

MANAGEMENT ISSUES FOR CLINICAL TRIALS OF MEDICINES IN NHS HOSPITALS WITH PARTICULAR REFERENCE TO THE PHARMACY

This paper has been prepared as part of the Medical Research Council/ Department of Health Joint Project to codify good practice in publicly-funded clinical trials. The following advice is offered in that spirit.

Introduction: relevant guidance

In the NHS, overall guidelines for the safe and secure handling of medicines in hospitals were given in a report drawn up in 1988 by a Joint Subcommittee of the Standing Medical, Nursing and Midwifery, and Pharmaceutical Advisory Committees chaired by Professor R B Duthie (the Duthie Report). At the time of drafting these guidelines are being revised.

As part of the NHS controls assurance arrangements in England, a set of standards have been published on Medicines Management (safe and secure handling) against which NHS bodies report. The first criterion of these standards is about board level responsibility and clear lines of accountability, and the guidance states that the organisation's Chief Executive has overall statutory responsibility for the safe and secure handling of medicines. It also states that the chief pharmacist should be responsible for ensuring that systems are in place to appropriately address all aspects of the safe and secure handling of medicines and report directly to the chief executive for this purpose across the whole of the organisation. Criterion 9 is that "the supply of medicines for clinical trials is undertaken in accordance with relevant legislation and best practice guidelines", with guidance that "all medicines, or constituent ingredients, for clinical trials should be ordered, stored and dispensed by the hospital pharmacy."

This note takes as a principle that all medicinal product clinical trial supplies in hospitals should be held in the hospital pharmacy unless there are specific reasons for particular supplies to be held on a ward, clinic or department – this may arise when, for example, the medicine has been dispensed as a supply for administration to an individual patient. There should be no ward or department stocks of such trial supplies unless urgent administration is a requirement of the trial, where the arrangements for storage would need to be agreed with the pharmacy.

General issues

Good relations are to be fostered between the hospital trust's R&D managers and trust pharmacy management, and procedures put in place to ensure that the pharmacy department is contacted in the early stages about proposals for a clinical trial which would be regulated by the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031). It is recommended that resources should be made available so that the appropriate level of pharmaceutical support can be provided for all such trials as part of Good Clinical Practice processes (in addition to the costs of manufacturing or assembly of investigational medicinal products used in individual trials).

Facilities devoted to clinical trials need to be appropriate to the volume of work involved. Equipment can be validated and checked as part of the normal NHS independent quality control audit at regular intervals.

For the purposes of maintaining Good Clinical Practice, all pharmacy, nursing and other staff involved in a clinical trial should be trained for undertaking their role in that trial. A record should be kept of such training.

Arrangements in relation to hospital pharmacies

Coordination and pharmacy staff

Information about a trial likely to be needed to be resolved with and understood by the pharmacy department includes:

- Purpose of the trial
- Explanation of the responsibilities of the various parties involved
- Codes including for participant randomisation
- Numbers and recruitment parameters of patients as trial participants
- Description of the marketed product or specification of the IMP to be used, and any relevant handling/COSHH data
- Source of products to be used
- Labelling to be used
- Name and contact details of the Chief Investigator, local investigators and others involved in organising, managing or administering the trial (including the involvement of any university based a clinical trials unit providing overall coordination as part of a trial)
- Documentation to be retained by the pharmacy.

Where the pharmacy is to assemble IMPs, or pharmacy manufacturing unit with IMP manufacturing authorisation to manufacture IMPs, for the trial, additional details will be necessary as part of the agreement for those activities.

Protocols of proposed clinical trials should be made available to the pharmacy department in advance of a request for a clinical trial authorisation or ethics committee opinion, so that practical details such as doses and method of administration, packaging, labelling and study documentation for pharmacy appropriate for each individual trial, can be confirmed. A copy of the up to date protocol of each approved clinical trial that involves a medicine, should be held for reference purposes by the pharmacy department that supplies the medicine.

It is recommended that a member of the pharmacy staff should have an assigned role as pharmaceutical coordinator in relation to each clinical trial involving a medicine in a hospital. In most cases this would be a designated clinical trials pharmacist.

This coordinator would be the contact person for any local or chief investigators, pharmaceutical companies or others involved in the

arrangements for supplies for the trial, including to ensure that the formulation, presentation, and storage of clinical trial medication are appropriate.

The pharmacy coordinator will need to liaise with the Trust R&D to confirm that the trial has received permission to take place in the Trust under research governance arrangements. He/she would also need to be provided with copies of the relevant documents about the trial and any subsequent amendments to documents including the protocol, and copy these on as appropriate to other staff involved, to support compliance with the principles of Good Clinical Practice in the trial.

There will ideally be a separation of responsibilities between:

- the pharmacist advising the Ethics Committee
- the clinical trials pharmacist (pharmaceutical coordinator) responsible for a trial, and (where there is a pharmacy manufacturing unit)
 - the production pharmacist responsible for the unit which manufactures the product
 - the qualified person responsible for the release of the locally manufactured product.

This will not always be practical in small units, but the principles of the separation of interest and responsibility is to be aimed for in all possible circumstances.

(There may be exceptional circumstances in a small unit where it may not be possible to separate the role of the advisor to the Ethics Committee and the clinical trials pharmacist, but in such circumstances a '*Declaration of Interests*' in full, including all costings, should be made, to the chairman, before any discussions occur.)

It is acknowledged that following the 'grandfather clause' of the Directive, that some clinical trial pharmacists may become Qualified Persons for IMPs. Units of sufficient size should be moving to separate these roles.

All pharmacy staff will need to receive training appropriate to their roles in clinical trials. All training should be documented, and be available for inspection.

Medicines storage and handling

All medicines should be managed by the pharmacy including clinical trial materials. It is recommended that specially manufactured or assembled IMPs (after QP release) be kept in a separate and secure storage area with sufficient room to ensure that there is no confusion between trial and other supplies. In trusts with a large number of clinical trials, holding stocks of marketed products intended for a trial (where the use is in accordance with the marketing authorisation), separate from supplies for normal outpatient dispensing, can facilitate control and work flow in the pharmacy.

Clinical trial medication should be supplied against an appropriate prescription form. There are advantages to the use of trial specific directions or prescription forms agreed between the trial investigators and the pharmacy; these would carry the title of the study and unique trial reference number (eg EUDRAct number).

Investigational medicinal products for administration to inpatients should be labelled in accordance with labelling requirements (see document [“Labelling of investigational medicinal products”](#)).

The pharmacy should be involved in the reconciliation of medicines returned by trial patients and the disposal of unused medication. Guidance can be obtained from the Regional Quality Assurance pharmacists’ document on Waste Disposal.

Documentation and Records

The clinical trials pharmacist/ pharmacy coordinator will need to ensure that appropriate records of dispensing and detailed drug accountability are kept in the pharmacy and appropriate arrangements made for clinical trial documentation to be retained in the pharmacy for the period as may be specified in the protocol. Storage after that time is the responsibility of the sponsor.

It is good practice for records of pharmacy storage conditions for the medicines involved in the trial to be kept.

Where agreed, randomisation of in-house clinical trials can be undertaken by pharmacists with access to appropriate statistical input. The randomisation codes would be held by the pharmacy, and arrangements would need to be made to allow for codes to be broken outside of normal pharmacy working hours according to the specified criteria. Records of any such intervention would need to be made in the relevant trial documentation.

As with other quality systems, all processes (including dispensing and agreed arrangements for administration to inpatients on the wards) will be described in standard operating procedures for the specific trial, which would be regularly reviewed.

Charging for Clinical Trials

The pharmacy department should have a standard method of charging for clinical trials agreed with the Trust’s R&D management, to cover the direct costs associated with the service provision.

Suitable arrangements should be made for the levy of prescription charges to outpatients in accordance with current guidance. Prescription charges do not apply to trials where one arm involves the use of a placebo. For trials that compare active substances, or different doses of an active substance, a prescription charge should be levied, subject to the usual prescription charge exemption criteria. Where a patient may be expected to pay a prescription

charge at regular intervals, they should be advised of the availability of a prescription charge prepayment certificate. Where prescription charges do apply, patients should not be expected to pay an abnormally high number of charges when, for the purposes of a trial, a greater number of medicines than would normally be the case are used simultaneously and in smaller quantities; the advice promulgated by the Department of Health is that, for the purposes of prescription charges, such a batch of trial medicines could be regarded as one item.

Audit

As with other preparative services there is a need for regular internal audit of the processes. This would include all aspects of the clinical trials process from receipt of the submission in pharmacy to the administration of the product to the patient. Pharmacies and their records may be inspected as part of the MHRA's Good Clinical Practice inspections. Licensed manufacturing units will be subjected to Good Manufacturing Practice audit by the MHRA inspectors.

Bio Hazards

Pharmacy departments will need to recognise their limits and not work beyond them. In certain cases it is necessary to call upon outside expertise e.g virologist in the case of contamination with gene therapy.

May 2004. The above is built upon the work of a previous pharmacy working party chaired by Mr V'lain Fenton-May.