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<td>Lead executive</td>
<td>Medical Director, NUH</td>
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<tr>
<td>Author</td>
<td>Medicines Management Committee, NUH</td>
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The **Here for You** standards have been introduced to ensure that employees are aware of the acceptable standards of behaviour that are expected and in doing so we have made a pledge to each other. We pledge that all day, everyday we will all do our very best to ensure:

- You are appreciated, with a polite and respectful attitude, from kind and helpful colleagues, who value everyone who takes responsibility for doing a good job
- You are supported to make the best use of your time, by simplifying processes, eliminating waste, and streamlining communication to ensure everyone can be focused on high quality care for patients
- You are encouraged to improve the quality of our service to patients, by listening to patients’ needs and through evidence-led improvement, team working, training and personal development
19.1 INTRODUCTION

This procedure sets out the standards required for the management of Investigational Medicinal Products (IMPs) at NUH Trust. It is applicable to both non-commercial, (including investigator initiated) and commercially sponsored protocols and all phases of clinical trials from Phase 1 human volunteer studies to Phase IV post-marketing studies. While some clinical trials will involve the use of existing marketed products used within their licensed indications, others will use new medicines, formulations or methods of administration unfamiliar to staff handling them. IMPs may also be coded to prevent ready identification by investigator or patient. Extra precautions need to be taken to ensure safety and security in their use.

Each clinical trial must have a sponsor responsible for the initiation, management and financial arrangements of the trial. The sponsor may be a pharmaceutical company, a research organisation, the Trust, an academic institution, or a combination of these. The sponsor may delegate responsibility for defined and agreed trial duties.

The role of the pharmacy service in relation to clinical trials is to safeguard the patients, healthcare professionals and the Trust by ensuring that the medicines are appropriate for use and are procured, handled, stored, used safely and correctly, and disposed of appropriately.

19.2 REGULATIONS

Statutory requirements for the conduct of all interventional trials involving medicines are imposed by the Medicines for Human Use (Clinical Trials) Amendment Regulations 2006 (1), the Medicines for Human Use (Clinical Trials) Amendment (no 2) Regulations 2006 (2), and the Medicines for Human Use (Clinical Trials) and Blood safety and Quality Amendment Regulations 2008 (3) which implement the requirements of EU directives 2001/20/EC and 2005/28/EC (4,5) The regulatory framework is supported by the Duthie report (6), Department of Health Controls Assurance (7), and the Research Governance Framework (8)
19.2.1 Approval processes

19.2.1.1 Regulatory authorisation

The use of medicines in a trial must be supported by a Clinical Trials Authorisation (CTA) issued by the Medicine and Healthcare Products Regulatory Agency (MHRA). All trials not conforming to all of the following conditions are considered to be interventional and will require a CTA.

A non-interventional study is defined as a study of one or more medicinal products which have a marketing authorisation (i.e. are licensed products), where the following conditions are met:

- the products are prescribed in the usual manner in accordance with the terms of the authorisation;
- the assignment of any patient involved in the study to a particular therapeutic strategy is not decided in advance by a protocol but falls within current practice;
- the decision to prescribe a particular medicinal product is clearly separated from the decision to include the patient in the study;
- no diagnostic or monitoring procedures are applied to patients included in the study, other than those than are normally applied in the course of the particular therapeutic strategy in question and
- epidemiological methods are to be used for the analysis of the data arising from the study

The trial sponsor is responsible for CTA application. This may be formally delegated to the investigator for protocols which are sponsored by the Trust or University.

The pharmacy clinical trials co-ordinator can assist with completion of the sections of the application form concerning the products to be used in the study.

19.2.1.2 Ethics approval
Before recruitment can begin, all studies must receive a favourable opinion from an Ethics committee. A comprehensive guide to the application process can be found on the National Research Ethics Service (NRES) website (9) www.nres.npsa.uk

19.2.1.3 Research and Development (R and D) approval

R and D approval will ensure compliance with the Research Governance framework. The site specific information (SSI) form is used to request R and D approval. Acknowledgement of approval from support services, where applicable, is required as part of the SSI application. R and D approval will not be granted until regulatory and ethics approval has been confirmed. The Trust R and D website provides further guidance. (10)

19.2.1.4 Final pharmacy sign off

This will be required before IMPs can be dispensed and will occur when all IMPs related procedures are in place.

19.3 RESPONSIBILITIES OF DESIGNATED RESEARCH STAFF IN THE RESEARCH PROCESS

19.3.1 Investigator responsibilities

These are detailed in the Good Clinical Practice (GCP) regulations (5) Particular vigilance is needed when operating protocols, which are sponsored, by the Trust or an academic institution in which Trust patients are to be recruited.

In summary, the investigator should

- be qualified by education, training and experience, including evidence of GCP awareness, to assume responsibility for proper conduct of the trial; (see R and D website for guidance (10)
- demonstrate adequate resources e.g. time, support staff and facilities to conduct the trial properly and safely within an agreed time period;
- ensure before the study begins that it has a favourable opinion from an Ethics committee;
- obtain and document informed subject consent, or if the subject is unable to provide informed consent, the subject’s legally acceptable representative, before any trial related procedures are performed. Subjects should have a clear understanding of the proposed treatments, the potential for harmful effects and any available alternative treatment. Written information and instructions which has Ethics committee approval, should be provided and the subject must have ample time to ask questions and decide whether or not to participate;
- ensure that all persons assisting with the study are adequately informed about the protocol, the investigational medicinal products and their trial related duties and functions;
- be responsible for reporting serious adverse events to the sponsor in accordance with the protocol;
- be responsible for all trial related medical decisions during and following a subjects participation in the study;
- be responsible for investigational product accountability at the trial site and delegate this responsibility to the pharmacy department;
- follow trial randomisation procedure if applicable and ensure that in blinded studies, the treatment code is broken only in accordance with the protocol;
- ensure the accuracy, completeness, legibility and timeliness of trial data and ensure that all other persons who have delegated responsibility for data collection are adequately trained in trial procedures and are aware of those responsibilities.

19.3.2 Pharmacy responsibilities

A designated member of pharmacy staff has overall responsibility for the pharmacy clinical trial service. The pharmacy clinical trials co-ordinator should:

- before the commencement of a clinical trial involving IMPs, ensure that the pharmacy department has copies of all essential regulatory and technical documents, a copy of the
protocol, an investigator brochure or Summary of Product Characteristics, if applicable and randomisation codes, if relevant;
- carry out risk assessments for each clinical trial and put procedures in place to minimise the predictable risks from trial medication to patients and staff;
- ensure that all clinical trial medicines provided or procured for use in non commercial studies are manufactured in accordance with Good Manufacturing Practice, by a holder of a manufacturing authorisation for investigational medicinal products, are of suitable quality and fit for purpose;
- ensure that packaging and labelling of clinical trial medication is acceptable for use within the Trust and complies with applicable legislation;
- be responsible for management of IMP stock, including IMP accountability and any other duties as delegated by the investigator. A written agreement or contract, detailing these delegated duties and pharmacy fees, should be in place for each clinical trial.

19.4 IMP MANAGEMENT

All medicines used in clinical trials at Nottingham University Hospitals NHS Trust must be stored and dispensed by the pharmacy department and managed to the same standards as other medicines used therapeutically (4).

All organisations supplying medicines and related products for use in clinical trials must do so through the Trust Pharmacy Department.

The investigators must delegate responsibilities to the pharmacy department for the:

- correct receipt and recording of deliveries of trial medicines;
- safe handling, storage and dispensing of trial medicines;
- maintenance of accurate accountability records for all clinical trial medicines;
- return of unused products to the trial sponsor or their disposal according to NUH policy;
- reconciliation of delivery records with usage and return of unused stock;
- safe keeping of randomisation information including emergency code breaks;
- provision of medicine information to trial subjects on administration of study medication;
- where necessary, the manufacture and/or assembly of study medication.

19.5 PRESCRIBING OF IMPs

The pharmacy clinical trials co-ordinator must be approached prior to Ethics and R and D submission to ensure the procedure and information necessary for prescribing IMPs are clarified.

IMP prescribing must be by study specific authorised prescribers only. A record of prescribers will be kept in the study specific pharmacy file.

IMP prescribing must be on an authorised, study specific prescription form or a clearly annotated NUH prescription chart. Authorised, study specific, stickers may be used to facilitate this. The pharmacy department can assist in the design and production of a suitable form.

Prescriptions must include:

- official trial name and protocol number;
- visit number;
- patient identifying details, name, address, date of birth, hospital number and trial subject number if relevant;
- dose, frequency, duration and route of administration;
- quantity of IMP required for the prescribed treatment period (this should correspond with prepacks designed to meet the requirements of the treatment protocol wherever possible).
19.6 STORAGE OF IMPs

All IMPs must be managed in a temperature controlled storage facility in the pharmacy department. It is inappropriate for separate stocks to be kept in wards, clinics or private offices. In exceptional circumstances investigators may need to store IMPs in a clinical area. The Pharmacy Trials Co-ordinator must authorise this deviation from the Policy and a procedure put in place to ensure the minimisation of risk and compliance with CL/MM/004 of this Medicines Code of Practice - Storage and security of medicines and controlled documentation.

The reasons for any alternative arrangements for storage of IMPs should be documented e.g. when 24 hour rapid access is required to IMPs and a delay in treatment initiation would result in a protocol violation and/or poor patient recruitment.

Alternative storage facilities should be designated for IMP storage only with appropriate security and temperature monitoring methods approved by the pharmacy department.

IMPs will be delivered to the pharmacy department. Issue to and return from the alternative storage facility will be documented as part of the IMP accountability records in the pharmacy file.

19.7 DISPENSING OF IMPs

The pharmacy department must have a study-specific dispensing procedure for all trials.

Labelling should comply with the requirements of the clinical trials directive and UK dispensed medicines (11) and will include patient name and study number (if applicable), dosage instructions, treatment period, batch number, expiry date, investigator name and contact details, hospital address, study identifier and sponsor details.

19.8 IMP ACCOUNTABILITY

The pharmacy department must have study specific accountability documents for all trials.
19.9 IMP ADMINISTRATION

Ward staff should be given reasonable notice of pending studies and provided with copies of all relevant documentation, including a protocol summary, information on IMP administration, study specific medication administration records, if applicable and any available information concerning possible adverse drug reactions. Ward staff must be informed of their responsibilities with respect to the confidentiality of study information.

Administration of IMPs is subject to the requirements of the NUH Medicines Code of Practice CL/MM/008- Administration of medicines. In most cases the IMP will be an unlicensed preparation or a licensed product administered outside the licensed indications.

Staff administering unlicensed or off-label medicines should be aware of their unlicensed status. Unlicensed medicines cannot be supplied or administered under a Patient Group Direction (PGD), unless in exceptional circumstances as approved by the Non Medical Prescribing, Administration and Supply Committee.

19.10 RETURN OF USED AND UNUSED IMPs TO PHARMACY

These processes are under pharmacy control and governed by pharmacy Standard Operating Procedures (SOPs).

19.11 DISPOSAL OF IMPs

These processes are under pharmacy control and governed by pharmacy SOPs.

19.12 RECALL OF IMPs

These processes are under pharmacy control and governed by pharmacy SOPs.
19.13 CODE BREAKING

Emergency code break information must be accessible 24 hours a day. Codes must only be broken in accordance with the procedures contained in the protocol. Out of hours the contact with pharmacy will be via the on call pharmacist.

The mechanism for code breaking will be:

either:

- a set of sealed envelopes containing individual subject treatment allocation. At least one complete set of envelopes must be provided to the Trust for storage in the pharmacy file;
- an alternative, if applicable is a randomisation list held on file in an unblinded pharmacy department, with access limited to those with written authorisation to perform a code break.

or:

- an interactive voice response (IVRS) telephone or a similar web based system with an option for named authorised study personnel to access the unblinding facility via a personal identification number (PIN). Where this responsibility is not directly delegated to the pharmacy, it is essential that a robust system is in place to ensure emergency unblinding, which is documented in the pharmacy SOP for the trial.

In the event of unblinding, whether accidental or deliberate e.g. due to a serious adverse event, the investigator must document the action taken and promptly notify the sponsor.

19.14 DEFINITIONS SPECIFIC TO CLINICAL TRIALS

Clinical Trial of an Investigational Medicinal Product (CTIMP): Any investigation in human subjects intended to discover or verify the clinical, pharmacological, and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an
investigational product(s) with the object of ascertaining its safety and/or efficacy.

**Clinical Trial Authorisation (CTA):** Authorisation given by the competent authority (MHRA in UK) to conduct a clinical trial.

**Disposal:** The removal of investigational products from the research site either by return to the trial sponsor or by destruction according to local policy. Destruction is usually performed by an external waste contractor.

**Good Clinical Practice (GCP):** A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.

**Good Manufacturing Practice (GMP):** The part of quality assurance which ensures that medicinal products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorisation (MA) or product specification. GMP is concerned with both production and quality control.

**Investigational Medicinal Product (IMP):** A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.

**Investigator:** A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.

**Medicines and Healthcare products Regulatory Agency (MHRA):** The government agency which is responsible for ensuring that medicines and medical devices work, and are acceptably safe.
**Research Ethics Committee (REC):** An independent body, constituted of medical / scientific professionals and nonmedical / non-scientific (lay) members, whose responsibility it is to ensure the protection of the rights, safety, and well-being of human subjects involved in a trial by, among other things, reviewing and providing a favourable opinion on the trial protocol, the suitability of the investigator(s), facilities, and the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

**Sponsor:** An individual, company, institution, or organisation that takes responsibility for the initiation, management, and/or financing of a clinical trial.

**Standard Operating Procedures (SOPs):** Detailed, written instructions to achieve uniformity of the performance of a specific function.

**19.15 REFERENCES**

2. Medicines for Human Use (Clinical Trials) Amendment (No 2) Regulations 2006 (SI 2006/2984)
3. Medicines for Human Use (Clinical Trials) and Blood safety and Quality Amendment Regulations 2008 (SI 2008/941)
Hospital Pharmacists Group of the Royal Pharmaceutical Society. March 2005
10. www.nuhrise.org
APPENDIX 1. EQUALITY IMPACT ASSESSMENT REPORT

OUTLINE

1. **Name of Policy or Service**
   
   Policy for Prescribing, Dispensing, and Administration of Clinical Trial Medicines Policy

2. **Responsible Manager**
   
   Medical Director, NUH

3. **Name of Person Completing Assessment**
   
   Sonia Gilmore

4. **Date EIA Completed**
   
   21\textsuperscript{st} December 2010

5. **Description and Aims of Policy/Service**
   
   This chapter of the Medicines Code of Practice has been developed to set out the standards required for the management of Investigational Medicinal Products at NUH Trust

6. **Brief Summary of Research and Relevant Data**

7. **Methods and Outcome of Consultation**
   
   Medicines Code of Practice Review Group

8. **Results of Initial Screening or Full Equality Impact Assessment:**

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9. Decisions and/or Recommendations

Following the initial impact assessment, it is my recommendation that this document does not require a full impact assessment.

10. Equality Action Plan

N/A

11. Monitoring and Review Arrangements

It is recommended that once implemented, this chapter is reviewed in line with NUH guidelines.

Equality Statement

All patients, employees and members of the public should be treated fairly and with respect, regardless of age, disability, gender, marital status, membership or non-membership of a trade union,
race, religion, domestic circumstances, sexual orientation, ethnic or national origin, social and employment status, HIV status, or gender re-assignment.

**Environmental Impact Assessment**

This policy has no detrimental environmental impact
Employee Record of Having Read the Policy

MEDICINES CODE OF PRACTICE
PRESCRIBING, DISPENSING, AND ADMINISTRATION OF
CLINICAL TRIALS MEDICINES POLICY

I have read and understand the principles contained in the named policy.

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