Standard of practice in clinical trials for pharmacy services

Peter Slobodian, BPharm, MClinPharm, MSHP 1, June Challen, B. Pharm, MSHP 2, Michael Ching, BPharm, MPharm, PhD, MSHP 3, Eugenia Hong, BPharm, GradDipRepSc, BSc, MSHP, AMACTA 4, Jasminka Nikolajevic-Sarunac, BPharm MsMedSc Pharmacoeconomics MFIP MEAHP MSHP 5, Brenda Shum, BSc (Hons), BPharm, MSHP 6, Claire Vosk, B.Pharm, BSc, MSHP 7, and Courtney Munro, BPharm, GradCertPharmPrac, MPharmPrac, MSHP, AACPA 8

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 Slobodian 1, 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 the SHPA Standards of Practice for Clinical Pharmacy Services 1 as the foremost Standard. This Standard supersedes the previous SHPA Standards of Practice for Pharmacy Investigational Drugs Services 2. 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 3 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 must abide. The Charter summarises the basic rights of patients and consumers when accessing healthcare services including access, safety, respect, partnership, information, privacy and the ability to give feedback. 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 complements the underpinnings of the Charter across five domains of competency for the pharmacy profession, namely: (1) professionalism and ethics; (2) communication and collaboration; (3) medicines management and patient care; (4) leadership and management; and (5) education and research.

Purpose and Definitions

The purpose of this Standard is to describe best practice for the provision of clinical trials pharmacy services by clinical trials pharmacists, technicians and, the pharmacy department or employer. 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. 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 this Standard 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 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. The SHPA supports both pharmacists and pharmacy technicians to operate at their full scope of practice in order to achieve optimal patient and pharmacy outcomes.

Objectives of the Service

The objectives of a clinical trials pharmacy service are to:

- 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 investigational product or medicines
- ensure pharmacy aspects of investigational product use comply with relevant legislative Acts, standards and guidelines and with local or institutional policies
- consider the safety and welfare of clinical trial participants and the 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-based 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. Users of the service include clinical trial participants and their carers, clinical trials investigator(s) and other health professionals.

The scope of services provided by clinical trials pharmacists will be dependent on a variety of factors including: the setting, 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.

The role of the clinical trials pharmacist should include: delivery of pharmacy services that improve patient/participant 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; and pharmacy research related to clinical trials.

The pharmacist should be a point of contact for other pharmacists and health professionals, sponsors and for the hospital or health service for investigational product or medicines inquiries related to clinical trials.

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

Operation

Coordination of the clinical trials pharmacy service should be the responsibility of the clinical trials pharmacist to ensure the maintenance of standards, consistency of service provision, and to ensure clinical trials involving investigational products are conducted according to the principles of GCP.

Clinical trials pharmacists should develop services specific to their departmental and institutional needs in accordance with each state policy (e.g. NSW public facilities as per NSW Ministry of Health), yet at a minimum, services should include:

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

The clinical trials pharmacists may be additionally be involved in:

• clinical trial design
• preparation of blinding plans and unblinding procedures
• 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 monitoring
• advising on regulatory and non-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 products to other study sites
• managing the financial aspects of the study.

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 4
• National Safety and Quality Health Service Standards 7 including the National Model Clinical Governance Framework 8
• Pharmacy Board of Australia Code of Conduct 9
• SHPA Code of Ethics 10
• National Competency Standards Framework for Pharmacists in Australia 3
• Professional Practice Standards 11
• Clinical Governance Principles for Pharmacy Services 12

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

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

Clinical Trials Protocol Development and Review

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

The Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice ICH E6(R2) recommends that an investigator should delegate responsibility for the investigational product(s) storage and accountability to an appropriate pharmacist.

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 service should develop and maintain written and up-to-date standard operating procedures (SOPs), including version control, for the handling of investigational products used in clinical trials.

Investigational Product Accountability Records

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

Investigational product accountability records should include full details of the following:

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

Investigational product accountability forms provided by the sponsor or purpose-designed forms may be used. Such forms should identify the protocol, clinical trial site, and principal investigator’s name.

Black ball-point pens should preferably be used for investigational product accountability records. Any corrections to accountability records should be crossed out with a single line, clearly signed and dated, and have 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 system (IxRS) are electronic systems using voice-telephone or web-based platforms for stock control and are 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. Personalised logins should not be shared or visible to other staff members.

Ordering and Receipt of Investigational Product

Methods of ordering investigational product vary depending on individual protocols. The clinical trials pharmacist should refer to the specific protocol and/or pharmacy manual for investigational product ordering requirements and procedures.

Investigational products should be sent by the sponsor directly to the pharmacy, and specifically to the Clinical Trials area of the pharmacy where possible, and addressed to the clinical trials pharmacist. When receiving investigational products, it is important that information on their safe handling is available to all pharmacy and other staff who may be involved, e.g. Safety Data Sheet (SDS). Occupational health and safety issues are paramount in the handling (i.e. receipt, manufacture, dispensing, disposal, etc.) of investigational products in the early stages of development.

The clinical trials pharmacist should physically examine receipts to ensure all investigational products are present, intact, correctly labelled as per shipment documentation and transported under appropriate conditions. It is advisable to inspect and 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 investigational product accountability record:

• 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 the investigational product 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 trials file.

Clinical trials pharmacists are sometimes involved in the importation of unregistered medicines. If the unregistered medicine is not available from an Australian sponsor, an overseas source should be found. When importing unregistered medicines from an overseas supplier it is important to obtain the appropriate type of licence and/or permit required, prior to placing an order. Examples of such include:

- an import licence and permit issued by the Office of Drug Control Section (DCS) which is required to import narcotic, psychotropic and precursor substances subject to Regulation 5 of the Customs Regulations 1956
- an import permit issued by the DCS which is required to import antibiotics subject to Regulation 5A of the Customs Regulations 1956
- an import permit issued by the DCS which is required to import anabolic and androgenic, hormones, genetically modified organisms, as well as other controlled drugs subject to Regulations 5G and 5H respectively
- an import permit through Biosecurity Import Conditions system (BICON) issued by the Department of Agriculture and Water Resources which is required to import biological products used for therapeutic or diagnostic use and containing or derived from microorganisms, animal, human, plant or viral material.

Manufacture of Investigational Products

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

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 trials pharmacists. 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, investigational product accountability recording, and security of the medicine.

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. They should additionally be stored according to the appropriate statutory regulations for registered medicines and in accordance with any special requirements (e.g. cytotoxic medicines).
Refrigerators and freezers used to store investigational products should meet local guidelines where they exist for medicines and the National standard for vaccines. All refrigerators, freezers and cold rooms must be connected to essential power.

There should be a regular monitoring program for all refrigerators, freezers and cold room storage as well as documentation of storage conditions. All refrigerators, freezers, cold rooms and ambient storage areas should be linked to the hospitals building management system and/or a stand-alone validated environmental monitoring system. 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 to the back-up facility as per the business continuity plan
- note the time of transfer and transfer a portable temperature data logger with the investigational product
- notify the sponsor as soon as practical (including a copy of the temperature readings)
- do not dispense the quarantined investigational product until authorised to do so by the sponsor
- contact an appropriate technician to investigate the alarm and/or excursion and if required to repair equipment. Obtain and file the technician’s report which may include preventative measures for future incidents
- write a file note or report of the alarm and/or excursion incident and file it with the relevant temperature records.

Quarantine of Investigational Products

In addition to storage temperature deviations that require the quarantine of investigational products (see above), other reasons for quarantine may include shipping temperature deviation, damage of investigational products, expiry of investigational products, or any event to cause questioning the integrity of the product. Quarantined investigational products should be clearly identified and segregated from working investigational products. The sponsor should be contacted as soon as practicable, and investigational products should only be made available for dispensation when authorised by the sponsor. A file note or record of correspondence regarding the quarantine incident should be kept in the clinical trials pharmacy folder.

Expiry date monitoring

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

Dispensing of Investigational Products

Specific dispensing instructions should be developed per-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 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, or if not listed that the prescriber is authorised by the Principal Investigator (PI). Approval for this authorisation from leading or local HREC is not necessary
- Addition: Verification that the prescriber is an authorised prescriber as per State & Territories legislation e.g. unregistered Schedule 8 medication must be authorised by state authority
- verification that the participant (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
- the requirement for a second check of all randomised prescriptions
- completion of accountability records
- completion of batch records for compounded items
- 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 PI
- name, strength and dosage form of the investigational product
- participant initials (as required)
- 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 participant-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 investigational product 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 investigational product accountability records. Returned investigational product should be stored such that it is clearly distinguishable from undispensed investigational product 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 participant confidentiality. Re-dispensing of returned investigational products should only be performed in exceptional circumstances.

For any potentially dangerous or contaminated products used or unused by participants (e.g. needles, syringes, broken ampoules) participants should be supplied with an appropriate sealed container provided by the sponsor. The handling of dangerous or contaminated investigational products should be consistent with work health and safety or occupational health and safety Acts and Regulations, as well as any relevant local, state, or Commonwealth policies. If a potentially dangerous or contaminated investigational product is returned to Pharmacy, it is recommended that this is destroyed as soon as possible after receipt, by usual pharmacy procedures.

For returned investigational products and particularly for oral cytotoxic and other hazardous medicines gloves should be worn and counting devices cleaned after each use as per relevant local guidance 22,23,27.

Transfer/Distribution to other Institutions

Investigational product should only be transferred to another site with the permission of the investigator and the sponsor. All transfers should be recorded on the investigational product 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. Transfer of cytotoxic medicines or genetically modified products that are also investigational products requires additional precautions 22,23.

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

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 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 investigational product is damaged
- the sponsor has requested the return of the investigational product.

Alternatively, the sponsor may authorise the destruction at the clinical trials 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 procedures.

All returns of investigational product approved for destruction should be recorded in the investigational product accountability records, with details recorded including batch/kit numbers, quantity, and date of destruction. Destruction records should also be completed and kept in the pharmacy file detailing the investigational product, strength, batch/kit number, expiry (re-test) date, quantity, and date of destruction. In addition, records of randomisation codes returned to the sponsor or destroyed should be recorded.

Retention and Archiving of Records

All records relating to the clinical trial should be retained in a secure accessible place following trial closure for a minimum of 15 years for adult participants and 25 years for paediatric participants, or for longer if required by the sponsor. The clinical trials pharmacy service should have an SOP for archiving of 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 have guidance regarding retention and archiving of records.

Documentation

Standard Operating Procedures (SOPs)

The clinical trials pharmacy service should have written SOPs for all standard services such as clinical trial set up, receipt of the investigational product, temperature monitoring, archiving, etc.

File Notes

Any event occurring during the administration of a clinical trial which is unexpected, unusual, or falls outside 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

Documentation of 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 re-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 the best practice to ensure protocol compliance and safe and appropriate use of investigational products.

An information leaflet may be used to assist this process, and verbal education should reinforce written information. Information leaflets provided to participants will require HREC and sponsor approval.

Monitoring Compliance

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 for the correct use of the investigational product
- counsel participants to return all investigational product 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 the 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 IB 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, IB (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. Liaison with clinical pharmacists, medical and nursing staff are encouraged to assist in the early detection of an unexpected participant admission to hospital (classified as a SAE). 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 notified.

Randomisation Codes

IWRS systems for randomisation are now 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 an 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 clinical trials 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, compounding and aseptic manufacture of investigational products
- sufficient and secure storage space (including refrigeration/freezers) to allow separation of the investigational product for each clinical trial (including investigational product 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
- a 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 and services
- 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: Resource documents required for use.
Recommended Staffing

The staffing structure and levels required for a clinical trials pharmacy service will be determined by four major factors: (1) the number of clinical trials undertaken at the institution, (2) the complexity and phase of those clinical trials; (3) the rate at which new trials are being opened and closed; and (4) participant recruitment.

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

Workload

Workload records can help in costing and determine staffing levels for clinical trials pharmacy services. Workload records could include:

- the number of dispensings by category e.g.
  - simple dispensing (average dispensing and recording time less than 15 minutes)
  - standard dispensing
  - complex dispensing (dispensing and recording time greater than 45 minutes)
  - sterile preparations
  - sterile cytotoxic preparations
- the number of clinical trials opened and closed
- the number of monitor visits
- the number of occasions and details of advice/education given concerning concomitant medications, protocol compliance, dose modifications, etc.

Training and Education

It is essential to develop the pharmacy workforce through the training and education of pharmacists and technicians to enable the delivery of best practice in clinical trials. 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. Ongoing education and training are important to ensure compliance with the requirements of state and federal legislation as well as professional standards and guidelines.

Clinical trials pharmacists should have a scope of practice competency profile with a continuing professional development (CPD) plan that covers the five domains of professional performance as per the National Competency Standards Framework for Pharmacists in Australia 2016. Although the framework itself is not tied to any area of specialisation, for clinical trials pharmacists there are qualifications, educational activities, knowledge, and skills that are recommended in addition to those of a clinical pharmacist. These have been informed by the SHPA Clinical Trials Leadership Committee.
Credentialing and Qualifications

Desirable certification, credentialing and qualifications for clinical trials pharmacists include:

- a postgraduate qualification in clinical pharmacy
- credentialing as an Advancing or Advanced Practice Pharmacist provided by Pharmacy Development Australia.

Educational Activities

Recommended continuing education activities for clinical trials pharmacists include those offered by the following organisations:

Domestic:
- SHPA Seminars and SHPA online 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.

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

- TGA publications, newsletters, and seminars
- NHMRC seminars and publications.

Educational material and resources are additionally provided on the SHPA Specialty Practice clinical trials stream page on the SHPA online CPD 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.

Knowledge, Skills and Experiential Learning

Pharmacists responsible for investigational products which are not currently registered for human use in Australia should have a detailed knowledge of the process of medicines regulation in Australia. Pharmacists in contact with participants will need to be knowledgeable about their specific protocol.

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

Desirable skills include:

---

1 This is a limited list offered for general information and does not represent endorsement of any particular provider; new providers may emerge, and this list is current as of July 2019.
knowledge of basic research methodology
• a postgraduate qualification in a field related to clinical trials e.g.
  o drug development or pharmacology
  o credentialing as an Advancing or Advanced Practice Pharmacist.
• training and education in manufacturing of cytotoxic and hazardous substances.

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

• undergraduate pharmacists
• provisionally registered pharmacists
• practising pharmacists involved with participants
• pharmacy technicians involved with participants
• research nurses and clinical trial co-ordinators
• research data managers
• other health professionals involved with participants.

Clinical trials pharmacists should undergo evaluation of their clinical skills through the clinCAT (version 2).

Training and education will predominately be work-based education and should follow adult learning principles. Further information can be found in Chapter 10 of the SHPA Standards of Practice for Clinical Pharmacy Services.

Key Performance Indicators

Key performance indicators (KPIs) should be developed for the major components of the clinical trials pharmacy service. Suggestions for KPIs 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 (number of scripts and participants/month)
• number of requests for costing quotes (services)
• number of SSVs
• number of SIVs
• number of compounded items/complexity of compounding
• uncovered leave (e.g. sick leave) and overtime
• protocol amendments and/or review
• performance at GCP audit and/or during monitoring visits.

The frequency of data collection and the number of indicators chosen will depend on the size and scope of the clinical trials pharmacy service. 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.

The Australian Commission on Safety and Quality in Health Care and the Australian Government Department of Health, in consultation with clinical trial experts and representatives from all Australian states and territories, is developing the National Clinical Trials Governance Framework for
public and private healthcare organisations and trials sites to support the delivery of high-quality clinical trials.

Research

Clinical trials pharmacists are encouraged to participate in and contribute towards advancing the knowledge and evidence for investigational products and research. Clinical trials pharmacists are likely to be well-positioned with opportunities for research, particularly so for investigator-driven studies where investigators may approach the clinical trials pharmacist for advice, resources, and solutions to address challenging clinical trials or investigational product issues. It is advisable to clarify and establish upfront if the work and services provided by the clinical trials pharmacist mean an invitation for formal collaboration on the protocol 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. investigational product encapsulation, blinded aseptic products)
- assessing the chemical stability of drug in an investigational or off-label formulation.

External funding enables larger and possibly multi-centre studies to be conducted. The SHPA 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/participant care.

The choice of a 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, including 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 for 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

<table>
<thead>
<tr>
<th>Resource documents required for use</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Therapeutic Goods Administration. ICH Harmonised Guideline. Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice-Annotated with TGA comments 2018 5</td>
</tr>
<tr>
<td>• Australian clinical trial handbook: Guidance on conducting clinical trials in Australia using 'unapproved' therapeutic goods ACT 2018 15</td>
</tr>
<tr>
<td>• NHMRC National Statement on Ethical Conduct in Human Research 16</td>
</tr>
<tr>
<td>• Protocols and investigator brochures (IB)/TGA approved product information for all clinical trials;</td>
</tr>
<tr>
<td>• Access to unapproved therapeutic goods - the special access scheme (SAS) 30</td>
</tr>
<tr>
<td>• Human research ethics committee and the therapeutic goods legislation 15,31</td>
</tr>
<tr>
<td>• NHMRC. Values and ethics: guidelines for ethical conduct in Aboriginal and Torres Strait Islander health research 32</td>
</tr>
</tbody>
</table>

Additional documents that may be of use

• European Association of Hospital Pharmacists (EAHP) Statement on Clinical Trials 2012 33

Useful Websites

<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Australian New Zealand Clinical Trials Registry (ANZCTR)</td>
<td><a href="http://www.anzctr.org.au/">http://www.anzctr.org.au/</a></td>
</tr>
</tbody>
</table>

Appendix 2: Definitions

<table>
<thead>
<tr>
<th>Clinical Trial Terms</th>
<th>Definition</th>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse Event (AE)</td>
<td>Any undesired action or effect of an investigational medicine that occurs during or within a proscribed 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>
</tbody>
</table>

765
766
768
| Phase I Study | 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 participants suffering from the condition the medicine is intended to treat | To determine the safety of the medicine, its pharmacological activity, pharmacokinetics, and tolerance. It may also identify routes of administration and appropriate doses. |
| Phase II study | The first trial of the medicine in a small number of closely supervised participants suffering from the condition for which the medicine is intended | To determine efficacy and safety, therapeutic dose range and maximum tolerated dose of the medicine |
| Phase III study | Extended clinical trials in greater numbers of participants | To generate clinical efficacy data and determine the incidence and nature of adverse events |
| Phase IV study | Postmarketing studies | To compare the medicine to a wider range of therapies and further investigate the use of the medicine in the normal clinical setting |
| Clinical Trial Exemption Scheme for Medicines (CTX) | A sponsor submits an application to conduct a clinical trial to the TGA for evaluation and comment | Notification under CTX or CTN is required for clinical investigation of  
a) Any medicine not entered in the Australian Register for Therapeutic Goods (ARTG)  
b) Any use of a marketed medicine beyond the conditions of its marketing approval |
<p>| Clinical Trial Notification Scheme (CTN) | The sponsor notifies the TGA that a clinical trial is to be conducted. The HREC takes responsibility for the review of the data |  |
| Good Clinical Practice (GCP) | A standard for the design, conduct, performance, monitoring, auditing, recording, analysis and reporting of clinical trials | 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 |</p>
<table>
<thead>
<tr>
<th><strong>Human Research Ethics Committee (HREC)</strong></th>
<th>An institutional committee whose composition and function is consistent with the National Statement on Ethical Conduct in Human Research and has notified its existence to the Australian Health Ethics Committee</th>
<th>To evaluate and monitor the conduct of clinical trials conducted within an institution</th>
</tr>
</thead>
<tbody>
<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>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>
</tr>
<tr>
<td><strong>Investigator</strong></td>
<td>The 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 Brochure (IB)</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>To direct the conduct and evaluation of a clinical trial</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</td>
<td></td>
</tr>
<tr>
<td>Persistent or significant disability/incapacity, or - is a 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>
<tr>
<td>---</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suspected Unexpected Serious Adverse Reaction (SUSAR)</td>
<td>Sometimes during a clinical trial for a certain investigational product, 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</td>
<td></td>
</tr>
</tbody>
</table>