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SOP 405
Obtaining and Maintaining Medicines and Healthcare Products Regulatory Agency (MHRA) Approval for a Clinical Trial

For Use in:	Research
By:	All staff
For:	All staff involved in the conduct of research
Division responsible for document:	Research & Development
Key words:	MHRA, Approval for Clinical Trials, Investigational Medicinal Product
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Date of approval:	26 June 2023
To be reviewed before: This document remains current after this date but will be under review	26 June 2026 (3 years, unless legislation or process changes)
Reference and / or Trust Docs ID No:	15249
Version No:	2
Description of changes:	EudraCT numbers no longer required but can be obtained. ISRCTN preferred. Minimum requirement for studies either IB or SmPC to ASMF. Combined review information added (page 5)

This Standard Operating Procedure (SOP) is available on the Research & Development pages on the NNUH website

Copies printed from the website are only valid on the day of printing.

Obtaining and Maintaining Medicines and Healthcare Products Regulatory Agency (MHRA) Approval for a Clinical Trial

1. Contents

2. Definitions of Terms Used / Glossary

CI	Chief Investigator
CTA	Clinical Trials Authorisation
CTIMP	Clinical Trial of an Investigational Medicinal Product
CTU	Clinical Trials Unit
DSUR	Development Safety Update Report
EMA	European Medicines Agency
EudraCT	European Union Drug Regulating Authorities Clinical Trials
GCP	Good Clinical Practice
IB	Investigator Brochure
IMP	Investigator Medicinal Product
IMPD	Investigational medicinal Product Dossier
IRAS	Integrated Research Application System
MHRA	Medicines and Healthcare Products Regulatory Agency
NCTU	Norwich Clinical Trials Unit
NNUH	Norfolk and Norwich University Hospitals NHS Foundation Trust
PI	Principal Investigator
QP	Qualified Person
R&D	Research and Development
REC	Research Ethics Committee
RIN	Research and Innovation Services
RSI	Reference Safety Information
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SUSARS	Serious Unexpected Adverse Reactions
UEA	University of East Anglia

3. Objectives

The aim of the SOP is to set-out the procedure for obtaining and maintaining approval for a Clinical Trial.

4. Scope

This SOP applies to all Clinical Trials of Investigational Medicinal Products (CTIMPs), which are sponsored by the NNUH.

5. Introduction

The MHRA is the government agency responsible for ensuring that medicines and medical devices are safe for use in clinical trials. These are substances, or combinations of substances, or methods/devices, which either prevent or treat disease in human beings or are administered to human beings with a view to making a medical diagnosis, or to restore, correct or modify physiological functions in humans.

Any research that fulfils the definition of a clinical trial, as described by the EU Clinical Trials Directive 2001/20/EC Article 2 (a) and update EU 536/2019, will require a Clinical Trials Authorisation (CTA) from the Competent Authority in the Member State in which research is being carried out. It will also require approval from an Ethics Committee. A CTA will only be issued by the Competent Authority (The MHRA in the UK) if it has no objections to the research proposal.

Clinical trials in the UK are regulated by The Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 1031) as amended. These regulations implement Directive 2001/20/EC ('The Clinical Trials Directive'). The current relevant legislation is given in Directive 2001/83/EC relating to medicinal products for human use, amended by Directives 2002/98/EC, 2003/63/EC, 2004/24/EC and 2004/27/EC.

Clinical trials involving only medical devices, food supplements or other non-medicinal therapies (such as surgical interventions) are **not** covered by the EU Directive, but may require other regulatory approvals. Studies of medical devices will, for example, usually fall within the remit of MHRA.

It is the responsibility of the Chief Investigator (CI) to establish whether regulatory approval is required for a study and that it is obtained prior to initiating the study. The Research and Development (R&D) Office at Norfolk and Norwich University Hospitals NHS Foundation Trust (NNUH), Research Innovation Services (RIN) at University of East Anglia (UEA) or Norwich Clinical Trials Unit (NCTU) can provide advice with the determination of whether or not it is a clinical trial, however the responsibility for whether regulatory approval is required remains with the CI. If there remains any uncertainty then the MHRA should be contacted for a written confirmation that a study does not require a CTA.

The clinical trial algorithm is attached at Appendix 1

6. Rules

Chief Investigator (CI)

- Responsible for establishing whether regulatory approval is required for a study and that it is obtained prior to initiating the study.

The application must be made by the Sponsor or by someone authorised to submit the request on behalf of the Sponsor. The activity of completing and submitting an application is frequently delegated to the CI/PI. The Sponsor should review and approve any applications. It is the CI/PI's responsibility to send a copy of all correspondence regarding regulatory approvals to the Sponsor. If the Sponsor is not established in the European Community then the Sponsor must have a legal representative which is based in the UK.

Sponsor

- Responsible for:
  - Obtaining an authorisation from the MHRA
  - Obtaining a favourable opinion from the Research Ethics Committee (REC) and HRA approval
  - Making arrangements to conduct the trial in accordance with the principles of Good Clinical Practice (GCP)
  - Complying with the requirements to report serious unexpected adverse reactions (SUSARs) to the MHRA and relevant REC within the required time limits
  - Providing the MHRA and relevant REC with an annual Development Safety Update Report (DSUR)
  - Allowing inspection of any trial premises by MHRA inspectors

7. Procedure NNUH

Procedure for obtaining an ISRCTN number

From 1 January 2022 the Health Research Authority (HRA) will automatically register clinical trials with ISRCTN Registry as one of the steps to ensure research transparency

Procedure for obtaining a EudraCT number
No longer required but can still be obtained

- If an EudraCT (European Union Drug Regulating Authorities Clinical Trials) number is required this number can be included on all clinical trial applications/regulatory forms

including applications to MHRA and those to the REC made through the Integrated Research Application System (IRAS)
- To obtain a EudraCT number, follow the process detailed at Eudract website (see reference information below)

Completing the CTA application form

In the UK, a Clinical Trial Authorisation (CTA) from the MHRA is required for a Clinical Trial of an Investigational Medicinal Product (CTIMP) and for combined trials of an investigational medicinal product and an investigational medical device (IMP/Device trials).

For these types of trial, there is now a single application for both Clinical Trial Authorisation and Research Ethics Committee (REC) opinion. Applications for combined review are prepared and submitted in a new part of the Integrated Research Application System (IRAS). The HRA website contains information on the combined review process.

Source: https://www.ct-toolkit.ac.uk/routemap/cta-submission

Submitting a notification for a trial to MHRA

- A CI wishing to have a trial considered for the Notification Scheme (in the majority of cases for type A, IMP studies) should contact the R&D Office for guidance before taking any further action to ascertain if the type of notification is appropriate
- A risk assessment based on the potential risks associated with the IMP should be made by the sponsor
- The MHRA website Notification Scheme for clinical trials should be used. Guidance for completion is also provided on the MHRA website (see reference information)

Reference Information:

Eudract website:	https://eudract.ema.europa.eu
MHRA website:	www.mhra.gov.uk
MHRA guidance:	https://www.gov.uk/guidance/clinical-trials-for-medicines-apply-for-authorisation-in-the-uk
IRAS website:	https://www.myresearchproject.org.uk/Help/HelpPage.aspx
The clinical trial algorithm and can be found at:	https://www.gov.uk/guidance/clinical-trials-for-medicines-apply-for-authorisation-in-the-uk - March 2023 *reproduced at Appendix 1 below*

Supporting documentation:

In addition to the completed application form, you are also required to send supporting documentation. The additional information required will depend on the design of the trial; this can be found in the MHRA guidance.

The minimum requirement for all studies is:

- Covering letter (titled for notification scheme)
- Completed CTA application form
- Protocol
- The exact version and section of the document being used for Pharmacovigilance Reference Safety Information (RSI) identification must be included within the cover letter as part of the CTA application. The exact location of the RSI must also be stated
- Investigator Brochure (IB), or Summary of Product Characterisation (SmPC) or Active Substance Master File (ASMF)
- Investigational Medicinal Product Dossier (IMPD) for product without a Marketing Authorisation (MA) or sIMPD for products with an MA
- A non-investigational product dossier (if required)
- Summary of scientific advice from any Member State or the European Medicines Agency (EMA)
- Manufacturer's authorisation, including the importer's authorisation and Qualified Person (QP) declaration on good manufacturing practice for each manufacturing site if the product is manufactured outside the EU
- Copy of the EMA's decision on the paediatric investigation plan and the opinion of the paediatric committee
- Example IMP label (or justification for its absence)
- Applicable fee

For non-commercial trials the MHRA has advised that the outline of all active trials should be submitted by the Chief Investigator for all studies with the same IMP in their department, and not by the Sponsor as indicated in the MHRA guidance.

Where appropriate the submission of the application activity may be delegated to a Clinical Trials Unit.

Confirmation of Approval

- Will be received via email
- Once received notify the NNUH R&D Office, providing a copy of the CTA.
- Some MHRA acceptance emails state conditions or remarks. These must be responded to prior to the start of the study
- The trial may only start if confirmation in writing to proceed has been received from the Sponsor (SOP 325 Study Start up Activities for Clinical Research Trials)
- The Sponsor will only provide this confirmation after receiving favourable opinions from the REC and approval from the NHS Trust(s) R&D Office and HRA
- If there are grounds for non-acceptance, the investigator should reply within 14 days (30 days for gene therapy, somatic cell therapy or products containing genetically modified organisms) to submit an amended request for authorisation.

- These periods may be extended in certain circumstances. The amended request is assessed within a total of 60 days from receipt of the initial application (90 days for gene therapy products)

Terms and conditions of approval

- For multi-centre trials an Investigator completing the Notification of an Amendment, will need to obtain a favourable opinion for each additional investigator, this will be issued by a REC. The project can begin at a site when REC approval and research governance authorisation is complete.
- In accordance with regulation 27 of the Clinical Trials Directive 2001/20/EC, the Sponsor must notify the Competent Authority within 90 days of the conclusion of the trial or a temporary halt to the trial.
- The MHRA may suspend or terminate a clinical trial when it feels the conditions for authorisation are not being met.

Amendments

Non-substantial Amendments

- The CI can make non-substantial amendments at any-time but an Amendment form must still be completed and signed by the sponsor. These must be filed along with the automated confirmation email
- It should not be assumed that an apparently small change in the protocol is necessarily non-substantial
- Where there is any doubt whether an amendment is substantial or not, the (MHRA, REC) should be contacted for advice

Substantial

- It is the responsibility of the Sponsor to ensure the decision of the substantiality of amendments is made

For further information see SOP 215 (Research Study Amendments).

Guidance on End of Trial reporting is available from the MHRA website (see references) and will follow the requirements of SOP 340 (Clinical Trial Reporting).

8. References and Related Documents

References
ICH GCP E6 / SI 2004/1041

SOP No.	SOP Title
SOP 215	Research Study Amendments
SOP 325	Study Start up Activities for Clinical Research Trials
SOP 340	Clinical Trial Reporting

9. Approval

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10. Reason for new version and Training Implication

This SOP replaces the previous version number V2

Changes made	What changes have been made to the contents of the document
Reason	• New layout • Revision in procedure (see page 1)
Training Implication	**Yes**
Actions required	• Additional training may be required

IS IT A CLINICAL TRIAL OF A MEDICINAL PRODUCT?[1]

This algorithm and its endnotes will help you answer that question. Please start in column A and follow the instructions. Additional information is provided in the notes at the end of the table. If you have doubts about the answer to any of the questions, contact the MHRA clinical trials unit.

A	B	C	D	E
A CLINICAL TRIAL OF A MEDICINAL PRODUCT?				**A NON-INTERVENTIONAL CLINICAL TRIAL?**
Is it a medicinal product (IMP)?[i]	**Is it not a medicinal product?**	**What effects of the medicine are you looking for?**	**Why are you looking for those effects?**	**How are you looking for those effects?**
If you answer no to <u>all</u> the questions in column A, the activity is not a clinical trial on a MP. If you answer yes to <u>any</u> of the questions below go to column B.	If you answer yes to the question below in column B the activity is not a clinical trial on a MP. If you answer no to this question below go to column C.	If you answer no to <u>all</u> the questions in column C the activity is not a clinical trial under the scope of SI 1031. If you answer yes to <u>any</u> of the questions below go to column D.	If you answer no to <u>all</u> the questions in column D the activity is not a clinical trial under the scope of SI 1031. If you answer yes to <u>any</u> of the questions below go to column E.	If you answer yes to all these questions the activity is a non-interventional trial which is outside the scope of SI 1031. If your answers in columns A,B,C & D brought you to column E and you answer no to any of these questions the activity is a clinical trial within the scope of the Directive.

[1] *Source: https://www.gov.uk/guidance/clinical-trials-for-medicines-apply-for-authorisation-in-the-uk - March 2023*

A.1 Is it a substance[ii] or combination of substances presented as having properties for treating or preventing disease in human beings? A.2 Does the substance function as a medicine? i.e. can it be administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action or to making a medical diagnosis or is otherwise administered for a medicinal purpose? A.3 Is it an active substance in a pharmaceutical form?	B.1 Are you only administering any of the following substances? • Human whole blood[iii]; • Human blood cells; • Human plasma; • Tissues except a somatic cell therapy medicinal product[iv]; • A food product (including dietary supplements) not presented as a medicine; • A cosmetic product[vi]; • A medical device	C.1 To discover or verify/compare its clinical effects? C.2 To discover or verify/compare its pharmacological effects, e.g. pharmacodynamics? C.3 To identify or verify/compare its adverse reactions? C.4 To study or verify/compare its absorption, distribution, metabolism or excretion?	D.1 To ascertain or verify/compare the efficacy[vii] of the medicine? D.2 To ascertain or verify/compare the safety of the medicine?	E.1 Is this a study of one or more medicinal products, which have a marketing authorisation in the UK? E.2 Are the products prescribed in the usual manner in accordance with the terms of that authorisation? E.3 Does the assignment of any patient involved in the study to a particular therapeutic strategy fall within current practice and is not decided in advance by a clinical trial protocol[viii]? E.4 Is the decision to prescribe a particular medicinal product clearly separated from the decision to include the patient in the study? E.5 Will no diagnostic or monitoring procedures be applied to the patients included in the study, other than those which are applied in the course of current practice? E.6 Will epidemiological methods be used for the analysis of the data arising from the study?

[i] Article 2 of The Human Medicines Regulations 2012 provides the definition of "medicinal product."

[ii] Substance is any matter irrespective of origin e.g. human, animal, vegetable or chemical that is being administered to a human being.

[iii] This does not include derivatives of human whole blood, human blood cells and human plasma that involve a manufacturing process.

[iv] Somatic cell therapy medicinal products use somatic living cells of human (or animal) origin, the biological characteristics of which have been substantially altered as a result of their manipulation to obtain a therapeutic, diagnostic or preventative effect (in humans) through metabolic, pharmacological and immunological means.

[v] Any ingested product which is not a medicine is regarded as a food. A food is unlikely to be classified as a medicine unless it contains one or more ingredients generally regarded as medicinal and indicative of a medicinal purpose.

[vi] The Cosmetic Directive 76/768/EC, as amended harmonises the requirements for cosmetics in the European Community. A "cosmetic product "means any substance or preparation intended for placing in contact with the various external parts of the human body (epidermis, hair system, nails, lips and external genital organs) or with the teeth and mucous membranes of the oral cavity with the view exclusively or principally to cleaning them, perfuming them or protecting them in order to keep them in good condition, change their appearance or correct body odours.

[vii] Efficacy is the concept of demonstrating scientifically whether and to what extent a medicine is capable of diagnosing, preventing or treating a disease.

[viii] Assignment of patients to a treatment group by randomisation planned by a clinical trial protocol cannot be considered as current practice.