Standard of practice in clinical trials for pharmacy services

Peter Slobodian, BPharm, MClinPharm, MSHP, June Challen, B. Pharm, MSHP, Michael Ching, post nominals MSHP, Eugenia Hong, post nominals MSHP, Jasminka Nikolajevic-Sarunac, BPharm, MsMedSc Pharmacoepidemiology MFIP MEAHP MSHP, Brenda Shum, post nominals MSHP, Claire Vosk, B.Pharm, BSc, MSHP, and Courtney Munro, BPharm, GradCertPharmPrac, MPharmPrac, MSHP, AACPAS

1 Royal Adelaide Hospital Pharmacy, Central Adelaide Local Health Network, SA Pharmacy, Adelaide, Australia
2 The Queen Elizabeth Hospital, Central Adelaide Local Health Network, Woodville, Australia
3 Austin Health, Heidelberg, Victoria, Australia
4 Melbourne Health, Parkville, Victoria, Australia
5 John Hunter Hospital, New Lambton Heights, New South Wales, Australia
6 Sir Charles Gairdner Hospital, Nedlands, Western Australia, Australia
7 Monash Health, Clayton, Victoria, Australia
8 The Society of Hospital Pharmacists of Australia, Collingwood, Victoria, Australia

Address for correspondence:
Peter Slobodian¹, Chair, Clinical Trials Leadership Committee, The Society of Hospital Pharmacists of Australia, Collingwood, Victoria, Australia. Email: specialtypractice@shpa.org.au

Preface

This Standard references and relies upon SHPA Standards of Practice for Clinical Pharmacy Services as the foremost Standard. This Standard supersedes the previous SHPA Standards of Practice for Pharmacy Investigational Drugs Services.

This Standard may overlap with others and depending on the area of specialty practice it may be advisable to refer to additional Standards of Practice.

The use of the word ‘specialisation’ in this standard is in line with the National Competency Standards Framework for Pharmacists in Australia where ‘specialisation’ refers to the scope of practice rather than the level of performance. ‘Specialisation’ of itself does not confer additional expertise.

This Standard is for professional practice and is not prepared or endorsed by Standards Australia. It is not legally binding.
Introduction

In Australia, everyone shares a fundamental right to safe and high-quality healthcare. This is enshrined in the *Australian Charter of Healthcare Rights*[^4] by which all healthcare systems, including the provision of advanced pharmacy care, must abide. The Charter summarises the basic rights of patients and consumers when accessing healthcare services including access, safety, respect, communication, participation, privacy and comment. The provision of pharmacy services must encompass the Charter to deliver effective, efficient, timely, and equitable patient-centred care.

The *National Competency Standards Framework for Pharmacists in Australia*[^3] complements the underpinnings of the Charter across five domains of competency for the pharmacy profession. These include professionalism and ethics, communication and collaboration, medicines management and patient care, leadership and management, as well as education and research.

This Standard, produced by The Society of Hospital Pharmacists of Australia (SHPA), refers to both the role of the pharmacy service and the pharmacists’ practice in clinical trials. It is intended for both pharmacists involved in clinical trial services and pharmacists whose area of specialisation is clinical trial services and for consistency refers to both as **clinical trials pharmacists**. The Standard predominantly refers to clinical trials pharmacists but does not intend to exclude suitably qualified pharmacy technicians where appropriate[^1]. SHPA supports both pharmacists and pharmacy technicians to operate at their full scope of practice in order to achieve optimal patient and pharmacy outcomes.

The Standard has been developed for pharmacists and pharmacy technicians involved with clinical trials in their institutions. It relates to the management of investigational products used in clinical trials and the facilities required for a clinical trials pharmacy services to align with the principles of Good Clinical Practice (GCP) which have their origin in the World Medical Association’s Declaration of Helsinki[^5,6]. Hospitals and other healthcare agencies are the major centres for clinical trials with investigational products and pharmacists in these institutions should be involved with policies and procedures for the safe and ethical use of investigational products. Implementation of these guidelines should ensure the provision of a clinical trials pharmacy service acceptable to the international community.

This Standard is intended to be used across hospital pharmacy services in Australia, irrespective of the service type (public or private) or location (metropolitan, regional or rural). While this Standard is intended for hospital pharmacy services, the principles and aspects of patient management discussed herein can be applied to broader pharmacy services that provide clinical trials services. It is acknowledged there are significant variations in pharmacy services that are dependent on organisational capacity, patient population, clinical trials service and pharmacy department priorities, and availability of clinical trials pharmacists; all of which may influence the scope of services.

The Standard describes current best care for the provision of clinical trials pharmacy services by clinical trials pharmacists, technicians and the pharmacy department or employer.

Objectives of the Service

The objectives of the clinical trials service provided by pharmacists are to:

[^4]: *Australian Charter of Healthcare Rights*
[^3]: *National Competency Standards Framework for Pharmacists in Australia*
[^1]: [1]
[^5]: [5]
[^6]: [6]
• provide safe and ethical use of investigational products by ensuring that they are appropriate for use and are procured, handled, stored and used safely and correctly
• apply the principles of best pharmacy practice to the evaluation of new medicines
• ensure pharmacy aspects of investigational drug use comply with relevant legislative Acts, standards and guidelines
• consider the safety and welfare of clinical trial participants and protection of their rights, confidentiality and privacy.

Clinical trials pharmacists must deliver the service as part of multidisciplinary collaboration and within the framework of evidence and patient-centred healthcare ensuring optimal patient care.

Scope

This Standard applies to all pharmacists working in clinical trials services. The service provided by the clinical trials pharmacist may be delivered across several settings including both public and private hospitals, in an inpatient, outpatient or ambulatory care setting, and in community or domiciliary settings.

In addition to providing Clinical Pharmacy services as outlined in SHPA Standards of Practice for Clinical Pharmacy Services, clinical trials pharmacists are expected to provide services relevant to their clinical area and scope of practice. The scope of services provided by clinical trials pharmacists will be dependent on a variety of factors including:

• the setting,
• the patient population,
• the services the hospital or health service provides,
• funding models,
• governance structures for clinical trials services,
• clinical trials service and pharmacy department priorities,
• organisational priorities, and
• the scope of practice of the individual pharmacist.

Whilst the range of services provided in clinical trials is primarily delivered by pharmacists, it is increasingly supported by pharmacy technicians in clinical and non-clinical roles.

The role of the clinical trials pharmacist should include:

• delivery of pharmacy services that improve patient medication outcomes and adds value to healthcare systems, while encouraging the financial sustainability of healthcare
• development of and input into policies, procedures, guidelines and resources
• comment on clinical trials protocols
• provision of education and training for healthcare professionals and students
• quality improvement activities; and
• pharmacy research related to clinical trials

It may additionally include involvement in compounding or manufacturing investigational products, services. The pharmacist should be a point of contact for other pharmacists and health professionals, and for the hospital or health service for medicines enquiries related to clinical trials.
Users of the service include clinical trial participants and their carers, investigators and other health professionals.

Coordination of the clinical trials pharmacy should be the responsibility of clinical trials pharmacist(s) within the pharmacy service to ensure the maintenance of practice standards and consistency of service provision and to ensure clinical trials involving investigational medicines are conducted according to the principles of GCP.

Clinical trials pharmacists should develop services specific to their departmental and institutional needs, but minimum services should include:

- stock management, storage, preparation and dispensing of all investigational products
- emergency 24-hour access to the service
- procedures to ensure compliance with clinical trial protocols
- counselling/educating clinical trial participants and monitoring compliance
- liaison with clinical trial investigator(s), trial coordinators and trial monitors
- providing information to participants and their carers, medical and nursing staff, other pharmacists
- pharmacy involvement in the institutional review of protocols (via membership of a scientific review committee and/or Human Research Ethics Committee (HREC)).

In addition, clinical trials pharmacists may be involved in:

- clinical trial design
- protocol development
- randomisation codes (e.g. for blinded clinical trials)
- preparation of placebos and special dosage forms
- adverse drug reaction reporting
- literature searches
- therapeutic drug level monitoring
- advising on regulatory aspects of conducting clinical trials
- collection and analysis of data
- education of pharmacists, pharmacy students and other healthcare professionals
- importation of investigational medicine material
- distribution of investigational medicines to other study sites.

**Operation**

**Policies, Procedures and Governance**

Pharmacists must have knowledge of the following documents which provide a framework within which they must practice:

- Australian Charter of Healthcare Rights
- National Safety and Quality Health Service Standards including the National Model Clinical Governance Framework
- Pharmacy Board of Australia Code of Conduct
- SHPA Code of Ethics
- National Competency Standards Framework for Pharmacists in Australia
- Professional Practice Standards
• Clinical Governance Principles for Pharmacy Services 12

All aspects of the clinical trials pharmacy service should be conducted according to the following standards and guidelines:

• Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice ICH E6(R2) - Annotated with TGA comments 5
• Access to Unapproved Therapeutic Goods - Clinical Trials in Australia 14
• Australian Clinical Trial Handbook: Guidance on conducting clinical trials in Australia using ‘unapproved’ therapeutic goods 15
• NHMRC National Statement on Ethical Conduct in Human Research 16
• NHMRC Australian Code for the Responsible Conduct of Research 17
• Code of Good Manufacturing Practice (GMP) 18
• Commonwealth and state and territory privacy principles and legislation 19.

Investigational products in clinical trials should be subject to the same standards of dispensing, labelling, stock management, participant counselling/education and drug information as those required for TGA-registered medicines, with additional requirements as outlined in this Standard.

**Trial Protocol Development and Review**

Pharmacists should be involved in the review of protocols either by the membership of an HREC or of a scientific review committee. If there is no clinical trials pharmacy membership of such committees, there should be an opportunity for prior review by clinical trials pharmacists of the clinical trial protocol, to assess the impact on the clinical trials pharmacy and other pharmacy services. There must be a Research Governance (RGO) Site Specific Assessment (SSA) prior to any study being conducted, which is signed by Head of, or Director of Pharmacy for any trial requiring pharmacy input.

Experienced clinical trials pharmacists may be involved in developing or advising on the design of new clinical trials particularly those generated within the institution or without external sponsorship. Other pharmacists with specialist knowledge should be involved as appropriate.

**Distribution and Control of Investigational Medicines**

The *Note for Guidance on Good Clinical Practice* recommends that an investigator should delegate responsibility for investigational drug(s) storage and accountability to an appropriate pharmacist 5.

The clinical trials pharmacist/s must sign the trial delegation log and training log held in the Investigator Site File (ISF) upon activation of the clinical trial.

The clinical trials pharmacy should develop and maintain written, and up to date standard operating procedures (SOPs), including version control, for the handling of medicines used in clinical trials.

**Drug Accountability Records**

Drug accountability records should be maintained by the clinical trial pharmacist to identify at all times the location and fate of all investigational product stock received by the site and details of all transactions.

Drug accountability records should include the full details of the following:

• Investigational product receipt and confirmation at the trial site
• Dispensing to individual clinical trial participants
stock disbursement to usage areas
participant returns
transfers to other institutions
returns to sponsor
authorised destruction by the sponsor
stock loss due to breakage, inappropriate storage conditions or unsuitability for use
errors and corrective action that is taken.

Forms provided by the sponsor or purpose-designed forms may be used. Such forms should have the identity of the clinical trial protocol, clinical trial site, principal investigator’s name and provision for the recording of all the above information.

Black ball-point pens should preferably be used for drug accountability records.

Any corrections to drug accountability records should be crossed out with a single line, clearly signed and dated, and an explanation/comment (if necessary), with the original entry still legible. “White-out” or blacking out on any documentation is not permitted.

Electronic accountability records may also be used and must be enabled to track all entries including changes by date and electronic login or signature.

**IVRS/IWRS/IxRS**

Interactive voice response system (IVRS)/Interactive web response system (IWRS) or Interactive voice/web response systems (IxRS) are electronic systems using voice-telephone or web-based platforms for stock control is routinely used for clinical trials. IxRS should have personalised logins which are password protected to allow for the identification of the person recording the entry.

**Ordering and Receipt of Investigational Product**

Methods of ordering vary with individual protocols. The clinical trials pharmacist should refer to the specific protocol for drug ordering requirements and procedures.

Investigational products should be sent by the sponsor directly to the pharmacy and addressed to the clinical trials pharmacist.

The clinical trials pharmacist should physically examine receipts to ensure all investigational products are present, intact, correctly labelled as per shipment documentation and transported in appropriate conditions. It is advisable to count every individual vial or bottle in multi-pack cartons rather than rely on an outer carton label for contents. The following should be checked and recorded in the drug accountability records:

- name or identification number of the investigational products
- name, strength and dosage form of the investigational products
- date of receipt
- quantity received
- expiry/retest date(s)
- batch/lot/serial number(s)
- unique code numbers assigned to the investigational product (if appropriate)
- numbers and quantity of any randomisation codes or envelopes received.

Any discrepancy should be reported to the sponsor directly and stock quarantined until the discrepancy is resolved.
Once shipment documentation has been checked and found correct or amended/annotated as required it should be signed and acknowledged as received by faxing or emailing and/or by IVRS/IWRS as required by the sponsor.

All shipment documentation should be retained in the pharmacy clinical trial file.

Clinical trials pharmacists are sometimes involved in the importation of unregistered drugs. If the unregistered medicine is not available from an Australian sponsor, an overseas source should be found. When importing the unregistered medicines from the overseas supplier, it is important to obtain appropriate types of licences and permits required prior to placing an order:

- import licence and permit issued by the Office of Chemical Safety are required to import narcotic, psychotropic and precursor substances subject to Regulation 5 of the Customs Regulations 1956
- import permit issued by the Office of Chemical Safety is required to import antibiotic and anabolic/androgenic substances, subject to Regulations 5A and 5H respectively
- import permit issued by the Australian Quarantine and Inspection Service is required to import biological products used for therapeutic or diagnostic use and containing and derived from microorganisms, animal, human, plant or viral material.

Manufacture of Investigational Products

To ensure high standards of quality assurance for manufactured products, the general standards for the manufacture of therapeutic goods as specified in the SHPA Guidelines for Medicines prepared in Australian Hospital Pharmacy 20 should be followed. The Australian Code of Good Manufacturing Practice for Medicinal Goods-Investigational Medicinal Products 18 particularly Annex 13 - Manufacture of Investigational Medicinal Products should also be considered. Guidelines for handling cytotoxic medicines and/or targeted therapies should be adhered to when appropriate 21-23.

It is important that information on the safe handling of investigational medicines is available to all pharmacy and other staff who may be involved. Occupational health and safety issues are paramount in the handling of products in the early stages of development.

Storage of Investigational Products

Investigational products should be stored separately from the normal pharmacy in an area with access restricted to pharmacy staff, and where possible, access only to clinical trial pharmacists.

Investigational products should be stored at the required temperature and environmental conditions, e.g. humidity as specified in the protocol, investigator’s brochure or approved product information and according to the appropriate statutory regulations for registered medicines and in accordance with special requirements e.g. cytotoxic medicines 20. Refrigerators and freezers used to store investigational products should meet the Australian standards for medical or vaccine refrigerators/freezers. All refrigerators, freezers and cold rooms must be connected to essential power.

There should be monitoring and documentation of storage conditions. All refrigerators, freezers, cold rooms and ambient storage areas should be linked to the hospital Building Management System (BMS) and/or a stand-alone validated Environmental Monitoring System (EMS). Alternatively, commercial individual temperature recorders with a back-up alarm system are recommended.

Temperature monitors should be serviced and re-calibrated annually and documentation of this kept. Temperature logs should be maintained either in paper form or electronically and made available to monitors, auditors or investigators on request.
In the event of a temperature alarm and/or excursion the following actions should be taken:

- check the temperature readings for deviations
- quarantine the investigational product and transfer stock to the back-up facility as per the Business Continuity Plan
- note the time of transfer and/or transfer a portable temperature data logger with the products
- notify the sponsors as soon as practicable (including a copy of the temperature readings)
- do not dispense quarantined investigational medicines until authorised by the sponsors
- contact the appropriate technician to investigate the alarm incident and/or to repair equipment. Obtain and file the technician’s report which may include preventative measures for future incidents
- write a file note/report of the alarm incident and file it with the relevant temperature records.

Quarantined investigational products should be clearly identified and segregated from working medicines.

Investigational products should be separated and labelled on a per protocol basis. Investigational products should preferably be stored in the pharmacy until needed. If the investigational products are stored outside the pharmacy as agreed upon by the service e.g. to permit emergency access, they should be regularly audited to ensure appropriate storage, drug accountability recording and security of the medicine.

**Expiry date monitoring**
Investigational products under development have limited stability data. The stock may have re-test dates instead of the expiry date. Re-test dates need to be regularly updated and stock relabelled as new storage stability data becomes available. A system for monitoring short-dated stock needs to be implemented.

**Dispensing of Investigational Products**
Specific dispensing instructions should be developed for each protocol (according to the Clinical Trials Pharmacy SOPs. The specific dispensing requirements for each visit should be detailed.

Requirements during dispensing include the following:

- verification that the clinical trial protocol has HREC approval (prior to first clinical trial dispensing)
- verification that the prescriber is an authorised investigator (i.e. listed on the HREC application/approval)
- verification that the patient (for whom the prescription is written) is registered on the clinical trial
- concordance of dosage and regimen with the protocol
- confirmation that the participant meets the requirements for treatment (if appropriate)
- compounding of sterile preparations (if required) as per the specific clinical trial requirements
- concordance of concomitant and disallowed therapy with the protocol
- verification of correct randomisation (if required)
- verification of IWRS allocation
- requirement for a second check of all randomised prescriptions
- completion of accountability record/s
labelling with a standard pharmacy dispensing label such that the clinical trial, investigator and institution can be identified at all times and in accordance with the protocol. Sponsor required information should not be obscured.

- retention of additional documentation such as original prescriptions and computer records in a readily accessible manner to allow verification of the dispensing records.

Investigational product accountability record(s) should be completed at the time of dispensing by the dispensing pharmacist. The following information should be included in the accountability form:

- identification of the clinical trial by protocol number
- clinical trial site
- name of the principal investigator
- name, strength and dosage form of the investigational product
- participant initials
- participant clinical trial assigned identification (ID) number
- date of dispensing
- dosage and quantity dispensed
- batch and re-test (expiry) date of investigational product
- dispensing pharmacist’s signature.

Accountability records for investigational products may also include:

- balance of investigational product at a site
- date and quantity of returned investigational product
- kit numbers and/or stickers for patient-specific investigational product
- date of the destruction of investigational product
- protocol specific information e.g. weight/BSA of the participant, the volume of medicine.

A clinical trial participant master list with full name and hospital record number (for pharmacy use), clinical trial ID number and randomisation arm/dose level (if appropriate) should be maintained. While the dispensing record may include specific participant details such as name and address, any records forwarded to the sponsor must not contain participant identifying information, other than initials and/or clinical trial assigned ID number.

Electronic accountability records may also be maintained by the pharmacy. The electronic system must have a personalised login system which identifies the pharmacist recording entries and contain security to prevent unauthorized access. If original data is modified the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change and date of the change. An adequate backup system must be employed to prevent loss of data. Originals or validated copies of all prescriptions or clinical trial drug orders should be kept to validate accountability records.

**Return of Investigational Products by Participants**

Clinical trial participants should return any unused investigational products or empty containers to the pharmacy. Date and quantity of participant returns (or the number of empty containers) and signature of person recording participant returns should be documented in the drug accountability records. Returned medicines should be stored such that it is clearly distinguishable from undispensed stock until confirmation by a trial monitor and returned to the sponsor or destroyed.

Any participant names or identifiers (other than initials and/or clinical trial ID numbers) on the
containers should be removed or blacked out before returning to the sponsor to maintain patient confidentiality. Reissue of returns with specific handling requirements should be discouraged.

Any potentially dangerous or contaminated products returned by participants, such as needles, syringes, broken ampoules, should be in appropriate sealed containers provided by sponsors. It is recommended that these be destroyed as soon as possible after receipt by the usual pharmacy procedures. Gloves should be worn and counting devices cleaned after each use for returned oral cytotoxic and other hazardous medicines as per relevant local guidelines.

Transfer/Distribution to other Institutions

Investigational products should only be transferred to another site with the permission of the investigator and the sponsor. All transfers should be recorded on drug accountability records and receipt should be acknowledged. Investigational products should be transferred under the required temperature storage conditions as specified in the protocol. Records of temperature during transit and upon receipt need to be kept and filed. Transfer of cytotoxic medicines or genetically modified products requires additional precautions.

An authorised recipient in the receiving institution should be responsible for the receipt of investigational products. The authorised recipient should be provided with pertinent information including participant details (if applicable), clinical trial protocol or relevant drug information, local investigator, storage and handling instructions, drug accountability details and forms, contact names and telephone numbers. Transfer records should be kept at both sites.

Pharmacy departments may be asked to act as a distribution centre for investigational products to other sites. This is not considered a standard service. If undertaken, detailed SOPs should be developed for each individual study.

Return and Disposal of Investigational Products

Investigational products may be returned to the sponsor due to the following reasons:

- the trial is completed or closed
- a participant has returned unused an investigational product to the pharmacy
- the investigational product has expired and re-test (expiry) date will not be extended
- the investigational product has been stored improperly
- the stock is damaged
- the sponsor has requested the return of the medicine.

Alternatively, the sponsor may authorise the destruction at the clinical trial site. This is usually done by incineration at high temperature or by appropriate destruction methods, in accordance with SOPs of the clinical trials pharmacy. The SOPs need to include specific details of the sites destruction procedure.

All returns or investigational products approved destruction, should be recorded in the drug accountability records, with details including batch/kit numbers and quantity recorded, date of destruction. Destruction logs documenting full details of name, strength, quantity, batch number, expiry (re-test) date, and date of destruction should be completed and kept in the pharmacy file. In addition, records of randomisation codes returned to the sponsor or destroyed should be recorded with other clinical trial records.
Retention and Archiving of Records

All records relating to the clinical trial should be retained following trial closure for a minimum of 15 years for adult participants and 25 years for paediatric participants in a secure accessible place, or for longer if required by the sponsor \(^5\). The clinical trials pharmacy service should have a documented procedure for archiving pharmacy records. The system used for archiving must allow for retrieval in a timely manner of any pharmacy study file or non-study specific documentation, such as temperature monitoring records, training records of pharmacy staff, etc. Increasingly, archiving of records may be off-site and pharmacy may choose to be responsible for original prescriptions and invoicing and return other documentation to the site for archiving. Some states and territories may have existing guidance regarding retention and archiving and should refer to such.

Documentation

Standard Operating Procedures (SOPs)
The clinical trials pharmacy should develop written SOP for all their standard services such as clinical trial set up, receipt of the drug, temperature monitoring, archiving etc.

File Notes
Any event occurring during the administration of a clinical trial which is unexpected, unusual or falls outside the requirements of the protocol, e.g. dispensing error, temperature excursion should be documented in a file note. This is important in explaining anomalies for monitoring and auditing purposes.

Training
Documented training should be kept for each protocol with a record of pharmacists and technicians trained. Protocol and investigator brochure (IB) amendments involving changes in pharmacy procedures require all pharmacists and technicians working with the trial to be retrained and a record of this training must be kept.

Clinical Trial Participant Care

Clinical Trial Participant Education
The clinical trials pharmacist needs to work closely with study staff involved with the participant’s treatment to ensure that education regarding investigational products is adequate and appropriate.

The participant will have been given written information by the investigator during the informed consent process. However, supplementary education by the clinical trials pharmacist is considered best practice to ensure protocol compliance and safe and appropriate use of investigational products.

Preparation of an information leaflet may be used to assist this process, and education should reinforce written information as per usual professional responsibility. Information leaflets provided to participants will require HREC approval and sponsor approval. Education should be based on the SHPA Standards of Practice for Clinical Pharmacy \(^2\).

Monitoring Compliance

Clinical trial participant compliance and its monitoring are important in clinical trials and clinical trials pharmacists should:

- Promote participant compliance by ensuring they understand the education given and the importance of investigational product compliance
• Check at regular intervals appropriate to the clinical trial (as per protocol/sponsor requirements) that each participant is following instructions about the correct use of the investigational product

• Counsel patients to return all investigational products at each visit

• Ensure that records are kept for returns of used and unused supplies and/or packaging, as required by the sponsor

• Notify the study staff if a participant has not adhered with protocol or sponsor requirements

• Attempt to recover all investigational products from participants (or other sources) at the end of each treatment period.

**Investigational Product Information**

Adequate investigational product information should be provided to ensure that the health professional can fulfil their duty of care to the participant. Issues of commercial confidence must be considered. Reproduction of any part of a commercially-sponsored protocol or investigator’s brochure is not permissible as a means of providing the required information without approval from the sponsor.

The clinical trials pharmacy should have access to the current protocol, Investigator’s Brochure (or equivalent) and pharmacy manual for each clinical trial.

Medical, nursing, pharmacy and study staff who will be involved in caring for the participants should have access to information about the investigational medicine(s) being used in the clinical trial.

**Serious Adverse Event Reporting**

Serious Adverse Events (SAE) need be reported as per regulatory requirements governed by the TGA and GCP requirements. The clinical trials pharmacist should be familiar with the Australian adverse event reporting system via the TGA and may assist the investigator in detecting and reporting adverse events.\(^5,14\)

Liaison with clinical pharmacists, medical and nursing staff are encouraged to assist in the early detection of any unexpected clinical trial participant admission to hospital (classified as a serious adverse event)\(^14\). The investigator or clinical trial coordinator should be notified as soon as possible. Hospital automatic electronic reporting systems may assist with this process. If clinical trial participants from other institutions are identified, the clinical trials pharmacist/trial coordinator or investigator at that institution should be contacted.

**Randomisation Codes**

IWRS systems for randomisation are now most commonly used. For studies not using IWRS a copy of the randomisation code should be retained by the study site or pharmacy in the pharmacy file as appropriate, to allow 24-hour access. The requirements to be met before breaking the code (emergency un-blinding) should be stated clearly to prevent inappropriate breaking of the code. Any premature un-blinding (e.g. accidental or due to a SAE) should be documented and explained to the sponsor by the investigator or clinical trials pharmacist.

A record of receipt and return to the sponsor of all randomisation codes should be kept in the Pharmacy File.

**Confidentiality**

The confidentiality of the participant and the research must be maintained at all times. Access to pharmacy study records should be provided only to authorised study staff including unblinded...
monitors and auditors. Compliance with privacy legislation (State and Commonwealth) is mandatory.

**Resources**

The resources recommended for the efficient provision of a clinical trials pharmacy service include:

- adequate staffing levels (see Recommended Staffing)
- facilities and equipment suitable for appropriate dispensing and compounding and aseptic manufacture of investigational products
- sufficient and secure storage space (including refrigeration/freezers) to allow separation of stock for each clinical trial (including medicines returned by participants) with restricted access to clinical trials pharmacy staff
- appropriate temperature and humidity control for all clinical trial storage areas including a 24-hour continuous temperature monitoring system
- dedicated and secure area with sufficient space for administration and monitoring/auditing of clinical trials as well as for counselling participants on investigational products
- space for archiving of records as appropriate
- access to information technology including PC, telephone, barcode scanner, printer
- access to participant medical records including pathology results as needed
- access to a Medicines Information Service
- copies of relevant documentation as listed in Appendix 1.

**Recommended Staffing**

The staffing structure and levels required for a clinical trials pharmacy service will be determined by four major factors; the number of clinical trials undertaken at the institution, the complexity and phase of those clinical trials, and the rate at which new trials are being opened and closed, and patient recruitment.

Support staff, under supervision, and with training, may be used for functions such as stock control, computer data entry, manufacturing, and clerical tasks. Qualified pharmacy technicians may assist with dispensing under supervision.

In June 2015 the Independent Hospital Pricing Authority (IHPA) released the report *Determination of standard costs associated with conducting clinical trials in Australia – Standard list of clinical trial items*.

This report determined the costs for a standard list of items (above those costs for standard care) necessary and associated with conducting clinical trials in Australia. The list of standard items was determined by the National Health and Medical Research Council (NHMRC). These items included services provided by clinical trials pharmacists and the report assigned a standard cost to each of these services. The standard list of items relevant to pharmacy is not limited to the major category of “Pharmacy/Investigation drug related”. The clinical trials pharmacist should refer to all the major categories and apply the relevant items and the standard cost listed when deciding pharmacy fees.

**Workload**

Workload records can help in costing a clinical trials pharmacy and determine staffing levels. Such records could include:
• number of dispensing, categorised as, e.g.:
  o simple dispensing (average dispensing and recording time less than 15 minutes)
  o standard dispensing
  o complex dispensing (dispensing and recording time greater than 45 minutes)
  o sterile preparations
  o sterile cytotoxic preparations

• number of clinical trials opened and closed
• monitor visits
• details of advice/education given concerning concomitant medications, protocol compliance, dose modifications etc.

**Training and Education (for the service, and of the individual)**

Training and education of clinical trials pharmacists will predominately be work-based education, should follow adult learning principles, and is documented in Chapter 10. Training and Education of the **SHPA Standards of Practice for Clinical Pharmacy Services**. Clinical trials pharmacists should have an annual learning plan that supports their development and performance along the continuum of advanced practice from transition level (stage 1), to consolidation level (stage 2), and to advanced level (stage 3). Credentialing of advanced practice pharmacists in Australia is provided by Pharmacy Development Australia.

Pharmacists responsible for medicines which are not currently registered for human use in Australia should have a detailed knowledge of the process of medicines regulation in Australia.

Ongoing education and training are important to ensure compliance with the requirements of state and federal legislation and professional standards and guidelines.

Pharmacists and pharmacy technicians starting practice in a clinical trial pharmacy service must be provided with an appropriate orientation and training program and be familiar with the documents listed in Appendix 1.

Pharmacists in contact with trial participants will need to be knowledgeable about their specific clinical trial protocols.

Additional sources of information, training and updates that should be available include:

- TGA publications, newsletters and seminars
- NHMRC seminars and publications
- Speciality Practice in investigational medicines seminars
- Speciality Practice in investigational medicines publications (available on SHPA website);
- SHPA publications and seminars
- Association of Regulatory and Clinical Scientists (ARCS) seminars and newsletters.

The skills and qualifications for clinical trials pharmacists have to date not been published. The recommended skills and qualifications listed below have been informed by the SHPA Clinical Trials Leadership Committee.

**Essential skills:**

- Good Clinical Practice (GCP) training every 3 years
- Good Manufacturing Practice (GMP) training.
Desirable skills:

- Knowledge of basic research methodology
- A postgraduate qualification in a field related to clinical trials e.g.
  - Drug development
  - Credentialing as an Advancing or Advanced Practice Pharmacist.
- Training and education in manufacturing of cytotoxic and hazardous substances.

Recommendations for education include the following:

Domestic:

- SHPA Seminars and CPD activities.
- Association of Regulatory and Clinical Scientists (ARCS)
- Praxis courses
- NHMRC eLearning Modules.

International:

- European Association of Hospital Pharmacy (EAHP) Clinical trial regulation
- TransCelerate.

Educational material and resources are additionally provided on the SHPA Specialty Practice clinical trials stream page on the SHPA eCPD website. For clinical trials pharmacists, joining and actively participating in the SHPA Specialty Practice clinical trials stream at the Practice Group level is strongly recommended.

Clinical trial pharmacists should additionally play an active role in the education and training of:

- undergraduate pharmacists
- pre-registration pharmacists
- practising pharmacists involved with clinical trial patients
- pharmacy technicians involved with clinical trial patients
- research nurses and clinical trial co-ordinators
- research data managers
- other health professionals involved with clinical trial patients;
- to ensure that all these groups are familiar with all the above.

Attendance at specialist conferences and educational meetings should be supported to maintain and update specialist knowledge in clinical trials. Relevant domestic conferences include those organised by SHPA, Australian Clinical Trials Alliance (ACTA). International conferences include Association of Regulatory and Clinical Scientists (ARCS).

Quality Improvement

Quality improvement activities should demonstrate that the clinical trials pharmacist is targeting and achieving optimal outcomes for all patient groups, including those at greatest risk for medicines misadventure in addition to advancing the practice of clinical trials. Quality improvement activities may include:

- Audit
- Performance review against this Standard
• Looking at current versus. future state for specific components of clinical trials pharmacy service
• Number of papers published per year

A quality assurance program incorporating pharmacy aspects of clinical trials should be developed and implemented. Quality control should be applied at each stage of data collection to ensure that data is reliable and has been processed correctly. Key performance indicators should be developed for the major components of the service.

Suggestions for KPIs may include:

• Full Time Equivalent (FTE) budget within 10% of revenue (aim for balanced) reviewed quarterly
• Start-up turnaround (from site selection visit [SSV] to site initiation visit [SIV])
• Dispensing statistics (amount of scripts and patient numbers/month)
• No. requests for costing quotes (services)
• Number of SSVs
• Number of SIVs
• Uncovered leave (e.g. sick leave) and overtime
• Protocol amendments and/or review
• Performance at audit.

The frequency and duration of data collection and the number of indicators chosen will depend on the size and scope of the pharmacy IMS.

Audits should be conducted by persons independent of those responsible for the clinical trial. All data and documentation should be available for inspection by regulatory authorities.

A quality improvement program should satisfy the requirements of an accreditation review. The following areas could be monitored:

• documentation of procedures
• completeness and accuracy of drug accountability records and dispensing records
• compliance with relevant aspects of the clinical trial protocol
• participant counselling/education
• assessment of participant compliance
• labelling of investigational medicines
• temperature recording procedures for storage areas
• expiry date checking
• procedures for breaking randomisation codes
• medicine information and education for staff
• recording of interventions and enquiries.

The quality of the clinical trial service is enhanced by pharmacist contribution towards ensuring standards of good clinical research practice by involvement in the following activities:
• review of protocols prior to ethics committee approval
• participation in research or ethics committee discussions
• participation in start-up and other trial meetings
• regular liaison with investigators, data managers and research nurses.

Further information on quality improvement can be found in Chapter 14 of the *SHPA Standards of Practice for Clinical Pharmacy Services*.¹

Research

Clinical trials pharmacists are encouraged to participate in and contribute towards advancing the knowledge and evidence of investigational products and clinical trial research. Clinical trials pharmacists are likely to be well positioned with opportunities for research, particularly with investigator-driven studies where investigators may approach the trials pharmacist for advice, resources and solutions to address challenging clinical trial or investigational drug issues. It is advisable to clarify and establish upfront if the work and services provided by the clinical trials pharmacist means an invitation for formal collaboration on clinical trial protocols and grants (e.g. co-investigator status, authorship on publications etc.). There are many areas where clinical trials pharmacists can significantly contribute to collaborative research, including the following:

• advice in clinical trial design, and stratification of treatment arms
• design, generation and implementation of randomisation schedules
• innovation and formulation of blinded dose forms (e.g. drug encapsulation, blinded aseptic products)
• assessing the chemical stability of drugs in investigational or off-label formulations.

External funding enables larger and possibly multi-centre studies to be conducted. The SHPA National Translational Research Collaborative (NTRC) funds research grants, practitioner grants and educational grants. Presentation and publication of studies by Australian pharmacists practising in clinical trials are imperative, to aid others and to illustrate where clinical trials pharmacists are involved in research and how they are improving patient care.

The choice of journal to publish in depends on consideration of the best audience for the study results. The Journal of Pharmacy Practice and Research (JPPR) presents findings to primarily an Australian pharmacy audience.

Further information on research can be found in Chapter 11 of the *SHPA Standards of Practice for Clinical Pharmacy Services*.¹

Acknowledgements

The SHPA additionally wish to acknowledge the work of the former SHPA Committee of Specialty Practice in Investigational Drugs on previous versions of this Standard Kay Hynes, Jillian Davis, Helen Kopp, Angela Morris, Carol Rice and Helen Matthews as well as Eugenia Hong, Michael Ching, Peta Breitag and Mei Grant of the former SHPA Committee of Specialty Practice in Investigational Drugs who contribution to a previous draft of this Standard.
References


2. SHPA Committee of Specialty Practice in Investigational Drugs. SHPA Standards of Practice for Pharmacy Investigational Drugs Services. 2006.


32. National Health and Medical Research Council. Ethical conduct in research with Aboriginal and Torres Strait Islander Peoples and communities: Guidelines for researchers and stakeholders. Canberra: Commonwealth of Australia., 2018.

Appendices

Appendix 1: Resources

Resource documents required for use

- Therapeutic Goods Administration. ICH Harmonised Guideline. Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice-Annotated with TGA comments 2018
- Australian clinical trial handbook: Guidance on conducting clinical trials in Australia using 'unapproved' therapeutic goods ACT 2018
- NHMRC National Statement on Ethical Conduct in Human Research
- Protocols and investigators brochures/TGA approved product information for all clinical trials;
- Access to unapproved therapeutic goods - the special access scheme (SAS)
- Human research ethics committee and the therapeutic goods legislation
- NHMRC. Values and ethics: guidelines for ethical conduct in aboriginal and Torres Strait islander health research

Additional documents that may be of use

- European Association of Hospital Pharmacists (EAHP) Statement on Clinical Trials 2012

Useful Websites


Appendix 2: Definitions

<table>
<thead>
<tr>
<th>Clinical Trial Terms</th>
<th>Definition</th>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE: Adverse Event</td>
<td>Any undesired action or effect of an investigational medicine that occurs during or within a prescribed period of time after a trial has ended</td>
<td>To investigate and report upon the safety and/or effectiveness of a diagnostic, therapeutic or prophylactic medicine</td>
</tr>
<tr>
<td>Clinical Trial/Clinical Study</td>
<td>A planned study in humans</td>
<td></td>
</tr>
<tr>
<td>Phase I Study</td>
<td>A study which involves the first administration of the medicine in humans. Usually administered to healthy volunteers however for certain medicine classes such as cytotoxic medicines may be conducted in patients suffering from the condition the medicine is intended to treat</td>
<td>To determine the safety of the medicine, its pharmacological activity, pharmacokinetics and tolerance. It may also identify routes of administration and appropriate doses.</td>
</tr>
<tr>
<td>Phase II study</td>
<td>First trial of the medicine in a small number of closely supervised patients suffering from the condition for which the medicine is intended</td>
<td>To determine efficacy and safety, therapeutic dose range and maximum tolerated dose of the medicine</td>
</tr>
<tr>
<td>Phase III study</td>
<td>Extended clinical trials in greater numbers of patients</td>
<td>To generate clinical efficacy data and determine incidence and nature of adverse events</td>
</tr>
<tr>
<td>Phase IV study</td>
<td>Post marketing studies</td>
<td>To compare the medicine to a wider range of therapies and further investigate the use of the medicine in the normal clinical setting</td>
</tr>
<tr>
<td>CTX: Clinical Trial Exemption Scheme for Medicines</td>
<td>A sponsor submits an application to conduct a clinical trial to the TGA for evaluation and comment</td>
<td>Notification under CTX or CTN is required for clinical investigation of</td>
</tr>
<tr>
<td>CTN: Clinical Trial Notification Scheme</td>
<td>The sponsor notifies the TGA that a clinical trial is to be conducted. The HREC takes responsibility for the review of the data</td>
<td>a) Any medicine not entered in the Australian Register for Therapeutic goods (ARTG)</td>
</tr>
<tr>
<td>GCP: Good Clinical Practice</td>
<td>A standard for the design, conduct, performance, monitoring, auditing, recording, analysis and reporting of clinical trials</td>
<td>To provide assurance that the data and reported results are credible and accurate and that the rights, integrity and confidentiality of the trial participants are protected</td>
</tr>
<tr>
<td>HREC: Human Research Ethics Committee</td>
<td>An institutional committee whose composition and</td>
<td>To evaluate and monitor the conduct of clinical trials</td>
</tr>
<tr>
<td><strong>function is consistent with the National Statement on Ethical Conduct in Human Research and has notified its existence to the Australian Health Ethics Committee</strong></td>
<td><strong>conducted within an institution</strong></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td><strong>Investigational product</strong></td>
<td>Any medicine, reference product or placebo which is being tested or used as a reference in a clinical trial</td>
<td></td>
</tr>
<tr>
<td>This may include a TGA-registered medicine used in a different formulation or used for an unapproved indication or in doses outside the approved range</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Investigator</strong></td>
<td>A person responsible for the conduct of a clinical trial at a trial site.</td>
<td></td>
</tr>
<tr>
<td><strong>Principal Investigator</strong></td>
<td>The responsible leader of a team of investigators of a clinical trial at a trial site</td>
<td></td>
</tr>
<tr>
<td><strong>Investigator’s Brochure</strong></td>
<td>A compilation of the clinical and non-clinical data on the investigational medicine(s) which is relevant to the study of the investigational medicine(s) in human subjects</td>
<td></td>
</tr>
<tr>
<td><strong>Protocol</strong></td>
<td>A document which describes the rationale, objectives, study design, identification of subjects, methodology, assessments, evaluation, ethical compliance and dissemination of results of a clinical trial</td>
<td></td>
</tr>
<tr>
<td>To direct the conduct and evaluation of a clinical trial</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Serious Adverse Event (SAE)</strong></td>
<td>Serious Adverse Event (SAE) or Serious Adverse Drug Reaction (Serious ADR) Any untoward medical occurrence that at any dose: - results in death, - is life-threatening, - requires inpatient hospitalization or prolongation of existing hospitalization, - results in persistent or significant disability/incapacity, or - is a</td>
<td></td>
</tr>
<tr>
<td>congenital anomaly/birth defect (see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Suspected Unexpected Serious Adverse Reaction (SUSAR) | Sometimes during a clinical trial for a certain drug, a subject may experience serious adverse reactions that may or may not be dose-related but are unexpected, as they are not consistent with current information. |