

Positively welcoming Actively respectful Clearly communicating Visibly reassuring

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This document supports: <i>Standards and legislation</i>	Medicines for Human Use (Clinical Trials) Regulations 2004 and all associated amendments. UK Policy Framework for Health and Social Care (2017)
Date equality analysis completed.	22/02/2018
<u>This is a controlled document</u>	
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Version Control

Version	Date	Author	Status	Comment
1	30/01/2018	Lucy Parker	Final	New Document
2	02/11/2018	Amanda Bidle	Updated	Causality Explanations and when to report
2.1	23/01/2018	Amanda Bidle	Draft	Causality Explanations (including safety reporting definitions) and when to report
2.2	30/01/2019	Rachel Fay	Final	Clarification of datix reporting requirements.

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1. INTRODUCTION

It is essential that all adverse events which occur during the course of study participants' involvement in a research project are appropriately recorded and reported in order to ensure their continuing safety. To ensure the interests and safety of subjects participating in clinical trials, this Standard Operating Procedure must be followed for all research studies that do not fall under the Clinical Trials Directive 2001/20/EC.

Studies that involve medical devices, diagnostic products and therapeutic interventions do not fall within the definition of investigational medicinal products (IMPs) in Directive 2001/20/EC. The UK Policy Framework for Health and Social Care (2017) also lays out the requirement for safety reporting during a study.

2. OBJECTIVE

This document defines the Trust's requirements with regards to Adverse Event Reporting; specifically this includes Investigators and Researchers involved in any part of the research process that lies outside of the normal pathway of care.

It is essential that all Adverse Events (AE) which occur during the participants' involvement in a research project are appropriately recorded and reported in order to ensure their continuing safety. Failure to report incidents, or deal with incidents adequately, can result in regulatory approval being withdrawn from an individual project, or, in extreme cases, from all research carried out by the Chief Investigator (CI) or Principal Investigator (PI).

The document aims to provide clear guidance on who takes overall responsibility for each process.

3. DEFINITIONS

Adverse Event

An adverse event (AE) is defined as any unfavourable and unintended sign including an abnormal laboratory finding, symptom or disease associated with the use of a medical intervention or procedure, regardless of whether it is considered related to the medical intervention or procedure, that occurs during the course of the study.

Serious Adverse Event

Any untoward medical occurrence that results in death, is life threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity, or in a congenital anomaly/birth defect. Important adverse events/reactions that are not immediately life threatening or do not result in death or hospitalisation, but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed above should also be considered serious.

Unexpected Related Serious Event

An Unexpected Related Serious Event is related to interventional studies with a procedure only. They are adverse events that are deemed serious, possibly related to the procedure and were not expected (as outlined in the protocol, manual or clinical practice). These should be reported to the Sponsor immediately. The Sponsor has an additional responsibility to report these to the REC within a set timeframe.

Severity

The term “severe” is often used to describe the intensity (severity) of a specific event. This is not the same as “serious”, which is based on patient/event outcome or action criteria. E.g. you can have a severe migraine; this would not constitute a serious adverse event.

Sponsor

An individual, company, institution or an organisation which takes on the responsibility for the initiation, management, and/or of the financing of a clinical trial.

Investigator

A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator (PI).

Chief Investigator (CI)

An investigator assigned the overall responsibility for the trial including the coordination of participating principal investigators at participating sites within a multicentre trial.

Adverse Incident

Adverse incidents are events which affect the health and safety of patients or service users, equipment users or operators, or other persons. An Adverse Incident in relation to a medical device is an event that causes or has the potential to cause, unexpected or unwanted effects involving the safety of device users (including patients) or other persons. E.g. a patient, user, carer or professional is injured as a result of a medical device failure or its misuse, or if a patient’s treatment is interrupted or compromised by a medical device failure or a misdiagnosis due to a medical device failure which leads to inappropriate treatment or a patient’s health deteriorates due to medical device failure. Causes may include: design; poor user instructions or training; inappropriate modifications; inadequate maintenance; and unsuitable storage and use conditions.

RFL - Royal Free London NHS Foundation Trust

RM&G - Research Management & Governance

R&D - Research & Development

4. SCOPE

This SOP describes the process for recording, managing safety and reporting Adverse Events or Incidents for Royal Free sponsored non-CTIMP studies or for non-CTIMP studies hosted at a Royal Free site.

This SOP does not cover safety reporting for CTIMPs hosted at RFL. Safety reporting for CTIMPs hosted at a Royal Free site is covered in SOP0063.

5. EQUALITY STATEMENT

The Royal Free London NHS Foundation Trust is committed to creating a positive culture of respect for all individuals, including job applicants, employees, patients, their families and carers as well as community partners. The intention is, as required by the Equality Act 2010, to identify, remove or minimise discriminatory practice in the nine named protected characteristics of age, disability (including HIV status), gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex or sexual orientation. It is also intended to use the Human Rights Act 1998 to treat fairly and value equality of

opportunity regardless of socio-economic status, domestic circumstances, employment status, political affiliation or trade union membership, and to promote positive practice and value the diversity of all individuals and communities.

This document forms part of the trust’s commitment. You are responsible for ensuring that the trust’s policies, procedures and obligation in respect of promoting equality and diversity are adhered to in relation to both staff and service delivery.

The equality analysis for this SOP is attached at Appendix (2).

6. DUTIES

The Trust is committed to the delivery of world class care and expertise to both staff and patients, and our values of positively welcoming, actively respectful, visibly reassuring and clearly communicating are fundamental to the delivery of this. This policy has been developed with our values in mind, and is intended to be implemented within the spirit of these values.

The Chief Investigator (CI) has overall responsibility for the conduct of the study. In a multi-site study, the CI has co-ordinating responsibility for reporting adverse events to the Sponsor and to the relevant Research Ethics Committee (REC).

The Principal Investigator (PI) has responsibility for the research at a local site where the study involves specified procedures requiring site-specific assessment. There should be one PI for each research site. In the case of a single-site study, the CI and the PI should be the same person. The PI is responsible for informing the CI or the organising research team and the RFL R&D Office of all adverse events that occur at their site. The duties are summarised below:

- PI to report all SAEs within agreed timelines, as per study protocol to the CI
- CI to report all SAEs within agreed timelines to Sponsor and relevant NHS Trust R&D.
- CI to provide the Sponsor with details of all AEs identified in the protocol as critical to the evaluation of safety within the agreed timeframes specified in the protocol.
- CI to supply the Sponsor, REC and relevant NHS Trust R&D with any supplementary information they request.

The Sponsor’s duties include:

- Promptly notifying all Investigators and REC(s) of any findings that may affect the health of subjects
- To keep detailed written reports of all AEs reported by PIs and performing an evaluation with respect to seriousness, causality and expectedness.
- Reporting all relevant safety information to the relevant REC.
- Ensure written SOPs and systems are in place to ensure quality standards and contractual agreements are met.

7. PROCEDURE

Person Responsible	Task
CI/PI at site	<p>7.1 Assessment of Event</p> <p>All protocols should list known side effects; adverse reactions contained within the manufacturer’s product information or</p>

	<p>technical specifications and expected events in relation to the disease or population being studied that would not require expedited reporting. A detailed explanation of SAE reporting procedures should also be included in the protocol.</p> <p>The CI can decide how to record and report adverse events, whether expected or not. Adverse events must be recorded in the first instance in the participant medical notes. The Case Report Forms (CRFs) should also include an Adverse Event report where the event should be clearly described. It should be clearly stated in the study protocol and the local SOP what will be recorded and how the onward reporting and the ongoing participant management should be processed.</p> <p>The management and reporting arrangements for SAEs should be in place for all trials. Agreements at the beginning of the trial should be made for such SAEs that can be defined as disease-related and therefore not subject to expedited reporting. The procedures for managing and reporting SAEs must be clearly defined in the protocol.</p> <p>As with all recording and reporting, subject confidentiality and adherence to the Data Protection Act (2018) must be maintained on all reports.</p> <p>Each AE must be evaluated for seriousness, causality, and expectedness. The responsibility for this evaluation can be shared between the CI and PIs. It may be most appropriate for the treating PI at each local site to evaluate whether each event is related and unexpected, before reporting it to the CI and Sponsor simultaneously. The definitions can be used below.</p>								
	<table border="1"> <thead> <tr> <th>Relationship</th> <th>Relationship</th> </tr> </thead> <tbody> <tr> <td>Unrelated</td> <td>There is no evidence of any causal relationship</td> </tr> <tr> <td>Unlikely</td> <td>There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment).</td> </tr> <tr> <td>Possible</td> <td>There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the patient's</td> </tr> </tbody> </table>	Relationship	Relationship	Unrelated	There is no evidence of any causal relationship	Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment).	Possible	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the patient's
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CI	<p>AEs that are not considered serious should be included in the patient notes and on the relevant case report forms (CRFLs). The completed form should be filed along with the other CRFLs for the study and a copy provided to the Sponsor as agreed.</p> <p>SAEs that are reportable are:</p> <ul style="list-style-type: none"> • Related: that is, it resulted from administration of any of the research procedures; and • Unexpected: that is, the type of event is not listed in the protocol as an expected occurrence. <p>Adverse events that occur during the course of the Research project should be recorded collectively with the use of an adverse event log. The log should be maintained and retained in the Investigator Site File. The Sponsor may require regular collection or periodic updates of AE occurrence.</p> <p>7.2 Adverse Event Reporting for Non-CTIMP Studies Sponsored by Royal Free – Event at a Royal Free Site</p> <p>A non-serious or unrelated adverse event does not need to be reported to the RLF R&D Office. All AE events that do occur during the course of the Research project should be recorded collectively e.g. RFLLRDLOG0019 Adverse Event Log - available to download from the website at www.royalfree.nhs.uk/research/for-investigators/standard-operating-procedures-sops/).</p> <p>If a research participant experiences a SAE, the CI should complete the SAE form (RFLRDDOC0012 - available to download from the website at www.royalfree.nhs.uk/research/for-investigators/standard-operating-procedures-sops/) and ensure the RFL R&D Office is informed within 48 hours of the CI becoming aware of the event.</p>								

	<p>It will be the CI's responsibility to forward the completed form to the relevant Ethics Committee and to the RFL R&D Office as Sponsor via email. The RFL R&D generic email mailbox should be included – rf.randd@nhs.net</p> <p>Reports of related and unexpected SAEs should be submitted to REC within 15 days of the CI becoming aware of the event.</p> <p>The REC will acknowledge receipt of the report within 30 days by signing the SAE form and returning a copy back to the person who made the submission.</p> <p>This signed copy will need to be retained in the appropriate section of the Investigator Site File.</p> <p>Adverse events that occur during the course of the Research project should be recorded collectively e.g. RFLRDLOG0019 Adverse Event Log - available to download from the website at www.royalfree.nhs.uk/research/for-investigators/standard-operating-procedures-sops/).</p> <p>The log should be maintained and retained in the Investigator Site File. The RFL R&D Office as Sponsor may require regular collection or periodic updates of AE occurrence.</p> <p>There is no need to enter a datix unless the SAE meets the trust-wide requirement for incident reporting: This applies to all studies including RFL sponsored studies. E.g. if there is a clinical incident that 'could have or did lead to unintended harm' that also met the definition of an SAE it should still be entered on datix. If there is an incident involving a research participant (SAE or not) please tick 'related to research' on datix.</p> <p>Definition of events that should be reported are: http://freenet/freenetcms/Default.aspx?S=41&M=1859&P=1322</p>
<p>PI at site</p>	<p>7.3 Non-CTIMPS Sponsored by Royal Free – Event at a non-Royal Free Site</p> <p>A non-serious or unrelated adverse event does not need to be reported to the RLF R&D Office. All AE events that do occur during the course of the Research project should be recorded collectively e.g. RFLRDLOG0019 Adverse Event Log - available to download from the website at www.royalfree.nhs.uk/research/for-investigators/standard-operating-procedures-sops/).</p> <p>If a research participant experiences a SAE, the PI at site should complete the SAE form (RFLRDDOC0012 - available to download from the website at</p>

	<p>www.royalfree.nhs.uk/research/for-investigators/standard-operating-procedures-sops/) and ensure the CI and Sponsor (the RFL R&D Office) is informed of the event within 48 hours of the PI becoming aware of the event.</p> <p>It will be the CI's responsibility to forward the completed form from the PI to the relevant Ethics Committee and to the RFL R&D Office as Sponsor via email. The RFL R&D generic email mailbox should also be included – rf.randd@nhs.net</p> <p>Reports of related and unexpected SAEs should be submitted within 15 days of the CI becoming aware of the event.</p> <p>The REC will acknowledge receipt of the report within 30 days by signing the SAE form and returning a copy back to the person who made the submission.</p> <p>This signed copy will need to be retained in the appropriate section of the Investigator Site File.</p> <p>SAEs that occur during the course of the Research project should be recorded collectively e.g. RFLRDLOG0019 Adverse Event Log - available to download from the website at www.royalfree.nhs.uk/research/for-investigators/standard-operating-procedures-sops/).</p> <p>The log should be maintained and retained in the Investigator Site File. The RFL R&D Office as Sponsor may require regular collection or periodic updates of AE occurrence.</p> <p>The Investigator at site must also inform the local R&D office of the SAE and follow their process of reporting at a local level e.g. through their Trust incidence reporting scheme.</p>
	<p>7.4 Non-CTIMPS hosted by Royal Free</p> <p>If a research participant at a Royal Free site experiences a SAE the PI should follow the Sponsor's SOPs on SAE reporting.</p> <p>A copy of the completed SAE form must sent to the RFL R&D Office as host site via email. The RFL R&D generic email mailbox should be used – rf.randd@nhs.net</p> <p>The Investigator must also raise a DATIX incidence (see section 7.5)</p>
CI	<p>7.5 DATIX Reporting</p> <p>You should also consider whether the event qualifies for reporting through the Trust's incidence system (DATIX). E.g.</p>

	<p>if there is a clinical incident that 'could have or did lead to unintended harm' that also met the definition of an SAE it should still be entered on datix. If there is an incident involving a research participant (SAE or not) please tick 'related to research' on datix. If the event requires a DATIX report, it can be accessed following this link:</p> <p>https://royalfree.datix.thirdparty.nhs.uk/Live/index.php</p> <p>The Adverse Incidents Reporting Policies and Procedures can be accessed following this link:</p> <p>http://freenet/freenetcms/Default.aspx?S=41&M=1859&P=1322</p>
<p>CI or PI at site</p>	<p>7.6 Events Involving Devices</p> <p>For Investigational studies that include a medical device a report must also be made to the device manufacturer in accordance with the protocol.</p>
<p>Assigned Research Portfolio Manager</p>	<p>7.7 Handling of SAEs</p> <p>The Assigned Research Portfolio Manager will work with the CI/PI to ensure that the SAE form is completed correctly and that the CI/PI sends the form to the REC within the stipulated timelines.</p> <p>The Assigned RPM will save a copy of the SAE form in the safety reporting section of the study record folder on the R&D study database.</p>

8. POLICY

This SOP is mandatory and non-compliance with it may result in disciplinary procedures.

9. RISK MANAGEMENT/ LIABILITY/MONITORING & AUDIT

- The SOP Working Group will ensure that this SOP and any future changes to this document are adequately disseminated.
- The R&D Office will monitor adherence to this SOP via the routine audit and monitoring of individual clinical trials and the Trust's auditors will monitor this SOP as part of their audit of Research Governance. From time to time, the SOP may also be inspected by external regulatory agencies (e.g. Care Quality Commission, Medicines and Healthcare Regulatory Agency).
- In exceptional circumstances it might be necessary to deviate from this SOP for which written approval of the R&D Manager/Deputy R&D Director should be gained before any action is taken.
- SOP deviations should be recorded including details of alternative procedures followed and filed in the Investigator and Sponsor Master File.
- The R&D Office is responsible for the ratification of this procedure.

SOP062: Safety Reporting for non CTIMPs

V2.2, 30/01/2019

Uncontrolled document when printed or downloaded. Current SOP versions available

<https://www.royalfree.nhs.uk/research/for-investigators/standard-operating-procedures-sops/>

10. FORMS/TEMPLATES TO BE USED

RFLRDDOC0012 – SAE reporting form non CTIMPs
RFLRDLOG0019 Adverse Event Log

11. FLOWCHART

None applicable

APPENDIX 1

SOP Reading Log

APPENDIX 2

Royal Free London NHS Foundation Trust Equality Analysis guide and Tool

An equality analysis is a review of a policy, practice, function, business case, project or service change which establishes whether there is a negative effect or impact on particular social groups. This In turn enables the organisation to demonstrate it does not discriminate and, where possible, it promotes equality to meet the needs of the diverse patients and communities we serve.

This check list is a way to help you think carefully about the likely impact on equality groups and take action to improve services. This is also an opportunity to evidence positive practices in our services and demonstrate strategic integrity to ensure that our services and employment practices are fair, accessible and appropriate for all patients, visitors and carers, as well as our talented and diverse workforce.

Name of the policy / function / service development being assessed	Safety Reporting for non CTIMP studies
Briefly describe its aims and objectives:	To define the Trust's requirements with regards to Adverse Event Reporting specifically this includes Investigators and Researchers involved in any part of the research process that lies outside of the normal pathway of care.
Directorate and Lead:	Rachel Fay, R&D Manager, R&D Office
Evidence sources: DH, legislation. JSNA, audits, patient and staff feedback	Medicines for Human Use (Clinical Trials) Regulations 2004 and all associated amendments. UK Policy Framework for Health and Social Care (2017)
Is the Trust Equality Statement present?	Yes No if no do not proceed with Equality Analysis (EA)

If you are conducting an EA on a procedural document please identify evidence sources and references, who has been involved in the development of the document, process or strategy, and identify positive or negative impacts. It is the discussion regarding the equality impact of the document that is important.

Equality Analysis Checklist

Go through each protected characteristic below and consider whether the policy, practice, function, business case, project or service change could have any impact on groups from the identified protected characteristic, involve service users where possible and get their opinion, use demographic / census data (available from public health and other sources), surveys (past or maybe carry one out), talk to staff in PALS and Complaints and Patient Experience.

Please ensure any remedial actions are Specific, Measureable, Achievable, Realistic, and Timely (SMART).

Equality Group	Identify negative impacts	What evidence, engagement or audit has been used?	How will you address the issues identified?	Identifies who will lead the work for the changes required and when?	Please list positive impacts and existing support structures
Age	None identified	R&D administrative document	NA	NA	This SOP includes the Trust Equality Statement, as well as the results from the Equality Assessment for this SOP. These actions are designed to embed the equality agenda and promote equality compliance within the Trust.
Disability	None identified	R&D administrative document	NA	NA	
Gender Reassignment	None identified	R&D administrative document	NA	NA	
Marriage and Civil Partnership	None identified	R&D administrative document	NA	NA	
Pregnancy and maternity	None identified	R&D administrative document	NA	NA	
Race	None identified	R&D administrative	NA	NA	

SOP062: Safety Reporting for non CTIMPs

Equality Group	Identify negative impacts	What evidence, engagement or audit has been used?	How will you address the issues identified?	Identifies who will lead the work for the changes required and when?	Please list positive impacts and existing support structures
		document			
Religion or Belief	None identified	R&D administrative document	NA	NA	
Sex	None identified	R&D administrative document	NA	NA	
Sexual Orientation	None identified	R&D administrative document	NA	NA	
Carers	None identified	R&D administrative document	NA	NA	

It is important to record the names of everyone who has contributed to the policy, practice, function, business case, and project or service change.

Equality Analysis completed by: (please include every person who has read or commented and approval committee(s). Add more lines if necessary)	Organisation	Date
QMS Working Group	Royal Free London NHS Foundation Trust	13/02/2018
R&D Committee	Royal Free London NHS Foundation Trust	22/02/2018

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V2.2, 30/01/2019

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