Submitting a CTA application to the MHRA

SOP Reference: RGIT_SOP_008	
Version Number: 14.0	
Effective Date: 14 Mar 2024	Review by: 14 Mar 2027
Author: Rinat Ezra, Clinical Trials Manager	
Approved by: Keith Boland, Senior Clinical Trial Manager	Date: 14 Mar 2024 Keith Boland Digitally signed by Keith Boland Date: 2024.03.14 14:33:50 Z

Version	Date	Reason for Change
Version 1.0	14 Sep 2006	MHRA updated processes
Version 2.0	10 May 2007	EudraCT link change
Version 2.1	27Jul 2007	Annual review
Version 3.0	19 Jun 2008	Annual review
Version 4.0	08 Feb 2010	Updates and Formation of Research Governance and Integrity Team
Version 5.0	14 Jul 2011	Annual Review
Version 6.0	30 Nov 2012	Annual Review
Version 7.0	18 Feb 2015	Scheduled Review
Version 8.0	28 Jul 2017	Scheduled Review
Version 9.0	10 Jan 2019	New version for minor updates
Version 10.0	19 Oct 2020	Scheduled Review Template removed and administrative changes to SOP. JRCO name change to RGIT.
Version 11.0	07 Jan 2021	Amendments due to leaving the European Union from 1st January 2021.

Version 12.0	25 Mar 2021	Remove of requirement for Annex 2 submission for amendments
Version 13.0	02 Nov 2021	Inclusion of submission via CWOW IRAS
Version 14.0	14 Mar 2024	Scheduled review

Table of Contents

1. PURPOSE 3
2. INTRODUCTION 3
3. PROCEDURE 4
3.1. Procedure for obtaining a EudraCT number 4
3.2. Completing the CTA application form 5
3.3. Supporting documentation 7
3.4. How and where to apply? 8
3.5. How do I pay the fees? 8
3.6. Do I have to apply anywhere else? 9
3.7. What happens next? 9
3.8. What is the timeframe? 10
3.9. What are the possible outcomes? 10
3.10. Terms and conditions of approval 10
3.11. Can I make changes after receiving an authorisation? 11
3.12. Who reports adverse drug reactions and adverse drug events? 12
3.13. Who reports suspected unexpected serious adverse reactions? 12
3.14. When is the annual safety report due? 12
4. REFERENCES 13
5. APPENDICES 13

1. PURPOSE

The EU Directive 2001/20/EC definition of a clinical trial is:
"…any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more investigational medicinal product(s), and/or to identify any adverse reactions to one or more investigational medicinal product(s) and/or to study absorption, distribution, metabolism and excretion of one or more investigational medicinal product(s) with the object of ascertaining its (their) safety and/or efficacy".

All research that fulfils the definition of a clinical trial, as described above requires a Clinical Trial Authorisation (CTA) from the Competent Authority in the Member State in which research is being carried out. The Competent Authority in the United Kingdom (UK) is the MHRA, the Medicines and Healthcare products Regulatory Agency.

This SOP describes the procedure for applying for a Clinical Trial Authorisation (CTA)- a regulatory approval- from the Medicines and Healthcare products Regulatory Agency (MHRA).

2. INTRODUCTION

The MHRA is the government agency responsible for ensuring that medicines and medical devices are safe.

A CTA is required only in trials of:

Investigational medicinal products,

Combined trials of Ionising Radiation for combined review of clinical trial of an investigational medicinal product,

Ionising Radiation and Devices form for combined review of combined trial of an investigational medicinal product and an investigational medical device

Investigational medicinal products are substances, or combinations of substances, 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.

Clinical studies 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. Please see other SOPs for further details.

It is the responsibility of the Chief Investigator (CI) to establish whether a regulatory approval is required for their study and that it is obtained prior to initiating the trial.

The Research Governance and Integrity Team (RGIT) can help with the determination of whether it is a clinical trial of an investigational medicinal product (CTIMP) or not. The clinical trial of a medicinal product algorithm should be reviewed in the first instance,

which can be found at: IS IT A CLINICAL TRIAL OF A MEDICINAL PRODUCT? *(cited 03 May 2023).*

Following review of the clinical trial of a medicinal product algorithm it is still uncertain whether the study is a CTIMP, you will be required to complete an ''RGIT CTIMP decision document'' -RGIT_TEMP_073, which will be reviewed by the RGIT CTIMP decision committee for confirmation of study categorisation.

3. PROCEDURE

3.1. Procedure for obtaining a EudraCT number

From 1st January 2021 it will not be mandatory for a EudraCT number to be needed for UK CT Applications (for European sites). However, from this date for the UK CTA submission the MHRA will still expect an EudraCT number to be in place until the MHRA confirms otherwise.

In order to provide a unique reference for clinical trials, each trial will need a EudraCT number. This number must be included on all clinical trial applications and as needed on other documents relating to the trial (e.g. safety reports). To obtain a EudraCT number, follow this process:

Apply for a security code *via* the EudraCT website

1. This will be sent to your email account and will expire after 24 hours.

2. Once you have your security code, request a EudraCT number *via* the EudraCT website by entering the security code along with:
   - Your organisation name
   - Organisation town/city
   - Organisation country
   - The sponsor's protocol code number
   - Your name
   - The email address to which the EudraCT number will be sent
   - Confirmation if EudraCT Number will be used for a Clinical Trial contained in a Paediatric Investigation Plan (PIP)
   - Confirmation if EudraCT Number will be used for a Clinical Trial conducted in a third country (outside of the EU/EEA)
   - Member state(s) where the trial is anticipated to be conducted

3. The EudraCT number will be sent by email, which you should then save locally.
   The EudraCT number has the format: YYYY-NNNNNN-CC
   (Y=the year in which the number is issued)
   (N = a 6 digit sequential number)
   (C = check digit)

4. You need to save a copy of the confirmation of EudraCT number, to be sent as confirmation with the CTA application form to the MHRA and Ethics Committee applications.

5. The EudraCT Number must be included on all Clinical Trial applications within the Community and as needed on other documents relating to the trials (e.g. SUSAR reports).

As of 31 January 2023, creation and submission of new Clinical Trial Applications (CTAs) for trials to be conducted in the EU/EEA is no longer allowed through EudraCT and must be performed through the Clinical Trials Information System Clinical Trials in the European Union - EMA (euclinicaltrials.eu)

3.2. Completing the CTA application form

The application is done via the Combined review at Step by step guide to using IRAS for combined review - Health Research Authority (hra.nhs.uk) which combines the ethics application along with an MHRA form.

Section A: Trial Identification
This section identifies your clinical trial by title and by EudraCT number. Where the Trust or College is acting as the sponsor The Research Governance and Integrity Team (RGIT) reference number can be used as the Sponsor's Protocol Code number. This number will be issued from the RGIT at the time of providing initial sponsorship review. The designated Competent Authority (CA) will be UK-MHRA for UK only studies. If studies are conducted elsewhere in the EU, a CTA should be submitted to each country's CA. In some circumstances, the RGIT reference number can be issued prior to sponsorship review.

Section B: Identification of the sponsor responsible for the request
This section identifies the name of the Sponsor organisation and relevant contact details. Hence you must have a sponsorship letter from Imperial College Academic Health Science Centre (AHSC) for your study before you can submit your application. You will be required to provide a copy of the letter with the completed form. For Imperial College AHSC Sponsored studies, the "name of the person to contact" is Keith Boland, Clinical Trials Managers, Research Governance and Integrity Team, Sherfield Building, Level 5, Exhibition Road, South Kensington, SW7 2AZ telephone: 020 7594 9480, email: rgit.ctimp.team@imperial.ac.uk

If the sponsor of the study is not based in a member state of the EU or the UK, then a legal representative who is based in the UK or on an approved country list: Importing investigational medicinal products into Great Britain from approved countries which currently includes EU/EEA countries (*cited on 05 Jan 2021*) (as described in B2).

Section C: Applicant Identification
This section identifies you, the Applicant. This section is split into two parts: C1 - Application to the MS Competent Authority and C2 - Application to the Ethics Committee. Both sections require completion. Sections should be completed with the relevant details of the person making the application to the CA and Research Ethics Committee. If you are applying on behalf of Imperial College AHSC who are acting as Sponsor (and this is

confirmed by the sponsor), then as such you are the person authorised by the Sponsor to make the application.

Section D: Information on each IMP

This section asks for a description of, and information about, the Investigational Medicinal Product(s) (IMP) being used in your study, including any comparator drug(s). You will need to repeat this section if more than one test or comparator product is being used. Much of the information required can be found on the Summary of Product Characteristics (SmPC) (if the drug is already licensed), Investigator Brochure (IB) or provided to you by your manufacturer. Each product will be given a number (e.g. PR1, PR2 etc) and should indicate whether this is a test product or a comparator.

Sections D1 to D3 should be completed for all products.

Sections D4 to D7 deals with specific types of products:

- D4 is for somatic cell therapy investigational medicinal product (no genetic modification) D5 is for gene therapy investigational medicinal products
- D6 is for tissue engineering product
- D7 for products containing devices
- D8 is for placebos

Section D9 asks about the release and supply of the investigational medicinal product(s) from their manufacturing source. The section is split into two parts: D.9.1 list IMPs and placebos for which no responsible site needs to be identified and D.9.2 add responsible site.

Section D.9.1 is used to identify IMPs and placebos that do not need to have responsible sites identified, i.e. which:

- Have a Marketing Authorisation in the EU **AND**
- Are sourced from the EU market **AND**
- Are used in the trial without modification (e.g. not over encapsulated) **AND**
- The packaging and labelling is carried out for local use only as per article 9.2 of the Directive 2005/28/EC (GCP Directive).

If all the above conditions are met, tick the appropriate box and indicate which IMP these refer to.

Section 9.2 is dedicated to finished IMPs, i.e. medicinal products randomised, packaged, labelled and certified for use in the clinical trial when conditions in 9.1 are not met. If there is more than one site, or more than one IMP is certified, then give each IMP its number from section D.1.1 or D.8.2. In the case of multiple sites indicate the product certified by each site.

For EU marketed products which are repackaged by a hospital pharmacy for use in a clinical trial (i.e., off the shelf) enter ‘Hospital Packaging’ as Name of the Organisation, along with the address of the Pharmacy Department for the hospital.

Section E: General Information on the trial

This section is concerned with general information about the trial – disease states, objectives, inclusion/exclusion criteria, end points, scope of the trial, study design, duration, drug dosage etc. The majority of this information can be taken from the study protocol.

Section F: Population of Trial Subjects
This section is concerned with the subject population – age, gender, vulnerable groups, numbers, treatment afterwards, etc. Again, this information can be taken from the study protocol.

Section G: Proposed Trial Sites/Investigators in the Member State
This Section should be completed for the Chief Investigator, as well as all Principal Investigators in the case of multi-centre studies, and collaborators.

Question G5, relating to the sponsor's delegation of duties to other organisations, should be answered in consultation with the RGIT as it will be project specific.

Section H: Competent Authority/Ethics Committee
This section asks for details regarding the ethics committee application. You will need to provide the name and address of the ethics committee as well as date of application (if already submitted) and the current status of the application, i.e. the date and opinion of the ethics committee, if available. A copy of the CTA application should be included in the ethics application.

3.3. 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. Appendix 1 outlines the additional data requirements for each type of trial. Appendix 2 demonstrates the supporting documents required for all Competent Authorities in the EU for all types of applications. Items that are shaded are not required to be sent to the MHRA. The minimum requirement for all studies is:

- Covering letter including title, phase of study, the identification of all Reference Safety Information and if appropriate detailing if the study falls under the notification scheme (See wording below regarding notification scheme). The cover letter also needs to include the purchase order number associated with the MHRA fees and if you are using a simplified IMPD to provide justification for this
- Clinical Trial Application + valid xml (not required for CWOW)
- Protocol
- IB or document replacing the IB
- IMPD/simplified IMPD
- NIMP Dossier (if required)
- Scientific advice - A summary of scientific advice from any Member State or the EMA with regard to the clinical trial (if available).
- EMA Decision - A copy the EMA's Decision on the decision of the Paediatric Investigation Plan and the opinion of the Paediatric Committee (if applicable).
- The content of the labeling of the IMP (or justification for its absence)
- Proof of payment

- Manufacturer's authorisation, including the importer's authorisation and Qualified Person declaration on good manufacturing practice for each manufacturing site if the product is manufactured outside the EU

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 Sponsor as indicated in the MHRA guidance. This has been agreed by the MHRA for non-commercial trials.

It is very important that all the required documentation for your particular application is submitted to the MHRA with the CTA application. If the application is received in the wrong format or with documentation missing, it may be returned as an 'invalid submission'. In CWOW all documentation can be uploaded to the Project Documents section.

It is best practice to include a cover letter with the CTA application. An example can be found in Appendix 2.

Notification Scheme:
The MHRA provide a notification scheme for certain lower-risk trials, defined as **'Type A' trials** may be made in place of a full CTA application. In these cases, the risk to the patient from the IMP is considered to be no greater than that of standard medical care.

- **Type A = No higher than the risk of standard medical care**
- Type B = Somewhat higher than the risk of standard medical care
- Type C = Markedly higher than the risk of standard medical car

Trials under the notification scheme also have simplified requirements for conducting the trial. More information can be found on Risk-adapted Approaches to the Management of Clinical Trials of Investigational Medicinal Products *(Cited on 03 May 2023).*

Type A trials 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
- 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

3.4. How and where to apply?

From 1st January 2022 UK clinical trial submissions have to be made through the IRAS CWOW system. This system provides streamlined review process with MHRA, REC and the HRA.

3.5. How are the fees paid?

Once the application has been validated, an invoice will be sent to make payment for the correct amount. PO details need to be included in the application so payments can be handled accordingly.

Invoices must be settled on receipt of invoice. Penalty fees can 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.

3.5.1 Payment Methods

Bank transfer

Account details:
account name: MHRA
account number: 10004386
sort code: 60-70-80
swift code: NWBKGB2L
IBAN: GB68NWBK60708010004386
National Westminster Bank,
RBS, London Corporate Service Centre, 2nd Floor
280 Bishopsgate,

Send remittance details to:
MHRA Accounts Receivable

Please send the remittance advice notices to Sales.Invoices@mhra.gov.uk
and ensure the relevant invoice number is quoted on the remittance advice.

The MHRA does not accept any documentation sent by post.

For more information see: Guidance Clinical trials for medicines: manage your authorisation, report safety issues *(cited 03 May 2023).*

Credit or debit card

Outstanding invoices can also be paid by credit and debit card.
See the terms and conditions for making a payment by credit and debit card on the MHRA using the following link: Making a payment to MHRA by credit or debit card - terms and conditions

3.6. Do I have to apply anywhere else?

All clinical trials also require a favourable opinion from an Ethics Committee and any other body where appropriate e.g. CAG (Confidentiality Advisory Group), GTAC (Gene Therapy Advisory Committee).

3.7. What happens next?

The CTA will be validated within 3 days of receipt the validation status will show on the CWOW dashboard. If the application is valid then the assessment period will begin. This starts from the date of receipt of a valid application. If the application is not valid then the

person making the application will be told of the deficiencies. Nothing will happen to the application until the missing components are provided.

The MHRA have issued guidance on common issues during the validation of Clinical Trial Applications at the following link:
MHRA - Guidance Common issues: Validation *(cited 03 May 2023).*

3.8. What is the timeframe?

The initial assessment will be completed within 30 days of being submitted. Applications for healthy volunteer trials and sponsor-determined phase I trials in non-oncology patients may qualify for a shortened assessment time (average 14 days). It should be stated on your covering letter if the trial is eligible. Note that trial designs that stretch to investigating the benefit of the treatment to subjects may not be eligible for the expedited assessment timeframe.
For the purposes of this calculation, the day of receipt of the valid application by the MHRA Clinical Trials Unit is day 0.

If a letter is not received within 35 days of sending the application, clintrialhelpline@mhra.gov.uk can be contacted for guidance. The MHRA will not accept calls or emails prior to 35 days to check the progress of the submission.

3.9. What are the possible outcomes?

There are two possible outcomes:

- Acceptance (with or without conditions)
- Grounds for non-acceptance (GNA).

Some acceptance letters state conditions or remarks. The conditions must be responded to prior to the start of the study.

If there are grounds for non-acceptance, the investigator should reply within 14 days via CWOW (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 upon request.

The amended request is assessed within a total of 60 days from receipt of the initial application (90 days for gene therapy products) and there are two possible outcomes:

- Acceptance (with or without conditions)
- Grounds for non-acceptance (GNA).

Once you have received approval from the MHRA you may start the trial, subject to receiving favourable opinion from the ethics committee and HRA (Health Research Authority) approval. Approvals (confirmation of capacities and capabilities- CCC from the participating NHS Trust(s) Research and Development Offices would also need to be in place.

3.10. Terms and conditions of approval

3.10.1 In accordance with regulation 27, you must notify the Competent Authority within 90 days of the conclusion/end of the trial (EOT) notification and within 15 days of the premature EOT.

The trigger for EOT notification should be defined under the approved study protocol and is usually considered as the last patient last follow up visit.

Whilst the EOT notification should usually be submitted via the CI and study team, in certain circumstances the Sponsor- via RGIT- may initiate the EOT notification from their end. The latter may occur if no responses are received from the CI and study team following Sponsor's monitoring queries or follow up requests.

The EOT notification can be submitted to the MHRA electronically via Home - MHRA Submissions (appiancloud.com) whilst uploading the completed EOT RGIT_TEMP_041_Notification-End-of-Clinical-Trial-Medicine_V1.0_19Oct2020.docx (live.com)

Submitting the completed EOT notification form to REC/HRA will still need to be completed via email to REC/HRA.

3.10.2 The MHRA may suspend or terminate a clinical trial where it feels the conditions for authorisation are not being met.

3.11. Can I make changes after receiving an authorisation?

3.11.1 Non-substantial amendments

The CI can make non-substantial amendments at any time but must notify the sponsor of these and keep records of these amendments. Please note that some non-substantial amendments may need to be submitted to the HRA/ethics committee for review. These will require review and sign off by the RGIT. Please see RGIT SOP 006 Amendments to healthcare research.

3.11.2 Substantial amendments

These changes count as a substantial amendment to your clinical trial authorisation. You need to send an amendment tool, a reviewed application form and other documents to the Medicines and Healthcare Products Regulatory Agency (MHRA):

- covering letter outlining the substantial and any non-substantial changes
- Signed pdf of the amendment tool
- updated XML and PDF versions of the clinical trial application form if it's changed since the last submission
- reasons for the proposed changes
- proposed changes to the protocol or other document (eg investigational medicinal product dossier), showing previous and new wording
- supporting data for the change, including:
    - summaries of data
    - updated overall risk-benefit assessment

- possible consequences for subjects already in the trial
- possible consequences for the evaluation of results

Please make the submission through the MHRA submissions portal.

For studies that used the CWOW application processed amendments should be submitted via CWOW.

Once approval from the MHRA has been received for the Substantial amendment, a favourable opinion from the ethics committee and HRA (Health Research Authority) approval may also be required.

Approvals (confirmation of capacities and capabilities- CCC from the participating NHS Trust(s) Research and Development Offices would also need to be in place if the Substantial amendment was categorised in need of UK wide review.

3.12. Who reports adverse drug reactions and adverse drug events?

All SAEs related to the medicinal product and unexpected events not listed in the protocol as an expected occurrence should be notified to the ethics committee, the MHRA and all Safety Reports should be forwarded to the sponsor annually (see 3.14). The CI shall keep detailed records of all adverse events relating to a clinical trial which are reported to him by the investigators for that trial.

3.13. Who reports suspected unexpected serious adverse reactions?

The Chief Investigator shall ensure that all relevant information about a suspected unexpected serious adverse reaction (SUSAR) which occurs during the course of a clinical trial in the United Kingdom is reported as soon as possible to the MHRA, the relevant ethics committee and the Sponsor. For fatal or life-threatening SUSARs, this needs to be done within 7 days of the CI becoming aware of the reaction. All other SUSARs should be reported within 15 days of the CI becoming aware of the event.

From 1st January 2021 SUSARs need to be reported via the ICSR submissions portal Reports | MHRA or the MHRA gateway. The eSUSAR portal will continue to be available to submit SUSARs. Further guidance can be found in the Safety Reporting SOP.

3.14. When is the annual safety report due?

The Development Safety Update Report (DSUR) must be compiled annually for the duration of the clinical trial until the regulator has been notified of the end of the trial. This process must commence on the anniversary of the first international regulatory approval regardless of the approval status in the UK. The annual time point is referred to as the Development International Birth Date (DIBD) in EMA guidance. Reporting must occur within 60 days of the defined DIBD.
From 1st January 2021 DSURs need to be submitted via the MHRA submissions portal Home - MHRA Submissions (appiancloud.com)*(cited 03 May 2023).*

For studies that have used the CWOW IRAS system for applications, the DSUR can be submitted via the CWOW system.

3.15. What happens when the trial ends?

A notification of the end of the trial should be sent by the CI and copied to the Sponsor within 90 days of its conclusion.

4. REFERENCES

1) EU Clinical Trials Directive 2001/20/EC
2) Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of a substantial amendment and declaration of the end of the trial, April 2004
3) Description of the Medicines for Human Use (Clinical Trials) Regulations 2004
4) SOP on Amendments to Healthcare Research, ref: RGIT_SOP_006
5) SOP on Safety Reporting, ref: RGIT_SOP_001
6) SOP on IMP Management and Accountability, ref: RGIT_SOP_026
7) https://www.gov.uk/guidance/clinical-trials-for-medicines-apply-for-authorisation-in-the-uk?utm_source=f41550fc-a35b-46fd-a3c4-5b0ab9dac3ae&utm_medium=email&utm_campaign=govuk-notifications&utm_content=daily

5. APPENDICES

The following Appendices list the following Templates associated to this SOP which can be found on the SOP, Associated Documents & Templates page.

Appendix 1: Summary of data required for CTA application and substantial amendments to a clinical trial

Authorisation of a clinical trial
Substantial Amendments to a Clinical Trial

Appendix 2: Amendment Tool – RGIT_TEMP_015

Appendix 3: RGIT CTIMP Decision – RGIT_TEMP_073