



National Pharmacy Clinical Trials Advisory Group

Professional Guidance on Pharmacy Services for Clinical Trials

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Endorsed by

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This guidance was initially prepared in 2005 on behalf of the Royal Pharmaceutical Society of Great Britain and the Institute of Clinical Research (ICR) by the Pharmacy Specialist Interest Group of the ICR. It has been reviewed and revised by the authors below as members of the Guidelines Subgroup of the National Pharmacy Clinical Trials Advisory Group (NPCTAG). This guidance has been reviewed by Jason Wakelin-Smith of the Medicines for Healthcare products Regulatory Agency (MHRA) Good Clinical Practice (GCP) Inspectorate. We would like to thank members of the NPCTAG for their valuable feedback and input during the update of this guidance.

This guidance will be reviewed and updated periodically by the NPCTAG to reflect changes in regulatory requirements. If you would like to feedback comments for suggested amendments or inclusion, please contact the NPCTAG joint-secretaries:

Mandy Wan: mandy.wan@gstt.nhs.uk

Julie Shenton: julie.shenton@nhr.ac.uk

Original authors: Claire Khalil, Caroline Bedford, Helen Bowler, Tracy Gazeley, John Gilroy, Sheila Hodgson, and Kim Ryalls.

Version 2 updated by: Caroline Bedford, Samantha Carmichael, and Mandy Wan on behalf of NPCTAG

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Introduction

This professional guidance on pharmacy services for clinical trials has been reviewed and revised by the National Pharmacy Clinical Trials Advisory Group (NPCTAG). It is intended for use by pharmacy staff involved with the provision of clinical trials services at policy, strategic and operational levels.

The guidance applies to all clinical trials that are regulated by the Medicines for Human Use (Clinical Trials) Regulations 2004 and subsequent amendments.¹⁻³ This includes commercial and non-commercial clinical trials. It does not specifically relate to pharmacy practice research unless this involves a Clinical Trial of an Investigational Medicinal Product (CTIMP).

This guidance specifically relates to the medicines management of Investigational Medicinal Products (IMPs), facilities required for the support of clinical trials services in accordance with regulatory requirements and informs operational, strategic and policy decisions relating to IMPs. It is underpinned by the principles of Good Clinical Practice (GCP) for the management of IMPs.^{4,5}

The generic terms "pharmacy" or "pharmacy staff" encompass pharmacists, pharmacy technicians and pharmacy assistants, although it is recognised that all may have different roles and responsibilities in relation to the provision of clinical trials services.

Pharmacy may support clinical trials involving medicinal products that are advanced therapy medicinal products (ATMPs)⁶ or radiopharmaceuticals. Specific guidance and regulations exist for the management of these products. It is the responsibility of the pharmacy staff involved to ensure working knowledge of all aspects of guidance and regulatory documents and compliance thereof. Legislation and guidance documents are subject to review and amendment; it is vital that only the current versions are referred to.

Where clinical trials take place in a hospital, all IMPs should be managed by the hospital pharmacy to the same standards as licensed medicines, in accordance with local medicines management policy.

For clinical trials conducted in other settings, for example Clinical Research Facilities, Clinical Trials Units and within the primary care sector, the principles of this practice guidance should be adhered to where possible.

Further guidance regarding clinical trials in community pharmacy settings is available through the Royal Pharmaceutical Society pharmacy accreditation scheme – Research Ready - for community pharmacies wishing to participate in health research, including clinical trials. The accreditation scheme is aligned with the principles of this practice guidance and provides essential support for pharmacy teams – enabling them to collaborate on and host clinical trial activity in community pharmacy settings.

Good Clinical Practice (GCP)

All clinical trials involving IMPs must be conducted according to the principles of GCP. These are outlined in articles 2 to 5 in the EU Directive 2005/28/EC.⁴

The definition of GCP in the EU Directive 2001/20/EC³ is as follows:

“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. 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.”⁴

GCP is a legal requirement for all CTIMPs in addition to the regulatory requirements stated in the UK (Medicines for Human Use) Clinical Trials regulations (as amended).¹⁻⁵ Guidance on GCP for CTIMPs is available from the MHRA.⁷

Individual staff members should ensure GCP competence commensurate with their roles and responsibilities in relation to CTIMPs.^{8,9} Whilst it may be the case that some pharmacy staff are carrying out tasks that are part of their normal role, it is recommended that they have an awareness of GCP, and that individual training is assessed as part of the organisation’s risk assessment for staff competency to participate in the conduct or support of clinical trials. The National Institute for Health Research (NIHR) has developed a [Delegation and Training Decision Aid](#) to help pharmacy staff to consider what individuals are being asked to do in the context of an individual research project and what training and learning they need to be effective. The approach is further explained by the MHRA ([refer to MHRA blog](#)). GCP training resources can be accessed through the NIHR Clinical Research Network (NIHR CRN), including:

- Introduction to GCP for IMP Management
- Fundamentals of Clinical Research for Pharmacy (Secondary) with IMPs
- Research Awareness (Secondary)
- Research and Pharmacy Community

Role of the Nations in Supporting Health Research

Clinical research is a vital part of improving treatments for patients. A commitment to promote, conduct and use research to improve the current and future health and care of the population is enshrined in the seven principles of the NHS Constitution for England and is embraced by all the devolved administrations - Scotland, Wales and Northern Ireland - which have developed similar approaches to supporting research (see useful web links).

England - National Institute for Health Research (NIHR) and the Clinical Research Network

The NIHR is funded by the Department of Health and Social Care. The NIHR CRN, which operates as the research delivery arm of NHS England, is of particular relevance to pharmacy services. The NIHR CRN funds the provision of research pharmacy staff, research nurses and other clinical research delivery staff across the country in order to develop clinical engagement in research activity, identify/recruit patients into suitable studies and carry out the clinical activities associated with studies on its portfolio. The Network also covers service support costs such as imaging, pathology sessions, lab costs etc associated with the completion of these studies.

A key role of the NIHR CRN is to ensure that studies on its portfolio are set-up quickly and delivered “to time and target” – that is to say they recruit the full quota of patients within the stipulated study period.

Scotland - the Chief Scientist for Health in Scotland and NHS Research Scotland

The Chief Scientist for Health in Scotland invests in NHS-related research and support. NHS Research Scotland (NRS) is a partnership involving Scottish NHS Boards and the Chief Scientist Office (CSO) of the Scottish Government. The overarching aim of NRS is to ensure that NHS Scotland provides the best environment to support clinical research.

Wales - Health and Care Research Wales

Health and Care Research Wales provides an infrastructure to support and increase capacity in research and development, runs a range of responsive funding schemes, and manages resources to promote, support and deliver research. It is funded and overseen by the Welsh Government's Division for Social Care and Health Research. The infrastructure includes Research Centres, Research Units, Clinical Trials Units, and the School for Social Care Research and allows a sharper focus on Wales' current and emerging areas of excellence.

Northern Ireland - The Northern Ireland Clinical Research Network (NICRN)

The NICRN is funded by the HSC Research & Development Division and supports high quality clinical trials across all HSC Trusts. Its mission is to develop and enable a well-resourced network of skilled staff which provides investigators and patients from throughout Northern Ireland with access to and help in developing high quality clinical research studies across all Health and Social Care (HSC) structures.

1. The Role of Pharmacy

1.1 The role of pharmacy in relation to clinical research is:

- a) To safeguard subjects, health care professionals and the Healthcare Provider Organisation (HPO) by ensuring that IMPs are appropriate for use and are procured, handled, stored, and used safely and correctly.
- b) To ensure that IMPs are managed and dispensed to subjects in accordance with the duly approved current protocol.
- c) To ensure that all pharmacy clinical trials procedures comply with relevant guidelines and regulations.

1.2 The HPO should have a policy for managing medicines used in clinical trials, including a statement defining the responsibilities that will be delegated to the pharmacy by the investigator. Pharmacy input into the development and review of this policy document is vital to ensure practicability and consistency with other pharmacy procedures.¹⁰

2. Pharmacy Staff

2.1 The Chief Pharmacist (or equivalent) is responsible for overall service provision although it is expected that a designated member of pharmacy staff will assume operational responsibility for the pharmacy clinical trial service. This individual will usually be the first point of contact within pharmacy when trials involving IMPs are under consideration by the host HPO.

2.2 Where the HPO retains the services of external individuals or organisations to perform IMP-related duties and functions, the Chief Pharmacist (or equivalent) must ensure the individual or organisation is qualified to perform those IMP-related duties and functions, and must implement processes for assessing their continuing suitability to ensure the integrity of the IMP-related duties and functions.

- 2.3 Designated pharmacy staff providing a clinical trial service must be adequately qualified, trained and experienced to assume clinical research responsibilities and should be able to provide up-to-date training records and/or curriculum vitae.^{1,4,5} Pharmacy staff job descriptions should provide clarity with regard to responsibility and accountability for clinical trials.
- 2.4 Pharmacy staff must ensure GCP competence and knowledge commensurate with their roles and responsibilities in relation to CTIMPs.^{8,9}
- 2.5 Pharmacy must hold training records and signature logs for those staff involved in clinical trial activity.⁷ These records may be held in a central location and should be readily available for inspection if required.
- 2.6 Clinical trials pharmacy staff must keep up to date with national guidance relating to clinical trials, GCP, Good Manufacturing Practice (GMP) and medicines management (see useful web links).

3. Pharmacy Facilities

- 3.1 It is essential to ensure appropriate facilities are available before agreeing to support a clinical trial particularly one involving radiopharmaceuticals or ATMPs (gene therapy, somatic-cell therapy, or tissue-engineered medicines). The pharmacy lead (or the designated member of pharmacy staff with operational responsibility) for clinical trials should liaise with, and seek advice from, other pharmacy staff (or individuals) with expert knowledge of or experience in handling these types of product.
- 3.2 Pharmacy should have facilities that allow for good segregation of IMPs and separate from normal pharmacy stock in an area with access restricted to pharmacy staff to minimise the risk of misidentification of trial stock. Licensed medicines (with a UK or EEA Marketing Authorisation) used as IMPs do not have to be stored separately as long as there is a process in place to ensure traceability.⁷
- 3.3 IMPs that are returned by subjects or have expired should be stored separately from unused IMPs. Quarantined medication should be clearly identified and segregated from working stock.
- 3.4 Regular temperature monitoring of IMP storage facilities should be undertaken and records maintained.⁷ All IMP storage areas should be fitted with calibrated temperature monitoring devices that record minimum and maximum temperatures, with a robust system to alert staff if the temperature falls outside of the specified range. Each temperature monitoring device must have a valid proof of calibration which is maintained for reference. Pharmacy should have written procedures in place for the actions to be taken when the storage conditions are outside of the specified range.
- 3.5 When using electronic data processing systems for trial data handling (e.g. e-prescribing, e-temperature recording system), HPO along with pharmacy input must base their approach to validation of such systems on a risk assessment that takes into consideration the intended use of the system and the potential of the system to affect human subject protection and reliability of trial results. These systems must be designed to prevent unauthorised access to the data, maintain data audit trail, maintain adequate backup of the data, safeguard the blinding, and maintain data integrity.⁵

- 3.6 Pharmacy must have suitable archiving arrangement for pharmacy trial files. The system used for archiving must allow for prompt retrieval of any pharmacy study file or of non-study specific documentation (such as pharmacy standard operating procedures, original pharmacy temperature monitoring records and training records of pharmacy staff).⁷

In practice it is desirable for the pharmacy file for a trial to be amalgamated back into the Investigator Site File for archiving purposes. This should be negotiated and agreed with the sponsor or local R&D Department.

4. Pharmacy and Resources

- 4.1 The Chief Pharmacist (or equivalent) must ensure that adequate resources are available to provide a pharmacy clinical trial service so that research does not inappropriately divert pharmacy NHS resources from the provision of routine patient care.¹¹⁻¹³
- 4.2 Pharmacy should receive funding for providing a clinical trial service. This funding should reflect the workload and cover costs involved and is separate to the prescription charge. As of October 2018, NHS England mandates the use of the standard costing methodology (the NIHR Industry Costing Template) to calculate the cost of supporting commercial trials.¹⁴ NHS Research Scotland and NHS Scotland have mandated the use of the NIHR Industry Costing Template since its launch and practice is established in national standard operating procedures. For non-commercial research the attribution of costs over and above usual NHS treatment costs are set out in AcoRD.¹³ It is advisable to maintain records of funding received and research activities undertaken per trial to provide transparent accounts for staffing resource and capacity planning.
- 4.3 For commercial-contract research, HPO must ensure that model Clinical Trial Agreement (mCTA) with trial sponsors include the appropriate fees for pharmacy clinical trial services and that the required pharmacy resources are available and appropriate for the clinical trial.¹⁵
- 4.4 For non-commercial research there must be an agreement in place between the trial sponsor and HPO that describes the obligations and responsibilities of each party. This model agreement for non-commercial research (mNCA) documents the relationship between and the responsibilities of the non-commercial sponsor(s) of a research study and the HPO where the study takes place.¹⁶
- 4.5 A management system should be established within an HPO whereby pharmacy input is actively sought in advance of the HPO agreeing and signing the model CTA.

5. Prescription Charges

- 5.1 Prescription charges apply only to England as they have been abolished in the rest of the UK. Where it is routine practice or policy to apply prescription charges these will also apply to clinical trial medicines unless the subject is exempt, or the clinical trial is placebo controlled.¹⁷
- 5.2 A sponsor may choose to pay the prescription charges on behalf of the subjects in a clinical trial. These charges should be handled separately from clinical trial payments as per department policy.

6. Communication Within and Outside the Healthcare Provider Organisation

6.1 Pharmacy should ensure that an effective working relationship is established with site investigators, research personnel, the Research & Development (R&D) department and other support services, including the clinical research network, to provide a responsive, high quality, comprehensive process for delivering the pharmacy clinical trial service.

A good working relationship should also be established and maintained with sponsors, monitors, auditors and regulatory authorities to:

- Ensure that protocol amendments, approvals and other relevant documents are provided to pharmacy for review of continued capacity and capability before the amendment is implemented.
- Ensure the safe supply of IMPs to clinical trial subjects.
- Ensure that all data and documentation (e.g. pharmacy study file, standard operating procedures) associated with a study are accurate, up-to-date and available for audit or inspection by an appropriate authority.
- Protect and maintain the blinded nature of treatment allocation where this is required.
- Ensure that medicines management systems for IMPs are robust.
- Represent and uphold the interests of the pharmacy and pharmacy professionals in clinical research.
- Ensure that the confidentiality and security of information and data about the subjects and the clinical trial are maintained and respected.
- Ensure any protocol deviations or serious breaches are reported in a timely manner to the research team, trial sponsor and the HPO.

6.2 Pharmacy staff must be aware of UK clinical trial legislation - Medicines for Human Use (Clinical Trials) Regulations 2004 - and subsequent amendments, and GCP¹⁻⁵ and local requirements for the reporting of suspected fraud, misconduct or other incidents involving a breach of the protocol or legislative requirements.¹⁸ If pharmacy staff become aware of any of these they must notify the investigator, sponsor and the local R&D department at the earliest opportunity.

7. Pharmacy and the R&D Department

7.1 Clinical trial pharmacy staff should foster a good working relationship with their local R&D Department. The pharmacy staff will be able to advice on issues such as:

- The source and quality of IMPs including comparators to be used.
- The cost of IMPs.
- The acceptability of the packaging and labelling of IMPs.
- Where the IMP is stored out of pharmacy custody, advice and risk assessment of the storage requirements for the IMPs.
- The regulatory approval process, providing support and assistance where necessary.
- The identification of possible clinical risk issues and how to address these where the use of an IMP may force changes to normal routine practice.
- The regulations and guidelines on GCP and GMP.
- Clinical risk assessments of individual clinical trials and on systems and procedures for HPO own-sponsored clinical trials.
- Health and safety aspects of drug handling, dispensing and reconstitution.

- Legacy after trial closure, i.e. what access will patients have to continuing treatment and what it could cost.
- 7.2 Where appropriate, pharmacy should be involved in the HPO peer review process of clinical trial protocols. Where there is a conflict of interest for pharmacy, it should be declared.

8. Ethics Committee

- 8.1 Ethics committees that are reviewing clinical trials involving IMPs should have a pharmacist as a member.¹⁹ The pharmacist must be aware of, and where appropriate, must declare any possible conflict of interest between her/his role on the ethics committee and involvement in providing pharmacy clinical trial services or in the clinical trial as a researcher/investigator, or any relationship to the sponsor. The ethics committee should ensure that trial subjects are informed about whether they will be able to continue to receive the trial medication at the end of the trial should they gain benefit from it.

9. Risk Management

- 9.1 As for licensed medicines, local risk assessments of new CTIMPs must be carried out. Potential sources of risk include, but not limited to, storage (see section 12.3), dispensing, reconstitution, clinical use, blinding and unblinding and treatment allocation, documentation, cost, and post-trial access to medicines.
- 9.2 Risk management procedures must be in place to minimise identified risks to trial subjects, staff and the organisation.
- 9.3 The risk-adapted approach (MRC/DH/MHRA Joint Project) provides a pragmatic approach to the management of CTIMPs.²⁰ The categorisation is based on the marketing authorisation status of the IMP and standard medical care:

Type A: no higher than the risk of standard medical care

Type B: somewhat higher than the risk of standard medical care

Type C: markedly higher than the risk of standard medical care

This risk assessment approach may be used to simplify the process for initiation and conducting some CTIMPs. It covers: the need for authorisation by the competent authority; the content of the Clinical Trials Authorisation (CTA) application; IMP management; safety surveillance; trial documentation; GCP Inspection.

- 9.4 Pharmacy should implement and document a risk reporting system for IMP-related activities to facilitate risk review and continual improvement.⁵
- 9.5 Pharmacy staff should periodically review risk control measures to ascertain whether the implemented quality management activities remain effective and relevant, taking into account of system changes, and emerging knowledge and experience.⁵

10. Set-up of a Study

- 10.1 Designated pharmacy staff must review each clinical trial protocol to assess and confirm local capacity and capability and cost the work to be undertaken by pharmacy. Where available the Health Research Authority (HRA) single pharmacy technical review should be used to facilitate

local feasibility assessments. In NHS Scotland, the Co-ordinated Pharmacy Review should be available in the absence of an HRA single technical review.

- 10.2 Pharmacy clinical trials staff should participate in investigator meetings or site selection visits and site initiation visits. A pre-initiation meeting is helpful in order to agree the details of the pharmacy arrangements with the sponsor. Pharmacy staff should use their professional expertise to review the protocol and explain the correct use and storage of any IMPs or auxiliary IMPs to other healthcare professionals (e.g. investigators and research nurses) who may not be familiar with these. This has particular importance when the study medication is not stored in pharmacy.
- 10.3 IMPs must be manufactured in accordance with GMP in a unit which holds a manufacturing authorisation.^{1,21-23} In the UK this authorisation is an MIA (IMP) granted by the Medicines and Healthcare Products Regulatory Agency (MHRA). Requirements for other EU states will be detailed in the clinical trial application. IMPs must be labelled in accordance with Annex 13 and certified by a QP(IMP) for release.^{1,21,22} The distinction between manufacture and assembly and the circumstances where a QP (IMP) is not required are defined in The Medicines for Human Use (Clinical Trials) Regulations 2004.¹ Regulation 37 of The Medicines for Human Use (Clinical Trials) Regulations 2004 provides an exemption from the need for hospitals and health centres participating in a trial to hold an MIA(IMP) in order to *assemble* IMPs for use in that trial.¹ Licensed medicines (with a UK or EEA Marketing Authorisation) may be used, unmodified, as IMPs without the requirement for QP (IMP) certification for release.¹ A risk assessment will determine whether such products require additional, clinical trial-specific labelling to comply with the regulations.
- 10.4 Pharmacy should request samples of the packaging and labelling of IMPs from the sponsor in advance of local confirmation of capacity and capability. Confirmation should be sought from the sponsor that additional routine dispensing labels may be added to the product if required. If samples are not available in advance pharmacy should check the suitability of the IMP packaging and labelling when the IMP is received on-site and prior to being issued. Sufficient time should be allowed for a risk assessment of the product and for additional pharmacy labels to be produced if necessary prior to any dispensing. Pharmacy should check that the packaging is child resistant, where appropriate, and that the label on the IMP complies with Annex 13 and with all other applicable legislation.^{1,21,22} Pharmacy should also ensure that the labelling of the dispensed products is legible and understandable by the subject.
- 10.5 Where drug accountability forms, prescription forms and other associated forms are supplied by the sponsor, the pharmacy should assess their appropriateness for the data they are designed to capture and for their suitability for use within the pharmacy.⁷ The pharmacy may instead use their own documentation with the sponsor's agreement.
- 10.6 With the information obtained in 10.4 and 10.5, local pharmacy procedures for the study should then be prepared and approved, in accordance with local practice, prior to the treatment of the first subject. It can be helpful to use the dispensing of the first prescription for a trial as a 'pilot' to ensure the procedures are applicable to the 'real life' situation.
- 10.7 Prior to the commencement of a clinical trial it should be determined whether adequate arrangements will be made to ensure that continuing treatment with the IMP(s) will be available to trial subjects if the trial IMP proves to be beneficial.
- 10.8 Pharmacy should agree with the sponsor whether unissued IMPs and returned used IMPs returned by clinical trial subjects are to be returned to the sponsor or disposed of locally, in

accordance with the sponsor's instructions and Trust procedures. If unused IMP is returned to the sponsor, the subject's identifiable information must be fully removed, to maintain confidentiality.

- 10.9 Although unblinding is the investigator's responsibility and decision, the pharmacy may be required to hold code break (unblinding/unmasking) envelopes or to have access to a telephone or web-based system for emergency unblinding of a subject's trial treatment. The code break procedure for each trial should be documented and tested prior to the first subject being recruited. In circumstances when the pharmacy does not hold the code break the pharmacy should ensure that there is a system in place for providing 24-hour cover for investigators or delegated medical staff to access the code-break for a clinical trial.

11. Approvals

- 11.1 HRA Approval brings together the assessment of governance and legal compliance, undertaken by dedicated HRA staff, with the independent ethical opinion by REC. HRA and Health and Care Research Wales (HCRW) Approval applies to all project-based research taking place in the NHS in England and Wales. It replaces the need for local checks of legal compliance and related matters by each participating organisation in England and Wales. This allows participating organisations to focus their resources on assessing, arranging and confirming their capacity and capability to deliver the study. The Generic Review process conducted in Scotland is considered to be equivalent to the HRA review process for England and Wales. R&D Generic and Local Permissions for Scotland are coordinated via the NHS Research Scotland Permissions Co-ordinating Centre.

- 11.2 Prior to the commencement of a clinical trial and the dispensing of any IMPs, pharmacy must be satisfied that the clinical trial has:

- Appropriate regulatory documentation in place i.e. MHRA Clinical Trial Authorisation
- A favourable opinion by REC
- HRA approval or the equivalent from any other devolved administration in the UK
- Confirmation of capacity and capability from the local R&D department

In addition, the pharmacy must be in receipt of the final approved version of the protocol and any approved amendments prior to dispensing any IMPs. Pharmacy should have access to the latest version of the investigator brochure (documenting its location with a file note if not kept in the pharmacy file).

12. IMP Management

- 12.1 The pharmacy should have written clinical trials standard operating procedures (SOPs) to cover the following essential procedures:

- Pharmacy approval of a clinical trial
- Receipt and recording of the safe delivery of IMPs
- Safe handling and storage of IMPs
- Temperature monitoring and reporting of temperature deviations
- Risk assessment of storage areas for IMPs outside pharmacy
- Quarantine of IMPs
- Expiry date relabelling
- Unblinding

- Preparation and dispensing of IMPs in accordance with professional standards (including dispensing against an appropriate prescription, maintaining drug accountability records and ensuring that all IMPs are labelled with the appropriate pharmacy label)
- Management and responsibilities of clinical trial stock and dispensing activities in an aseptic/ manufacturing unit
- Return and disposal of unused IMPs
- Reconciliation of IMPs
- Drug alerts and recalls of IMPs
- Maintaining a pharmacy study file
- Training of clinical trial pharmacy staff
- Archiving of clinical trials documentation

SOPs must be authorised and reviewed at regular intervals and when new legislation or guidance is published. Trial-specific SOPs must be reviewed with each protocol amendment. SOPs and other documents produced by pharmacy must be version-controlled to ensure that the correct documents are used. Superseded documents must be clearly marked as such.

12.2 Pharmacy is responsible for keeping accurate records with sufficient information to provide a full audit trail from the receipt of the IMPs to their issue and/or return and/or removal from site or destruction.^{4,5} This source data should be attributable, legible, contemporaneous, original, accurate, and complete. Any changes and alterations to source data should be traceable, must not obscure the original entry, and should be explained if necessary.⁵

12.3 Where possible, IMPs should be stored in pharmacy. However, it may be clinically necessary to store IMPs on wards or in other departments (e.g. if IMPs are to be used in emergency situations or for inpatients). It may also be logistically necessary to store IMPs outside of pharmacy (e.g. ATIMPs will routinely be required to be stored within facilities that have liquid nitrogen tanks – often Stem Cell Laboratories or Cellular Therapy Units). If IMPs are to be stored outside of pharmacy, a risk assessment should be performed to determine the following:

- Where the IMP will be stored on the ward / department
- If the IMP storage is suitable, for example if the IMP storage is secure and separate from routine stock
- If the storage area temperature is within the appropriate range, and regularly monitored
- What records will be maintained and by whom

This process should be documented and filed in the pharmacy file.

Pharmacy must ensure that any IMPs stored outside of pharmacy are stored appropriately throughout the conduct of the trial according to local policy. Where storage conditions are not met or associated documentation (eg. temperature logs or IMP accountability) is not completed consideration should be given to returning the IMP to a suitable facility within pharmacy until the issues are resolved. Care should be taken that the impact to the trial/ product/ supply of medication to trial subjects is minimised.

12.4 It is good practice for pharmacy staff to assess whether any IMPs in the possession of a trial subject and intended for continued use when the subject is admitted to hospital are suitable for use. Pharmacy staff, when made aware, should ensure that the investigator is notified of these hospital admissions. This may require contacting an investigator who is located at a different hospital to the one of admission.

- 12.5 Dispensed IMPs should be labelled with the trial subject's name or initials, and date of dispensing. Any post-certification labelling should be agreed with the sponsor. However, to maintain confidentiality, the trial subject's identity must be fully removed when the IMP is returned to the pharmacy and before onward return to the sponsor.
- 12.6 Trial subjects should be counselled on the correct use of the IMP. This should reflect the written information provided e.g. trial-specific Patient Information Sheet, as licensed IMP may be used outside of the terms of its marketing authorisation.
- 12.7 Pharmacy staff must promptly notify all reported adverse events experienced by trial subjects to the investigator.

13. Prescriptions for IMPs

- 13.1 Only qualified and registered medical practitioners and health care professionals who are supplementary or independent prescribers* can prescribe IMPs.^{7,24,25} All prescribers for a clinical trial must be named on the delegation log for the study which is retained within the investigator site file. HPO must assess the risk and decide whether prescribing by non-medical supplementary or independent prescribers is acceptable and in line with local policy.

*If a non-medical supplementary or independent prescriber prescribes for a clinical trial, then the pharmacy department should be provided with written confirmation of this arrangement signed by the principal investigator and the sponsor. This document should be included in the pharmacy study file and may be in the form of a delegation log.

- 13.2 Although not a requirement of the Clinical Trials Regulations¹, it is good practice for IMPs to be prescribed on a prescription form (paper or electronic) or a hospital drug chart.⁷ A record in a patient's medical notes or clinical trial case report form (CRF) by the investigator (or delegated prescriber) is also acceptable, however local record keeping practice may require the organisation to document on a prescription form as with other medicinal products. Auxiliary Medicinal Products (AxMPs formerly referred to as Non-IMPs) however fall under general medicines legislation and must comply with the requirements of The Human Medicines Regulations 2012.^{25,26}
- 13.2 Where possible, study-specific clinical trial prescription forms should be used to facilitate the prompt identification of the clinical trial and dispensing procedures and to reduce the risk of dispensing errors.
- 13.3 Where an IMP is a licensed medicinal product used in the trial within its marketing authorisation, clinical trial labelling requirements as stipulated by the Medicines for Human Use (Clinical Trials) Regulations is not required.^{1,21,22} In this situation, the IMP can be dispensed against a normal prescription and labelled in accordance with the requirements for dispensed relevant medicinal products.^{1,25} This activity is covered by Regulation 46 of the Medicines for Human Use (Clinical Trials) Regulations (as amended).^{1,25}
- 13.4 It is acceptable to use electronic prescribing system for IMPs prescribing.⁷ Pharmacy must implement a robust internally documented quality control process when using such systems and should be aware of how information is managed and archived from such systems as this constitutes source data.

- 13.5 It is essential that prescriptions for IMPs clearly identify the clinical trial, the subject, and product(s) required. When an IMP is prescribed in an in-patient setting, the hospital drug chart should clearly identify the clinical trial and the IMP and include the words "Clinical Trial".
- 13.6 Where possible, IMP doses should be validated by a pharmacist before dispensing to ensure that the IMP is being prescribed in accordance with the approved protocol and that the prescribed has been appropriately delegated this activity.
- 13.7 Prescription charges may apply (see section 5).

Glossary of Terms (For a full explanation of each term consult the appropriate reference source):

ADVANCED THERAPY MEDICINAL PRODUCTS (ATMPs) Gene therapy, somatic cell therapy and tissue engineered products.

ADVANCED THERAPY INVESTIGATIONAL MEDICINAL PRODUCTS (ATIMPs) An advanced therapy medicinal product (ATMP) tested or used within a clinical trial.

AUXILIARY MEDICINAL PRODUCT (AxMP) A medicinal product used for the needs of a clinical trial as described in the protocol, but not as an investigational medicinal product (IMP). Examples include rescue medication, challenge agents, background treatment and medicines used to assess end points in a clinical trial. Concomitant medications are not classed as auxiliary medicinal products.

CASE REPORT FORM (CRF) A case report form is a paper or electronic document specifically used in clinical trial research. The Case Report Form is designed to record all of the protocol required information to be reported to the sponsor on each trial subject.

CLINICAL TRIAL OF AN INVESTIGATIONAL MEDICINAL PRODUCT (CTIMP) A interventional trial of a medicinal product that is conducted in accordance with the Medicines for Human Use (Clinical Trials) Regulations and subsequent amendments.

DELEGATION LOG A list of roles and responsibilities for the various members of the research team that are delegated and authorised by the Chief or Principal Investigator at the site.

GOOD CLINICAL PRACTICE (GCP) A set of internationally recognised ethical and scientific quality standards which must be observed for designing, conducting, recording and reporting clinical trials that involve the participation of human subjects.

GOOD MANUFACTURING PRACTICE (GMP) That 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.

HEALTHCARE PROVIDER ORGANISATION (HPO) Any healthcare organisation responsible for provision of healthcare including medicines and IMPs or a pharmacy providing medicines and IMPs, to patients directly or via another HPO.

HEALTH RESEARCH AUTHORITY The Health Research Authority (HRA) is a NHS organisation established on 1st December 2011 as a Special Health Authority. The purpose of the HRA is to protect and promote the interests of patients and the public in health research.

INVESTIGATOR¹ An authorised health care professional responsible for the conduct of a clinical trial at a clinical trial site. If this trial is conducted by a team of authorised health professionals at a clinical trial site, the investigator is the leader responsible for that team. Often the investigator within the hospital setting is a medically qualified consultant and in primary care, a medically qualified general practitioner.

INVESTIGATOR BROCHURE¹ A document of the clinical and non-clinical data on the investigational product(s) which is relevant to the study of the investigational products in human subjects.

INVESTIGATIONAL MEDICINAL PRODUCT (IMP)¹ A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial.

MHRA Medicines and Healthcare products Regulatory Agency

MONITOR A person who has been trained to oversee the progress of a clinical trial, and to ensure that the clinical trial is conducted in accordance with the clinical trial protocol, standard operating procedures, good clinical practice and applicable regulatory requirements.

NATIONAL PHARMACY CLINICAL TRIALS ADVISORY GROUP (NPCTAG) A partnership group of the Royal Pharmaceutical Society established in 2010. Membership includes representatives from a range of hospital pharmacy disciplines and other relevant specialist groups, MHRA and the NIHR. The group's objectives are to provide advice to NHS pharmacy services, to the NIHR Clinical Research Networks Coordinating Centre, to support education & training of pharmacy staff, and to provide a forum for communication with MHRA about clinical trial issues.

PHARMACY STUDY FILE The pharmacy file is a sub folder of the Investigator Site File which contains all the documents pertaining to the IMP management. It is kept in Pharmacy throughout the trial, until the close out visit where it may be reconciled with the Investigator Site File or archived in pharmacy in accordance with the clinical trial agreement. This usually includes, but is not limited to clinical trial protocol and amendments, investigator brochure, copies of approval documents (ethics, MHRA, NHS R&D), clinical trial agreement, pharmacy dispensing procedures, pharmacy signature list, monitoring visit log, drug accountability forms, receipt and return of IMPs, unblinding procedure, key contact details, subject I.D. logs and any relevant correspondence (including hard copies of e-mails).

PROTOCOL¹ A document that describes the objective(s), design, methodology, statistical considerations, and organisation of a trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol reference documents.

RESEARCH ETHICS COMMITTEE (REC) In the NHS NRES Research Ethics Committees are established by The Health Research Authority. A REC is an independent body consisting of healthcare professionals and lay members, whose responsibility it is to safeguard the rights, safety, dignity and well-being of people participating in research in the NHS, and to provide public assurance of that protection by, among other things, expressing an opinion on the trial protocol, the suitability of the investigators and the adequacy of facilities, and on the methods and documents to be used to inform trial subjects and obtain their informed consent.

SERIOUS BREACH A breach of a clinical trial protocol or good clinical practice in connection with a trial, which is likely to affect, to a significant degree, the safety or physical or mental integrity of trial subjects or the scientific value of the trial.

SPONSOR A sponsor is, in relation to a clinical trial, a person/organisation who takes responsibility for the initiation, management and financing (or arranging the financing) of that clinical trial.

References:

1. The Medicines for Human Use (Clinical Trials) Regulations 2004 ([SI 2004/1031](#))
2. The Medicines for Human Use (Clinical Trials) Amendment Regulation 2004 as amended ([SI 2006/1928](#), [SI 2006/2984](#) and [SI 2008/941](#))
3. The European Parliament and the Council of the European Union. (2001) [Directive 2001/20/EC](#) on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use.
4. The Commission of the European Communities. (2005) [Directive 2005/28/EC](#) laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products.
5. European Medicines Agency. (2016) [Guideline for good clinical practice E6\(R2\)](#).
6. The European Parliament and the Council of the European Union. (2007) [Regulation \(EC\) No 1394/2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation \(EC\) No 726/2004](#).
7. The Medicines for Healthcare products and Regulatory Agency. (2012) Good Clinical Practice Guide.
8. Health Research Authority & The Medicines for Healthcare products and Regulatory Agency & UK Health Departments. (2017) [Joint statement on the application of good clinical practice to training for researchers](#).
9. The Medicines for Healthcare products and Regulatory Agency. (2014) [Competence in Clinical Trials – the Regulators Perspective](#).
10. Royal Pharmaceutical Society. (2019) [Professional guidance on the safe and secure handling of medicines](#).
11. Department of Health. (1997) HSG (97)32: Responsibilities for meeting Patient Care Costs associated with Research and Development in the NHS.
12. UK Health Departments and Health Research Authority. (2018) [UK Policy Framework for Health and Social Care Research](#).
13. Department of Health and Social Care. (2012) [Attributing the costs of health and social care research and development](#) (AcoRD).
14. NHS England. (2018) [National Directive on Commercial Contract Research Studies](#).
15. The Association of the British Pharmaceutical Industry and Department of Health. (2018) [Commercial Model Clinical Trial Agreements \(mCTA and CRO-mCTA\)](#).
16. Department of Health & Partners. (2018) [UK-wide model Non-Commercial Agreement \(mNCA\)](#).
17. Department of Health. (1975) Prescription Charges for Drugs Given to Outpatients in Clinical Trials (DS21/75, ref. G/P25/66B).
18. The Medicines and Healthcare products Regulatory Agency. (2018) [Guidance for the Notification of Serious Breaches of GCP or the Trial Protocol. Version 5](#).
19. UK Health Departments and Health Research Authority. (2018) [Standard Operating Procedures for Research Ethics Committees](#).
20. MRC/DH/MHRA Joint Project (2011) [Risk-adapted Approaches to the Management of Clinical Trials of Investigational Medicinal Products](#).
21. The Commission of the European Communities. (2003) [Directive 2003/94/EC](#) laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use.
22. European Commission. (2010) [Guidelines to Good Manufacturing Practice Medicinal Products for Human and Veterinary Use, Investigational Medicinal Products. Vol. 4, Annex 13](#).
23. The Medicines and Healthcare products Regulatory Agency. (2017) Rules and Guidance for Pharmaceutical Manufacturers and Distributors.
24. The Prescription Only Medicines (Human Use) Amendment Order 2003 ([SI 20103/696](#))
25. The Human Medicines Regulations 2012 ([SI 2012/1916](#))
26. Recommendations of the expert group on clinical trials for the implementation of Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use. (2017) [Auxiliary Medicinal Products in Clinical Trials](#).

Useful Web Links

ABPI Guidelines

<http://www.abpi.org.uk/what-we-do/research-medical-and-innovation/clinical-research-and-late-phase-clinical-trials/>

Attributing the costs of health and social care research

http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_133882

Auxiliary Medicinal Products

https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/2017_06_28_recommendation_on_axmps.pdf

Clinical Trials Tool Kit (NIHR)

www.ct-toolkit.ac.uk

Direct to Patient Distribution of IMPs

<https://drive.google.com/file/d/0B5U38hPHhLioWHZESmloenRIUHc/view>

EudraLex Clinical Trials Guidelines - European Commission

http://ec.europa.eu/health/documents/eudralex/vol-10/index_en.htm

GCP Delegation and Training Decision aid

<https://sites.google.com/a/nih.ac.uk/dandtda/>

GCP training - NIHR

<https://www.nihr.ac.uk/our-research-community/clinical-research-staff/learning-and-development/national-directory/good-clinical-practice/>

MHRA GCP pages

<https://www.gov.uk/government/collections/good-clinical-practice-guidance-and-inspections>

MHRA Clinical Trials for Medicines pages

<https://www.gov.uk/topic/medicines-medical-devices-blood/clinical-trials-investigations>

MHRA Inspectorate Blog: Manufacture of Investigational Medicinal Products - FAQs

<https://mhrainspectorate.blog.gov.uk/>

Model Clinical Trial Agreement

<https://www.myresearchproject.org.uk/help/hlptemplatesfor.aspx#mNCA>

Position statement on the use of dispensing label on investigational medicinal products in clinical trials

<https://drive.google.com/file/d/0B5U38hPHhLiodmVOXzF1eVBvblppSXY3MFgyRE00eIBLclJR/view>

Risk-adapted Approaches to the Management of Clinical Trials of Investigational Medicinal Products

https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/343677/Risk-adapted_approaches_to_the_management_of_clinical_trials_of_investigational_medicinal_products.pdf

Supply of aseptically - prepared doses of IMPs across legal boundaries

<https://drive.google.com/file/d/0B70TkSojU9fiSU1oZ0tYRjI3UXlpbFFIZnNSZm1SRlJ1bEpz/view>

Chief Scientist Office

<http://www.cso.scot.nhs.uk/>

Department of Health

www.dh.gov.uk

Health and Care Research Wales

<https://www.healthandcareresearch.gov.wales/>

Health Research Authority

<http://www.hra.nhs.uk>

HRA Research Ethics Service

<https://www.hra.nhs.uk/about-us/committees-and-services/res-and-recs/>

Institute of Clinical Research

<http://www.icr-global.org/>

Medicines and Healthcare products Regulatory Agency (MHRA)

<https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency>

National Institute for Health Research (NIHR)

www.nihr.ac.uk

NHS Research Scotland

<http://www.nhsresearchscotland.org.uk/>

NIHR Clinical Research Network

<https://www.nihr.ac.uk/about-us/how-we-are-managed/managing-centres/crn/>

NIHR Clinical Research Network: Research and Pharmacy

<https://sites.google.com/nihr.ac.uk/researchandpharmacy/home>

Northern Ireland Clinical Research Network (NICRN)

<http://www.nicrn.hscni.net/>

Research and Development Forum

www.rdforum.nhs.uk

Royal Pharmaceutical Society

www.rpharms.com

RPS National Pharmacy Clinical Trials Network

<https://www.rpharms.com/network/activity/groupid/60>

The Medical Research Council

www.mrc.ac.uk