Chapter 5

Clinical trials

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Clinical trial regulations

Clinical trials form a fundamental part in the research, development, and licensing of new medicines. Research of how the drug interacts in humans is essential to ensure safe and effective medicines are licensed as new treatments. It is an exciting and varied role at the cutting edge of modern research with trials ranging across all therapeutic specialities. Clinical Trial pharmacists are therefore required to have a broad clinical knowledge and a specialist knowledge of the regulations that clinical trials have to follow.

New regulations were introduced in 2004 to help regulate the field of clinical trials in human subjects. The European Clinical Trials Directive (2001/20/EC) was implemented across the European Union (EU) in 2004 and transposed into local law (Statutory Instrument (SI)1031 in the UK). Its primary aim is to ensure that patient safety is paramount in all clinical trials. Its secondary aim is to ensure the integrity of the data that is collected so that the decisions that are made from the outcomes of the trial are representative of true effects of the medicine and not due to bias in the trial.

All clinical trials involving investigational medicinal products (unlicensed drugs in a clinical trial) have to follow the principles outlined as good clinical practice (GCP). This is a defined quality standard devised by the International Conference on Harmonisation (ICH) which provides guidelines on how clinical trials should be conducted and defines the roles and responsibilities of clinical trial sponsors, clinical research investigators, and monitors.

GCP aims to ensure that the safety of the patient and the integrity of the data collected are paramount at all times. The guidelines include protection of the human rights of subjects in a clinical trial and provide assurance of the safety and efficacy of the newly developed compounds. Everyone involved in running a clinical trial (clinicians, nursing staff, pharmacists, radiologists, etc.) must have GCP training to ensure that they complete their role to the required standard.

Licensing of a clinical trial

Before a clinical trial starts, the following authorizations/approvals must be obtained:

- Clinical trial authorization from a competent authority—in the UK this is the Medicines and Healthcare Products Regulatory Agency (MHRA).
  - The competent authority must consider the application within 60 days (maximum). This application can run in parallel with the ethics opinion.
  - This application outlines the design and outcomes of the trial so that the competent authority can assess whether the trial safe to conduct.
  - The competent authority must notify the sponsor within 35 days if there are grounds for refusal.
- A favourable opinion from one ethics committee, if the trial is deemed ethical to complete.
- Permission from the NHS trust for the trial to take place within that trust (R&D approval) for each site. This now also includes an opinion on the suitability of the local investigator and facilities (used to be obtained from the local research ethics committee).
- A EudraCT number must be obtained from the EudraCT database. The EudraCT number is a unique number allocated to each trial by the competent authority (MHRA). The EudraCT database registers details of all trials approved in the EU.
- The MHRA enforces these standards in the UK by performing inspections of GCP and good manufacturing practice (GMP). The MHRA is also responsible for ensuring that suitable safety monitoring occurs in all clinical trials.
- There is no distinction between commercial and non-commercial trials, and there are no exemptions for any trials using a drug that is prescribed outside of its licence.
- All clinical trials will follow a protocol which will contain detailed information about the design of the trial and the drugs involved. All processes and requirements outlined in the trial must be followed as the protocol will have been written in compliance with GCP to ensure the study follows the required regulations.

Clinical trial development phases

The development of new drugs has four phases of clinical trials in humans. These trials can only occur following extensive modelling of the effects of drugs and testing in animals.

Phase I trials

- First time that the drug is given to humans.
- Provide data on the tolerability of a range of doses and assess Maximum tolerated dose (MTD) and toxicity of a drug used for the first time in humans.
- Provide data on pharmacokinetics and pharmacodynamics of the drug.
- Often designed to start at a single low dose, which is gradually increased depending on the side effects until the MTD is reached.
- Usually only involve small numbers of participants, and are usually undertaken in healthy volunteers unless it is unethical (e.g. cytotoxic drugs must be tested in cancer patients).

Phase II trials

- Usually the first time that the drug is given to a patient with the disease state it is thought to treat (with the exception of anti-cancer drugs). Often called proof of concept studies.
- Assess efficacy and define therapeutic dose range and dosing regimen for a specific indication, with minimum side effects.
- Provide further information on safety, pharmacokinetics, and pharmacodynamics in the presence of the disease process.
- Provide information on the doses that should be tested in phase III studies.
- Relatively small numbers of patients are studied under close supervision, usually by specialized investigators.

Phase III trials

- Assess treatment outcomes in a variety of patients approximating to the population of patients who will receive the drug once it is launched.
- Often compare new treatments with existing treatments.
- Aim to demonstrate long-term safety and tolerance.
- Undertaken in large numbers of patients, often in multiple centres across the globe.

Phase IV trials

- Performed after a product licence is obtained.
- Aim to investigate the incidence of relatively rare ADRs or to compare drugs with comparative treatments, often to extend the range of approved indications.

Trial design, randomization, and blinding

- The most robust trials include blinding and randomization.
- Controlled clinical trials compare a test treatment with another treatment or placebo agent. These can be designed as parallel or crossover studies.
  - Parallel studies assign patients to receive one study treatment only. They do not receive the other agent during the trial, i.e. the two groups of patients continue in the study 'in parallel'.
  - Crossover studies assign patients to receive one study treatment for a set period of time and, following a washout period, the same patients receive the second treatment.
- Randomized trials assign treatments to successive patients in a predetermined random way.
  - Randomized trials aim to show that one treatment is superior to another, and they avoid investigator bias.
  - Patients are randomly allocated to the new drug, or an existing recognized treatment, or a placebo agent, which provides comparisions for treatment outcomes.
- These trials are often blinded.
  - Open-label studies—no one is blinded and everyone is aware of which treatment has been administered.
  - Single-blind study—the investigator or assessor does not know which treatment has been administered but the patient is aware.
  - Double-blind study—neither the subject nor the investigator knows which treatment has been given. This is the preferred type of study. Often the pharmacist is the only person who is aware of which subject is receiving which treatment. ► Care must be taken to ensure that participants in the trial are not inadvertently unblinded as this can introduce bias to the outcomes of the study and invalidate the trial.

Controlled randomized double-blind parallel-group studies are the reference standard for comparing treatments.

- There can be problems with blinding in a clinical trial.
  - If the drugs have obvious differences—e.g. IV versus oral forms, different looking or tasting tablets/capsules.
  - When ADRs are associated with only one arm of the trial.
  - Ethical issues of withholding information from patients on the exact treatment they are receiving.
- When trials are blinded, mechanisms must be in place (ideally accessible 24 hours a day) to ensure that individuals can be unblinded in the case of emergencies.
- If an attending clinician needs information about a patient participating and needs information about treatment options, the worst-case scenario is usually to treat as if the patient is on active treatment.
  - Many clinical trials now have web pages containg information on the treatments involved and contact information for emergencies. There is usually a study identifier (a shortened name of the title) which can be researched on Google to provide additional information.

European Clinical Trials Directive

The Clinical Trials Directive provides regulations that need to be followed for all clinical trials to ensure patient safety. The Clinical Trials Directive was first implemented in 2004 and there have been three subsequent amendments to ensure that it covers current requirements and has been expanded to include blood products used in a clinical trial. The latest amendment was completed in 2008 and was transposed in the UK in SI 2008/941.

There are some specific requirements within the Directive that are particularly relevant to pharmacy or are in areas where pharmacists can help ensure compliance:

- Trials have to be under the control of a named sponsor. The sponsor is the person legally responsible for the conduct of a clinical trial. This is usually the chief executive of the body registered as the sponsor (this can be a pharmaceutical company or a clinician in a hospital trust or university department). This person is responsible for ensuring that the required systems are in place and that all the regulations are complied with.
- All staff involved in clinical trials must have evidence of suitable training in their CPD log.
- All sites who manufacture, label, or assemble clinical trial materials must hold an Investigational Medicinal Product Manufacturing Authorization (MIA(IMP)).
- Hospitals or healthcare centres with patients who are participating in a clinical trial fall under the Section 37 exemption within SI 1030. This allows a pharmacist (or a person under their authorization) to reconstitute, assemble, or label a clinical trial material without this license. This does not allow pharmacies to manufacture a drug. Definitions of what constitutes manufacture and what is reconstitution are available from the MHRA.
- An individual in the pharmacy department will be named as the responsible pharmacist for clinical trials within that hospital or trust. This pharmacist must liaise with the trust's research and development department to ensure that the trials are valid and acceptable. They are also the contact person for any pharmaceutical company or investigator who wish to run a clinical trial within that hospital.
- Clinical trial protocols must be made available to the pharmacy department in advance of consideration by an ethics committee, so that the practical details, such as doses and method of administration, packaging, labelling, and study documentation appropriate for each individual trial, can be checked. The protocol must specify the duration of and responsibility for the storage of all pharmacy records relating to the trial.
- Failure to comply with the EU clinical trials directive is a criminal offence.
- On completion of a clinical trial the sponsor must notify the competent authority within 90 days of the conclusion of the trial.

  - If the trial terminates early, the sponsor must notify the competent authority within 15 days.
- The competent authority can suspend or terminate any trial if there are doubts about the safety or scientific validity.

In summary, the Clinical Trials Directive sets standards to ensure the following.

- Safety of clinical trial participants.
- Quality assurance of clinical trials and investigational medicinal products (IMPs).
- An appropriate regulatory approval system for clinical trials in the EU.
- Ethics committees were established on a statutory basis.
- Appropriate requirements for the manufacture, import, and labelling of IMPs.
- Manufacture and labelling of clinical trial drugs are compliant with GMP.
- Adequate safety monitoring of patients participating in trials.
- Procedures for reporting and recording ADRs.

Clinical trials: hospital pharmacy guidance

All investigational medicinal products (IMPs) used in a clinical trial should be received from an approved EU supplier and must be verified by a qualified person (QP) from within the EU. Any supplies manufactured outside the EU must be imported into the EU with an import licence.

Receipt of supplies

The pharmacy department is responsible for maintaining the traceability of all IMPs used in the trial.

- All clinical trial supplies should be checked on receipt to ensure that they have been received in good condition and are in accordance with the shipping paperwork.
- Receipt of supplies may need to be acknowledged. This can be done using an electronic system or by faxing the paperwork back to the company who shipped the drug. This is to ensure that the supplies reached their intended destination.

Storage and handling

- All IMPs must be handled by the pharmacy department in a hospital/trust.
- IMPs must be kept in a separate secure storage area, with sufficient segregation to ensure that there is no confusion between trial materials.
- The designated pharmacist should ensure that the formulation, presentation, and storage of clinical trial medications are appropriate.
- Records of storage conditions must be kept.
- Clinical trial medication must be dispensed against appropriate prescription forms, which have been agreed by the trial investigators and pharmacy department and which help to identify clearly that the subject is participating in a clinical trial.
- Each clinical trial drug prescription must contain the agreed title of the study and a protocol number unique to the study to enable the study to be easily identified and avoid confusion.
- The pharmacy department should be involved in the reconciliation and disposal of unused medication. Guidance is available from the regional quality assurance pharmacists' document on waste disposal.

Labelling, packaging, and stability issues

- All IMP labels must comply with labelling requirements for IMPs, as outlined in Annex 13 of the GMP guide.
- Pharmacists, and those working under their supervision, do not need to hold a manufacturing authorization to repackage or change the packaging of clinical trial materials if this is done in a hospital or health centre for patients of that establishment.

Documentation and records

- The pharmacy department must keep appropriate records of the dispensing of clinical trial drugs and detailed drug accountability.

- Clinical trial documentation should be retained in the pharmacy for the life of the trial, and must be retained for a minimum of 15 years and in the case of a paediatric trial until the subject is 21 years of age.
- All training must be documented and available for inspection. Only people who are suitably trained in the trial procedures should be involved in the running of the trial.
- Clinical trial randomization codes should be held in the pharmacy department. Arrangements for the codes to be broken outside normal pharmacy working hours must be made. Criteria for code breaking should be available and records made in the relevant trial documentation.
- Departmental standard operating procedures must be in place, which are suitably version-controlled and reviewed at regular intervals.

Charging for clinical trials

- The pharmacy department should have a standard method of charging for clinical trials, which has been agreed with the R&D department.
- Arrangements should be made for the levy of prescription charges in accordance with current guidance.
  - Prescription charges do not apply in trials where patients could receive a placebo substance.
  - A prescription charge should be levied (subject to the usual prescription charge exemption criteria) for trials comparing active substances or different doses of an active substance.

Ethical committees

The EU directive (2001/20/EC) ensures that there are national ethics committees operating within a legal framework, with firm deadlines for approval. The UK ethics review system is the National Research Ethics Service (NRES).

The composition of a research ethics committee is as follows.

- 12–18 members (lay and medical).
- Balanced age and gender distribution.
- Subcommittees encouraged.
- Lead reviewers suggested.
- Quorum of seven members stipulated and defined.
- Co-opted members allowed, as defined, to ensure the balance of the committee is maintained.

Ethics committees consider the following.

- The relevance of the clinical trial and trial design.
- Whether the evaluation of the anticipated benefits and risks are satisfactory and conclusions justified.
- The protocol.
- The suitability of the investigator and supporting staff.
- The Investigators' Brochure (document that details results of previous trials and the chemical composition of the IMP).
- The quality of the facilities.
- The consent form and patient information sheet.
- The procedure to be followed for obtaining informed consent.
- Justification for research on persons incapable of giving informed consent.
- The arrangements for the recruitment of subjects.
- Provision for indemnity or compensation in the event of injury or death.
- Insurance or indemnity to cover the liability of the investigator and sponsor.
- The arrangements for rewarding or compensating investigators and trial subjects, including the amount, and the relevant aspects of any agreement between the sponsor and the site.

Timelines for ethics committees

- Ethics committees meet monthly.
- The ethics committee has a maximum of 60 days from the date of receipt of the valid application to give its 'reasoned opinion'.
- Ethics committees must give favourable opinions within 35 days.
- There might be a single request for supplementary information.
- There is no extension to the 60-day period except for trials involving gene therapy, somatic cell therapy, or xenogenic cell therapy.

Pharmacists advising ethics committees

Pharmacists advising ethics committees should be able to use their pharmaceutical expertise to advise on issues including the following.

- Quality assurance.
- GCP issues.
- GMP issues.
- Storage.
- Issues surrounding drug administration—e.g. blinding.
- Monitoring ADRs.
- Clinical trial design and randomization.
- Licensing arrangements for the trial.
- Indemnity arrangements for the trial.
- Safety and efficacy of any drugs involved.
- Appropriateness of the proposed dosage regimens.
- Appropriateness of the formulation.
- The method of monitoring compliance with drug regimens.
- Patient education.
- Continuing supply of medications for 2 years following the trial.
- Availability of a QP (if required).

Further reading

Medicines Healthcare Regulatory Agency: www.mhra.gov.uk.
Clinical Trials Toolkit: www.ct-toolkit.ac.uk.
NRES website: www.nres.npsa.nhs.uk.
Royal Pharmaceutical Society: www.rpharms.com.
European Clinical Trials Directive (2001/20/EC).
The Medicines for Human Use (Clinical Trials) Regulations 2004 – SI 2004/1031.
The Medicines for Human Use (Clinical Trials) Amendment Regulations 2006–SI 2006/1928..
The Medicines for Human Use (Clinical Trials) Amendment (No. 2) Regulations 2006–SI 2006/2984.
The Medicines for Human Use (Clinical Trials) and Blood Safety and Quality (Amendment) Regulations 2008 – SI 2008/941.
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Chapter 6

Controlled drugs

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Suspected loss of controlled drugs within hospitals

Ward or clinic level

On discovering a discrepancy in a stock balance two nurses, midwives, or operating department practitioners (ODPs) must immediately check the following.

- All requisitions received have been entered on the correct page of the record book(s).
- Administered controlled drugs prescribed for in-patients have been entered into the Controlled Drug Record Book (or Patients' Own Controlled Drug Record Book).
- No item has been accidentally put in the wrong place or cupboard.
- All calculations of previous balance checks are correct.

If the error or omission is traced, the two nurses, midwives, or ODPs must make an entry in the Controlled Drug Record Book (or the Patients' Own Controlled Drug Record Book), clearly stating the reasons for the entry and the correct balance, and sign the entry.

If no reason for the error or omission is found it must be reported to the ward pharmacist (if available—resident pharmacist out of hours) without delay, and an incident form and suspected loss of controlled drug form completed.

If the pharmacist confirms the discrepancy, the Accountable Officer must be informed immediately by the pharmacist.

The Health Act 2006 created a new role of Accountable Officer for controlled drugs who is charged with the responsibility for the safe, appropriate, and effective management and use of controlled drugs within their organization.

It is the responsibility of the Accountable Officer or Chief Pharmacist to inform the police if criminal activity is reasonably suspected. The police should NOT be contacted by ward staff unless instructed to do so.

If theft by a member of staff involving controlled drugs is witnessed or there is strong suspicion that a member of staff has diverted a controlled drug for their own purposes, the senior nurse, midwife, or ODP in charge of the shift should deal with the issue as for any other witnessed or suspicion of theft situation as this falls under a performance and conduct issue. They must also inform the pharmacist (if available—resident pharmacist out of hours) without delay who will immediately inform the senior pharmacist on call who will in turn inform security, the Accountable Officer, and the Chief Pharmacist. The police should not be involved without prior permission from the Accountable Officer and the Chief Pharmacist.

The record of suspected losses should be reported to the clinical governance committee, or a similar body, that has responsibility for the administration of medicines.

Notes for the investigating pharmacist

On investigating identified discrepancies, it is good practice to check the following initially.

- Arithmetic details in the register.
- Identify the time interval when the suspected drug balance was correct.
- Enquire about the probable number of staff who could have had access to the keys for controlled drug storage during the investigated period.
- Check whether the senior nurse has organized all administrations for the drug to be checked against the patient's drug chart during the time period being investigated.
- Ensure that regular checks of controlled drug stocks have been performed.
- Check when nurse and pharmacist stock accountability was last undertaken.

Note that small discrepancies involving liquid preparations are not uncommon, but could need to be monitored in case a pattern emerges.

If an arithmetical error explains the loss, it is not usually considered necessary to complete an incident form or report the incident to senior managers.

Hospital pharmacy department

Suspicion of loss must be reported immediately to the appropriate manager—e.g. the dispensary manager or stores manager. The manager must undertake an inventory check and decide if staff are following the department's standing operating procedures for receipt and supply of controlled drugs. It is GCP to check the following.

- Arithmetic details in the register.
- Identify the time interval when the suspected drug balance was correct.
- Department's standard operating procedures have been complied with—e.g. only designated staff have access to operate in controlled drug preparation area, including out-of-hours staff, and that all such staff have received appropriate training.
- Receipt and invoice procedures are in place.
- Access to the department by visitors is enforced and visitors have no access to controlled drug preparation areas.
- All supply requisitions are checked.

If a discrepancy exists, the loss should be submitted in writing to the Chief Pharmacist and Accountable Officer, who should review the standard operating procedures. The incident should be reported to the clinical governance committee, or a similar body, that has responsibility for medicine management.

The decision to involve an external investigator must be undertaken with the involvement of the Chief Pharmacist and the Accountable Officer.

Patients' own controlled drugs in a hospital setting

Patients admitted into hospital

Patients' own controlled drugs refer to those drugs brought in by patients when admitted to hospital and those that may be supplied as part of discharge medication (TTO).

Whenever a patient is admitted with his/her own controlled drug(s) they should be encouraged to return these home via an identified adult. Responsibility for security is given to the adult, and therefore it is essential that this is recorded in the patient notes/care plan. They do not need to be entered in the Patients Own Controlled Drug Record Book unless considered as an added documented precaution.

If a patient is admitted with his/her own controlled drugs and it has been decided to retain the patient on the ward, two registered nurses should check these into the ward's Patients' Own Controlled Drugs Register.

The drug and its form, strength, and quantity should be checked, and the drug(s) should then placed in a controlled drugs cupboard, with the details entered in a separate Patients' Own Controlled Drugs Record Book.

The patients name must be written on the label. If unlabelled strips of medicine are brought in, these should not be administered to the patient and the supplies should be highlighted to a pharmacist, who should organize their destruction or return to the patient, or their relative, on discharge.

Use of patients' own controlled drugs

Ideally, the use of the patients own supplies for in-patients should be restricted to the following.

- Non-formulary drugs or drugs which are otherwise unavailable.
- While awaiting supplies from the pharmacy.
- Administration records should be completed on the relevant page of the Patients' Own Controlled Drugs Record Book.

Nurses should be encouraged to order supplies from their pharmacy as soon as feasible.

Return of patients' own controlled drugs

When the patient goes home, their medicines must be signed out of the Patients' Own Controlled Drug Record Book by the patient's nurse/midwife, which should be checked by a second nurse/midwife and handed directly to the patient, assuming that the nurse has previously checked that the patient's drug and labelled dose schedule hasn't changed during the in-patient stay.

A patient's own controlled drug should never be used to treat other patients but must be returned to the patient before their discharge if there is no change to the prescription. If they have been issued with a new and revised prescription for controlled drugs, those brought in with them must be returned to pharmacy as soon as is practical after the patient has been discharged.

Disposal and destruction of controlled drugs including patients own medicines

A controlled drug ceases to be classified as a controlled drug once it has been rendered irretrievable, i.e. all controlled drugs, once disposed of, should be unrecognizable as controlled drugs and non-usable as a controlled drug.

Only small amounts of controlled drugs can be destroyed on wards—e.g. the surplus when a dose smaller than the total ampoule or vial is drawn up, when a dose is drawn up but not used, broken ampoules of controlled drugs, or left-over syringe/opiate infusion residue.

For all other controlled drugs (e.g. expired stocks, PODs, and excess stock) the pharmacist responsible for the ward or department MUST be notified. these controlled drugs MUST NOT be destroyed on the ward.

Wards and departments who do not receive a routine pharmacy visit, must either arrange for a pharmacist to come to the ward or agree a mutually convenient time for the nurse, midwife, or ODP to take their controlled drugs and the Controlled Drug Record Book to the Pharmacy, where a pharmacist will sign for their return.

The process for destruction of controlled drugs in pharmacy should be found in your Local Standard Operating Procedure

Records of destruction

All destruction must be documented in the appropriate section of the Controlled Drug Record Book or the Patients' Own Controlled Drug Record Book. It must be witnessed by a second person who may be another nurse, midwife, ODP, doctor, or pharmacist.

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