MANCHESTER 1824
The University of Manchester

Standard Operating Procedure

Number:	UoMCTSOP07/2025/V7.0		
Title:	Preparation and Submission of a Clinical Trial Authorisation (CTA)		
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Version	Date	Summary of Changes
2.0	January 2013	Update of web links and office details.
3.0	May 2014	Addition version control statement for SOP and contractual obligations (Appendix I)
4.0	October 2015	Update of weblinks and office details
5.0	August 2016	Update of weblinks and office details
6.0	March 2018	Updated to reflect current processes
7.0	February 2025	Updates to reflect changes to MRHA submissions, following Brexit

1.0 Introduction

The European Clinical Trials Directive 2001/20/EC ("the Directive") was introduced to establish standardisation of research activity in Clinical Trials throughout the European Union. It was transposed into UK law as the Medicines for Human Use (Clinical Trial) Regulations 2004, (SI 2004/1031), which came into force on 1st May 2004. The Medicines for Human Use (Clinical Trials) Regulations together with subsequent amendments, will be referred to as "the Regulations" in the rest of the document.

All proposed research which falls under the above stated regulations, requires a Sponsor (Confirmation of Sponsorship SOP03). A research Sponsor takes responsibility for the initiation, management and financing (or arranging the financing) of a trial. It is the Sponsor's role to seek authorisation from the Medicines and Healthcare products Regulatory Agency (MHRA). The UK Clinical Trial Regulations, Part 3, Reg 17, state that the request for a clinical trial "…shall be in writing and signed by or on behalf of the Sponsor."

Where there is doubt if a clinical trial falls under the regulations, and may require regulatory approval by the MHRA, the Chief Investigator should refer to the clinical trial algorithm. When necessary RGEIT can provide further clarification as to whether a proposed study is considered to meet CTIMP/Medical Device criteria.

2.0 Scope

This SOP relates to CTIMPs/Devices/ATIMPs – (i.e. all Trials which come under the Regulations, in which The University of Manchester has accepted the role of Sponsor or co-sponsor), and refers to the procedure for applying for:

- a CTA for trials starting before January 1st 2021,
- a CTA starting on or after January 1st 2021
- and applying for MHRA approval, starting January 1st 2022 using the combined system known as CWOW.

The requirements of this SOP should be applied as a minimum to such trials and in conjunction with all applicable University policies and procedures and the policies and procedures of the relevant NHS Trust.

3.0 Responsibilities

The Chief Investigator, in liaison with the Sponsor, will prepare and submit the application to the MHRA, in line with the specific delegated responsibility by the Sponsor. The Chief Investigator cannot submit the application to the MHRAuntil the Sponsor has reviewed and approved the application in writing. In addition, written confirmation of full Sponsorship needs to be obtained prior to application submission. All fees associated with the CTA application are to be met by the Chief Investigator.

4 Procedures

4.1 Combined review application process – CWOW (Combined way of working) – after January 1st 2022 the following rules apply

Any new Clinical Trials of Investigational Medicinal Products (CTIMPs) and combined IMP/device trials submission must be done using the new Combined Way of Working. For this purpose, the new part of IRAS has been developed, which will require separate log in details (accessible from the IRAS homepage).
There is only need for 1 submission, both to MHRA and REC, using the same portal for preparation, submission and review.
A comprehensive, step-by-step guidance is available on HRA website:
https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/clinical-trials-investigational-medicinal-products-ctimps/combined-ways-working-pilot/step-step-guide-using-iras-combined-ways-working-cwow/#preparing
The guidance covers:

- application preparation
- validation and possible re-submission
- creating amendment
- reporting – DSUR (Development Safety Update Reports), USM (Urgent Safety Measures), EOT (End of Trial) and Final report.

The system does not send automated emails, therefore any submission in the CWOW system, that are for Sponsor action, are to be followed by email to: clinicaltrials@manchester.ac.uk

4.2 Obtaining a EudraCT Number

CTIMPs that started before January 2021, will still need to register and report results on EudraCT. CTIMPs that started after January 2021, will only need to apply but not report the results. CTIMPs that have sites in EU, must register on the EudraCT database, as well as CTIMPs contained in Paediatric Investigation Plan. If the EudraCT is still required for the application, it can be applied for at: https://eudract.ema.europa.eu/index.html. The EudraCT number is the unique reference given to each trial. The number is to be included on all CTA applications, and other relevant documents relating to the trial.

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4.3 Completing the CTA form

The CTA application is an electronic process and is to be completed in parallel with the ethics application online through the New Integrated Research Application System (IRAS) - CWOW, where guidance notes on the completion of the form can also be found (https://www.myresearchproject.org.uk/).

In order for an application to be considered valid by the MHRA, a submission should also contain the following supporting documentation via the copy and paste functionality as described on the MHRA website: (https://www.gov.uk/guidance/clinical-trials-for-medicines-apply-for-authorisation-in-the-uk)
The IRAS portal includes a list of documentation to submit for combined review of your application. The following provides some further guidance on the content of some of the specific MHRA documents:

- covering letter: When applicable, the subject line should state that the submission is for a Phase I healthy volunteer trial and is eligible for a shortened assessment time, or if you are using risk proportionate approaches to the conduct of the study. Your covering letter should clearly highlight your Purchase Order (PO) number; this will help us to invoice and allocate your payments promptly and efficiently
- investigational medical product dossier (IMPD): please note that an active substance master file (ASMF) is not acceptable as a substitute for an IMPD
- 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. Further guidance covering this area.
- content of the labelling of the investigational medicinal product (IMP): where this has not been provided please provide a justification for its absence

4.4 Submission of the CTA form

CTIMP submissions (initial applications, substantial amendments, end of trial notifications and developmental safety update reports (DSURs) to MHRA from 1 January 2021 will need to use 'MHRA Submissions'.using MHRA Submissions portal https://www.gov.uk/guidance/register-to-make-submissions-to-the-mhra

The MHRA will not accept paper documents.

4.5 Following Submission of the CTA form

For every approved CTA application the MHRA will provide a letter of acceptance. The Chief Investigator must also obtain relevant approvals from the main REC, NHS Trust and sponsor green light before recruiting the first patient to the clinical trial.

4.6 Amendments to the CTA

The Chief Investigator must maintain a record of all non-substantial amendments made to the CTA following authorisation from the MHRA and notify the Sponsor via the annex associated with SOP09: Substantial and non-Substantial Amendments, using the IRAS or CWOW path as applicable to the trial. Where amendments are considered to be substantial, following consultation with the Sponsor, a request must be made to the MHRA (and the REC if appropriate) seeking approval for the amendment. All amendments submitted to the MHRA must be done electronically.
Please view the MHRA guidance on amendments to the CTA. Please also see the University of Manchester SOP09 on Substantial and non-Substantial Amendments.

A protocol amendment can only be implemented after receiving authorisation from the MHRA, the main REC and HRA Approval as appropriate.

Urgent amendments to a protocol can be made at any time and do not require prior MHRA and main REC approval if the safety of one or more study participants is at risk (see SOP11 on Urgent Safety Measures). The Chief Investigator must inform the MHRA, the main REC and the sponsor as soon as possible.

4.7 End of Trial Notification

A 'Declaration of the end of a Clinical Trial' form (https://view.officeapps.live.com/op/view.aspx?src=https%3A%2F%2Fassets.publishing.service.gov.uk%2Fgovernment%2Fuploads%2Fsystem%2Fuploads%2Fattachment_data%2Ffile%2F1022119%2Fdeclaration_end_trial_form_final_29.09.21.doc&wdOrigin=BROWSELINK) must be sent to the MHRA at the end of the clinical trial. This form should be submitted by the Chief Investigator within 90 days of the trial's conclusion as defined by the protocol, alongside with covering letter.
Submission is done, using MHRA Submissions via the Human Medicines Tile. No further amendments or DSUR are possible once the declaration is received by the MHRA.
The trials submitted via CWOW will do their submission using this platform.

5 References

- Directive 2001/20/EC
- Directive 2005/28/EC
- The Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 1031)
- The Medicines for Human Use (Clinical Trials) Amendment Regulations 2006 (SI 1928)

The above can be accessed via/ downloaded from the MHRA website:
http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Clinicaltrials/IsaclinicaltrialauthorisationCTArequired/index.htm

- Clinical Trials Toolkit information on 'Substantial Protocol Amendments', which can be accessed via/downloaded from http://www.ct-toolkit.ac.uk/routemap/substantial-amendments/
- UK Policy Framework for Health and Social Care Research

Related SOPs:

- UoMSOP03: UoM Sponsorship
- UoMSOP09: Amendments
- UoMSOP11: Urgent Safety Measures