Document Title: Gaining Regulatory Approval from the MHRA

Document Number: PTUC SOP014

Staff involved in development: *Job titles only*	Senior R&D Manager, R&D Administration Manager, Clinical Project Managers
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Summary of Significant Change(s) (for this version only)

Section(s):	Modification:
	Minor administrative changes throughout the document

Key Points of this Document

- This document sets out the procedures to be followed by all Royal Papworth Staff who are involved in the initiation and set-up of projects managed by Royal Papworth Trials Unit Collaboration (PTUC) or sponsored by Royal Papworth NHS Foundation Trust which involve investigational medicinal products (CTIMPs) or non-CE marked devices which require regulatory approval from the Medicines and Healthcare Regulatory Agency (MHRA).

- It provides guidance on how the necessary regulatory approvals should be obtained prior to commencement of the study to ensure compliance with the Trust's wider research policies.

1 Purpose and Content

a. This document defines the Trust's procedures for applying for and obtaining MHRA authorisation of clinical trials that investigate medicinal products or non-CE marked devices which are managed by Royal Papworth Trials Unit Collaboration (PTUC) or sponsored by Royal Papworth NHS Foundation Trust.

b. Proof of approval for the study, as issued by the MHRA prior to the study commencing, must be recorded as part of the study's essential documents as described in Good Clinical Practice (GCP: 'a 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').

c. The document provides guidance on how approval should be obtained and recorded so as to comply with the Trust's procedures on Research Governance and Sponsor Files (Royal Papworth sponsored studies).

d. The subsequent gaining of R&D permissions for a research study is outside the scope of this SOP and is described in SOP034: Trust Approval and Research Governance.

2 Roles & Responsibilities

a. This Policy applies to all personnel who are conducting research at the Trust.

b. Staff involved in research trials concerning CTIMPs or non-CE marked devices that are subject to MHRA regulation must comply with the requirements set out in section 4.

c. The Chief Investigator (CI), in conjunction with the Sponsor's representative, is responsible for applying for MHRA approval.

d. The Principal Investigator must ensure that a trial of IMPs or non-CE marked devices has received regulatory approval from the MHRA prior to any study related activity being performed at Royal Papworth Hospital NHS Foundation Trust.

3 Policy

a. This SOP is mandatory and, as per the Trust's Information Governance and Records Management framework, non-compliance with may result in disciplinary procedures.

4 Procedure

a. According to the European Clinical Trials Directive (2001/20/EC), clinical trials of either non-CE marked devices or medicinal products in human subjects require authorisation by the competent authority (MHRA in the UK) in addition to a favourable opinion by an ethics committee. Medicinal trials are those in which an investigational medicinal product (IMP) is being assessed, e.g. to verify its efficacy or safety. For full definitions see: https://www.gov.uk/guidance/clinical-trials-for-medicines-apply-for-authorisation-in-the-uk

b. Under the EC Medical Devices Directives manufacturers are obliged to ensure that their devices are safe and fit for their intended purpose before they are CE marked and placed on the market in any EC member state. For further details regarding the regulation of non-CE marked devices please see https://www.gov.uk/topic/medicines-medical-devices-blood/medical-devices-regulation-safety

c. The MHRA authorisation is granted in the form of a clinical trial authorisation (CTA).Therefore, no clinical activity can take place on a medicinal clinical trial until written approval has been received from the MHRA. A complete copy of the CTA application (including the covering letter) must be forwarded to the Research Governance Team and kept in the Trial Master File

4.1 Making an application for Regulatory Approval

a. At the earliest opportunity an investigator should contact PTUC / R&D, who will assign a Clinical Project Manager to give guidance on what is required to complete the application.

b. All applications for studies requiring authorisation from Royal Papworth as Sponsor (including Ethics) must be sent to R&D for review (as in section 4.4a) and agreed by the

Trust prior to submission. The application must be signed on behalf of the Trust by the Clinical Director of R&D, or their delegated representative of the Trust. The CI, or their delegated representative, is responsible for ensuring that all documentation is submitted to R&D Enquiries in accordance with SOP048 Papworth Sponsorship of Research Studies.

c. A risk assessment must be undertaken by the investigators as preparation for the application to the MHRA and for running the study at Royal Papworth Hospital. This assessment, and actions put in place to mitigate any risks, should be documented accordingly and the outcomes of this assessment included in the CTA application. A template (FRM024: Risk Assessment Form of Royal Papworth Sponsored Clinical Trials of Investigational Medicinal Products) can be found on the intranet.

d. Pharmacy must be actively involved in the CTIMP risk assessment process. In addition a full review of the pharmacy requirements for the proposed trial must be conducted as part of the application process.

4.2 Completing the application

a. All CTIMPs must have a EudraCT number before an application to the MHRA must be made. The EudraCT number is a unique reference number for the clinical trial and will appear on all applications and documents such as Suspected Unexpected Serious Adverse Reactions (SUSAR) reports. The Sponsor applies for a EudraCT number through the EudraCT website: https://eudract.ema.europa.eu/

b. It is strongly recommended that the applicant reads the available guidance on the application process that can be found at: https://www.gov.uk/guidance/clinical-trials-for-medicines-apply-for-authorisation-in-the-uk

c. A clearly written Clinical Trials Authorisation (CTA) application will mean the MHRA is more likely to approve the application without requesting further information or conditions. The application must include:

1. A detailed covering letter to explain the application and to justify any exclusions.
2. A clear description of the IMP, its use and certification
3. A protocol
4. An Investigator Brochure or Summary of Product Characteristics, including information on expectedness of adverse reactions
5. Labelling which complies with Annex 13, EudraLex Volume 4
6. Authorisations for all EU sites of manufacture and assembly, and Qualified Person (QP) release
7. Any further scientific advice
8. If available, the REC opinion.

The investigator must ensure consistency between all the submitted documents.

d. All applications must be made using the web based Integrated Research Application System (IRAS) application form at http://www.myresearchproject.org.uk. The Clinical Project Manager will provide guidance on the completion of the application form and the submission process; this can also be found on the IRAS website

4.3 MHRA Review

a. The initial assessment of the validity of the CTA application will be performed by the MHRA within 10 days of receipt of the application and an acknowledgement letter will be sent to the person who made the application: this will be the person named in Section C of the Clinical Trial Application form (i.e. CI or Sponsor's representative).

b. If the application is not valid then the person named in C1 will be asked to supply what is missing. If there are large discrepancies they will be asked to submit a new application. The application will not be processed further until all the missing components of the application have been provided.

c. Valid CTA applications are assessed within 30 days of the receipt of the validated application.

4.4 Outcomes from the MHRA

a. Following assessment of the valid application the applicant named in section C1 will be sent a letter informing them of:

1. Acceptance of the request for a CTA
   OR
2. Acceptance of the request for a CTA subject to conditions
   OR
3. Grounds for non-acceptance of the request for a CTA.

If a letter has not been received within 35 days of sending the application, see the MHRA website for details on who to contact.

b. The structure of the notification letters from the MHRA is such that only one IMP can be named on the letter, even where there may be several IMPs used within the trial. Since the CTA is for a protocol and not for individual products, the notice of acceptance covers all IMPs listed in the application form even although only one is named on the letter. The

product which appears first in Section C of the Clinical Trial Application Form is the product which will be named on the letter.

4.5 After MHRA Approval

a. The CI is responsible for ensuring that a copy of the MHRA approval letter is forwarded to PTUC (papworth.ptuc@nhs.net and the Research Governance Team in R&D viapapworth.randdenquiries@nhs.net as it will be required for the Trust Approval of a study.

b. Documentary evidence that the conditions for a CTA have been met is required prior to Trust Approval and study green light being issued.

c. All subsequent amendments must be reviewed to see if they require MHRA approval (see SOP037: Amendments to Research Documents of Royal Papworth Sponsored Studies post Trust Approval).

d. The CI is responsible for forwarding copies of any MHRA approval letters relating to substantial amendments to R&D as in section 4.4a.

e. The CI is responsible for ensuring that reports to the MHRA must be sent with a covering letter and this letter should also be forwarded to R&D.

5 Risk Management / Liability / Monitoring & Audit

a. The R&D SOP Committee will ensure that this SOP and any future changes to this document are adequately disseminated.

b. The R&D Department 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).

c. In exceptional circumstances it might be necessary to deviate from this SOP for which written approval of the Senior R&D Manager 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.

d. The Research and Development Directorate is responsible for the ratification of this procedure.

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Further Document Information

Approved by: *Managment/Clinical Directorate Group*	Research and Development Directorate
Approval date: *(this version)*	Current active version approved date.
Ratified by Board of Directors/ Committee of the Board of Directors:	STET
Date:	N/A
This document supports: *Standards and legislation*	Medicines for Human Use (Clinical Trials) Regulations 2004 and all associated amendments. UK policy framework for health and social care research
Key related documents:	Trust Research Policy

Equality Impact Assessment: Does this document impact on any of the following groups? If YES, state positive or negative, complete Equality Impact Assessment Form available in Disability Equality Scheme document DN192 and attach.

Groups	Disability	Race	Gender	Age	Sexual orientation	Religious & belief	Other
Yes/No	NO	NO	NO	NO	NO	NO	NO
Positive/Negative							

Review date:	March 2021

Version Control

Version	Date effective	Valid to	Approved by	Date of approval
1.0	5 August 2009	July 2011	RDD	5 August 2009
2.0	5 June 2013	March 2016	RDD (Chairman's action)	10 May 2013
3.0				
4.0				

I certify the contents of this SOP has been reviewed and ratified

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Signed by Dr Ian Smith, Clinical Director of R&D

23rd January 2019

Date

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