STANDARD OPERATING PROCEDURE 5 Part 2
Gaining Initial Regulatory Approvals

Version:	5.0	Effective Date:	27 February 2024
Issue Date:	13 February 2024	Review Date:	27 February 2026
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Revision Chronology:	Effective date:	Reason for change:
Version 5.0	27 February 2024	Biennial review: Updates to application process, new process flowcharts added. Clarification of trial registry for CTIMPs with UK and EU sites.
Version 4.0	21 December 2021	Updated to include the new HRA/MHRA Combined Review process for applying for a clinical trial authorisation. Addition of new process to apply for Clinical Research Network (CRN) support for CTIMPs using the Combined Review process. Addition of new form to use to contact the MHRA for an opinion as to whether a trial will require a CTA.
Version 3.0	3 December 2020	Title, scope and format change to detail how to obtain initial regulatory approvals only. Amendments and ongoing communications with authorities are now covered in SOP 5 part 3 'Communication with Regulatory Authorities' and SOP 6 'Amendments'
Version 2.7	22 January 2020	Minor update to text regarding submission of an APR, not a DSUR for Type A trials. Plus, the requirement to send substantial amendments to WCTU QA team for review prior to submission to sponsors. Change to new format.
Version 2.6	25 March 2019	Biennial review: Updates to text and web links throughout the document to reflect current practice.
Version 2.5	19 July 2016	Biennial review: Web links updated. Application and submission process updated. Change to new format.
Version 2.4	3 February 2014	Biennial review: Web links updated. Details of fees updated.
Version 2.3	1 December 2011	Introduction of the new DSUR, changes to the approval system for low-risk trials and changes to the EudraCT number application system
Version 2.2	21 March 2011	New guidance on notifying protocol amendments (section 3.3.4.1). Change of address for MHRA. Updated information on safety reporting using MHRA's eSUSAR system. Updated website links.
Version 2.1	September 2009	Introduction of IRAS system
Version 2.0	8 April 2008	SOP 5 v1.0 split into two separate documents; MHRA Authorisation remains as SOP 5. Registration of a trial for publication is now SOP 28.
Version 1.0	March 2006	

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1. Purpose and Scope

This Standard Operating Procedure (SOP) details which clinical trials require a Clinical Trial Authorisation (CTA) from the Medicines and Healthcare products Regulatory Authority (MHRA) and how regulatory authorisation within the UK is acquired.

This SOP is applicable to all University of Warwick research staff involved in the set-up or management of a Clinical Trial of an Investigational Medicinal Product (CTIMP) or a clinical trial involving a medicine and/or a medical device. It applies for all Warwick sponsored trials or those managed by WCTU which have an external sponsor where the use of Warwick SOPs has been agreed.

2. Definitions

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.
Investigator's Brochure (IB)	A compilation of the clinical and nonclinical data on the investigational product(s) which is relevant to the study of the investigational product(s) in human subjects
Summary of Product Characteristics (SmPC)	A document describing the properties and the officially approved conditions of use of a medicine. SmPCs form the basis of information for healthcare professionals on how to use the medicine safely and effectively.
Integrated Research Application System (IRAS)	System for applying for the permissions and approvals for health, social and community care research in the UK.
Regulatory Authorities	Bodies having the power to regulate. In the ICH GCP guidelines, the expression Regulatory Authorities includes the authorities that review submitted clinical data and those that conduct inspections. These bodies are sometimes referred to as competent authorities (CA) and in the UK, this is the MHRA
Medicines and Healthcare products Regulatory Agency (MHRA)	The UK's Competent Authority (CA)- regulator of medicines, medical devices and blood components for transfusion, responsible for ensuring their safety, quality and effectiveness.

3. Background

It is a legal requirement of the Medicines for Human Use (Clinical Trials) Regulations 2004 that all CTIMPs and clinical trials involving a medicine and/or a medical device must obtain a CTA from the CA.

International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) section 5.10 regarding sponsors responsibilities states that;

"Before initiating the clinical trial, the sponsor (or the sponsor and the investigator) should submit any required application to the appropriate authority for review, acceptance, and/or permission to begin the trial."

Responsibility for the submission of applications to the appropriate regulatory authorities and ensuring that the necessary approvals are received before the trial begins must be determined at an early stage and appropriately delegated. The trial sponsor may delegate responsibility to an accredited CTU.

Clinical studies involving only licensed medical devices, food supplements or other non-medicinal therapies (such as surgical/physiotherapy interventions) are not covered by the UK Regulations and therefore do not need a CTA to be submitted to the CA.

Clinical trials involving a medicine and a medical device are subject to the regulations and may also be subject to medical devices regulations. Advice should be sought from the MHRA's Devices Division about trials involving non-CE marked devices or CE marked devices used outside of the conditions of the CE mark via devices.regulatory@mhra.gov.uk

Failure to comply with the relevant legislation, including the Medicines for Human Use (Clinical Trials) Regulations 2004 may have serious consequences and you are advised to refer to the University of Warwick Research Code of Practice for further information.

4. Procedure

4.1 Responsibilities

Chief Investigator (CI) (or delegate)	• Submission of all trial documentation for approval (Preparation of the application forms may be delegated to the Trial Manager or other team member, but the CI retains responsibility for its accuracy and completeness). • Ensuring compliance with the funding body's requirements. • Ensuring that all required authorisations are in place prior to the recruitment of any participants.
Sponsor	• Review and approval of trial protocol and supporting documents • Completion of a risk assessment • Determine the risk-adapted approach category • Sign-off of the application forms in IRAS • Oversight of the trial

4.2 When?

Clinical Trial Authorisation (CTA) must be obtained before a trial can commence (i.e., before any drugs can be released, recruitment of the first participant etc.).

4.3 How?

4.3.1 Determining whether a CTA is required

Not all clinical trials will require a CTA. An algorithm is available on the MHRA website to help determine if a clinical trial is covered by the UK regulations.

If, after using the algorithm, it is still unclear whether or not the clinical trial is covered by the regulations, researchers can contact the MHRA for an opinion using the Scope - protocol review -

request form available from Clinical trials for medicines: apply for authorisation in the UK. Complete the form and email it with a copy of the protocol to clintrialhelpline@mhra.gov.uk, with 'Scope - protocol review' followed by the study title (shortened)' as the subject line.

Where possible, the MHRA will respond to such queries within 14 days.

4.3.2 Apply for a CTA

All applications are processed through the MHRA and HRA's combined review service. **Please note the combined review service uses a new part of IRAS which requires a new account.** The application should not be started in the standard part of IRAS.

The combined review service offers a single application route and coordinated review leading to a single UK decision for CTIMPs.

The service is available to all CTIMP sponsors and applicants. To register, make a submission, or to get more information, refer to the combined review page on the Health Research Authority's website.

The HRA have produced a step-by-step guide to using the combined review system in IRAS.
The guidance includes:

- Creating an IRAS account
- IRAS user roles and tasks
- Making an initial submission:
    - Preparing your application
    - Validation
    - Responding to Requests for Further Information
    - Withdrawing a submission
    - Downloading documents
- Amendments and Reporting:
    - Developmental Safety Update Reports (DSURs)
    - Urgent Safety Measures (USMs)
    - End of trial notifications
    - Final reports can be submitted via IRAS and will be sent to the relevant body.

There is also a comprehensive guide on the use of the area in IRAS for submission of CTIMP applications.

The guide is to help those who apply for and manage approvals, as well as those who review and/or authorise projects. It's recommended to work through the whole guide before using the system for the first time.

Applicants are reminded to ensure common issues identified during clinical trial applications are addressed before submitting an application.

First-time users, can contact the HRA for initial advice and support at: cwow@hra.nhs.uk.

The system is designed so that individuals can view and revise the application information directly in the system rather than by generating a pdf of an in-progress application. Other collaborators to the system can be added with view-only or read-write access for this purpose.

For WCTU managed trials, the initial application forms generated in the new part of IRAS, along with the study protocol and any other supporting documentation should be sent to the QA team for review and quality control checks for consistency before being submitted for approval.

If there are requests for further information after the review, these should be returned within 14 days.

Documents to send with your application:

The IRAS portal includes a list of documentation to submit for combined review of your application with further information available from the MHRA. All applications should include:

- covering letter
- investigational medical product dossier (IMPD)
- manufacturer's authorisation
- content of the labelling of the investigational medicinal product (IMP)

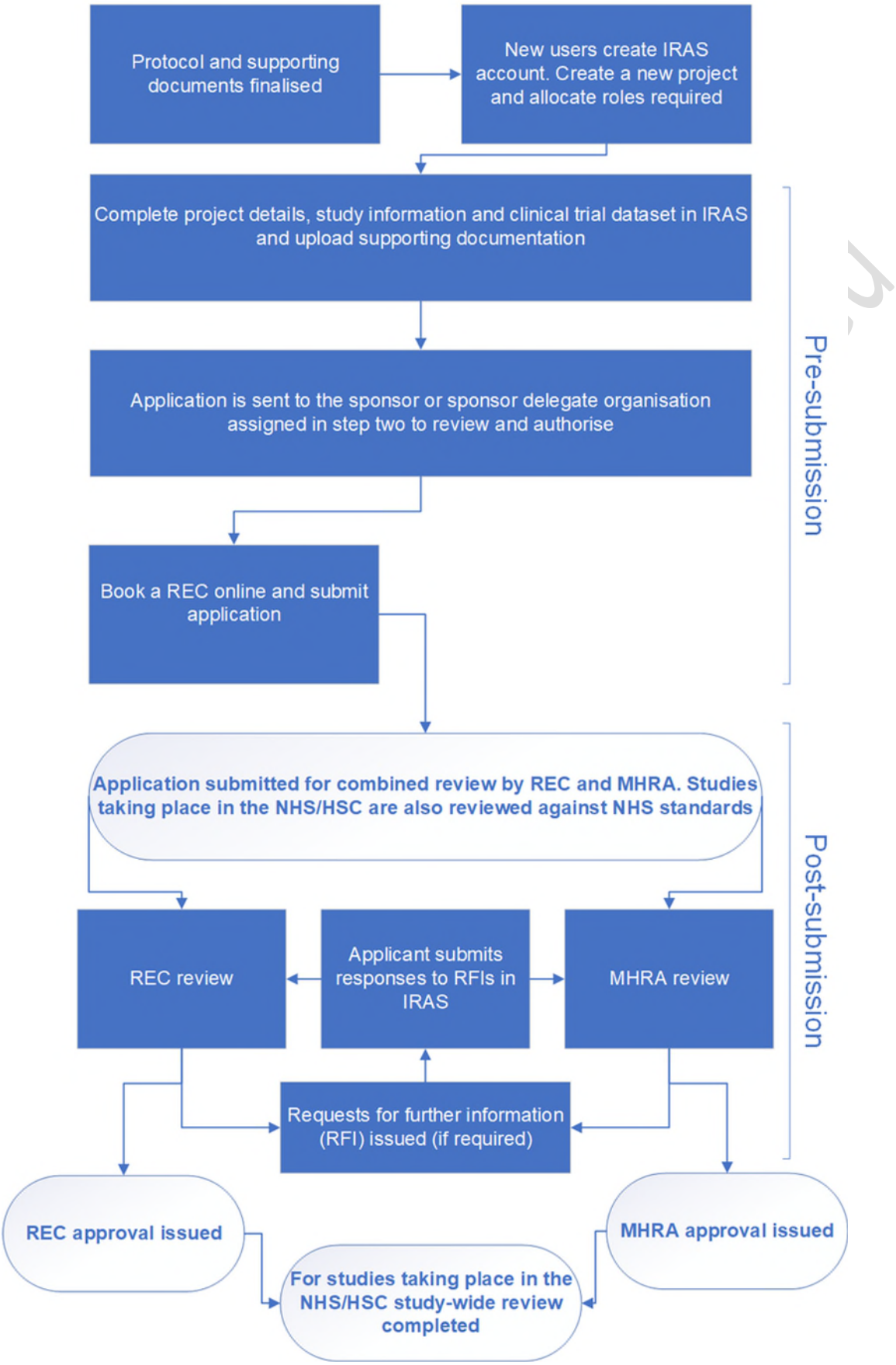
All documents must have copy and paste functionality. Password-protected documents are not accepted. Other published guidance remains relevant and should be consulted for further information on the submission requirements (with consideration of the MHRA as a sovereign regulator).

Contact:
For information about a submission, including status and tracking enquiries, contact the clinical trials helpline on 020 3080 6456 (Monday to Friday 8:30am to 4.30pm) or email clintrialhelpline@mhra.gov.uk.

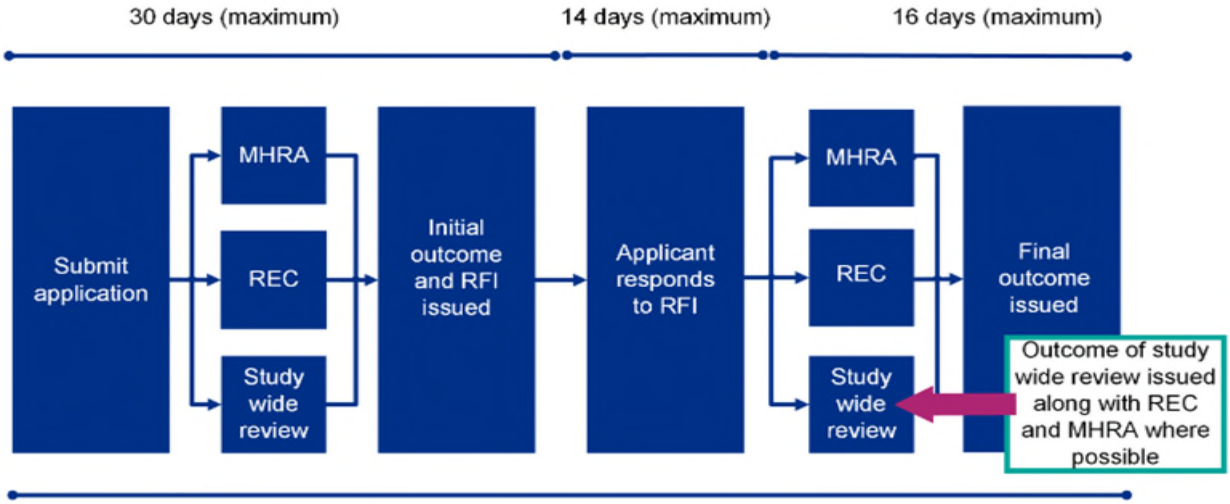
The flowchart below provides an overview of the application process.

N.B. For WCTU managed studies, all documentation prepared for an application must be sent to the QA team for Quality control checks prior to submission and booking the REC meeting slot.

Overview of the application process



Initial review process and timelines



A risk adapted approach to the approval of CTIMPs is in force. This guidance allows for a proportionate approach to approving trials and introduces a 'notification' system for low-risk trials rather than requiring a full application.

Risk Proportionate Approaches:
A risk proportionate approach to the initiation, management and monitoring of certain clinical trials is possible. The sponsor should carry out a risk assessment based on the potential risks associated with the IMP. The MHRA's guidance on risk-adapted approaches to the management of clinical trials of investigational medicinal products should be referred to.

The MHRA perform a risk adapted assessment of certain 'Type A' trials in which the risk to the patient from the IMP is considered to be no greater than that of standard medical care. These are trials involving medicinal products licensed in any EU Member State if:

- the trial relates to the licensed range of indications, dosage and form of the product, or;
- the trial involves off-label use (such as in paediatrics and oncology) that is established practice and supported by enough published evidence and/or guidelines.

The guidance categorises CTIMPs as risk types 'A', 'B' or 'C'. For examples and explanations of the categories, see Table 1 below.

Table 1:

Trial Categories based upon the potential risk associated with the IMP	**Examples of types of clinical trials**
***Type A: no higher than* that of standard medical care**	Trials involving medicinal products licensed in any EU Member State if: • they relate to the licensed range of indications, dosage and form or, • they involve off-label use (such as in paediatrics and in

	oncology etc.) if this off-label use is established practice and supported by sufficient published evidence and/or guidelines
***Type B: somewhat higher* than that of standard medical care**	Trials involving medicinal products licensed in any EU Member State if: • such products are used for a new indication (different patient population/disease group) or • substantial dosage modifications are made for the licensed indication or • if they are used in combinations for which interactions are suspected Trials involving medicinal products not licensed in any EU Member State if • the active substance is part of a medicinal product licensed in the EU (A grading of Type A may be justified if there is extensive clinical experience with the product and no reason to suspect a different safety profile in the trial population) *
***Type C: markedly higher* than that of standard medical care**	Trials involving a medicinal product not licensed in any EU Member State (A grading other than Type C may be justified if there is extensive class data or pre-clinical and clinical evidence) *

**If a grading other than those indicated is felt to be justified, the rationale and evidence should be presented in the CTA application*

The trial sponsor is responsible for reviewing the level of risk associated with the trial to establish the appropriate category and delegate ongoing review as appropriate.

For WCTU managed studies, this will be delegated to WCTU. In the event that a study is managed by an external CTU, this responsibility would be delegated to the external CTU.

The full guidance document including how to assess the risk is available and should be referred to early on the planning stage of a trial.

Notification Scheme:
The MHRA's Notification Scheme enables a more streamlined and risk-proportionate approach to processing clinical trial authorisation (CTA) for "initial" applications.

The scheme only applies to CTA applications for Phase 4 and certain Phase 3 clinical trials deemed to be of lower risk; it does not include CTA applications for first in human (FIH), Phase 1 or Phase 2, or amendments.

CTA applications submitted under this scheme will be processed by the MHRA within 14 days, instead of the statutory 30 days, provided the sponsor can demonstrate the trial meets the inclusion criteria.

Registering interest in the Notification Scheme:
Applications under the Notification Scheme are submitted via the combined review process using IRAS; there are no documentation exemptions. The complete submission package should be prepared and submitted in the new part of IRAS as described above.

All applicants (commercials and non-commercials) whose trials meet these criteria should participate in the scheme by registering their interest via this form.

MHRA acceptance of an application under the Notification Scheme will be confirmed within 14 calendar days from the application received effective date, and authorisation by the MHRA will be granted unless any criterion is not suitably met . If the MHRA considers the application does not meet the Notification Scheme criteria, an objection decision will be communicated within 14 calendar days from the application received effective date, and the application will continue under full CTA assessment with a decision communicated within the 30-day statutory timeframe.

The Notification Scheme is subject to existing fees.

Contact the MHRA if you have any questions about the Notification Scheme.

Fees:
There are different fees based on the type of clinical trial application. The fees applied (including for the New Notification Scheme) are listed under Clinical trials: applications fees.

Invoices for Clinical Trial Authorisation applications, Substantial Amendment applications, and Annual Safety Reports are sent directly to the applicant shortly after a valid submission has been established. The covering letter for the application should clearly highlight your Purchase Order (PO) number where available. The applicant is the person listed in section C1 of the Application form, or section D1 of the Amendment form. The MHRA are unable to address the invoice to someone other than those listed in the sections above.

It is the responsibility of the applicant to ensure timely payment of invoices for their submissions. Invoices must be settled on receipt of invoice. Penalty fees may be incurred for non-payment, details of the penalties are set out in the Fees Regulations. Non-payment may also result in suspension of any licence or authorisation, followed by legal proceedings for unpaid amounts, as a debt due to the Crown.

Contact MHRA Finance Department on 020 3080 6533 or email sales.invoices@mhra.gov.uk for more information on how to pay fees.

4.3.2.1 Trial Registration

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

CTIMPs with recruiting sites in the UK and the European Union (EU) or European Economic Area (EEA), need to register the trial with a registry such as ISRCTN and Clinical Trials.gov. This is because the Clinical Trials Information System (CTIS), the online system for the regulatory submission, authorisation and supervision of clinical trials in the EU and the EEA, does not allow users to submit information about UK CTIMPs conducted as part of a multinational trial. This means that the UK component of such trials is not visible which is not in line with the research transparency requirements for trusted information from health and social care research studies to be publicly available for the benefit of all.

It is a standard condition of a Research Ethics Committee (REC) favourable opinion for clinical trials to be registered on a publicly accessible database.

To defer registration of a trial (for example if it is an adult phase I trial), contact the HRA at study.registration@hra.nhs.uk.

The registry number(s) should be included, if available, in section A.5. of the application form in IRAS. If this is not available at the time of application, an email must be sent to the MHRA at clintrialhelpline@mhra.gov.uk with the subject line "Clinical Trial Registration" within six weeks of recruiting the first research participant and the relevant REC should also be informed as soon as possible.

4.3.2.2 Non-commercial application for Clinical Research Network (CRN) Support

For CTIMPS with non-commercial sponsors using the combined review system, there is a new system to apply for support from the CRN called the Non-commercial Portfolio Application service which is available within the Central Portfolio Management System (CPMS).

The service allows investigators to apply earlier and receive an eligibility decision sooner to benefit from the full range of support that the study support service offers. See here for full details.

4.3.2.3 Withdrawing a request before the final decision

An application may be withdrawn at any point before an assessment decision on the clinical trial authorisation application is reached. It is not possible to withdraw an application once grounds for non-acceptance have been issued.

To withdraw an application, please refer to the guidance on the HRA website.

4.3.2.4 Further guidance and support

The HRA provide comprehensive guidance on making an application where additional approvals or more information is required including:

- Pharmacy and Radiation Technical Assurance Submission Guidelines
- Instructions for studies with ionising radiation
- How and when to submit to ARSAC
- Guidance for combined IMP and device trials
- Information on registration of studies
- Current legislation and regulations
- Recorded webinars for applicants, sponsors and NHS/HSC organisations
- REC directory to search meeting dates (filter by RECs recognised to review CTIMPs)

This is all available on the HRA website

After initial approvals have been gained to commence a new trial, the Chief Investigator (CI) will have ongoing obligations to report to the MHRA. Details of these ongoing requirements can be found in SOP 17 Part 2 'Safety Reporting for CTIMPs, SOP 6 'Amendments to Approved Study Documents and SOP 5 part 3 'Communication with Approval Bodies'.

List of abbreviations

CA	Competent Authority
CI	Chief Investigator
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of an Investigational Medicinal Product
CTU	Clinical Trials Unit
DSUR	Development Safety Update Report
GNA	Grounds for Non-Acceptance
HCRW	Health and Care Research Wales
HRA	Health Research Authority
IB	Investigator Brochure
ICH GCP	International Conference on Harmonisation Good Clinical Practice
IMP	Investigational Medicinal Product
IRAS	Integrated Research Application System
MHRA	Medicines and Healthcare products Regulatory Agency
QA	Quality Assurance
REC	Research Ethics Committee
RFI	Request for further information
R&IS	Research & Impact Services
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
WCTU	Warwick Clinical Trials Unit