process and, if applicable, any required concomitant medication. The Sponsor is responsible for determining the need for, duration and nature of follow up based on the risk assessment. This could include follow-up that takes place after the end of study.

If the Sponsor has not provided the above information, the requirements must be clarified with the Sponsor and documented.

5.2.4 Summary Reports (CTIMPs Only)

A Development Safety Update Report (DSUR) must be submitted by the Sponsor to the relevant authorities annually. The Sponsor is responsible for the preparation, content and submission of the DSUR.

The DSUR should present a comprehensive and meaningful review of safety information that has been received during the DSUR period and an assessment of whether this information is consistent with the previous knowledge for that IMP. The DSUR should also summarise the current understanding of the identified and potential risks to study participants and/or patients taking the product in the post-marketing setting.

At the end of the DSUR reporting period the Sponsor may assess the new safety information that has been generated and submit any proposed safety changes to the Investigator's Brochure or SmPC as a substantial amendment. This amendment should be supported by the DSUR and approved before the reference safety information (RSI) is changed.

The RSI for an IMP must remain consistent during each reporting period.

Information on the content, submission processes to approving bodies and timelines can be found on the MHRA and HRA websites.

5.3 Progress Reporting

5.3.1 Key Study Dates and Recruitment (EDGE and EPR)

EDGE information is used for reporting to the NIHR and Department of Health and Social Care (DHSC) to determine Trust's research performance and to allocate funding. It is therefore essential that this is accurate.

The PI is responsible for ensuring key study dates and recruitment are recorded in EDGE in a timely manner and these are updated as required throughout the study. The study team must input the key study dates into EDGE as required. The Research Systems and Data Management team will provide EDGE training.

Key Study Dates required in EDGE:

- Site SIV Date - Date of Site Initiation Visit (SIV).
- Site Open to Recruitment
- Site Recruitment End Dates (Planned and Actual)
- Site Closure Dates (Planned and Actual)

Study recruitment will be recorded in EPR by the study team. These recruitment data will be regularly uploaded to EDGE by the Research Systems and Data Management team. For this to work, participants must be allocated to the study and their study ID must be included in EPR in the format [R&D number]_[Participant study ID] (e.g. 19CM04_001).

5.3.2 Progress

Depending on the approvals received, the Sponsor/CI is required to submit annual progress reports to the HRA and (if applicable) to the REC and the Confidentiality Advisory Group (CAG). Copies of these annual reports should also be sent to the R&D Office(s) and PI(s).

Information on the submission process can be found on the HRA website.

5.4 Reporting Site Closure, End of Study and Study Outcomes

5.4.1 Site Closure and End of Study

When the site and/or study closes, the PI must inform the R&D Office (contact: Research.Governance@gosh.nhs.uk).

The definition of the end of the study should be documented in the protocol. If it is not, this must be clarified with the Sponsor and documented. Any change to this definition after approval has been given for the research must be notified as an amendment to the appropriate review body(ies) (see Section 5.1.1).

The end of study will have to be declared to all approving bodies using the appropriate form(s) within defined timelines. This should be done as soon as possible but within a maximum of 90 days of the end of study. If the research is terminated early or is temporarily suspended, all relevant review bodies must be notified within 15 days (unless this is an urgent safety measure where the timeline is 3 days, see Section 5.1.2).

Information on the submission processes can be found on the MHRA and HRA websites.

Before the end of the study declaration is submitted, the study team should review any plans that have been approved by the REC for the use of tissue and data, providing information to participants, or dissemination of results. If any changes to the approved arrangements are needed, the PI should discuss with the Sponsor whether an amendment is required before submitting the end of study notification (amendments will not be accepted after the end of study is submitted).

5.4.2 Final Report on the Research

At the end of a study, the Sponsor is responsible for providing a final report to the appropriate body(ies) within defined timelines.

For CTIMPs, the Sponsor is responsible for uploading summary results to EudraCT within 6 months of the end of study for paediatric CTIMPs or within 12 months for other CTIMPs. The Sponsor should send confirmation of the upload to all approving bodies.

For non-CTIMPs, the Sponsor is responsible for submitting the final report to the REC within 12 months of the end of study. There is no standard format for the report. As a minimum, the Sponsor should inform the REC whether the study achieved its objectives, the main findings, and the arrangements for publication or dissemination of the research, including any feedback to participants.

The MHRA may request a copy of the final report of a device study.

Information on the submission processes can be found on the MHRA and HRA websites.

It is good practice to disseminate the results to participants to provide feedback on the outcome of research towards which they have contributed. Guidance can be found on the HRA website.

5.5 Support and Escalation

Support is available for staff from more experienced colleagues or their line manager. If the query is related to a specific study, then the study research nurse, PI and/or CRA may also be able to help.

Escalation is necessary if a staff member becomes aware of an issue or has any concerns that they feel are outstanding, are not being addressed appropriately or may relate to more than one study. Escalation must be to the appropriate person(s) in a timely manner (see Section 8.1). It is good practice for staff to include their line manager and/or area lead (e.g. relevant Band 8a or above) in escalation so that they can provide support and will have oversight of issues.

5.6 Compliance

Reporting and escalation will be reviewed during routine monitoring/audit.

Systematic or persistent failure to comply with the study procedures and/or this SOP will be seen as non-compliance to GCP and must be brought to the attention of the Head of Governance, Clinical Trials and Contracts who will decide the appropriate action.

6. Related Documents

- GOSH/ICH/TMP/R/013: Amendment tracker – If not provided by Sponsor
- GOSH/ICH/TMP/R/012: Deviation log – If not provided by Sponsor
- GOSH/ICH/FRM/R/004: Deviation report – If not provided by Sponsor
- GOSH/ICH/FRM/R/003: Safety Reporting form – If not provided by Sponsor
- Trust Incident Reporting and Management Policy
- Trust Performance Management Policy
- Trust Disciplinary Policy
- Trust Conduct Capability, III Health and Appeals Policies and Procedures for Medical Practitioners (MHPS)
- Trust Countering Fraud, Bribery and Corruption Policy
- Trust Resuscitation Policy
- Trust Safeguarding Adults at Risk of Abuse or Neglect Policy
- Trust Safeguarding Children and Young People Policy

7. References

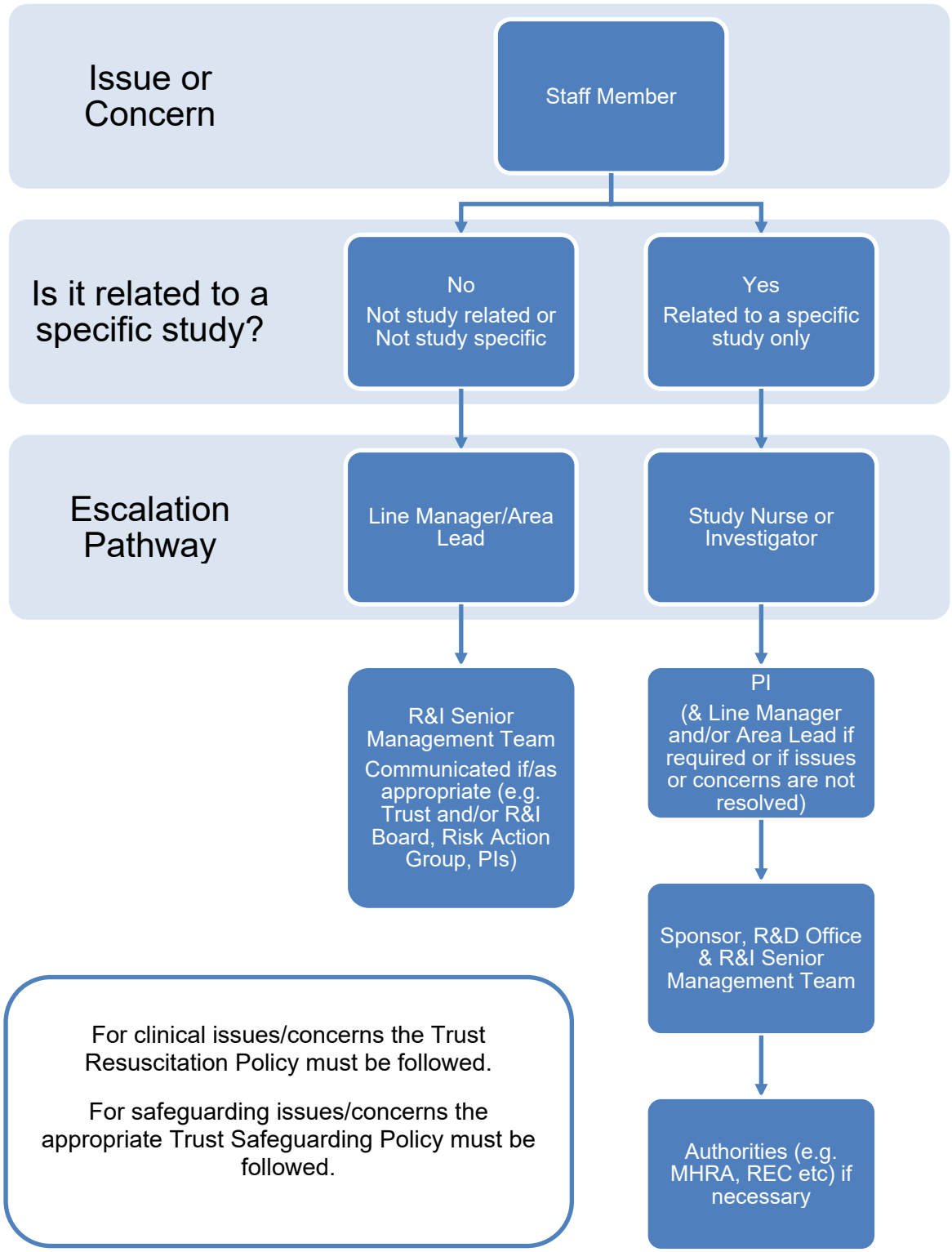
- MHRA and HRA websites
- UK policy framework for health and social care research
- ICH Harmonised Guideline - Guideline For Good Clinical Practice E6(R2)
- MHRA Good Clinical Practice Guide (Grey Guide) – Chapters 1, 2, 5 and Annex 3
- Guidelines On Medical Devices - MEDDEV 2.7/3
- Clinical Trial Facilitation Group (CTFG) Q&A Document – RSI
- Guidelines on Good Clinical Practice specific to Advanced Therapy Medicinal Products
- The concordat to support research integrity
- HRA Guidance on Information for participants at the end of a study

8. Appendices

- Appendix 1: Escalation pathway
- Appendix 2: Reporting Summary Best Practice

- Appendix 3: Safety Reporting Definitions Decision Tree
- Appendix 4: Safety Reporting Best Practice
- Appendix 5: Datix Notification List for Research and Innovation

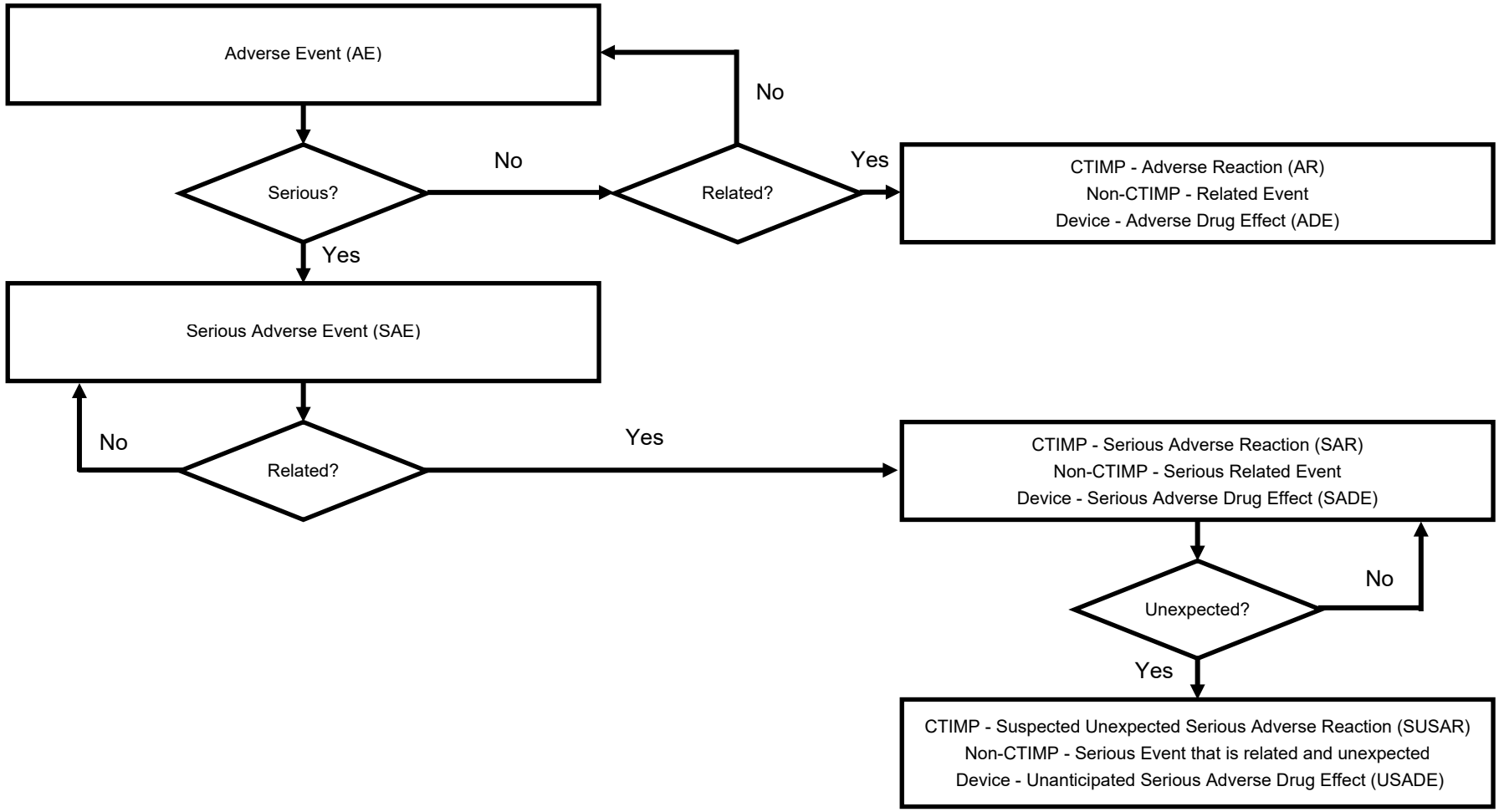
8.1 Appendix 1: Escalation Pathway



8.2 Appendix 2: Reporting Summary Best Practice – Study specific reporting requirements must be followed.

Reporting purpose		Reporting		Types of report	Timeframes
		Person responsible	Reported to		
Significant Changes Affecting the Study or Increasing Subject Risk		PI	Sponsor and R&D	Substantial Amendment Urgent Safety Measures (see 8.4) Serious Breaches	Promptly as needed < 24hrs for Serious Breach or Urgent Safety Measures
		Sponsor/CI	All approving bodies Other sites (if applicable)		
Any other changes to the study		PI	Sponsor and R&D	Non substantial amendments Deviations Changes in funding	Promptly as needed
		Sponsor/CI	HRA Other sites (if applicable)		
Safety (see 8.4)	**Individual Reports**	PI	Sponsor and R&D	SAE/Pregnancy Report Form	< 24hrs of event
		Sponsor	All approving bodies/PI/CI	SUSAR Report	< 7 - 15 days
	Summary	Sponsor	All approving bodies/PI/CI	DSUR/Annual Safety Report	Annually
Progress		Study Team	EDGE / EPR	Recruitment numbers (EPR) & key dates (EDGE)	Promptly as needed
		Sponsor/CI	R&D, HRA, REC, CAG, PI	Progress report	Annually
Site Closure		PI	R&D	Close out letter	Promptly as needed
End of Study	**Suspension/ Premature Termination**	PI	R&D Participants	As appropriate	Promptly as needed
		Sponsor	All approving bodies	Substantial Amendment/End of study declaration	≤ 15 days
	As Expected	PI	R&D Participants	End of study declaration As appropriate	Promptly as needed
		Sponsor	All approving bodies	End of study declaration	≤ 90 days
Summary of Study & Outcomes		Sponsor/CI	The Public	Report published on publically accessible register	≤ 6-12 months
		Sponsor/CI	MHRA, REC, R&D & PI	Clinical Study Report	≤ 6-12 months

8.3 Appendix 3: Safety Definitions Decision Tree (CTIMPs, Non-CTIMPs and Devices) – For reporting timelines see Appendix 4



8.4 Appendix 4: Safety Reporting Best Practice – Study specific safety reporting requirements must be followed. In addition to the reporting below; all AEs must be recorded in the participant's medical notes (unless otherwise specified by Sponsor).

	Reporting to Sponsor and R&D		Reporting to REC		Reporting to MHRA	
	Person responsible	**Timeframe**	**Person responsible**	**Timeframe**	**Person responsible**	**Timeframe**
Individual Reports						
Non-serious (e.g. AE/R, ADE)						
• All research	NA	NA	NA	NA	NA	NA
Serious (e.g. SAE/R, IME) **& Pregnancy**						
• CTIMPs & Non-CTIMPs	PI	< 24hrs	NA	NA	NA	NA
• Devices (regardless of causality) see MEDDEV 2.7/3	PI	< 24hrs	NA	NA	Sponsor	< 2 days (risk of death, serious injury or illness) < 7 days (all others)
Serious, Related and Unexpected						
• CTIMP (SUSAR)	PI	< 24hrs	Sponsor/CI	< 7 days (death or life threatening) < 15 days (all others)	Sponsor	< 7 days (death or life threatening) < 15 days (all others)
• Non-CTIMP (Related & Unexpected SAE)	PI	< 24hrs	Sponsor/CI	< 15 days	Not required	Not required
• Devices (USADE) see MEDDEV 2.7/3	PI	< 24hrs	Sponsor or Manufacturer	< 15 days	Sponsor	< 2 days (risk of death, serious injury or illness) < 7 days (all others)
Urgent Safety Measures						
• All research	PI	< 24hrs	Sponsor/CI	< 3 days	Sponsor	< 3 days
Summary Reports						
Quarterly Report (Devices ONLY)	NA	NA	Sponsor	Quarterly	Sponsor	Quarterly
DSUR (CTIMPs ONLY)	NA	NA	Sponsor	Annual	Sponsor	Annual

8.5 Appendix 5: Datix Notification List for Research and Innovation Directorate and/or Research as a (additional) Speciality

Deputy Director of R&I

Head of Governance, Clinical Trials and Contracts

Principal Pharmacist Clinical Trials & Audit

Director of CRF

Head of Clinical Research Operations

R&I QA Manager

Clinical Research Delivery Manager

CRF Service Manager

Head of Nursing for Research and Innovation

Matron for Research and Innovation

Band 7 Research Nurses

CRF Pharmacist

Advanced Nurse Practitioner (ANP) for Research

Critical Care Senior Research Nurse