<table>
<thead>
<tr>
<th>Title:</th>
<th>Conducting Clinical Trials of Investigational Medicinal Products</th>
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<tbody>
<tr>
<td>Outcome Statement:</td>
<td>Researchers in the Trust and research partners will be informed about the procedures involved in conducting Clinical trials of Investigational Medicinal Products in the Trust.</td>
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<tr>
<td>Written By:</td>
<td>Bonnie Teague, Research Manager</td>
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<tr>
<td>Reviewed By:</td>
<td>Kayte Russell, Research Quality Lead. Tom Rhodes, Senior Research Facilitator Dennis Liew, Clinical Trials Pharmacist</td>
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<tr>
<td>In Consultation With:</td>
<td>NIHR GCP Facilitators, Pharmacy Department</td>
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<tr>
<td>Approved By and Date:</td>
<td>V1.0 Research Governance Committee 29th March 2012 V 2.0 Research Governance Committee 26th June 2014 V 3.0 Research Committee, 29th June 2017</td>
</tr>
<tr>
<td>References and Bibliography:</td>
<td>• The Medicines for Human Use (Clinical Trials) Amendment Regulations 2006 (External link) Statutory Instrument 2006 No. 1928 • The Medicines for Human Use (Clinical Trials) Amendment (No.2) Regulations 2006 (External link) – Statutory Instrument 2006 No. 2984 • The Medicines for Human Use (Clinical Trials) and Blood Safety and Quality (Amendment) (External link) Statutory Instruments 2008 No. 941 • The Medicines for Human Use (Clinical Trials) Regulations 2004 (External link) – Statutory Instrument 2004 No. 1031 • Memorandum of Understanding (MoU) between MHRA, NRES, GTAC and AAPEC on clinical trials of investigational medicinal products (CTIMPs) (pdf) • Clinical Trials of Investigational Medicinal Products (CTIMPS): EU Legislation Note this resource page includes information about the EU Clinical Trials Regulation, which was published on 27 May 2014.</td>
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<td>Associated Trust Policies and Documents:</td>
<td>Applicable To: All research staff involved in the set-up and delivery of drug trials in the Trust. For Use By: Research team members, Pharmacy, R&amp;D, Sponsors, Auditors. Reference Number: R&amp;D005 Version: 2.0 Published Date: 1st July 2017 Review Date: 3 years Impact Assessment: Yes – no impact identified Implementation: Routine distribution procedures (publication on the Trust intranet, email notification to identified senior staff for distribution throughout the team and inclusion in the weekly Trust Update e-bulletin).</td>
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### Review and Amendment Log

<table>
<thead>
<tr>
<th>Version</th>
<th>Reasons for Development/Review</th>
<th>Date</th>
<th>Description of Change(s)</th>
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<tbody>
<tr>
<td>V1.0</td>
<td>To clearly state the local requirements for the conduct of drug trial research within the NSFT.</td>
<td>23rd February 2012</td>
<td>N/A</td>
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<tr>
<td>V2.0</td>
<td>Review required to update legislative changes and include Pharmacy practice recommendations</td>
<td>27th June 2014</td>
<td>1. Inclusion of UKCHC/UK guidance 2. Clarification regarding Trial management and dispensing arrangements</td>
</tr>
<tr>
<td>V3.0</td>
<td>Review required to update Research approval requirements and Pharmacy dispensing arrangements.</td>
<td>27th June 2017</td>
<td>1. Change in terminology from R&amp;D approvals to HRA/CCC. 2. Adding CTIMP study personnel roles and employment. 3. Update of EU Clinical Trial Regulation timelines.</td>
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</table>
1.0 Introduction

This policy applies to all clinical trials of investigational medicinal products (CTIMPs) which are being conducted within the Norfolk and Suffolk NHS Foundation Trust. The definition of a clinical trial is:

“A clinical trial is an investigation in human subjects which is intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more medicinal products, identify any adverse reactions or study the absorption, distribution, metabolism and excretion, with the object of ascertaining the safety and/or efficacy of those products. This definition includes pharmacokinetic studies.

Clinical studies involving only medical devices, food supplements or other non-medicinal therapies (such as surgical interventions) are not covered by the Directive. The regulations do not apply to non-interventional trials. In such trials, no additional diagnostic or monitoring procedure should be applied. Epidemiological methods should be used for the data analysis.”

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’).

According to the Clinical Trials Directive, clinical trials of medicinal products in human subjects requires authorisation by the competent authority (MHRA in the UK) and a favourable opinion by an ethics committee. This authorisation is granted in the form of a clinical trial authorisation (CTA).

From October 2018, the EU Clinical Trials Directive is due to be replaced by the EU Clinical Trials Regulation (EU Regulation No 536/2014, Published by the Official Journal of the EU (OJEU)) which will streamline and harmonise requirements for clinical trial authorisation across Europe.

In the UK, this will currently mean that a single decision on a clinical trial will replace the current separate approvals given by the Medicines and Healthcare products Regulatory Agency (MHRA) and the Research Ethics Committee (REC). Implementation of the Clinical Trials Regulation will be led by the Health Research Authority. This policy will be updated as implementation guidance is made available in the UK.

2.0 Purpose

To clearly inform Trust research teams and external research partners about local requirements for conducting research involving a Clinical Trial of an Investigational Medicinal Product within NSFT, and setting out the responsibilities of each partner for the study.

3.0 Definitions

Clinical Trial of an Investigational Medicinal Product (CTIMP)

A Clinical Trial of an Investigational Medicinal Product (CTIMP) is defined in the Medicines for Human Use (Clinical Trial) Regulations 2004 as any investigation in human subjects, other than a non-interventional trial intended:

- To discover or verify the clinical, pharmacological or other pharmacodynamic effects of one or more medicinal products
- To identify one or more adverse effects of these medicinal products
- To study absorption, excretion or distribution of medicinal products with a view of ascertaining the safety or efficacy of such products.

Since May 2004 when the Trial Regulations came into force, CTIMPs have been regulated by the Medicines and Healthcare Products Regulatory Agency (MHRA) who needs to give explicit authorisation for a CTIMP to be conducted in addition to the standard approvals required for clinical studies. This is termed “Clinical Trial Authorisation” or CTA.
EudraCT (European Union Drug Regulating Authorities Clinical Trials) is the European Clinical Trials Database of all clinical trials commencing in the European Union from 1 May 2004 onwards. The EudraCT database has been established in accordance with Directive 2001/20/EC.

Each clinical trial with at least one site in the European Union receives a unique number for identification, the EudraCT Number. The EudraCT Number must be included on all Clinical Trial applications within the European Community and as needed on other documents relating to the trials (e.g. SUSAR reports).

GCP: Good Clinical Practice.

“Good clinical practice is a set of internationally recognised ethical and scientific quality requirements which must be observed for designing, conducting, recording and reporting clinical trials that involve the participation of human subjects.” [Definition from EU Directive 2001/20/EC, article 1, clause 2]

Compliance with this good practice provides assurance that the rights, safety and well-being of trial subjects are protected, and that the results of the clinical trials are credible and accurate.

Investigational Medicinal Product (IMP)

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 authorization 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. [EU 2011/C 172/01]

MHRA: Medicines and Healthcare Products Regulatory Authority.

The MHRA’s Good Clinical Practice (GCP) Inspectorate is part of the Inspection, Standards and Enforcement Division of the MHRA. The function of the GCP Inspectorate is to assess the compliance of organisations with UK and EU legislation relating to the conduct of clinical trials in investigational medicinal products. This is achieved through carrying out inspections of sponsor organisations that hold clinical trial authorisations (CTA) or organisations that provide services to clinical trial sponsors (host organisations).

Trial Manager: A representative of the main research team (within the sponsor organisation or contracted partner) who has received delegated management duties from the Chief Investigator for the conduct of the trial across all research sites.

CI Chief Investigator. The lead researcher who has overall responsibility for the conduct of the research study across all sites.

PI: Principal Investigator: The named researcher who has delegated responsibility for the conduct of the research study at each individual participating research site.

Clinical Trial Regulation Definition: Principal Investigator means an investigator who is the responsible leader of a team of investigators who conduct a clinical trial at a clinical trial site;

4.0 Duties

Sponsor: The organisation with overall responsibility for the conduct of the clinical trial. The sponsor will arrange for indemnity, regulatory and R&D approvals to be in place by the start of the study, will set-up and provide full trial documentation and study training to local research teams, will ensure that appropriate emergency reporting procedures are in place, will provide study medication to be sent to local Pharmacy sites where required, will perform comprehensive monitoring and audit functions throughout the study by arrangement with local teams.

CI – Chief Investigator: The lead researcher with responsibility for the conduct of the clinical trial across all research sites, including but not limited to the following areas.
1. Qualifications and agreements (Good Clinical Practice (GCP) Training, delegation of trial-related duties)
2. Adequate Resources to conduct the overall study – time, funding, demonstrate ability to recruit (via pilot etc)
3. Medical care of trial subjects: A qualified clinician, who is an investigator or a sub-investigator for the trial, should be responsible for all trial-related medical decisions
4. On-going communication with Ethics/MHRA/R&D throughout trial (amendments, annual reports etc)
5. Ensure full compliance with protocol and document deviations and submit amendments to Ethics and R&D.
6. Investigational Product (if applicable) - responsible for IMP accountability at site/s (can be assigned to appropriate pharmacist)
7. Randomization Procedures and Unblinding – responsible for following trial’s randomization and blinding/unblinding procedures (if applicable)
8. Informed consent – responsible for following GCP guidelines on informed consent
9. Records and Reports – follow GCP guidelines on Case Report Forms and source documentation, maintenance of trial documentation, financial agreements and archiving
10. Progress Reports – provide written summaries to Ethics (annually or more frequently if requested) and sponsor and Ethics and R&D regarding substantial changes to trial
11. Serious Adverse Events (SAEs) - responsible for ensuring all SAEs reported to sponsor
12. Premature Termination or Suspension of Trial – Responsible for ensuring trial subjects, institution sponsor, Ethics and R&D are promptly informed if trial ends prematurely or is suspended
13. Final Report – ensure that final report provided to institution, Ethics and R&D, regulatory authorities and sponsor

The CI will be responsible for the integrity of the study protocol and publications resulting from the study

**PI:** The lead researcher with delegated responsibility for the conduct of the clinical trial aligned with the responsibilities of the chief investigator (listed above) across the local site only. The PI will report any adverse events or serious adverse events to the sponsor/CI, will be responsible for the set-up and conduct of the study at the local site and ensure that all trial documentation and appropriate training has been received and passed onto the study team. Duties will include set-up and maintenance of trial documentation, patient identification and recruitment, patient follow-up, arrangement and collection of prescribed study medication from Pharmacy and ensuring that the study is being conducted to study protocol, trust policy and GCP standards.

**Local Research Team:** The local research team, as named on approval documentation, have delegated duties from the CI and PI to conduct the clinical trial at the local site. Duties will include set-up and maintenance of trial documentation, patient identification and recruitment, patient follow-up, arrangement and collection of prescribed study medication from Pharmacy and ensuring that the study is being conducted to study protocol, trust policy and GCP standards.

**Pharmacy:** To ensure that drug prescribing for clinical trials is performed in a way which is consistent with study protocol GCP regulations and trust policies, and that full records are maintained and kept accurate by the Trial Pharmacist.

**R&D:** To conduct thorough research governance checks of a study prior to commencement in the Trust, and ensure that the trial is being conducted to be compliant to approved protocol, GCP and Trust policies, and undertake local research audits of clinical trials where appropriate.

The host NHS organisation is required to have procedures in place for conducting the trial in accordance with Good Clinical Practice and the Clinical Trials Regulations, including:
- Adequate training for all site staff and adequate training records;
- Ensuring clarity of roles and responsibilities (e.g. contracts and agreement, delegation log)
- Appropriate knowledge of the trial and quality systems in all peripheral departments (e.g. laboratories, radiology, medical records);
- Ensure systems and facilities are fit for purpose (e.g. computer systems, equipment)
Conducting the trial in accordance with the protocol, including: informed consent; reporting of adverse events / reactions as per protocol (and urgent safety measures); unblinding procedures; and IMP accountability at the trial site; and

Adequate trial documentation and archiving of trial documentation.

5.0 Guidance to Good practice

5.1 Sponsorship

The Trust will support the conduct of CTIMPs in the Trust (Phase II, III, IV) as a research site, providing that sponsorship responsibilities are held by, or delegated to, an external recognised legal institution within the UK (such as a commercial company, a higher education institute, an NHS Trust or healthcare provider).

The Trust will not accept sponsorship responsibilities for clinical trials of investigational medicinal products or medical devices.

Evidence of acceptance of sponsorship must be received by the Trust R&D Office along with Insurance/Indemnity documents for the study before the project is authorised to start in the Trust.

5.2 Approvals and Set-up

All CTIMPs and Device Trials must have gained full approval from the regulatory authority (MHRA), an NHS Ethics Committee and the Health Research Authority (HRA Approval) before the start of the study. Researchers will need to obtain Confirmation of Capacity and Capability from the Trust Research Office prior to study start in the organization.

It is the expectation of the Trust that a feasibility meeting will be set-up by the Sponsor organisation in the Trust to discuss the study. This meeting should minimally include the Principal Investigator, a representative from R&D, and input from Trust Pharmacy.

For Commercially-sponsored Portfolio studies, the Trust expects that the NIHR Industry Costing Template and NCTA templates are used for financial and contractual negotiations respectively, and these should be made available to the Trust R&D Office for review prior to a full submission for Research Governance approval being received.

For non-Portfolio or non-commercial studies, the sponsor must negotiate with R&D in writing regarding preferred financial and contractual arrangements prior to a full submission for Research Governance approval.

5.3 Trial Management

It is the responsibility of the Sponsor, or sponsor’s representative, to provide the named Trust research staff with comprehensive Trial Management documentation including, but not limited to:

- Site file set-up instructions,
- All Ethically-approved patient-related documentation
- Delegation and signature logs,
- Adverse event reporting procedures,
- Emergency contact information,
- Randomisation procedures,
• Pharmacy dispensing instructions
• Blood-taking and storage instructions
• Communication logs
• Up-to-date CVs and Training logs
• Ethically-approved Investigator Brochure (IB) or Summary of Product Characteristics (SmPC).

If trial management documentation is not made available, it is the expectation of the Trust that local Trust templates available from R&D will be used by the local research team until study documentation is provided.

It is the responsibility of the Principal Investigator that all documentation is correct, and maintained in accordance to GCP Guidelines. The duty of maintaining Trial Documentation can be delegated to a named Trust staff member, but the overall local responsibility remains with the PI.

The sponsor must inform R&D of any amendments to the study protocol, study documentation and IMP data as soon as possible. No amendments can be implemented on site until approval for the amendment has been received from R&D.

All site-specific information in the local site file must be sent to the Trial Manager for inclusion in the Trial Master File held by the Sponsor Organisation. A nominated member of staff of the local research team should have delegated responsibility to set-up and maintain the site file.

5.4 CTIMP Study Personnel

The selected Principal Investigator for CTIMPs is required to be a GMC-registered clinician, who is able to provide due diligence and oversight for NSFT Research participants. The Investigator is required to hold a substantive contract with NSFT, or, in exceptional circumstances where no NSFT-employed clinician is available to act as principal investigator, through honorary research contract arrangements and by agreement of the Research management.

Local study staff are required to have appropriate training, supervision and resource to manage all delegated aspects of the study, as confirmed by delegation of duties and training logs.

Any non-NSFT research team member who will have access to NSFT participants or identifiable data for the purposes of the study will be required to hold an honorary research contract or letter of access for the duration of the study.

5.4 Training

The sponsor, research network, R&D Office and Principal Investigator will ensure through discussions and documentation that named Trust staff members are suitably trained and qualified to perform their delegated roles in the study.

All Trust research team members must hold a contract of employment or an honorary contract/letter of access with the Trust, and provide evidence of undertaking Good Clinical Practice training prior to working on the study. All training records and certificates will be held in the central site file.

All researchers in the Trust, delegated to work on CTIMPs, must hold a valid GCP certificate and have completed training within the previous 24 months. Due to the complexity and regulation involved in CTIMPs, it is good practice that GCP Training should be undertaken every 12 months by local research team members involved in the delivery of drug trial research.

Pharmacy staff involved in the delivery of clinical trials should also have completed appropriate and current training.
5.5 Trial Management for UKCRN Portfolio Studies

For Portfolio studies, the local research team will report to the Trial Manager and R&D the recruitment on the study on a monthly basis.

It is the expectation of the Trust that the first participant will be recruited into the study within 30 days of the Trust providing Confirmation of Capacity and Capability. If there are any sponsor-related issues to be resolved which will delay recruitment locally, R&D and the PI must be informed immediately. If there are local/Trust issues which may delay recruitment into the study, it is the responsibility of the PI to inform the sponsor and R&D. These issues will be reported to the NIHR by R&D as required via quarterly PID reporting.

5.6 Monitoring and Auditing

5.6.1 Sponsor Monitoring

According to the ICH-GCP framework, the purpose of study monitoring is to verify that:
- The rights and well-being of research participants is being protected.
- Reported trial data is complete, accurate and verifiable from source data.
- The conduct of the trial is compliant with the current protocol, regulatory authority regulations and GCP guidelines.

A monitoring visit conducted by a representative of the Sponsor involves source data verification to compare the case report form entries with information available from source documents i.e. patient notes, files and test results.

The monitor should inform the research team about the visit in advance, including details about the monitoring schedule for the study and the expected duration of the visit. The research team and Monitor should jointly find a suitable location for the conduct of the Monitoring visit.

The research team should make all study documentation and source data available to the monitor for the duration of the visit, and any supporting departments contacted in advance.

After the visit, the Monitor will complete the study Monitoring Report Form and make a copy available to the PI/CI stating what has been reviewed, and the findings of the visit, including information about any areas which need corrective action.

The research team should file a copy of the Monitoring Report Form in the study file, plus document any corrective action or subsequent communication about the findings.

5.6.2 Auditing by Regulatory Authorities

Audits and Inspections performed by sponsor organisations or regulatory authorities have three primary functions:
- To assure integrity of clinical and research data
- To assure participants’ rights, well-being and safety
- To allow sound decision making regarding efficacy and safety of the investigational product(s).

The above functions are assessed through thorough checking of study and clinical documentation to ensure compliance with GCP guidelines and regulations, and ensure that monitoring responsibilities have been undertaken to a satisfactory level. A check is also made to ensure that data received by regulatory authorities can be verified/evidenced through source data at each site.
The regulatory authorities, such as the MHRA, have the legal right to enter premises involved in the conduct of CTIMPs to undertake inspections, take samples or copies of research materials and seize research documents. It is a criminal offence to obstruct this process.

Once an investigator has received notification of an upcoming audit/inspection, they should notify all local research team members involved in the study across all sites as soon as possible. This notification should include the date, duration and nature of the prospective audit/inspection.

The local research team should conduct a thorough review of all study materials to ensure compliance prior to the audit/inspection. This review should include, but not limited to,

- Study protocol
- Study procedures
- Trial Master File/Site File including Patient-specific documentation and Pharmacy arrangements/records.
- Source Data
- Case Report Forms

The local research team should inform R&D of the pre-audit review, who will lead review preparation and arrangements. Any findings of the review which require corrective action will be clearly documented by the research team and R&D, with a clear and timely management plan put in place where required. A copy of the actions and plan should be placed in the site files, with a copy being sent to the sponsor organisation.

### 5.7 Pharmacy:

Approval from a senior Trust Pharmacy representative must be obtained for study procedures and IMP protocol before Confirmation of Capacity and Capability is granted. The feasibility and risk assessment involving Pharmacy in Trust CTIMPs must be conducted through Research and Development in conjunction with the local research team and sponsor organisation.

For a CTIMP to be conducted in the Trust, clear Pharmacy management procedures must be in place and evidenced in the following areas:

- Service Authorisations
- Stock Management
- Systems and Records
- Storage of Trial Medication
- Destruction of Trial Medication
- Study Data Queries
- Approvals (including Regulatory Authority and Trust) and Contracts
- Labelling of Trial Medication
- Dispensing of Trial Medication.
- Transportation
- Nominated Individuals/Pharmacy Delegation log.

Pharmacy Research Policies and Procedures will be authorised by the Chief Pharmacist.

#### 5.7.1. Storage and Dispensing

All trial medication and placebo products must be received, stored and dispensed through the Central Pharmacy facilities. Internal Policies regarding the transfer and storage of pharmaceutical materials will be followed if IMPs are transported to other areas of the Trust.

Under no circumstances will IMPs be administered to Trust research participants directly by Trust staff or research team members without dispensing from Trust Pharmacy facilities.
It is the responsibility of the Research study nurse/clinical study officer/assistant and/or PI to provide the clinical trial prescription to Pharmacy in a timely manner, stating clearly the time and date that the medication is required.

If trial medication is transferred from the Pharmacy to off-site premises (such as participants’ homes), this must be performed by a named member of research study staff not before the day of the dispensing appointment and the medication transferred in a suitable environment/storage as stated in the study protocol. Any medication transfer arrangements in this manner should receive written approval by the study sponsor and Pharmacy.

All IMPs will be dispensed, stored, recorded and destroyed in accordance with existing Trust Pharmacy policies for medicinal products and the approved study protocol.

Any unused IMPs must be counted and recorded by the research staff and returned to Trust Pharmacy for destruction by the named Study Pharmacist.

5.7.2 Study Management

Each study will have a nominated individual Trust Pharmacist listed on the delegation log, who will be appropriately trained for administering IMPs and will have attended Good Clinical Practice Training. Responsibility for clinical trials cannot be delegated to other Pharmacist staff unless they have been trained for the study, attended GCP and have been added to the Study delegation log.

The study Pharmacist should make themselves available for any monitoring or audit visits, and be able to provide information regarding all study paperwork, IMP storage, temperature logs and policies as required by the monitors and auditing representatives.

5.8 Study Shut-down procedures

It is the legal responsibility of the study sponsor to inform regulatory authorities and research ethics committee of early termination of a study at a research site within 15 days of the termination. This information should be communicated to the CI, PI and R&D Offices where necessary. Sponsor and Trust study close-down/termination procedures should be followed.

The Research office is required to keep accurate records of study end-dates and should update databases with the status of the study as soon as possible.

5.9 Archiving

In line with Good Clinical Practice guidelines, all Essential Documents should be archived in a way which allows for recall of files, accurate reporting, interpretation and verification of data.

The sponsor will make arrangements for archiving study materials in accordance with study protocol.

Local documentation will be archived according to local Trust policy and stored for the duration stated in the study protocol. Responsibility for arranging Trust archiving will remain with the Principal Investigator unless otherwise delegated.