This policy has been approved by Senate

Policy for Compliance with The Medicines for Human Use (Clinical Trials) Regulations 2004 and subsequent amendments (Investigational Medicinal Products) and other Clinical Research

UM/10/POL/CT004

1.0 Background

1.1 The University of Manchester’s research has real-world impact beyond academia and is at the forefront of the search for solutions to some of the world’s most pressing problems, seeking to be a global force for positive change. This includes tackling health related issues to improve patient well-being and quality of life. Clinical trials are an essential tool to determine if treatments could be beneficial to patients. Research studies in which medicines are tested and/or compared against known treatment in humans are referred to as clinical trials of investigational medicinal products (CTIMPs) and such trials are regulated under UK law by the Medicines Healthcare Products Regulatory Agency (MHRA). The University of Manchester is committed to seeking to bridge the drive for research and ensuring regulatory compliance. This policy sets out how the University of Manchester works to achieve this balance for CTIMPs From 2017, this policy extends to the design and conduct of applicable clinical investigations of medical devices

This policy should be read, alongside The University of Manchester’s Code of Good Research Conduct, by all University staff who are either working on, or are likely to work on, research projects, that are covered by the UK Clinical Trials Regulations.

1.2 The European Clinical Trials Directive 2001/20/EC (“the Directive”) was introduced to establish a standardised framework for good practice in the management of Clinical Trials throughout the European Community. The Directive sets out how clinical trials investigating the safety or efficacy of a medicinal product for use in humans must be conducted, and includes clinical trials involving healthy volunteers as well as small scale or pilot studies. The Directive also requires clinical trials to be conducted in compliance with the principles of Good Clinical Practice (GCP), with detailed standards subsequently published as the European Directive
2005/28/EC (usually referred to as “the GCP Directive”).

The Directive was transposed into UK law as the Medicines for Human Use (Clinical Trial) Regulations 2004, statutory instrument SI 2004/1031, which came into force on 1 May 2004. This statutory instrument and all its subsequent Amendments (including SI 2006/1928, which transposed into UK law the GCP Directive), will be referred to as “the Regulations” in the rest of the document.

1.3 The Regulations are intended to protect the rights, safety and well-being of research participants in CTIMPs and to harmonise, and make transparent, regulatory processes relating to clinical trials of medicines for human use.

1.4 In order to be compliant with the law, organisations conducting CTIMPs must have clearly documented Standard Operating Procedures (SOPs) covering all aspects of conducting Clinical Trials. The University of Manchester SOPs for clinical trials can be found on the Research Governance, Ethics and Integrity intranet pages:

http://www.staffnet.manchester.ac.uk/services/rbess/governance/clinicaltrials/policies andprocedures/

2.0 Purpose

2.1 This policy outlines the responsibilities of the University where it is the sponsor of CTIMPs led by its staff. This policy is underpinned by separate procedures outlined as SOPs, which provide the structure which should be applied when undertaking and managing CTIMPs.

2.2 Failure to follow this policy could result in the instigation of the UoM Disciplinary/Research Misconduct processes in line with the Code of Practice for Investigating Concerns about the Conduct of Research (http://www.staffnet.manchester.ac.uk/services/rbess/governance/research-misconduct/).

3.0 Roles and Responsibilities

3.1 The University of Manchester, as sponsor of a CTIMP, has specified legal responsibilities which are defined in SI 2004/1031 and relate to obtaining and maintaining the authorisation for clinical trials (from the MHRA) research ethics committee (REC) opinion and Health Research Authority (HRA) approval; following Good Clinical Practice (GCP) and practices; trial conduct; pharmacovigilance; and investigational medicinal product (IMP) manufacture and labelling. The Clinical Trials Management Group (CTMG) undertakes all sponsorship responsibilities to
ensure the University meets its obligations to comply with the Medicines for Human Use (Clinical Trials) Regulations (2004 and subsequent amendments) for regulated trials. The CTMG also oversees the fulfillment of the sponsor role for unregulated, high risk trials on behalf of the University of Manchester. The CTMG has the power to suspend and/or terminate a trial where it is deemed necessary and/or appropriate, and reports to the Research Compliance Committee (RCC). The RCC reports to the University of Manchester Policy and Review Committee (PRC). All sponsor roles and responsibilities of the University, as detailed in this policy, are conducted by CTMG on behalf of the University.

3.2 The Chair of the University CTMG will be responsible for implementing the current clinical trials policy (as ratified by the University of Manchester Senior Leadership Team) relating to the approval of sponsorship arrangements and oversight for CTIMPs.

3.3 The Research Governance, Ethics and Integrity Manager (Clinical Trials) is accountable to the Chair of the CTMG and will act on his/her behalf to oversee adherence to this policy.

3.4 Chief Investigators (In this policy document, the term Chief Investigator refers to the person responsible for conducting the research project) are responsible for ensuring that this policy is observed for any CTIMPs for which they are the Chief Investigator, and to abide by the relevant University wide and/or local SOPs.

3.5 All University members of staff working on CTIMPs are accountable to the Chief Investigator for undertaking activity in adherence with this policy.

4.0 Compliance with the UK Clinical Trials Regulations

4.1 Research covered by the Regulations

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”.

The EU Directive 2001/20/EC definition of an investigational medicinal product is:
“a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorisation but used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form”.

The EU Directive 2001/83/EC definition of an investigational medicinal product is:
(a) Any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or

(b) Any substance or combination of substances which may be used in or 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.

4.2 Determining whether a study comes under the Regulations

4.2.1 Where it is not clear whether or not a study is a CTIMP as defined in 4.1 above, the MHRA algorithm should be consulted and, if necessary, further clarification sought via the MHRA Helpline in accordance with the SOP ‘University Sponsorship of a Clinical Trial’ (Processing requests for confirmation of sponsorship for funding applications).

Guidance and advice on the correct definition of a clinical trial can also be accessed via the Research Governance Ethics and Integrity Team in Research & Business Engagement Support Services.

4.3 Gaining the necessary approvals

4.3.1 The University of Manchester Registration

The Chief Investigator must inform the University of Manchester’s Research Governance, Ethics and Integrity Manager (Clinical Trials) of any intention to submit a funding application for a CTIMP, whether or not the University of Manchester has been identified as a probable sponsor.

The Chief Investigator must keep the Research Governance, Ethics and Integrity Manager (Clinical Trials) informed of the funding outcome, even in cases where the application is unsuccessful or where there will be a re-submission for funding.

For successfully funded CTIMPs, the CI must, at all stages, keep the Research Governance, Ethics and Integrity Manager (Clinical Trials) informed of progress and any intended start dates.
4.3.2 Sponsorship

Sponsorship and the associated financial aspects of sponsorship must be agreed in principle before any funding application is made. The University requires a lead time of 12 weeks before submission to risk assess, evaluate the proposed delegation of responsibilities and costings, and provide a decision regarding sponsorship in principle.

The University of Manchester will only sponsor CTIMPs for which the Chief Investigator is an employee or honorary contract holder of the University.

If the University of Manchester is requested to act as the sponsor, a risk assessment will be undertaken.

4.3.3 Authorisation of the original protocol, all required trial documentation and all subsequent amendments from a National Research Ethics Committee (REC).

The Chief Investigator must obtain a favourable opinion from an appropriate research ethics committee before starting recruitment to the trial.

The Chief Investigator cannot apply to any research ethics committee until the sponsor has signed the relevant documents agreeing to undertake sponsorship responsibilities. Applications to a NHS REC are made via the IRAS (Integrated Research Application) system.

4.3.4 Authorisation of the original protocol, all required trial documentation and all subsequent amendments from the MHRA.

The Chief Investigator, in liaison with the sponsor, has to complete the Clinical Trial Authorisation (CTA) form which can be accessed via the IRAS portal.

The Chief Investigator will submit the CTA, following review and sign off from the Sponsor.

4.3.5 Authorisation of the original protocol, all required trial documentation and subsequent amendments must be obtained from the HRA.

The Chief Investigator will complete all documentation and submit to the HRA for approval following review and sign off from the Sponsor (https://www.hra.nhs.uk/approvals-amendments/what-approvals-do-i-need/hra-approval/).
4.4 Responsibility of the University of Manchester as the Sponsor

4.4.1 In accordance with Regulation 3 of the UK Clinical Trials Regulations “sponsor” means, in relation to clinical trials, the organisation which takes responsibility for the initiation, management and financing (or arranging the financing) of that trial.

4.4.2 Before it agrees to act as sponsor, and accept the responsibilities as set out in Parts 3, 4 and 5 of the UK Clinical Trial Regulations, The University of Manchester will determine whether it has adequate systems in place to undertake the responsibilities of a sponsor.

The University of Manchester will only act as the sole sponsor for a trial when it is able to provide sufficient oversight of all activities detailed in the Regulations as listed below in Sections 4.43 - 4.45. This will usually involve the use of a UK Clinical Research Collaboration (UKCRC) registered clinical trials unit (CTU) (see Appendix 1a), in which case the relevant activities will be contracted to the named CTU and detailed in a contract. In the case of First in Human (FIH) studies, the expectation is that all FIH studies will be conducted in or with the oversight of a University approved clinical research facility (CRF) (see Appendix 1b and 1c). Where an MHRA accredited Phase I CRF (see Appendix 1b) or a National Institute of Health Research (NIHR) CRF (see Appendix 1c) is likely to be involved, a contract will need to be agreed between the University and the CRF.

Study Agreements/Contracts detailing responsibilities of all parties will need to be established with all host institutions, IMP manufacturers and other associated vendors. All critical suppliers will be sent a vendor assessment to provide an assurance to the University of the services to be provided. An onsite visit will follow if required.

Where The University of Manchester is being asked to co-sponsor a study, it will need to be satisfied that it can provide sufficient oversight of the activities delegated and specified in a sponsorship agreement. The University of Manchester as a sponsor will also need to be satisfied that the co-sponsor has adequate systems in place to take on the responsibilities delegated to it in the sponsorship agreement.

4.4.3 Where The University of Manchester takes on the responsibilities of the sponsor as outlined in Part 3 of the regulations, "Authorisation and Ethics Committee Opinion" The University will: take responsibility for ensuring that all necessary approvals are in place before allowing the trial to commence. The University will approve submission to request a Clinical Trials Authorisation (CTA) from the MHRA. The University will not grant approval for a clinical trial to commence until it has received a favourable opinion from an appropriate REC, notification that the clinical trial has been authorised by the competent authority (MHRA) and HRA approval.
1. Undertake to allow inspection of its premises by the Regulator.

2. Give notice to the MHRA of amendments to the CTA and make representations to the MHRA in relation to amendments.

3. Give notice of amendments to the protocol to the MHRA and REC.

4. Give notice to the MHRA, HRA and REC that the trial has ended.

5. Ensure the relevant insurance and indemnity cover is in place (UoM/NHS/Other) for the conduct, management and design of the trial.

4.4.4 Where the University of Manchester takes on the responsibilities of the sponsor outlined in Part 4 of the regulations “Good Clinical Practice and Conduct”, the University will:

1. Put and keep in place arrangements to adhere to Good Clinical Practice

2. Ensure Investigational Medicinal Products are made available to subjects free of charge.

3. Take appropriate urgent safety measures (if no other person is delegated to do so) in accordance with its SOP on Urgent Safety Measures.

4. Notify the competent authorities as well as the REC that the clinical trial has ended within 90 days of the end of the trial as defined in the protocol.

4.4.5 Where the University of Manchester takes on the responsibilities of the sponsor outlined in Part 5 of the regulations “Pharmacovigilance”, the University will adhere to these responsibilities in accordance with its SOP on Pharmacovigilance: Serious Adverse Events (SAEs) and drug safety update reports (DSURs), which includes:

1. Keeping records of all adverse events reported by investigators.

2. Ensuring the recording and prompt reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs) to the MHRA.

3. Ensuring investigators are informed of SUSARs.

4. Ensuring all SUSARs, including those in third countries, are entered into a European database.

5. Providing an annual list of suspected adverse reactions and a safety report to the MHRA.
4.5 Responsibility and requirements of the Chief Investigator where the University of Manchester is acting as sponsor

4.5.1 The Chief Investigator in line with University Ordinance XVIII requires all Members of the University to declare any personal interest that might reasonably be deemed to compromise impartiality, conflict with duty as an employee, or result in private benefit.

4.5.2 The Chief Investigator is responsible for making an application for a research ethics committee opinion from an appropriate NHS REC.

4.5.3 The Chief Investigator cannot commence the clinical trial until the University as Sponsor has given its approval for the trial to start (a formal green light document will be issued by the CTMG). This will not be until the relevant Faculty has given its approval, a favourable opinion has been received from the REC, the clinical trial has been authorised by the licensing authority (MHRA) and HRA approval has been received.

4.5.4 The Chief Investigator will be required to sign and adhere to an Investigator Agreement which sets out the responsibilities delegated to Investigators by The University of Manchester.

4.5.5 The Chief Investigator must abide by the relevant University wide and/or local SOPs as detailed in the Investigator Agreement.

4.5.6 Co-sponsor – The Chief Investigator must adhere to his/her responsibilities as delegated in the division of responsibilities as agreed collaboratively between the University of Manchester and the co-sponsor(s).

4.5.7 The Chief Investigator must comply with the reporting requirements of the regulator (MHRA), REC, Funder and oversight committees and provide the CTMG with copies of any such reports including annual reports. Chief Investigators are also required to submit quarterly reports to the CTMG in a timely manner.

4.5.8 The Chief Investigator is required to maintain a Trial Master File (TMF) for each CTIMP. The contents of the TMF should conform to the requirements set out in The University of Manchester SOP on Creating and Maintaining a TMF. The TMF must include the quality management documentation required by CTMG as specified in the University of Manchester SOP on Creating and Maintaining a TMF.

4.5.9 The Chief Investigator must co-operate with audits that the University will
undertake of a CTIMP as may be detailed in the University issued Investigator Agreement.

4.5.10 The Chief Investigator will co-operate with University preparations for an inspection by the MHRA and make him/herself available during the dates specified for the inspection.

4.5.11 The Chief Investigator is required to undertake regular GCP training and to ensure that all persons involved in a CTIMP are also GCP trained. The University expects that the Chief Investigator and all relevant trial staff undergo retraining a minimum of every 3 years. Training records should be documented in the TMF. Links to a GCP training course can be found on the Research Governance, Ethics and Integrity webpages.

4.5.12 The Chief Investigator is responsible for ensuring that any adverse events are reported to The University (Sponsor) in adherence to its SOP on Pharmacovigilance (SAEs) and that annual safety reports are completed and returned to the main REC and MHRA and copied to the University as detailed in the Investigator Agreement.

4.5.13 The Chief Investigator cannot negotiate his/her own agreements/contracts. All agreements/contracts with an external organisation or body must be negotiated via the University Contracts Team in the University Research and Business Engagement Support Services Office. The Chief Investigator must complete and pass to Research Governance, Ethics and Integrity Manager (Clinical Trials) and the Contracts Team the ‘Checklist for Clinical Trials-Third Party Contracts’.

4.5.14 The Chief Investigator must ensure that all data are collected, stored, verified and analysed in a secure and appropriate manner and in accordance with the ethically approved protocol and University SOP for Data Management. Personal data must be handled in accordance with the UK Data Protection Act and in line with the University of Manchester Good Research Practice Guide.

4.5.15 Arrangements for the archiving of essential documents and research data must be detailed in the protocol before the CTIMP commences and these arrangements must be adhered to by the Chief Investigator.

Where records are to be stored at The University of Manchester this must be in accordance with The University of Manchester SOP on Archiving which requires that records must be maintained in appropriate conditions and that all appropriate documentation is available and transferred for archiving at the appropriate and agreed time.

In line with the maximum retention period (ATIMPs) all CTMG documentation will be retained for

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UoM Policy on CTIMPs and other Clinical Research  
Version 4.0 Feb 2018  

Please see the intranet for the latest version: [http://www.staffnet.manchester.ac.uk/services/rbess/governance/clinicaltrials/policiesandprocedures/](http://www.staffnet.manchester.ac.uk/services/rbess/governance/clinicaltrials/policiesandprocedures/)
4.5.16 The Chief investigator must ensure that their clinical trial is registered on a publically accessible register before they apply for their CTA and recruitment commences.

4.5.17 The Chief investigator must nominate a deputy to take on the role of the Chief Investigator and the associated responsibilities should unforeseen circumstances require the original Chief Investigator to step down or be absent for a prolonged period.

4.6 Expectations of an organisation that enters into a co-sponsorship arrangement with the University of Manchester

4.6.1 Where the University of Manchester is being asked to co-sponsor a study, it will need to be satisfied that the co-sponsor has adequate systems in place to take on the responsibilities delegated to it in the sponsorship agreement.

4.6.2 The University will assess the suitability of the co-sponsor in accordance with its SOP on Assessing the Suitability of a co-Sponsor, checking that the standards and expectations are at least equivalent to the standards and expectations of the University as set out in this Policy and supporting SOPs.

4.7 The role of the University of Manchester where an external organisation undertakes sponsorship of a CTIMP

4.7.1 Where an external organisation agrees to be a sponsor for a CTIMP, (irrespective of whether the research is commercial or non-commercial research), The University of Manchester requires that the Chief Investigator inform and negotiate all contracts in co-operation with the University Contracts Team.

Where there is a breach of GCP involving the Chief Investigator or any other member of staff employed by the University, that this be reported both to the sponsor and the University immediately to the Research Governance, Ethics and Integrity Manager (Clinical Trials).

5 Consultation, Approval and Ratification Process

5.1 Consultation and Communication with Stakeholders

5.1.1 All University of Manchester Clinical Trials documents should be written by members of staff with relevant expertise and experience. Additional advice should be
sought from members of the research community within the University or external advisors, as necessary.

5.2 Document Approval Process

5.2.1 All University of Manchester SOPs related to the conduct and management of CTIMPs are approved by the CTMG.

5.2.2 All University of Manchester policies related to the conduct and management of CTIMPs should be ratified by the University of Manchester Senior Leadership Team.

6 Dissemination and Implementation

6.1 Dissemination
6.1.1 When approved, this document will be posted on the Clinical Trials pages of the University’s Research Governance, Ethics and Integrity website. Only the current version will be available.

6.1.2 All Chief Investigators will be notified by email when the latest version of the document is available.

6.2 Implementation of Procedural Documents

6.2.1 Training covering the content of this document and trial related SOPs will be included in any in-house Clinical Trial training delivered by the Research Governance, Ethics and Integrity Manager (Clinical Trials) and the Research and Business Engagement Support Services Office.

6.2.2 Support and advice on the implementation of this document can be obtained from the Research Governance, Ethics and Integrity Manager (Clinical Trials) or Chair of the Clinical Trials Management Group.

7 Review, Monitoring Compliance with and the Effectiveness of Procedural Documents

7.1 Process for Monitoring Compliance and Effectiveness

7.1.1 The Chair of the Clinical Trials Management Group or Research Governance, Ethics and Integrity Manager (Clinical Trials) will monitor compliance to this policy and to the UK Clinical Trials Regulations via the quarterly reports from individual trials to CTMG, regular audits and monitoring visits, in line with the relevant SOPs.

7.1.2 Document content will be reviewed against any changes to the applicable GCP
guidelines and UK Clinical Trials Regulations and taking into account any feedback received from the Chief Investigators.

7.1.3 The outcome of any review, and any resulting amendments, will be reported to the Research Conduct and Accountability Committee.

7.2 Standards and Key Performance Indicators ‘KPIs’

7.2.1 This document will be available on the University intranet.

7.2.2 This document will be reviewed by the CTMG at least every two years or when there are significant changes. All changes will require ratification by the CTMG.
Appendix

Appendix 1a – UKCRC registered clinical trials unit in Manchester

Manchester Academic Health Science Centre - Trials Coordination Unit (MAHSC-CTU) http://www.mahsc.ac.uk/our-work/scope/mahsc-clinical-trials-unit/

(www.ukcrc-ctu.org.uk)

Appendix 1b - MHRA accredited Phase I clinical research facility (CRF) in Manchester

Medicines Evaluation Unit (MEU)

http://www.meu.org.uk/Manchester

Appendix 1c - National Institute of Health Research (NIHR) CRFs

https://www.nihr.ac.uk/about-us/how-we-are-managed/our-structure/infrastructure/clinical-research-facilities-for-experimental-medicine.htm

NIHR/Wellcome Trust Manchester CRF(Central Manchester University Hospitals NHS Foundation Trust)
https://research.cmft.nhs.uk/facilities-services/clinical-research-facility

- NIHR/Cancer Research UK Christie CRF (The Christie NHS Foundation Trust)
http://www.christie.nhs.uk/professionals/research/research-and-development/research-facilities-and-infrastructure/nihrcancer-research-uk-christie-clinical-research-facility/

- NIHR/South Manchester Respiratory and Allergy CRF (University Hospital of South Manchester NHS Foundation Trust)
https://www.uhsm.nhs.uk/about/research/respiratory-hub/
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Related Statutes, Ordinances, General Regulations: Medicines for Human Use (Clinical Trial) Regulations 2004, statutory instrument SI 2004/1031; subsequent Amendments including SI 2006/1928;

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Related policies:

Related procedures: All CTIMP related SOPs

Related guidance and or codes of practice: European Directives 2001/20/EC & 2005/28/EC

Related information: See ‘References’ section of policy

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