11 Clinical Trials

11.1 Conduct of clinical trials involving medication: General Principles

11.1.1 The testing of medication under clinical trial is regulated by the European Clinical Trials Directive (EC Directive 2001/20/EC), published in April 2001, transposed into UK legislation in 2004 as Statutory Instrument 2004:1031 The Medicines for Human Use (Clinical Trials) Regulations, and further amended in 2006 to incorporate Good Clinical Practice (GCP) as set out within EC Directive 2005/28/EC. Further updated with minor amendments in 2008:941 (Medicine for Human Use (Clinical Trials) and Blood Safety and Quality (Amendment) Regulations.

11.1.2 The investigation of a medicine in a clinical trial is regulated by the Medicines and Healthcare products Regulatory Agency (MHRA) which is responsible for assessing the compliance of organisations using investigational medicinal products with UK and EU legislation. Trusts have a statutory obligation to comply with the principles of Good Clinical Practice (GCP). Detailed guidance can be found at www.mhra.gov.uk and http://ec.europa.eu/health/documents/eudralex/vol-10/index_en.htm

11.1.3 All clinical trials involving medication (commercial, non-commercial and Investigator initiated clinical research) fall under the Clinical Trial regulations, including those on (healthy) human volunteers, and will require a favourable opinion from the appropriate Research Ethics Committee (REC) and a Clinical Trials Authorisation (CTA) from the MHRA before Trust approval and commencement of the study. The Health Research Authority (HRA) review the REC and CTA centrally and provide HRA approval to local Trusts to proceed.

Application for both is via the Integrated Research Application System (IRAS) website. https://www.myresearchproject.org.uk and further advice is available from the organisation/Trust's Research and Innovation (R&I) Office.

11.1.4 All Investigational Medicinal Products (IMPs) must be manufactured to Good Manufacturing Practice (GMP) standards, and all trial sites are subject to statutory MHRA Good Clinical Practice (GCP) inspection.

11.1.5 Patient Information Sheets (part of the informed consent package) must be available to the patient when medicines are given as a part of a clinical trial. These are provided for use in the study by the Investigator or trial Sponsor to highlight the risks associated with using an IMP.

11.1.6 Investigators should contact their local clinical trial pharmacist when the study is at the design stage, or in the case of protocols provided by external Sponsors as soon after receipt as possible, so that appropriate advice may be obtained and implications for pharmacy identified at the earliest opportunity. This may include advice on the appropriate sourcing / procurement of an IMP, including placebos.

11.1.7 Further guidance on the conduct of clinical trials can be obtained from the Trust Research and Innovation website r local R&I office.

11.2 Pharmacy considerations

11.2.1 All clinical trials involving medication will normally be handled through the local pharmacy

department and the medication stored in the clinical trials pharmacy.

11.2.2 As storage of clinical trial medication is highly regulated, it is inappropriate for stocks of trial medication to be stored outside of Pharmacy (e.g. on wards, in clinics, in University departments or in private offices) except in exceptional circumstances (e.g. if it involves a medicine used in an emergency situation or involves out of hours recruitment). Even in exceptional circumstances, only sufficient medication for immediate use should be held outside Pharmacy. The explicit agreement of the clinical trial pharmacist will be required in these circumstances; exceptions will normally be agreed with the Investigator before Trust Approval for the Trial is granted following inspection & assessment of the area by the clinical trial pharmacist. Where storage is agreed outside Pharmacy there will be an ongoing monitoring requirement of storage temperature, accountability records etc. by Pharmacy staff.

11.2.3 Records must be kept of receipt, dispensing, issue, administration, and disposal of all IMPs to facilitate reconciliation and to comply with GCP and statutory requirements. The handling, storage and dispensing must be covered by Standard Operating Procedures (SOPs) and must follow GCP guidelines prepared by the Institute for Clinical Research - SOPs and checklists for Pharmacy personnel. http://www.icr-global.org/community/special-interest-groups/pharmacy-special-interest-group/pharmacy-publications

11.2.4 The identities of all those involved with receipt, dispensing, issue, administration, and disposal of all IMPs must be recorded. Records on an appropriate trial delegation/responsibility log must be regularly audited by pharmacy staff, with reconciliation. They will also be subject to external audit by e.g. the MHRA, independent clinical trials monitors and the organisation's own R & I Staff.

11.2.5 SOPs must be in place to describe the procedure for code breaks / unblinding of Pharmacy Clinical Trials. An unblinding procedure (if appropriate) must be available in each pharmacy trial file detailing the unblinding method (e.g. code break envelope, automated system or other process). This must be agreed & signed by the Principal Investigator (PI). In most cases the PI or trial Sponsor may be the only ones authorised to unblind a study, in which case contact details for this will be in the trial specific unblinding procedure. N.B. Pharmacy can only unblind a trial if authorised to do so by the Sponsor.

11.2.6 Professional Guidance on Pharmacy Services for Clinical Trials which has been issued by the Royal Pharmaceutical Society and the National Pharmacy Clinical Trials Advisory Group (2013) should be followed. http://www.rpharms.com/support-pdfs/professional-guidance--n-pharmacy-services-for-clinical-trials-141013.pdf

11.2.7 Any request for an individual patient's trial medication to be supplied in a compliance aid e.g. Dosette box, must be discussed in the first instance with the clinical trial pharmacist. It has to be accepted that depending on the nature of the IMP, its stability outside its original packaging, and/or the study design, this may not be possible.

11.3 Risk Management

11.3.1 Risk Management measures should follow the local risk management policy. Risk assessments should be carried out in connection with the drug products and procedures (including the use of delivery devices) to determine potential risks to patients and staff.
Risk Management procedures should be in place to minimise the risks from trial medicines or procedures to patients and staff

11.3.2 It will be the responsibility of the clinical trial pharmacist to ensure that clinical trials involving medication have been assessed for clinical and safe handling risks, as well as for compliance with Trust clinical policies & guidelines, before Trust approval is granted.

11.4 Considerations for Inpatients receiving Investigational Medicinal Products

11.4.1 Inpatients may receive clinical trial medication as follows:-

- Initiation of treatment on the ward
- Continuation of treatment on admission
- TTO supply on discharge

11.4.2 It is the Principal Investigator's (PI) responsibility to ensure that relevant ward staff are informed and have had at least basic GCP training prior to initiating clinical trial treatment for an inpatient. Training may only need to be specific to the trial in question, but must be recorded in the investigator site file together with evidence of appropriate qualification / registration.

11.4.3 Ward staff should be aware of information relating to the IMP's administration, adverse drug reactions and side effects, as well as how to report these to the investigator. Ward staff should have access to the investigator's and research team's contact details. Ward staff should be aware of the need for proper documentation to record administration of the IMP. Ward staff should be aware of the need to ensure that the IMP is supplied on patient discharge from the ward for continuity of treatment, and that this is documented. Ward staff should be aware of the need to return any unused or discontinued IMP to Pharmacy clearly labelled as clinical trial material, and preferably contact the clinical trial pharmacist beforehand.

11.4.4 For patients admitted on clinical trial medication, the Principal Investigator or research team should be contacted at the earliest opportunity (this may be from another organisation or NHS Trust). Unless otherwise instructed by the PI or delegate, or due to the overriding clinical condition of the patient, continuity of treatment should be maintained. It is the PI's responsibility to ensure that ward staff have adequate GCP training (see 11.4.2), as well as providing information relating to the IMP (see 11.4.3).

11.4.5 Arrangements should be made for patients admitted on clinical trial medication, and continuing on the study, for their trial supplies to be brought into hospital if they have been left at home to enable continuation of treatment.

11.5 Prescribing

11.5.1 It is the responsibility of the PI to ensure that prescribers are appropriately delegated for the study and have a current GCP certificate.

11.5.2 Qualified and registered medical practitioners and health care professionals who are supplementary prescribers* can prescribe IMPs. The IMPs must be prescribed on a hospital drug chart, via the Electronic Prescribing and Medicines Administration (ePMA) system, or on a prescription form which is signed by a prescriber who is recognised as

participating in the clinical trial.

*A supplementary prescriber can prescribe unlicensed medicines if part of a clinical trial. If a supplementary prescriber prescribes for a clinical trial, then the pharmacy department should be provided with written confirmation of this arrangement which is signed by the PI and the trial Sponsor. This document should be included in the pharmacy study file

11.5.3 When prescribing IMPs on inpatient drug charts or EPMA, the prescription should make it clear that the medication is a trial drug, and be clear that only trial medications can be used for that specific patient in the study in accordance with the trial protocol. How individual IMPs are prescribed in these circumstances will depend on study design (e.g. blinded medication) and advice should be sought from the clinical trial pharmacist.

11.5.4 Non-Medical Prescribers can prescribe IMPs on a case by case basis. Approval can be sought from the Sponsor to support this practice for an individual study. The Non-Medical Prescriber must have undertaken the appropriate training, be working within the remit of their job role, have support by the host site and have the responsibility delegated by the PI. However, the decision to dose a trial patient, in line with MHRA guidance, remains the responsibility of medically qualified doctor.

11.6 Administration of IMPs

11.6.1 In instances, where the IMP trial involves the preparation of an intravenous injection that must remain blinded and pharmacy are unable to prepare aseptically (due to expiry issues, logistics etc). There may be occasions where a study requires the use of both a blinded and an unblinded nursing team. It is recognised and accepted practice, that the preparation will be prepared by the unblinded nursing team but administered to the patient by the blinded nursing team. Approval will have been granted from the Sponsor and this practice will be approved by the PI.

11.7 Consideration for studies involving Advanced Therapy Medicinal Products (ATMPs)

11.7.1 Use of ATMPs in clinical trials is regulated under the above guidance but under additional guidance, Advanced Therapy Medicinal Products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004. The Chief Pharmacist has overall responsibility for the use of ATMPs

11.7.2. Clinical Trials involving ATMPs must be identified to the clinical trials pharmacy team as soon as possible to ensure adequate time is allocated for all internal assurance processes to be undertaken before trial approval can be granted. The Trust Genetic Safety Materials Committee (GSMC) must be convened to review evidence, study protocols and health and safety implications of the use of the agents within the Trust.