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<u>This is a controlled document</u>	
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Version Control

Version	Date	Author	Status	Comment
1.0	24/06/2017	Heidi Saunders	Final	New document
2.0	07 OCT 2017	Lucy Parker	Final	Update to v3.0 of SOP template Clarification that the SOP covers audits and inspections by external parties only. Addition of the R&D Office must be invited to the close out meeting. Replacement of reference from Research Governance Framework to UK Policy Framework for Health and Social Care (2017)

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1. INTRODUCTION

As an NHS organisation (host site), the RF R&D office is responsible for allowing external access to research conducted at RF sites such as external Sponsor audits or monitoring visits as well as inspections from regulatory authorities such as the MHRA.

2. OBJECTIVE

The aim of this SOP is to describe to research staff the process for preparing for an external audit or inspection either by the Sponsor's independent audit function or by the Competent Authority (CA) for clinical trials that fall under the UK Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031) and the European Clinical Trials Directive. The SOP will cover the processes necessary to prepare, host and participate in a regulatory inspection by the Competent Authority.

Both audits and inspections take place to examine 'systems' and look for good control of processes and opportunities for process improvement.

This SOP also describes the internal audit procedure of RF R&D research activity. This SOP specifically describes the processes for selecting those studies and processes for audit that fall under the UK Policy Framework for Health and Social Care Research (2017) and/or the Medicines for Human Use (Clinical Trials) Regulations 2004 and subsequent amendments; Human Tissue Act (2008) the procedures for carrying out internal audits; and reporting audit results. This SOP also describes the requirements corrective and preventative action plans. As a sponsor and host organisation under section 3.10 of the UK Policy Framework for Health and Social Care Research (2017) RFL has a responsibility for auditing research practice and assuring adherence to current legislation and guidelines.

3. DEFINITIONS

RF Royal Free London NHS Foundation Trust

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.

Essential documents - These are documents which permit evaluation of the conduct of the trial and the quality of the data produced. These documents serve to demonstrate the compliance of the investigator, Sponsor and the monitor with the standards of GCP and with regulatory requirements'

4. SCOPE

This document sets out the procedures to be followed by all Staff members who are involved in the initiation, set-up and running of research.

This SOP describes the procedures relating to the preparation required, prior to, during and after the conduct of a site audit and/or inspection by authorized internal and/or external regulatory body and/or a Sponsor. The organisation providing care is responsible for permitting and assisting with monitoring, audit and inspection by relevant authorities.

RF R&D Office will be implementing a research audit programme in 2018. Therefore, this SOP will not cover auditing conducted by the RF R&D Office.

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.

7. PROCEDURE

An audit is:

“A systematic and independent examination of trial related activities and documents to determine whether the evaluated trial related activities were conducted, and the data were recorded, analysed and accurately reported according to the protocol, Sponsor's Standard Operating Procedures (SOPs), Good Clinical Practice (GCP) and the applicable regulatory requirements.” (ICH GCP 1.6)

Throughout the audit, general information exchange between the auditor and the person(s)/institution being audited is acceptable and essentially is used as an evaluation tool. Any results obtained from an audit should be used to train staff and improve upon the quality of research conducted.

Copies of the audit report should be sent to the R&D Office. Trials are audited to verify that:

- a) The rights and well-being of human subjects are protected
- b) The reported trial data are accurate, complete, and verifiable from source documents.
- c) The conduct of the trial is in compliance with the currently approved protocol/amendments(s), the GCP and with the applicable

An inspection is:

“The act by a Competent Authority of conducting an official review of documents, facilities, records, quality assurance arrangements and any other resources that are deemed by the authority to be related to the clinical trial and that may be located at

the site of the trial, at the Sponsor and/or Contract Research Organisation's (CRO's) facilities or at other establishments that the Competent Authority sees fit to inspect". (ICH 1.29)

An inspection is a formal process that has legal implications if non-compliance with the regulations is found. It is therefore imperative that all trial related documentation is maintained and continually updated in readiness for an inspection.

Part 1. EXTERNAL AUDITS and INSPECTIONS	
Person Responsible	Task
Auditor/Regulatory Authority Inspector	<p>7.1. The Audit/Inspection Timetable</p> <p>The Auditor/ Regulatory Authority will contact the PI directly to inform him/her that an audit/inspection is to take place, together with a suggested date and agenda.</p> <p>In the case of audit by an external auditor/Sponsor the PI should inform RFL R&D Office immediately that an audit/inspection is to be undertaken.</p>
PI	<p>7.2. Prior to the Audit/Inspection</p> <p>If a study is being audited by a Sponsor, the PI should inform the R&D office but should coordinate the audit themselves. The R&D office will be notified of external audits/inspection open and close out meeting as a minimum and will attend where possible.</p> <p>If the study is being inspected, the PI should notify all those personnel who need to be aware that an inspection is to take place e.g. Departmental director, R&D Office, Sponsor, REC, co-investigator(s), study coordinator, study administrator, research nurse, pharmacy, laboratory and technical departments (Radiology, Pathology, etc.) as appropriate and ensure that everyone is aware of the following:</p> <ol style="list-style-type: none"> a) That there is to be an inspection b) The purpose of the inspection c) When the inspection is to take place d) Who should be present, or be available if required <p>Prior to an inspection taking place a co-ordinator should be appointed to organise and plan the visit. All records must be made available (direct access) for monitors, auditors and regulatory authorities. It is</p>

	<p>important to address the following:</p> <ul style="list-style-type: none"> • Establish the name(s) of the inspector(s), the scope of the inspection and agree all dates in advance. It is essential that sufficient notice should be given to those expected to attend the inspection, with dates for availability of all involved agreed well in advance. • The inspection co-ordinator should be given a timetable of events and all roles and responsibilities agreed. For commercial trials that have been assigned an external monitor, they will act as a key liaison between the Sponsor (if commercial company) and the Investigator's study team, providing support to ensure that the personnel and site are ready for an inspection. • Identify and book suitable accommodation for the inspection to be conducted in, including space for all trial documents to be reviewed. Ensure that the room is tidy before the inspection. • Provide photocopying facilities • Organise refreshments • Respond to requests for specific documents, visits to specific departments eg labs, pharmacy. • Provide Inspection training/mock interviews for staff to prepare for an inspection and document in their training records.
<p>PI/Inspection Coordinator</p>	<p>7.3 Preparation for the Audit /Inspection</p> <p>RF policy is that the PI and core members of the study team must undergo inspection training before the inspection takes place. The training will be organised through the R&D Office.</p> <p>The PI/Inspection Co-ordinator should ensure that all the requested documentation is available for the Auditor / Inspector. Any missing data or forms should be covered by appropriate signed and dated file notes.</p> <p>The PI/Inspection Co-ordinator should ensure that all required study team personnel will be available on the day of the audit / inspection either in person, by pager, or telephone.</p> <p>An inspector will be looking for a number of things during the inspection process including:</p> <ul style="list-style-type: none"> • Essential Documents.

	<ul style="list-style-type: none">• Source Data<ul style="list-style-type: none">○ Records should be accurate, complete, legible and timely○ Data should be consistent with the source documents, or discrepancies explained.○ Document all deviations from protocol and explain.○ Any changes should be initialled, dated and signed○ Document all dose/therapy modifications, visits and tests not conducted○ Data verification will check CRF's for completeness, looking at data queries, lab results, ECG's , X-rays etc., protocol details/ number in notes, date of birth, vital signs, all visit dates, medical examinations, concomitant medication and changes,○ Adherence to study specific procedures. • Recorded in patient notes<ul style="list-style-type: none">○ Signed and dated copy of consent form and Patient Information Leaflet○ Laboratory results, X-ray results etc. related to participation in the clinical trial○ Title of the trial including the drug to be received○ Visit dates○ Concomitant medicines taken○ Any adverse events○ A letter informing the GP that the patient has been enrolled in the clinical trial if applicable • Complete Investigator File as per the Sponsor's SOP <p>It is important that:</p> <ul style="list-style-type: none">• Documents are up to date, reviewed and staff familiar with location and content• There is a clear Audit trail• Relevant documents bear dates and version numbers• A Tracking log is kept, if documents are updated (evidence of distribution and receipt)• Patient hospital notes should include up to date annotations, copy of consent form, General Practitioner (GP) letters, laboratory results, X-ray results etc. related to participation in the clinical trial• There are Pharmacy/drug accountability records
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	<p>The PI and each member of the study team are aware that the Auditor will be looking for evidence that each person dealing with the study, particularly the PI, can clearly identify the extent of their knowledge and degree of participation throughout the whole study.</p>
<p>PI/Inspection Coordinator</p>	<p>7.4 During the Audit / Inspection</p> <p>The PI/Inspection Co-ordinator should ensure that suitable facilities are made available for the Auditor / Inspectors.</p> <p>The PI/Inspection Co-ordinator should ensure that the appropriate study site personnel are available on the day of the audit / inspection in person, by pager, or telephone to answer any questions during the on-going audit / inspection.</p> <p>The PI/Inspection Co-ordinator should ensure the following:</p> <ul style="list-style-type: none"> • Details of the study team responsibilities are listed and available in the Investigator Site File • Research team is familiar and confident about their areas of responsibility in order to answer questions by the auditor/inspector. • Research team can provide up to date and accurate information to the auditor / inspector in a timely manner. • Unsupported information should not be offered • Members of the research team should seek clarification if they do not fully understand any questions raised by the auditor/inspector • Members of the research team do not answer questions if they are not the correct person to give a proper answer.
<p>PI/Inspection Coordinator</p>	<p>7.5 Close-out of the inspection</p> <p>At the end of the inspection a close out meeting will take place and the inspector will provide verbal feedback of the findings, followed by a detailed written inspection report. Each finding will be labelled, 'Critical, major, minor or For Note'. Each finding is referred to the particular regulation/guideline to which it is attributed. A reply to the report is required.</p> <p>The Research Portfolio Manager assigned to the study and relevant R&D staff must be invited by the</p>

	<p>PI/Inspection/Audit Coordinator to attend the close out meeting.</p> <p>The R&D office must receive a copy of any findings in order to send the completed report to the RFL R&D Committee, HTA Committee as appropriate</p> <p>Dissemination of Inspection findings should be used to evaluate research practices, and assist in staff training and update RFL R&D SOPs. Improving upon the quality of research conducted by implementing solutions to remedy the findings should be a priority after an inspection</p>
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PART 2: INTERNAL R&D AUDITS	
R&D Office	<p>Selection and role of auditors</p> <p>R&D auditors will be suitably trained as per RFL SOP reading log SOP 004 Training Records).</p> <p>R&D auditors will be asked to provide evidence of their training by the R&D Manager, and are responsible for filing accordingly (e.g. with audit reports). It is the auditor's primary role to collect evidence of research practice and compare it against the requirements of Good Clinical Practice UK Policy Framework for Health and Social Care Research (2017) and , RFL SOPs . The auditor is responsible for documenting observations and conclusions, safeguarding audit documents, records and reports, assessing whether requirements are being met, and developing reports including recommendations for change or adherence and corrective and preventative plans.</p> <p>Auditors should be independent to the research project team and/or from the R&D process they are auditing.</p>
R&D Manager	<p>The extent and nature of audits will be proportional to the R&D portfolio of research activity. A schedule will be created by the R&D Manager which is to be approved by the R&D Deputy Director (Operations). The R&D Manager will review the schedule periodically.</p>

	<p>Audits can be but are not restricted to :</p> <ul style="list-style-type: none"> • R&D SOP audit <ul style="list-style-type: none"> • Study essential documentation audits • Laboratory audits • Computer system / trial database audits • Investigational Medicinal Product (IMP) audits • Project audits 		
R&D Auditor	<p>Audit Plan:</p> <p>The Auditor will schedule the audit at a mutually convenient time, 'ideally' allowing the auditee 4 weeks' notice. This will be in writing and detailing as follows:</p> <ul style="list-style-type: none"> • Define the scope and objectives for audit. • Provide timelines for audit conduct. • Identify where and when the audit will take place. • Identify requirements to be audited against. • Identify groups and areas to be audited. • List documents and records to be reviewed. • List responsible people whose functions will be audited. • Clarify who will get the final report and when it will be ready 		
R&D Auditor	<p>During Audit: The auditor will perform the audit using relevant audit tools</p> <p>All audits will consist of an open and close out meeting with the auditee (s) present.</p> <p>The auditee (s) should be made aware of a summary of findings during the close out meeting.</p>		
R&D Auditor	<p>Audit Findings</p> <table border="1" data-bbox="603 1682 1406 1921"> <tr> <td data-bbox="603 1682 762 1921">Critical</td> <td data-bbox="762 1682 1406 1921"> <ul style="list-style-type: none"> • Where evidence exists that the safety, well being or confidentiality of study subjects has been jeopardised, and/or; • Where evidence exists that reported data are unreliable and/or; • Where inappropriate, insufficient, or untimely corrective action has taken place </td> </tr> </table>	Critical	<ul style="list-style-type: none"> • Where evidence exists that the safety, well being or confidentiality of study subjects has been jeopardised, and/or; • Where evidence exists that reported data are unreliable and/or; • Where inappropriate, insufficient, or untimely corrective action has taken place
Critical	<ul style="list-style-type: none"> • Where evidence exists that the safety, well being or confidentiality of study subjects has been jeopardised, and/or; • Where evidence exists that reported data are unreliable and/or; • Where inappropriate, insufficient, or untimely corrective action has taken place 		

		<p>regarding major non compliances and/or;</p> <ul style="list-style-type: none"> That reveals a significant failure to comply with relevant legislative requirements.
	Major	<p>A non-critical finding:</p> <ul style="list-style-type: none"> That reveals a significant and unjustified departure from the ICH GCP guidelines or other relevant established guidance, or failure to meet one of the principles of GCP, or; Where evidence exists that reported data may be unreliable and/or; That consists of a number of minor departures from the ICH GCP guidelines or other relevant established guidance, suggesting a systematic quality assurance failure, and/or; That reveals a failure to comply with relevant legislative requirements.
	Other	<ul style="list-style-type: none"> Any other inspection finding, excluding observations and recommendations.
R&D Auditor	<p>Post Audit:</p> <p>The audit report should be completed and passed to the auditor’s manager (for the R&D this should be the R&D manager or Deputy Director (Operations) for review and comment, prior to dissemination.</p> <p>The auditee should expect the audit report within 3 weeks of an audit being conducted.</p> <p>The audit will work with the auditor to explain CAPA plan but it is the auditees who is responsible resolving the findings (see below).</p> <p>Findings Review: Depending on the seriousness of audit findings, findings will be escalated, by the R&D Deputy Director (Operations), to the R&D Directors Depending or as per R&D escalation policy.</p> <p>Audit reports and CAPA plan will be shared with R&D Committee</p>	
Auditee	<p>The auditee is to follow up on the actions: corrective and preventive until resolved.</p> <p>If the actions have not been carried out in a timely manner, R&D Manager is to be notified, who will if necessary escalate to the Deputy R&D Director (Operations).</p>	

Auditor	The auditor will deem closed once all findings and CAPA has been completed and followed up to resolution. Issues with closing an audit will be escalated as per R&D escalation policy.
R&D Manager	There will be a R&D centralised log of audit findings – which is to be kept up to date by R&D Manager. This will be used as part of trend analysis and further audit plans.

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

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	Research Audits and Inspections			
Briefly describe its aims and objectives:	The aim of this SOP is to describe to research staff the process for preparing for an external audit or inspection either by the Sponsor’s independent audit function or by the Competent Authority (CA) for clinical trials that fall under the UK Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031) and the European Clinical Trials Directive. The SOP will cover the processes necessary to prepare, host and participate in a regulatory inspection by the Competent Authority.			
Directorate and Lead:	Rachel Fay, R&D Manger, 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
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	

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
Pregnancy and maternity	None identified	R&D administrative document	NA	NA	equality compliance within the Trust.
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	

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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

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