

Document Title: SOP for Handling of Non-Compliance: Recording and Reporting of Deviations, Violations and Urgent Safety Measure

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Version Control

Version	Date	Author	Status	Comment
1.1	24_FEB_2017	Rachel Fay	FINAL	Non-substantial amendments to correct date of review and amend to SOP template V2.0.
2	03 OCT 2017	Lucy Parker	Final	Update to SOP template V3.0 Replacement of reference from Research Governance Framework to UK Policy Framework for Health and Social Care (2017)
3	13 NOV 2018	Danielle Read	Final	Update requirements for non-compliance reporting.
3.1	05 MAR 2019	Danielle Read	Final	Correction of Typos.

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1. INTRODUCTION

This document sets out the standardised process to be followed by all RFL Staff who are involved in clinical research within the Trust.

It aims to provide clear guidance on how non-compliance with the trial protocol, Standard Operating Procedures or regulatory requirements should be identified and managed.

2. OBJECTIVE

The document states the procedures to be followed to protect patients, maintain the integrity of the trial and comply with legal and Good Clinical Practice (GCP) guidelines.

3. DEFINITIONS

RFL Royal Free London NHS Foundation Trust

Serious Breach - is a breach which is likely to effect to a significant degree:

- a) the safety or physical or mental integrity of the subjects of the trial; or
- b) the scientific value of the trial.

USM - Urgent Safety Measure (USM) is an appropriate measure required to be taken in order to protect the subjects of a clinical trial against any immediate hazard to their health or safety.

Deviation - is usually an un-intended departure from the expected conduct of the trial protocol or SOPs, which does not need to be reported to the Sponsor.

Violation - can occur when there is a consistent variation in practice from trial protocol, SOPs. A violation can be classified as major if there is a significant occurrence which affects participant safety or integrity of the research.

RM&G - Research Management & Governance

R&D - Research & Development

Clinical Trial of Investigational Medicinal Product (CTIMP) - Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamics effects of one or more investigational medicinal product(s), and/or to identify any adverse reactions to one or more investigational medicinal products(s) and/or Study absorption, distribution, metabolism and excretion of one or more investigational product(s) with the object of ascertaining its (their) safety and/or efficacy.

Sponsor - Individual, organisation or group taking on responsibility for securing the arrangements to initiate, manage and finance a study. A group of individuals and/or organisations may take on Sponsorship responsibilities and distribute them by agreement among the members of the group, provided that, collectively, they make arrangements to allocate all the responsibilities that are relevant to the study.

CI - Chief Investigator (CI) is the authorised health care professional who takes primary responsibility for the conduct of the trial. There is only one Chief Investigator per Member State.

PI - Principal Investigator (PI) is the person who takes responsibility for the initiation and conduct of the study at site. There is one Principal Investigator at each site participating in a research study. For a single site study the Chief investigator may also take on the role of Principal investigator

GCP - Good Clinical Practice (GCP) is 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 reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.

TMF - The Trial Master File (TMF) contains all essential documents held by the Sponsor/Chief Investigator which individually and collectively permits the evaluation of the conduct of a trial and the quality of the data produced.

ISF - The Investigator Site File (ISF) contains all essential documents held by Principal Investigator(s) conducting a trial which individually and collectively permit the evaluation of the conduct of a trial and the quality of the data produced.

CRF – Case Report Form (CRF) is a printed, optical, or electronic document designed to record all of the protocol required information to be reported to the Sponsor on each trial subject.

4. SCOPE

This document defines the Trust's procedures for identifying and managing protocol deviations, violations and urgent safety measures in Research Studies and Clinical Trials of Investigational Medicinal Products (CTIMPs) at Royal Free London NHS Foundation Trust.

The management of serious breaches of protocol or GCP is outside the scope of this SOP and is described in SOP033: Reporting Serious Breaches of Protocol or GCP.

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.

This SOP applies to all personnel that are conducting research at the Trust including: staff that are full or part-time employees of the Trust, those working at the Trust with employment contracts funded partially or wholly by third parties, those working at the trust under honorary contract or under the remit of a valid research passport, those seconded to and providing consultancy to the Trust, and to students undertaking training at the Trust.

The Sponsor is responsible for implementing and maintaining quality assurance and control systems to ensure that research studies are conducted and data generated, documented and reported in compliance with the protocol.

The CI is responsible for the overall conduct of the research on behalf of the Sponsor. This includes ensuring the research is conducted in accordance with the approved protocol.

The PI (or other investigators) should not implement any deviation from or changes to the protocol/procedures, without the prior agreement of the Sponsor and approval from the relevant regulatory bodies and RFL R&D office, except to eliminate an immediate hazard to research subject.

Staff working on research studies must comply with the requirements set out in section 7.

7. PROCEDURE

Person Responsible	Task
All research staff	<p>7.1 Episodes of Non-Compliance</p> <p>Episodes of non-compliance can occur for a number of reasons and depending on the occurrence can be classes as either a protocol deviation, a protocol violation, a serious breach, or an urgent safety measure. When using the term 'protocol', this includes the detailed protocol, any summary document, standard operating procedures, consent forms, and any other information relating to the research study.</p> <p>A protocol deviation occurs when a process or criteria has not been actioned in line with the approved protocol. For example, a study visit outside defined visit schedule, or a variation in the management of a participant due to minor safety</p>

	<p>concerns. Deviations are occurrences which can be classed as minor and not affect participant safety or the integrity of the research.</p> <p>A protocol deviation may become a violation if it occurs on multiple occasions and/or affects multiple participants.</p> <p>A protocol violation occurs when there is a consistent variation in practice from the defined protocol. For example, changes to the protocol that have not been approved by an ethics committee or regulator that are classed as substantial amendments. A violation is a significant occurrence or event which may affect participant safety or the integrity of the research.</p> <p>Non-compliance with the inclusion and exclusion criteria is always classed as a significant protocol violation regardless of how minor the deviation appears to be, as these criteria define the participant group in relation to the scientific requirements of the protocol.</p> <p>An urgent safety measure occurs when a research participant has been identified as being at risk of harm in relation to their involvement in a research project and urgent action, which deviates from the protocol, is required to manage the event and protect the participant.</p>
<p>All research staff/PI/CI</p>	<p>7.2 Identification of an episode of non-compliance</p> <p>Where an episode of non-compliance is suspected, further information should be gathered detailing the nature and extent of the episode. The trial team should collate any supporting documentation. The PI or a member of the trial team must:</p> <ul style="list-style-type: none"> • Record full details of the episode and any corrective action that was taken • Inform the site PI/CI of the episode of non-compliance. • Gather and add any additional comments or explanatory notes as appropriate. <p>All events of non-compliance must be reviewed by the PI/CI to assess whether participant safety or study integrity has been affected by the deviation and to what extent the deviation has affected the project.</p> <p>The PI/CI will notify the Sponsor and the Sponsor will advise whether the event is a protocol violation and</p>

	<p>take appropriate measures to address the occurrence.</p> <p>If the PI/CI is unsure whether an occurrence is a deviation or violation they should seek advice from the Sponsor to ensure appropriate action is taken.</p>
<p>PI</p>	<p>7.3 Episodes that are classified as Deviations</p> <p>It is important that any deviation from the protocol is recorded and assessed and, where necessary, steps are taken to mitigate any harm to subjects or any loss of integrity to the trial data and information.</p> <p>These cases should be documented in the CRF or in a file note and appropriate corrective and preventative action taken in order to ensure they do not recur.</p> <p>The episode should be evaluated to identify any underlying problems; especially if there have been other episodes of a similar nature. Frequently recurring deviations can accumulate into a serious non-compliance. It is recommended that reoccurring deviations be discussed at any trial meetings to ensure any necessary corrective and preventative actions to be implemented.</p> <p>Consideration of the need for further training on trial procedures at the site where the episode occurred should be made.</p> <p>Where the PI/CI judges the deviation not to impact on safety or research integrity, it is not necessary to notify the RFL R&D office, but a file note should be added to the ISF and/or CRF and source documents explaining the action taken and its justification.</p> <p><u>RFL sponsored studies</u></p> <p>Deviations on RFL sponsored studies should be recorded on RFLRDLOG0005 Protocol Violations_Deviations Log.</p>
<p>PI</p>	<p>7.4 Episodes that are classified as Protocol Violation</p> <p>When a protocol violation is identified, it is essential to inform the appropriate parties of the occurrence and any corrective actions that have been implemented.</p> <p>Protocol violations should be recorded in the CRF or in a file note and appropriate corrective and preventative action (CAPA) taken in order to ensure they do not recur.</p> <p>The PI/CI must notify the Sponsor of the violation</p>

	<p>immediately upon identifying the issue. The Sponsor will advise on what action is required. The PI is responsible for notifying the R&D manager or research portfolio manager for the theme. R&D will confirm whether a datix incident needs to be completed and/or whether the violation and CAPA needs to be reviewed at R&Ds Quality Management Systems (QMS) Group meeting.</p> <p>Once a violation has been identified it may be necessary to inform the ethics committee and/or regulator of the incident and any corrective actions.</p> <p>Royal Free sponsored studies</p> <p>Violations on RFL sponsored studies should also be recorded on RFLRDLOG0005 Protocol Violations_Deviations Log.</p> <p>The R&D as sponsor will inform the CI of reporting requirements and direct them to submit a report explaining the event. Key areas in a report are:</p> <ul style="list-style-type: none"> • An overview of the incident and its cause • Description of corrective action • An assessment of likelihood of reoccurrence • Outline of any changes to the protocol that may be required • Time line for corrective action and amendment approval (if applicable) <p>All episodes classed as protocol violations on RFL sponsored studies are classed reportable Trust incidents and must be reported as a trial-related incident on Datix and a notification email sent to rf.randd@nhs.net.</p>
PI	<p>7.5 Episodes that are classified as a Serious Breach</p> <p>Strict guidelines and time limits apply to serious breaches. Reference should be made to SOP033: Reporting Serious Breaches of Protocol or GCP, which describes the procedures that must be followed.</p>
PI	<p>7.6 Episodes that are classified as Urgent Safety Measures</p> <p>Under the Medicine for Human Use (Clinical Trials) Regulations the Sponsor, Chief Investigator or Principal Investigator may carry out urgent safety measures (USM) to protect trial subject from immediate harm. This means that a deviation from, or a change of the protocol to eliminate an immediate</p>

	<p>hazard(s) to trial subjects may be implemented without prior approval from the REC/MHRA.</p> <p>The Sponsor, REC, MHRA (in the case of CTIMPs) and R&D office should be notified within 3 days of taking the USM. The notification should describe:</p> <ul style="list-style-type: none">• the event• the measures taken• justification for the measures taken <p>In the case of CTIMPs, the notification to the MHRA should be submitted electronically via email marked 'Urgent Safety Measure' to clinicaltrialhelpine@mhra.gsi.gov.uk.</p>
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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

11. FLOWCHART

None applicable

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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	Handling Non Compliance in research			
Briefly describe its aims and objectives:	The document states the procedures to be followed to protect patients, maintain the integrity of the trial and comply with legal and Good Clinical Practice (GCP) guidelines.			
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?	<table style="width: 100%; border: none;"> <tr> <td style="text-align: center; width: 33%;">Yes</td> <td style="text-align: center; width: 33%;">No</td> <td style="text-align: center; width: 33%;">if no do not proceed with Equality Analysis (EA)</td> </tr> </table>	Yes	No	if no do not proceed with Equality Analysis (EA)
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	

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, 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	10/11/2017
R&D Committee	Royal Free London NHS Foundation Trust	21/12/2017