

Document Title: Safety Reporting for CTIMPS hosted at Royal Free

Document Number: 063

Version:	1
Ratified by:	R&D Committee
Date ratified:	25/01/2018
Name of originator/author:	Lucy Parker
Directorate:	Corporate Services
Department:	Research and Development
Name of responsible individual:	Rachel Fay, R&D Manager
Date issued:	05/02/2018
Review date:	05/02/2021
Target audience:	All research staff
Intranet:	NA
Key related documents:	SOP062 Safety Reporting for non CTIMPS Royal Free Adverse Incidents Reporting Policies and Procedures
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.	25/01/2018
<u>This is a controlled document</u>	
Whilst this document may be printed, the electronic version maintained on the RFL website is the controlled copy. Any printed copies of this document are not controlled.	

Version Control

Version	Date	Author	Status	Comment
1	07 Nov 2017	Lucy Parker	Final	New Document

Contents

Section		Page
1	Introduction	4
2	Objective	4
3	Definitions	4
4	Scope	7
5	Equality statement	7
6	Duties	8
7	Details of procedure	8
8	Policy	19
9	Risk management/liability/monitoring & audit	19
10	Forms/templates to be used	20
11	Flowcharts	20
Appendices		
Appendix (1)	Reporting Responsibilities	22
Appendix (2)	SOP reading log	24
Appendix (3)	Equality analysis guide and tool	25

1. INTRODUCTION

The European Clinical Trials Directive (EUCTD) 2001/20/EC was transposed into UK Regulations by The Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031) on the 1st May 2004. 'UK Regulations' will be the term used to cover the UK legislation and the EUCTD in this document. UK Regulations and its subsequent amendments set out the legal requirements for Adverse Event (AE) recording, management and reporting in clinical trials. These regulations apply to all Clinical Trials of Investigational Medicinal Products (CTIMPs) and specify 'Pharmacovigilance (PCV)' reporting requirements. To breach these requirements constitutes a breach in criminal law. The requirements have been incorporated into this Standard Operating Procedure (SOP) to define procedures undertaken by Royal Free London NHS Foundation Trust for CTIMPS hosted at a Royal Free site in order comply with the UK Regulations.

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.

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

3. DEFINITIONS

GCP - Good Clinical Practice An international ethical and scientific quality standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and equality statement

RF Royal Free London NHS Foundation Trust

RM&G - Research Management & Governance

R&D - Research & Development

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 responsibility for the coordination of participating principal investigators at participating sites in a multicentre trial.

Investigational Medicinal Product (IMP) A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorisation when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.

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.

Adverse Event (AE) Any untoward medical occurrence in a patient or clinical trial subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IMP whether or not related to that IMP.

AESI Adverse Event of Special Interest For some trials the IMP manufacturer/funder may identify AEs of special interest (AESI). An adverse event of special interest (serious or non-serious) is one of scientific and medical concern specific to the IMP or trial, for which ongoing monitoring and rapid communication by the investigator to the sponsor/IMP manufacturer maybe appropriate. Such an event might warrant further investigation in order to characterise and understand it. Depending on the nature of the event, rapid communication by the trial sponsor to other parties (e.g. regulators) might also be warranted

Adverse Reaction (AR) Any noxious and unintended response to an IMP where a causal relationship between the IMP and an AE cannot be ruled out.

Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR) Any untoward medical occurrence that at any dose: results in death, is life threatening, requires inpatient hospitalisation or prolongation of hospitalisation, results in persistent or significant disability/incapacity or is a congenital anomaly or birth defect. NB: hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Therefore subjects do not need to be hospitalised overnight to meet the hospitalisation criteria. Hospitalisation for an elective procedure or for a pre-existing (prior to study entry) condition which has not worsened is not defined as an SAE.

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.

Other SAEs or SARs Important medical events that may jeopardise the subject or may require intervention to prevent one of the outcomes listed in the definition of a Serious Adverse Event should also be considered as serious e.g. overdoses (accidental or intentional), pregnancy (of subject or their partner), AE and/or laboratory abnormalities which are listed in the trial protocol as critical to safety evaluations and require reporting.

Suspected Serious Adverse Reaction (SSAR) An AR that is classed in nature as serious and which is consistent with the information about the IMP listed in the relevant reference documentation e.g. Summary of medicinal characteristics (SmPC) for a licensed product being used according to licensed doses and indications or an Investigator’s brochure (IB) for any other IMP or for an IMP being used outside of its SmPC.

Unexpected Adverse Reaction (UAR) An adverse reaction, the nature or severity of which is not consistent with the applicable product information (SmPC or IB).

Suspected Unexpected Serious Adverse Reaction (SUSAR) An adverse reaction that is classed in nature as both serious and unexpected.

Other Serious Safety issues Other safety issues that might materially alter the current risk-benefit assessment of an IMP or that would be sufficient to consider changes in the IMP administration or in the overall conduct of the trial also need to be considered serious, e.g.:

- An increase in the rate of occurrence or qualitative change of an expected SAR which is judged clinically important;
- Post study SUSARs that occur after the patient has completed a clinical trial and are reported by the Investigator to the Sponsor;
- New events related to the conduct of the trial or the development of the IMPs and likely to affect the safety of the subjects, such as:
 - An SAE which could be associated with the trial procedures and which could modify the conduct of the trial;
 - A significant hazard to the subject population such as lack of efficacy of an IMP used for a life threatening disease;
 - A major safety finding from a newly completed animal study (e.g. carcinogenicity);
 - Any anticipated end or temporal halt of a trial for safety reasons and conducted with the same IMP in another country by the same Sponsor;
- Recommendations of the Data Monitoring Committee (DMC), if any, where relevant for the safety of subjects.
- Any pregnancies that occur in clinical trial subjects as soon as the investigator becomes aware of the event. It may be necessary to monitor the pregnancy of a woman whose male partner is the trial subject.

Urgent Safety Measure It may be necessary to undertake a procedure that is not defined in the protocol but has to be taken without any authorisation from the MHRA and/or REC, in order to protect the trial subjects from any immediate hazard to their health or safety. The PI/CI/Lab will need to report this immediately to the Sponsor to enable reporting to the MHRA and REC within 3 days of the measure being taken. During the course of a Clinical Trial involving an IMP, new safety information in the form of a Serious Adverse Event or information received from an external source may necessitate an immediate change in the study procedures or a temporary halt to the study in order to protect clinical trial subjects from any immediate hazard to their health and safety

Adverse Incident An 'adverse incident' is any event, circumstance, activity or action which has caused, or has been identified as potentially causing harm, loss or damage to patients, members of the public or staff. This includes breaches of confidentiality, serious adverse events, serious adverse reactions, which requires a hospital admission and has a severity grading of severe or critical.

Reference Safety Information RSI a list of medical events that defines which reactions are expected for the Investigational Medicinal Product (IMP) being administered to clinical trial participants.

Independent Data Monitoring Committee IDMC - The role of the IDMC is to review interim study results and determine whether or not there are any safety issues or any reason why the study should not continue e.g. if interim results are showing strong evidence that the treatment/intervention is superior or inferior to the control.

4. SCOPE

This SOP describes the procedure to be used by all Investigators for recording and reporting of Adverse Events (AEs), including Adverse Reactions (ARs), Serious Adverse Events (SAEs), Serious Adverse Reactions (SARs) and Suspected Unexpected Serious Adverse Reactions (SUSARs) that require reporting in accordance with the UK Regulation and that occur in subjects participating in CTIMPs hosted at a RF site. It also provides details of the responsibilities of the Investigator (Section 6).

This SOP will not describe the process for submitting Development Update Safety Reports (DSURs) as this remains the responsibility of the Sponsor.

This SOP does not describe the procedure for reporting of Adverse Incidents (AIs) to the Trust Risk Management Department Database "DATIX" by Investigators for all clinical research registered with the RF R&D Office.

Adverse Incidents Reporting Policies and Procedures can be accessed following this link:

<http://freenet/freenetcms/Default.aspx?S=41&M=1859&P=1322>

And the DATIX link can be found at

<https://royalfree.datix.thirdparty.nhs.uk/Live/index.php>

This SOP also does not cover safety reporting for non CTIMP studies. That is covered by SOP062.

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 (3).

SOP 063: Safety Reporting for CTIMPS hosted at RF

V1, 07 NOV 2017

Uncontrolled document when printed or downloaded. Current SOP versions available

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

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.

There are a number of responsibilities when managing adverse events. Below is a list of responsibilities for the Investigator

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 Medicines and Healthcare products Regulatory Agency (MHRA) 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 only be one PI for each research site. In the case of a single-site study, the CI and the PI should normally be the same person. The PI is responsible for informing the CI, or the organising research team, of all adverse events that occur at their site following the guidelines given in Appendix (1)

Any CI/PI who has agreed to undertake duties for pharmacovigilance delegated by the Sponsor must undertake both Investigator's and Sponsor's responsibilities as described in appendix 1.

7. PROCEDURE

Person Responsible	Task
CI	<p>7.1 Study Planning</p> <p>All Protocols should list known side effects and adverse reactions contained within the manufacturer's product information. This should be written in agreement with the relevant drug/device company where applicable. Rare/very rare events may or may not be included depending on individual study requirements.</p> <p>A detailed explanation of SAE reporting procedures should also be included in the Protocol.</p> <p>7.1.1 Which AE to Record?</p> <p>The sponsor or delegate can decide how to record and report adverse events, whether expected or not. Adverse events are usually described on case report forms (CRFs), unless they are classified as serious, in</p>

	<p>which case, these should be reported on a specific SAE form It should be clearly stated in the study protocol what will be recorded and how the reporting is to be managed.</p> <p>It may be decided that all, or only some, non-serious AEs are to be recorded. Whatever option is chosen, it must be consistent with the purpose of the trial and any toxicity and efficacy end points.</p> <p>7.1.2 Which SAE to Report?</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>It is recommended that an Independent Data Monitoring Committee (IDMC) is appointed in order to review safety data regularly throughout the trial and when necessary, recommend to the Sponsor whether to continue, modify or terminate the trial. Again, this procedure must be defined in the protocol.</p> <p>As with all recording and reporting, subject confidentiality and adherence to the Data Protection Act (1998) must be maintained on all reports.</p>
PI	<p>Use external sponsor’s forms and SOPs, report <u>incidents</u> via RFL datix systems .</p> <p>Report SAEs and SUSARs as per external sponsor’s procedures using the external sponsor’s forms or electronic data capture systems.</p> <p>Ensure that research team is trained and complies with the study specific pharmacovigilance reporting requirements.</p> <p>If any SAE or SUSAR meets RFL incident reporting standards, ensure that appropriate procedures are followed. Please see RFL trust intranet for the Adverse Incident Policy for details of how to report these events/incidents</p>
PI	<p>7.2 During the Trial</p> <p>Each AE must be evaluated for seriousness (see the definition of this in section 3 of this SOP), 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 each event, before reporting it to</p>

	<p>the CI. It must be stated in the clinical trial protocol who will take responsibility for the assessment and reporting of such events to the Sponsor and CI simultaneously. As expedited reporting may be required, this SOP assumes that responsibility of initial assessment and reporting to the CI lies with the PI.</p> <p>7.2.1 Causality Adverse reactions should be assessed for causality. The protocol should stipulate the causality definitions. The below is an example:</p> <table border="1"> <thead> <tr> <th>Relationship</th> <th>Description</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 clinical condition, other concomitant treatments).</td> </tr> <tr> <td>Probable*</td> <td>There is evidence to suggest a causal relationship and the influence of other factors is unlikely</td> </tr> <tr> <td>Definitely*</td> <td>There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out</td> </tr> <tr> <td>Not assessable</td> <td>There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship.</td> </tr> </tbody> </table>	Relationship	Description	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 clinical condition, other concomitant treatments).	Probable*	There is evidence to suggest a causal relationship and the influence of other factors is unlikely	Definitely*	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out	Not assessable	There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship.
Relationship	Description														
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 clinical condition, other concomitant treatments).														
Probable*	There is evidence to suggest a causal relationship and the influence of other factors is unlikely														
Definitely*	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out														
Not assessable	There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship.														

	<p>* If the AE is serious and unexpected, the possible, probable, not assessable and definitely related should be notified to the CI as a possible SUSAR.</p> <p>Where different causality definitions are specified in the Protocol, it must be clear which definitions constitute a 'related' event.</p> <p>7.2.2 Expectedness</p> <p>The PI must assess the event against the known undesirable effects of trial medication. The RSI will contain the known effects. The event will either be assessed as expected or unexpected.</p>
<p>PI/CI</p>	<p>7.3 Reporting Guidelines</p> <p>The CI/PI has evaluated and determined the AE in terms of seriousness, causality and expectedness. The PI of a hosted CTIMP study at a Royal Free site must be aware of and follow the Sponsor's process for reporting AEs. The following guidelines are standard but should be checked against the Sponsor's SOP.</p> <p>AEs</p> <p>AEs that are not considered serious should be included in the patient notes and on the relevant case report forms (CRFs). The completed form should be filed along with the other CRFs for the study and a copy provided to the Sponsor as agreed.</p> <p>SAEs</p> <p>If the AE is assessed as serious, the PI must report the event to the CI immediately or within 24 hours of being made aware of the event (other than those SAEs identified in the protocol as not requiring immediate reporting). The initial report can be made verbally but must be promptly followed with a detailed, written report. The PI must record the event with their assessment of seriousness, (along with causality, expectedness and severity) on a trial SAE form provided by the CI or Sponsor. (see an example www.hra.nhs.uk/approvals-amendments/managing-your-approval/safety-reporting/) The PI should ensure that follow-up information is provided when available.</p> <p>SUSARs</p>

	<p>Any AE that the PI evaluate as serious, is suspected of having a causal relationship to the trial medication and is unexpected, will require expedited reporting to the sponsor and to other organisations as required under the terms of the individual contracts (e.g. relevant Pharmaceutical Companies, CRO, NHS Trusts). The PI must report the event to the sponsor (or as per sponsor pharmacovigilance SOP) immediately or within 24 hour of being made aware of the event.</p> <p>Firstly the PI must assess whether a Serious Adverse Reaction (SAR) is expected (see reference safety information 7.6); whether the reaction to the IMP or NIMP was expected. To make the expectedness assessment the PI must review the trial specific Reference Safety Information (RSI) together with the protocol. The RSI is listed in the Investigators Brochure (IB) or the Summary of Product Characteristics (SmPC).</p> <p>If the SAR is expected in the IB/SmPC and protocol Report the expected SAR to Sponsor (see SAE process).</p> <p>If the PI has assessed that the SAR as unexpected it should be classified as a SUSAR (Suspected Unexpected Serious Adverse Reaction). A SUSAR is an SAE which is suspected to be a reaction to the medicinal product and is UNEXPECTED i.e. it has not been seen before in the RSI.</p> <p>If the CI, or Trial Management Group if appropriate, is not in agreement with the “expectedness” decision of the PI, the CI cannot overrule the PI’s decision. Both opinions should be recorded on the relevant SAE form. SUSARs should be reported to the MHRA and REC within 7 calendar days if the SUSAR was fatal or life threatening or within 15 calendar days if non- fatal or non-life threatening. For the REC notification, the submission must also have a covering document completed which can be located at www.hra.nhs.uk/approvals-amendments/managing-your-approval/safety-reporting/</p> <p>The minimum data required for reporting SUSARs to the MHRA and REC are:</p> <ol style="list-style-type: none">i) The suspected Investigational Medicinal Product (IMP)ii) Subject trial Identificationiii) An adverse event assessed as serious and
--	--

	<p>unexpected, and for which there is a reasonable suspected causal relationship iv) An identifiable reporting source</p>
<p>PI/CI</p>	<p>7.4 Timeframes for Expedited Reporting</p> <p>The PI of a hosted CTIMP study at a Royal Free site must be aware of and follow the Sponsor’s process for expedited reporting. This normally requires notifying the CI/Sponsor within 24 hours of becoming aware of the event.</p> <p>In addition to informing the CI/Sponsor, the PI at the Royal Free site must inform the RF R&D Office as soon as possible as well as completing a DATIX.</p> <p>The CI must then:</p> <p><i>Fatal/life threatening SUSARs</i></p> <p>The CI must inform all sites where the study is currently active the MHRA, REC, and relevant Pharmaceutical Companies (if required under the terms of the contract) of fatal or life threatening SUSARs as soon as possible, but no later than 7 calendar days after the CI has first knowledge of the minimum criteria for expedited reporting. In each case, relevant follow-up information should be sought and a report completed as soon as possible. This should be sent within an additional 8 calendar days.</p> <p><i>Non- fatal and non-life threatening SUSARs</i></p> <p>The CI must report all other SUSARs and safety issues to all sites where the study is currently active the MHRA, REC, and relevant pharmaceutical companies (if required under the terms of the contract) as soon as possible, but no later than 15 calendar days after the CI has first knowledge of the minimum criteria for expedited reporting. Further relevant information should be given as soon as possible.</p>
<p>PI and research delivery team</p>	<p>7.5 When Sponsor’s electronic data capture systems (EDCs) are used for pharmacovigilance (reporting SAEs and SUSARs)</p> <p>Where a sponsor is using the EDC for the site to record AEs, and/or report serious adverse events</p>

	<p>(SAEs) and SUSARs to the sponsor there should be evidence in the database that the PI, or delegated medic has logged in to review and approve before they were submitted to the sponsor.</p> <p>The PI should log into the EDC and review SAEs in a timely manner.</p> <p>Non-medical staff must not login, submit or 'approve' aspects of the EDC that require medical review i.e. evaluating AEs, SAEs or eligibility decisions. The sponsor EDC system would normally require a separate login for the PI or medic to authorise medical decision. There must be evidence that site staff have completed data that is appropriate to their delegated role.</p> <p>If the sponsor's EDC does not have separate login for the PI or medic to review of approve AEs, SAEs or SUSARs the research team should complete the EDC as per sponsor SOPs AND:</p> <ul style="list-style-type: none"> • Print off the relevant pharmacovigilance section of the EDC for the PI or delegated medic to wet-sign in a timely manner and save a copy in the site file as evidence medical oversight. <p style="text-align: center;">OR</p> <ul style="list-style-type: none"> • Use a SAE proforma (hardcopy version of the E-SAE form) for the PI or delegated medic to wet-sign. The proforma should be version controlled and reviewed by the sponsor to ensure it captures all the required information for the IMP. The PI or delegated medic should sign the proforma in a timely manner and a copy should be saved in the site file as evidence medical oversight. <p>(See SOP058 Research Data)</p>
<p>PI</p>	<p>7.6 Urgent Safety Measures</p> <p>The Chief and Principal Investigators have the authority to deviate from the protocol if doing so relates to the immediate safety of a participant, where continuing to follow protocol would put that participant at risk. This is classed as an urgent safety measure and must be reported to the RF R&D Office and CI/Sponsor as soon as the PI makes the decision to deviate for safety reasons.</p>

	<p>On becoming aware of a potential hazard the PI or delegate must contact the sponsor immediately with the full decision making process information that lead to the implementation of the urgent safety measure. The PI or CI may report this verbally to the Clinical Trial Unit at the MHRA and discuss the issue with a medical assessor immediately (see MHRA website for telephone contact details). But Urgent Safety measure must be supported by a written report as soon as information is available. If the PI is unable to contact the sponsor or MHRA an Urgent Safety Measure can be implemented to protect the subject.</p> <p>The sponsor must then notify (in the form of a substantial amendment) the MHRA and the REC, in writing, of the measures taken and the reason for the measures within three calendar days of taking the Urgent Safety Measure or as soon as possible for any period during which a disease is pandemic and is a serious risk to human health or potentially serious risk to human health. This notification must include a covering letter detailing the measures taken, the reason for them, the medical assessor contacted and any supporting documentation. The notification must be submitted to the MHRA as per their current submission guidelines on the MHRA website. Should the trial be temporarily halted, or an amendment is required following an event for any reason (please see SOP 003 Implementing Amendments).</p> <p>.</p>
<p>PI</p>	<p>7.7 Unblinding</p> <p>PIs of hosted CTIMP studies at RF are responsible for ensuring that they are aware and understand the process of unblinding for a particular study.</p> <p>Systems for SUSAR and SAR reporting should, as far as possible, maintain blinding of individual clinicians and of trials staff involved in the day-to-day running of the trial. It is important that the details of the unblinding process are included in the trial protocol.</p> <p>For blinded trials involving a placebo and an active drug, seriousness, causality and expectedness should be evaluated as though the patient was on active drug. Cases that are considered serious, unexpected and possibly, probably or definitely related (i.e. possible SUSARs) would have to be unblinded. Only those events occurring among patients on the active drug (unless thought to be due to the excipient in the placebo) should be considered</p>

	<p>to be SUSARs requiring reporting to the MHRA, RECs, RF R&D and DATIX. It may be that individuals who are not directly involved in the management of the trial could perform unblinding.</p> <p>For blinded trials involving two active drugs, the person responsible for the evaluation for causality and expectedness might be able to state that if the patient were on drug A the event would be causal and/or unexpected, but if on drug B it would be expected. If the event were unexpected for either of the active drugs, the case should be unblinded by the individual charged with unblinding, who would then classify the event accordingly. An IDMC has access to semi-blinded or unblinded data and can oversee the assessment of emerging risks, such as an increase in frequency or severity of adverse events. The committee's assessments are carried out without disclosure to the trial team. They may recommend protocol amendments, or termination of the study, if they detect serious safety issues. In addition, the chairman of an IDMC might be able to play a role in unblinding individual reports of SUSARs for expedited reporting (if this could be managed within the requisite timeframes) and SSARs for annual reports.</p>
<p>PI/CI</p>	<p>7.8 Reference Safety information (RSI)</p> <p>If the PI or CI has been delegated the 'expectedness' decision of a Serious Adverse Reaction (SAR) by the sponsor, they must be able to identify the MHRA approved Reference Safety Information (RSI) to make the decision. The RSI should be a list of medical events that defines which reactions are expected for the Investigational Medicinal Product (IMP) being administered to clinical trial subjects, and so do not require expedited reporting to the sponsor and MHRA.</p> <p>When designing the study, the sponsor is responsible for ensuring the RSI is clearly defined in the protocol and, once the trial is active review the RSI every year.</p> <p>If the RFL investigator has been delegated 'expectedness' decision they must know which documents to refer to decide whether or not the reaction is an expected side effect of the IMP, thus determining whether it does or does not need reporting in an expedited fashion as a SUSAR to the sponsor (or as per sponsor SOP). To be categorised as expected the reaction must be clearly listed in the RSI.</p> <p>The sponsor is responsible for identifying the RSI in</p>

	<p>the original CTA application. For example, the RSI is often a specific section of the SmPC (version/date) if the product is licenced, or the IB (version/date) if the product is unlicensed.</p> <p>All clinicians who is delegated the ‘expectedness’ decision must know which <u>version</u> of the RSI is approved by the MHRA. Once your trial’s initial CTA has been approved, that is the RSI that must be used unless the regulator agrees otherwise. To change the RSI the sponsor must submit a substantial amendment to the MHRA to change it (see SOP 003 Implementing Amendments) Therefore, if the sponsor has submitted SmPC version 2.0 dated 01/01/2010 with the initial MHRA application that is the version of the SmPC that must be used as the RSI by the investigator. If a new SmPC is released, the sponsor must submit a substantial amendment to the MHRA and wait for the approval before the site make the switch the RSI. The same applies for IB updates.</p> <p>Serious Adverse Events (SAEs) that are not related to the IMP do not need an expectedness assessment against the RSI to assess whether they meet the criteria for a SUSAR.</p> <p>When investigators are conducting the expectedness assessment it important that the RSI is controlled so that all sites are using the same version of the RSI at the same time.</p> <p>International trials: it is advisable that new versions of SmPCs and IBS are submitted in parallel to the UK and non-UK competent authorities. This is to ensure that the same version of the RSI is relevant in all countries during the DSUR reporting period</p>
<p>CIs/PIs</p>	<p>Investigators who have been delegated DSUR submission by the sponsor</p> <p>The DSUR must be submitted no later than 60-days after the anniversary of the trial’s MHRA approval (date on the “Notice of acceptance letter). The DSUR should cover a one year period and no longer. The reporting period ends on the anniversary of the trial’s MHRA approval.</p> <p>The reference safety information (RSI) must be assessed annually as part of the DSUR submission.</p> <p>The DSUR submission normally include the following but investigators should follow sponsor’s SOPs and</p>

	<p>guidance:</p> <ul style="list-style-type: none">• A cover letter listing all EudraCT numbers of trials covered by the DSUR, including any trials approved via the Voluntary Harmonisation Procedure (VHP) process.• An analysis of the subjects' safety in the concerned clinical trial(s) with an appraisal of its ongoing risk/benefit.• A line listing of all suspected serious adverse reactions (including all SUSARs) that occurred in the trial(s), including all SUSARs from third countries.• An aggregate summary tabulation of SUSARs that occurred in the concerned trial(s). Full details of what to include in a DSUR are on the European Commission website <p>RSI review in the DSUR</p> <p>At the end of the DSUR reporting period the delegate must assess the new safety information that has been generated and submit any proposed safety changes to the investigator's brochure 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 any investigational medicinal product involved in a clinical trial must stay consistent during each reporting period. The development safety update reports (DSURs) should take into account all new available safety information received during the reporting period.</p> <p>If there are any changes to the (RSI) during the trial the CI must assess along with the sponsor whether or not the protocol and patient facing documents (patient information sheet and consent forms) need to be formally amended.</p> <p>Once a decision has been made that an update to the RSI document is required it is important that the change is managed in a timely fashion. The overall process to change the RSI requires several steps, such as a review of the evidence of the proposed change, agreeing the wording, compiling a variation document (where required) awaiting approval by the Competent Authority (where required), notifying relevant parties of approved updates and implementing changes within an appropriate timeframe. It is not possible to define the timeline for</p>
--	---

	<p>the whole process but the investigator should ensure that the updates of the SmPCs and IBs are performed without undue delay, as they provide vital information to patients and prescribers that will impact upon patient safety. The Investigator brochures or SmPC must be reviewed periodically, to ensure that it is up to data and accurately reflects the knowledge currently available about the product.</p> <p>IBs should be reviewed at least annually and revised as necessary. The requirements for reviewing SmPCs is less well defined, although the Directive 2001/83/EC requires that the information should be updated on a 'regular basis,' which JRMO has set the standard as being at least annually. Once approved by the sponsor and Competent Authority (where required), the sponsor must ensure that the latest version of the RSI, i.e. the SmPC or IB, is distributed to the PI at each site at the commencement of the trial and when updated. The previous version must be superseded in the TMF and a copy of the updated document placed in the file.</p>
<p>PI</p>	<p>Inform the sponsor about Adverse Event of Special Interest (AESI), as per protocol/CTA.</p> <p>If the event is not classed as serious, but is deemed to be an AESI, the PI must inform the sponsor who will report this to the MHRA following the same timelines as for reporting a SUSAR. AESI may be:</p> <ol style="list-style-type: none"> 1. An increase in the rate of occurrence of an expected serious adverse event, which is judged to be clinically important 2. Post-study SUSARs that occur after the patient has completed a trial 3. A new event, related to the conduct of the trial or the development of the investigational medicinal product (IMP), that is likely to affect the safety of subjects, such as: <ul style="list-style-type: none"> • A serious adverse event that could be associated with the trial procedures and which could modify the conduct of the trial; • A significant hazard to the subject's population such as lack of efficacy of an IMP used for the treatment of a life-threatening disease; a major safety finding (for example, carcinogenicity) from a newly completed animal study; • Any anticipated end to a trial or temporary halt for safety reasons where the trial is conducted by the same sponsor with the same IMP in another country;

	<ul style="list-style-type: none"> • The conclusions or recommendations of a data monitoring committee, where relevant for the safety of subjects. The MHRA recommends expedited reporting both to MHRA and the REC of any information that materially alters the current risk/benefit assessment of the IMP or merits changes in the way the IMP is administered or the overall conduct of the trial.
Externally Sponsored trials	<p>There is no regulatory requirement to send the R&D reports and SAEs for externally sponsored studies, i.e. sponsored by pharmaceutical company or another university or Trust.</p> <p>The R&D office does not require SAE reports or SUSAR reports, or Development Safety Update for externally sponsored CTIMPs or SAEs for externally sponsored non-CTIMPs. These documents need to be processed according to the external sponsor's SOP. The R&D office does not review nor is it obliged to keep copies of these documents.</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.

10. FORMS/TEMPLATES TO BE USED

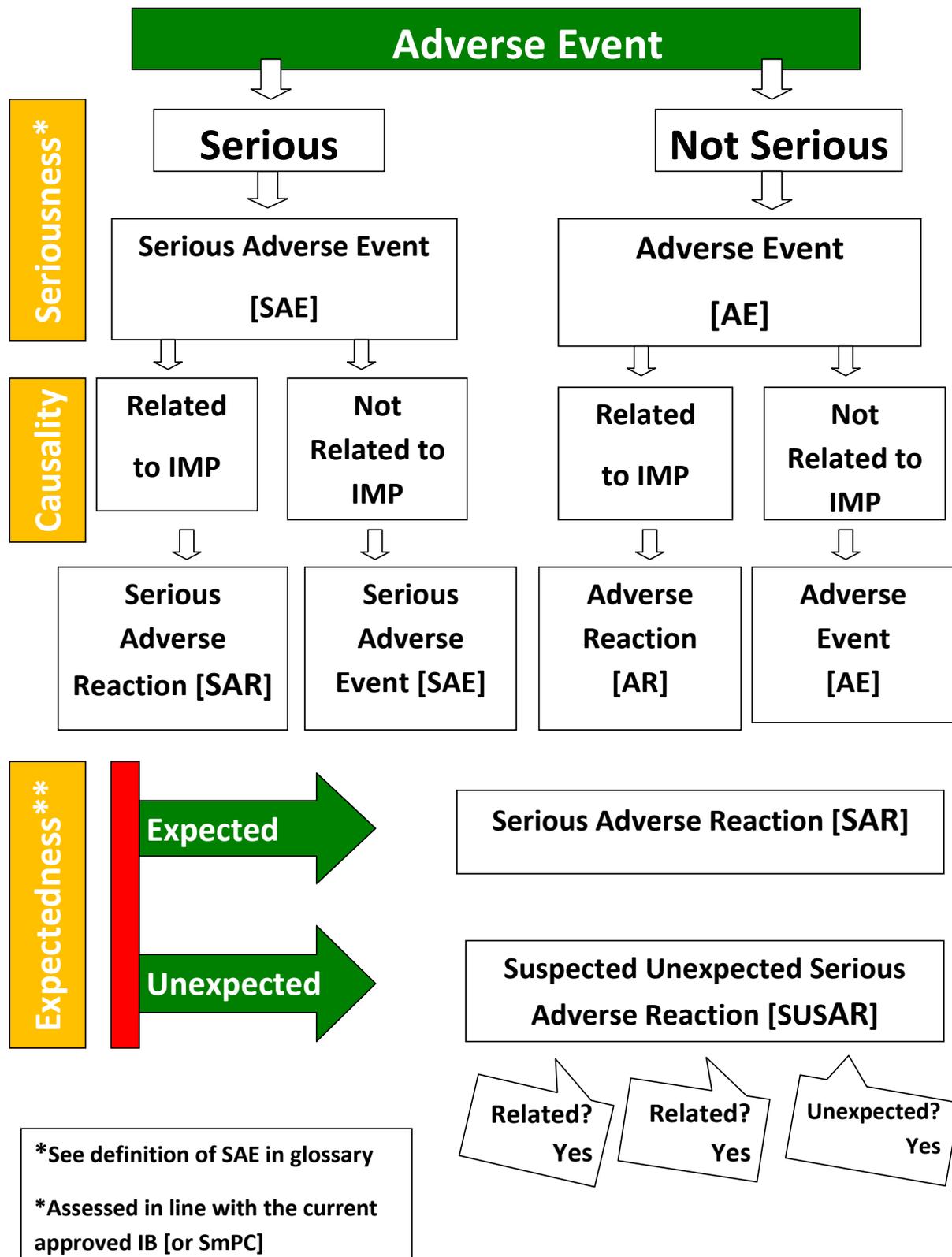
None applicable

11. FLOWCHART – Safety Reporting

SOP 063: Safety Reporting for CTIMPS hosted at RF

V1, 07 NOV 2017

Uncontrolled document when printed or downloaded. Current SOP versions available
<https://www.royalfree.nhs.uk/research/for-investigators/standard-operating-procedures-sops/>



APPENDIX 1 REPORTING RESPONSIBILITIES

1.1 Investigator's Responsibilities

1. PI to report all SAEs and SUSARs within agreed timelines to the CI (see section 7).
2. RF Trust related SUSARs are to be reported via Trust Intranet DATIX Reporting by PI
3. PI to ensure that the RF R&D has been notified about SUSARs that have occurred in any RF trial patients.
4. PI to complete trial specific SAE reporting form and submit to the CI following the initial SAE report. Ensuring that as much detail as possible is included in the report. Providing the CI with details of all AEs identified in the protocol as critical to the evaluation of safety within the agreed timeframes specified in the protocol.
5. Assess each event for causality and expectedness
6. Sign and date the SAE form (if required)
7. CI to report all SAEs within agreed timelines to Sponsor
8. CI to report SUSARs within agreed timelines to Sponsor, MHRA, REC and relevant NHS Trust Research and Development Office (R&D)
9. 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.
10. CI to also assess each event for causality and seriousness between the IMP and/or concomitant therapy and the adverse event.
11. CI to supply the Sponsor, MHRA, REC and relevant NHS Trust R&D with any supplementary information they request.

It is acknowledged that all these activities (except **(4 and 5)** are often undertaken by the Research Nurse (RN), Clinical Trials Practitioner (CTP) or Data Manager (DM) where appropriate, and where this has been delegated by the PI in the site delegation/participants log that the person is suitably qualified. As important as it is to report SAE's in urgent situations, every effort must be made by the RN/CTP/DM to discuss the SAE with the PI.

1.2 Responsibilities of other members of the research team e.g. Registrars, Junior Doctors (FY2/3/4/5) Ward Sister etc.

1. To report details of an SAE as defined in the study protocol as soon as possible to the PI or research support staff.

1.3 Responsibilities of Research Nurse /Clinical Trials Practitioner

- 1 As soon as they are made aware of an SAE in a subject who has consented to a trial being conducted at RFL they must inform the PI of the trial immediately within **24 hours**
- 2 If the RN or CTP is unsure whether an event should be defined as serious they should ask the CI/PI or a sub investigator for clarification.

1.4 Sponsor's Responsibilities

1. Ongoing safety evaluation of any IMP(s), including trend analyses.
2. Promptly notify all Investigators, REC(s) and MHRA, of any findings that may affect the health of subjects. This may include informing investigators using the same IMP in different studies.
3. Keep detailed written reports of all AEs reported by PIs and performing an evaluation with respect to seriousness, causality and expectedness.
4. Report all relevant safety information to the relevant REC and MHRA.
5. Report all SUSARs to the MHRA, REC and relevant NHS Trust R&D in concerned Member States associated with comparator product(s) and Marketing Authorisation (MA) holder(s), within given timelines.
6. Break treatment codes before submitting expedited reports to MHRA and REC for specific subjects, even if the Investigator has not broken the code. (Note: A system for maintaining blinding for the CI/PI and trial staff may need to be agreed in advance).
7. Submit the development update safety report (DSUR) to Sponsor, MHRA and REC.
8. Encourage the set-up of Independent Data Monitoring Committees (IDMC) for phase III clinical trials that have high morbidity/mortality and describe their function in the protocol.
9. Ensure written SOPs and systems are in place to ensure quality standards are met.
10. Register users for pharmacovigilance data entry with the European Medicines Evaluation Agency (EMA) if required.

APPENDIX 3

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 CTIMPS hosted at a Royal Free site.
Briefly describe its aims and objectives:	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.
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	

SOP 063: Safety Reporting for CTIMPs hosted at Royal Free

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
Race	None identified	R&D administrative document	NA	NA	
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
SOP Working Group	Royal Free London NHS Foundation Trust	06/12/2017
R&D Committee	Royal Free London NHS Foundation Trust	25/01/2018

SOP 063: Safety Reporting for CTIMPS hosted at RF

V1, 07 NOV 2017

Uncontrolled document when printed or downloaded. Current SOP versions available <https://www.royalfree.nhs.uk/research/for-investigators/standard-operating-procedures-sops/>