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Clinical Trials: Guidelines for Pharmacies in Healthcare Institutions

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Clinical Trials: Guidelines for Pharmacies in Healthcare Institutions

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Introduction

This is the 2013 version of the Canadian Society of Hospital Pharmacists (CSHP) Official Publication entitled *Clinical Trials: Guidelines for Pharmacies in Healthcare Institutions*. These consensus-based guidelines, approved by the CSHP Council in 2013, replace the 2001 version of *Clinical Trials: Guidelines for Pharmacies in Healthcare Facilities* (originally entitled *Guidelines for Use of Drugs in Clinical Trials in Health Care Facilities*).

CSHP acknowledges the contributions of a group of CSHP members in the development of these guidelines.

High-quality systems that support clinical trials without compromising the participants stand to improve the quality and efficiency of such trials. With such systems in place, investigators, regulators, and others are better positioned to draw meaningful conclusions and interpretations about the safety and efficacy of a treatment on the basis of high quality data.[1] These guidelines have been written to assist pharmacy departments of healthcare institutions in developing their own high-quality systems in support of clinical trials involving investigational products.

1 Scope

Building on the Guideline for Good Clinical Practice[2] of the International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH), the current guidelines define the roles and responsibilities of pharmacists and other pharmacy personnel with regard to supporting clinical trials involving investigational products.

These guidelines detail the policies and procedures that should be in place for the role of pharmacy in managing a clinical trial in a healthcare institution (hereafter referred to as an institution), to help promote safety and to ensure the integrity of the research data; they do not replace federal or provincial legislation governing the use of investigational drugs.

These guidelines do not address the procedures for designing drug trials or for accessing drugs through Health Canada's Special Access Programme, nor do they describe how to undertake a clinical trial or other research. For information regarding how to undertake a study, the reader is referred to CSHP's official publication entitled Research: Guidelines on Conducting Research in Pharmacy, published in 2011. For information regarding Canada's Special Access Programme, the reader is referred to Health Canada.

2 Glossary

The following definitions apply to terms used in these guidelines. They may have different meanings in other contexts.

Audit	A review or inspection of the conduct of a clinical trial, including documentation, to evaluate whether the protocol, sponsor's standard operating procedures, Good Clinical Practice, and regulatory requirements were followed.
Clinical trial	"Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy. The terms clinical trial and clinical study are synonymous."[2]
Good Clinical Practice	"A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected."[2]
Informed consent	A formal process by which an individual agrees to be a trial participant, after being informed appropriately and thoroughly about the study.
Institutional review board (IRB)	"An independent body constituted of medical, scientific, and non-scientific members, whose responsibility is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial by, among other things, reviewing, approving, and providing continuing review of trial protocol and amendments and of the methods and material to be used in obtaining and documenting informed consent of the trial subjects."[2]
Investigational product	"A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use."[2]
Investigator's brochure	Document (developed by the sponsor) that includes preclinical and clinical data for an investigational product.[3] Note: The reader is referred to the Food and Drugs Regulations for a complete list of the information to be included in the brochure.

Monitor	An individual who oversees the conduct of a clinical trial on behalf of the sponsor to ensure that the investigators and others are following all applicable regulatory requirements.
Participant	"An individual whose data, or responses to interventions, stimuli, or questions by a researcher are relevant to answering a research question; also referred to as "human participant," and in other policies/guidance as "subject" or "research subject."[4] Note: In keeping with spirit of the Tri-council policy statement,[4] this set of guidelines prefers the term "participant" over "subject" because the term reflects a more active role played by individuals, rather than the more passive role that the term "subject" connotes.
Phase I	"Initial safety studies on a new drug, including the first administration of the drug into humans, usually conducted in healthy volunteers. These trials may be conducted in patients when administration of the drug to healthy volunteers is not ethical. Phase I trials are designed mainly to determine the pharmacological actions of the drug and the side effects associated with increasing doses. Pharmacokinetic as well as drug-drug interaction studies are usually considered as Phase I trials regardless of when they are conducted during drug development as these are generally conducted in healthy volunteers. Phase I trials also include trials in which new drugs are used as research tools to explore biological phenomena or disease processes."[5]
Phase II	"Clinical trials to evaluate the efficacy of the drug in patients with medical conditions to be treated, diagnosed or prevented and to determine the side effects and risks associated with [the] drug. If a new indication for a marketed drug is to be investigated, then those clinical trials may generally be considered Phase II trials."[5]
Phase III	"Controlled or uncontrolled trials conducted after preliminary evidence suggesting efficacy of the drug has been demonstrated. These are intended to gather the additional information about efficacy and safety that is needed for further risk/benefit assessment of the drug. In this phase, clinical trials are also conducted in special patient populations (e.g., renal failure patients), or under special conditions dictated by the nature of the drug and disease."[5]

Phase IV	"All studies performed after the drug has been authorized by the regulator for the market, and related to the authorized indication. These studies are often important for optimizing the drug's use. They may be of any type but must have valid scientific objectives. Commonly conducted studies include safety studies and studies designed to support use under the authorized indication such as mortality and morbidity studies, or epidemiological studies."[5]
Principal investigator	"The leader of a research team who is responsible for the conduct of the research, and for the actions of any member of the research team."[2] Where the clinical trial is funded by a sponsor, the principal investigator is responsible to the sponsor.
Protocol	The document that outlines the procedures of a clinical trial.
Sponsor	"An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial."[2]

3 Administration and Governance

The use of investigational products is subject to the authority of Health Canada, and as such must comply with ICH's *Guideline for Good Clinical Practice*.[2] Each investigational product shall be used only according to a pertinent clinical trial protocol that has been approved by an institutional review board (IRB), with determination and evaluation of participants' rights, ethical issues, investigators' responsibilities, scientific validity, and legal and therapeutic issues.

Subject to the decision of Health Canada, the institution shall have final authority as to whether a particular clinical trial will be run under its auspices.

All clinical trials shall be reviewed and approved by at least one IRB before the trial may start.

3.1 Institutional Review Board

The institution's IRB should include at least one pharmacist, to help identify drug-related issues (e.g., pharmacokinetics, drug interactions, adverse events, medication safety issues, general knowledge of drugs) that might arise in the conduct of clinical trials. The IRB should request disclosure of any (real or perceived) conflict of interest before discussions of any protocols begin.[6] To minimize conflicts of interest, the pharmacist who is a member of the IRB should ideally not be the clinical trials pharmacist, nor should this person be involved in the manufacture of the investigational product.

Note: For more information about IRBs, refer to Chapter 6, Governance of Research Ethics Review, in the Tri-Council Policy Statement: Ethical Conduct for Research involving Humans[4] and the ICH Guideline for Good Clinical Practice E6(R1).[2]

3.2 Institutional Policies and Procedures

Each institution should develop a set of policies and procedures for using, processing, and handling investigational products.[7] Such policies and procedures shall be endorsed and upheld by the institution's administration and medical authority.

The policies and procedures manual should cover the following topics:

a) review of proposals for clinical trials;[1]
b) protection of participants;[1]
c) inventory management for clinical trials;
d) prescribing, dispensing, and administering of investigational products;
e) access to breaking the randomization codes;
f) managing data,[1] documentation and record-keeping;
g) quality control;
h) conflict of interest;
i) handling misconduct;[1]
j) reimbursement for services; and
k) other topics as deemed appropriate to the particular institution.

All institutions, including those that do not run clinical trials, should have policies and procedures to address how an investigational product will be handled when a trial participant is admitted to the institution.

3.3 Role of Principal Investigator

The ultimate responsibility for use of an investigational product for a participant shall reside with the principal investigator.

In accordance with the ICH Good Clinical Practice guidelines E6 (section 4.3), the principal investigator shall be a "qualified physician (or dentist, when appropriate), who is an investigator or sub-investigator for the trial [and who] should be responsible for all trial-related medical (or dental) decision.";[2] this applies to clinical trials in Phases I to III.

The principal investigator should secure the resources necessary to cover the costs of the study.

3.4 Role of the Pharmacy Department

The pharmacy department is responsible for providing the following services related to clinical trials:

a) managing the inventory of investigational products, including acquisition, storage, and dispensing;
b) promoting the safe handling and administration of investigational products;
c) promoting compliance with the study protocol and legislative framework in all matters related to investigational products;
d) maintaining a drug information file on each investigational product being prescribed in the institution; and
e) ensuring that patients who are participants in a clinical trial are assessed by a pharmacist in the context of their respective conditions and total drug therapy, as would be the case for any other patient.

Pharmacy personnel actively involved in a particular study should participate in the site selection meeting, the site initiation meeting, and/or the investigator meeting to help determine the resources required to support the clinical trial and to gain insight regarding the particulars of the investigational product and the study protocol.

The pharmacy department may also play a role in the following activities:

a) developing the clinical trial protocol;
b) coordinating the study across multiple sites;
c) preparing randomization codes;
d) preparing and packaging special dosage forms;
e) developing information for healthcare providers who will be administering the investigational product and/or monitoring the participants;
f) developing information for participants;
g) enrolling persons as participants in the study;
h) monitoring participants' responses to treatment;
i) analyzing the results; and
j) disseminating the results of the trial (e.g., poster presentations, manuscripts for publication).

3.5 Relationship between Pharmacy Services and Research Team

To facilitate the fulfilment of responsibilities by pharmacy personnel, the pharmacy department should have an effective working relationship with the IRB, the principal investigator, the research team (including sponsors and auditors), and the pertinent regulatory authorities.[6]

The roles and responsibilities of each team member shall be clearly articulated (by the Qualified Investigator) and shall be understood and accepted by the research team.[1, 8] The research team should also document the delegation of duties that may occur during the clinical trial; this log should be routinely reviewed and revised as needed.[1]

The pharmacy department should establish a service agreement with the principal investigator, outlining the services to be provided by the department and the costs (if any) to be reimbursed by the study sponsor.

4 Pharmacy Resources

Before participating in any study, the pharmacy department should ensure that it has adequate resources (people, space, equipment, and supplies) and infrastructure to support the clinical trial according to the ICH's Guidelines for Good Clinical Practice, the institution's policies and procedures, and the study protocol.

4.1 Human Resources

The pharmacy department should have a designated staff member who is responsible for the overall provision of pharmacy services for clinical trials involving investigational products. Additional pharmacy personnel may be assigned as needed, to give further support to clinical trials.

The designated person shall be appropriately trained to execute the responsibilities associated with this role.

All pharmacy personnel involved in clinical trials shall be knowledgeable and trained regarding the relevant procedures and the risks associated with non-compliance with those procedures. Personnel should have a working knowledge in the following topics, as they relate to clinical trials:

a) regulatory requirements;[9]
b) IRB review procedures;[9]
c) protection of human participants;[1]
d) ethical conduct,[9] guidelines, principles, and philosophical presuppositions (e.g., clinical equipoise, uncertainty principle) relating to clinical trials;
e) misconduct and fraud (types, implications, preventive measures, response to suspicions);[9]
f) conflicts of interest;[9]
g) data management;[9]
h) Good Clinical Practice;
i) IRBs;[9] and
j) all applicable policies and procedures.

The pharmacy department should maintain records of the qualifications and training of pharmacy personnel involved in clinical trials. Such personnel should undergo testing of their skills and knowledge.[1]

All pharmacy personnel actively involved in a particular study should be adequately trained to execute their responsibilities before the study begins. Records of training specific to the study protocol should be archived with the pharmacy's records for that study, for reference during subsequent audits or other reviews.[6]

In instances where pharmacy personnel who are actively managing clinical trials need to delegate certain responsibilities to other pharmacy personnel, adequate training and education must be provided or made readily available. Such education can be implemented in various ways, including written formats and in-service programs.

4.2 Facilities

The design of the pharmacy department's premises should provide sufficient space to support the anticipated volume of work and the orderly and suitable storage of investigational products and records.

4.3 Policies and Procedures

The pharmacy department shall implement policies and procedures that comply with legislative and local requirements relating to clinical trials. The policies and procedures should address the following topics:

a) training of staff;
b) review of draft protocols by pharmacy personnel;
c) inventory management of investigational products (including acquisition, receipt, storage, dispensing, removal, destruction, or return);
d) review of prescriptions by a pharmacist;
e) drug information;
f) controlled substances;
g) hazardous substances;
h) audits;
i) records management;
j) access to pharmacy after hours to dispense investigational products or to break the randomization code;
k) reimbursement for pharmacy services (see section 4.4); and
l) quality management.

The policies and procedures should be critically reviewed on a scheduled, periodic basis and revised as needed.[1]

4.4 Reimbursement of Expenses

The pharmacy department should establish a fee schedule that reflects the general costs of workload and supplies for most studies. The schedule should be reviewed annually.

Expenses related to obtaining, preparing, and distributing the investigational product and to collecting and analyzing the data should be reimbursed (e.g., from a grant source or by the pharmaceutical manufacturer). Estimates of these expenses (based on the fee schedule) should be provided to the principal investigator, as part of the service agreement (see section 3.5), before the study begins. The pharmacy department should ensure that the service agreement describes the arrangements for reimbursement.

Pharmacy management should work with the healthcare organization's finance department to create procedures for invoicing and collecting payment for clinical trials.

5 Review of Protocols for Clinical Trials Involving Investigational Products

Designated pharmacy staff shall review each clinical trial protocol before the trial begins. The review should include an assessment of the feasibility of the study,[6] the extent of the work to be done, and an estimate of the costs to the pharmacy department of providing the service.[6]

The pharmacy's designated clinical trials personnel shall ensure that an up-to-date version of each investigator's brochure and associated study protocol are received and kept by pharmacy.

For each clinical trial, the pharmacy's designated clinical trials personnel should understand the following aspects of the trial and should engage in discussions with the principal investigator (or designate) as needed. The personnel should be given enough time to allow a risk assessment of the product (including the label) before any dispensing of the product occurs.[6]

General information about the trial:

a) purpose of the trial;

b) content of the investigator's brochure;
c) enrolment criteria and expected number of trial participants, including whether the study is limited to participants who have been hospitalized or those being seen in a clinic or ambulatory setting;
d) anticipated timeline for the study;
e) responsibilities of the parties involved in the study;
f) how the investigational product will be prescribed (e.g., according to template forms) and by whom;
g) who is authorized to administer the investigational product;
h) known clinical risks of how the investigational product might differ from products used in routine practice;[6]
i) medication safety issues for the participant;
j) applicability of regulations and guidelines for Good Clinical Practice to the study;[6]
k) specific training requirements for pharmacy staff;
l) management of ongoing treatment after the study is completed (if relevant);
m) forms to be completed and retained by pharmacy personnel;
n) requirements for record storage; and
o) cost of pharmacy services to support the trial in accordance with Good Clinical Practice guidelines, local procedures, and the study protocol.

Information about the investigational product:

a) source and quality of the investigational product and any comparators that will be used;[6]
b) process for procurement of the investigational product and any comparators to be used;
c) additional supplies related to the study that will be provided by the study sponsor;
d) storage requirements for the investigational product[10] (location, space, environmental conditions, and methods of access);
e) how the investigational product is to be prepared, dispensed, and administered, including information about any special equipment required or to be avoided (e.g., closed system drug transfer device, in-line filters);
f) occupational health and safety concerns related to the handling, preparation, and administration of the investigational product;[6]
g) requirements for labelling and packaging of the investigational product;[6]
h) cost of the investigational product to the hospital or participant;[6] and
i) procedures for handling any returned, unused, or contaminated investigational products.

Randomization and breaking the randomization code (if applicable):

a) method of and responsibility for randomization;
b) use of codes for randomization; and
c) procedures for holding and breaking codes.[6]

6 Inventory Management

The pharmacy department shall be responsible for managing the inventory of investigational products within the healthcare organization.

In particular, a system should be in place to ensure an adequate supply of the investigational product for the duration of the study.

6.1 Location of Investigational Products

Investigational products shall be stored in a secure storage area within the pharmacy, separate from the inventory areas for non-investigational products, to prevent or minimize errors in product selection. When the same investigational product is being used in more than one concurrent clinical trial at the institution, care shall be taken to not draw stock from one central location; rather, separate stocks of the product should be stored according to each clinical trial protocol.[11]

Provisions should be in place to prevent unauthorized personnel from entering any area where investigational products are stored.

An investigational product should not be held outside the pharmacy's storage area (e.g., inpatient care unit or clinic area) unless the study protocol stipulates the possible need for urgent administration of the product.[7]

Regardless of storage location, policies and procedures should be in place to provide for urgent access to investigational products, as relevant.

When an investigational product is held outside of the pharmacy for potential urgent administration, a sufficient volume of stock should be maintained. In such situations, adequate controls shall be in place to ensure that the investigational product is securely and safely stored. All arrangements for storing, packaging, labelling, dispensing, and disposing of, or returning investigational products stored outside of the usual pharmacy storage area should conform to the relevant study protocol and should be subject to the approval of the pharmacy department. Compliance with the study protocol and with departmental policies and procedures to secure and account for the investigational product is the responsibility of the principal investigator.

Under all circumstances, the pharmacy department should maintain the necessary controls (including documents for record-keeping and conducting routine audits) to secure and account for investigational products held in the pharmacy and any satellite areas where investigational products are stored for urgent use.

6.2 Storage Conditions

Investigational products shall be stored as required by the sponsor and in accordance with applicable legislation.[2]

The areas used to store and handle investigational products should be kept clean and orderly.

Environmental controls shall be used to maintain the temperature and humidity of these areas within acceptable limits. Refrigerators and freezers should have temperature-recording devices with alarms to signal when the temperature deviates outside acceptable limits.

The environmental conditions of refrigerators, freezers, and the storage area in general shall be regularly monitored and recorded. All deviations from acceptable limits shall be investigated according to established policies and procedures.

6.3 Reconciliation of Inventory

Upon receipt of any investigational product, pharmacy personnel should reconcile the quantity of drug received against the sponsor's records of what was to be shipped. Shipments that are incomplete or otherwise faulty (e.g., breaking a cold chain) shall be promptly investigated by authorized pharmacy personnel. Periodically, staff should count inventory stock on hand and compare the resulting value with the book records for the investigational products. All discrepancies shall be investigated, and any unaccountable differences shall be promptly reported in accordance with the study protocol (or to the principal investigator if the protocol does not address this issue).

6.4 Unused or Unusable Investigational Products

All returned, unused, or contaminated investigational products shall be quarantined, away from other investigational products and regular pharmacy inventory and then properly disposed of, or returned to the sponsor, as per the study protocol.

7 Records Management

The pharmacy shall implement policies and procedures to manage records arising from clinical trials, in accordance with legislative and local requirements and the respective study protocols.

Standardized procedures should be employed for handling documents, including naming conventions, tracking, filing, back-up of data, and version controls.[1] These procedures should support the prompt retrieval of current and archived study files and operational documents (policies and procedures, quality control forms, etc.)

Records that account for each investigational product, and such other records as specified in the clinical trial protocol, shall be kept. The systems used to record the information may be electronic or paper-based.

7.1 Records to be Maintained

The pharmacy department shall maintain a variety of documents, including amendments, relevant to any clinical trials in which the institution participates.[6]

These records shall include information about the following topics:

a) the investigational product (see more detailed information below in this section);
    i) receipt of the investigational product in pharmacy (see more detailed information below in this section);
    ii) quantities of inventory (physical and records of stock on hand);
    iii) activities related to the dispensing of the investigational product (see more detailed information below in this section);
    iv) expired product, wastage, and other forms of stock loss (see more detailed information below in this section);
    v) returns to the sponsor or alternative authorized disposition or destruction of unused product(s) (see more detailed information below in this section)
b) training records (see section 4, Pharmacy Resources);
c) signature logs for staff involved in clinical trials;[6]
d) activities to be performed to reconcile all inventory records.

If the investigational product was not provided by the study sponsor, the pharmacy department should also maintain records of all orders and shipments received and subsequently used for investigational purposes.

The pharmacy department should also record the storage conditions under which the investigational product is stored.[6]

At a minimum, the following information specific to the investigational product shall be maintained:

a) name of the product;
b) dosage form and strength;
c) lot number;
d) expiry date;
e) protocol number;
f) name of the sponsor; and
g) information for re-ordering the drug.

The following information about receipt of the investigational product shall be maintained:

a) date of receipt;
b) quantity received; and
c) identity of the person who accepted the shipment.

Information about the dispensing (or return to stock) of the investigational product should be maintained, including but not limited to the following records:

a) protocol number assigned to the clinical trial;
b) name of the clinical trial site;
c) identity of every trial participant (e.g., name, initials, or code number assigned);
d) dose and quantity of the investigational product dispensed (or returned to stock);
e) quantity of product transferred to other institutions and date of transfer (if applicable); and

f) identity of any persons involved in the dispensing (or return) of the investigational product.

Dispensing information for an investigational product given on an outpatient basis shall be entered in the patient's provincial record of prescriptions (e.g., in PharmaNet).

The following records shall be maintained regarding any expired investigational product, wastage, and other forms of stock loss (including dispensing or handling errors), as well as destruction and disposal of investigational products:

a) date;
b) quantity expired, wasted, destroyed, or otherwise disposed of;
c) lot number;
d) expiry date (if applicable);
e) unique code numbers assigned to the investigational product and trial participants (as applicable); and
f) identity of any persons involved in the disposal of the investigational product.[7]

The following records shall be maintained regarding investigational products returned to the sponsor:[2]

a) date;
b) quantity returned;
c) serial/batch number;
d) expiry date (if applicable); and
e) unique code numbers assigned to the investigational product and trial participants (if applicable).

7.2 Retention of Records

Drug accountability records shall be retained for the period of time specified by the protocol and appropriate regulations.

Note: The Food and Drug Regulations stipulate that certain records relating to a clinical trial must be retained for 25 years.[3]

7.3 Data Integrity

Pharmacy personnel shall maintain the scientific integrity of every study by maintaining accurate and complete records as per the protocol, and by ensuring that the correct product (as it relates to the relevant study arm) is dispensed, according to treatment allocation.

In blinded studies, treatment allocation should not be revealed unless the conditions set forth in the study protocol are met.

Safeguards should be in place to prevent breaches of confidentiality. Records relating to the clinical trial should be accessible only to authorized personnel. Swift corrective action shall follow any breach of participant confidentiality; such corrective action must include reporting the incident to the IRB.[1]

7.4 Privacy and Confidentiality of Information about Participants

Pharmacy personnel shall ensure that the privacy and confidentiality of participants' information are safeguarded. Documents or materials about the study that are taken out of the institution should not contain any information of a personal health nature.

8 The Start of a Clinical Trial

Pharmacy staff shall not dispense any doses of an investigational product for a clinical trial until the pharmacy department has received written confirmation that the following conditions have been met:

a) the IRB has authorized the start of the trial at the study site;
b) the granting or contracting agency has approved funding for the study (if applicable); and
c) for clinical trials of Phases I to III of drug development and comparative bioavailability, Health Canada has issued a "No Objection Letter," which is required regardless of

whether the investigational product is already marketed in Canada or if the use of the product under investigation would be outside the authorization given under a Notice of Compliance or Notice of Compliance with Conditions (not required for Phase IV trials).[12]

Before the study begins, pharmacy personnel should review the final copy of the study protocol, the latest version of the investigator brochure, and related policies and procedures. Beta-testing of the procedures should be conducted before the first participant is enrolled in the study.[1] Corrective measures should be taken as required to ensure that pharmacy personnel can follow the protocol correctly.

8.1 Dispensing for a Clinical Trial

Clinical trials may involve drugs with or without prior market authorization. As such, some investigational products may be unfamiliar to personnel who are required to handle them. In this situation, additional precautions should be taken to ensure that the products are handled safely and securely.[7]

Investigational products shall be dispensed only under the following conditions:

a) receipt of a written (i.e. non-verbal) prescription from an investigator who is authorized to prescribe for the clinical trial for which the products are intended; and
b) receipt of evidence that the person for whom the prescription is provided is enrolled as a participant in the study.

Consideration should be given to using a standardized order form for prescribing investigational products, to reduce the potential for medication incidents involving these products.[13, 14] The following information should be included in the standardized order:[14]

a) study protocol number and/or name;
b) participant identifier (participant number or randomization number);
c) study visit (as defined in the protocol) number;
d) sponsor identity (e.g., pharmaceutical manufacturer);
e) designation given to the investigational product (e.g., code name);
f) dosage and quantity to be dispensed per study protocol;
g) names and contact information of persons authorized to prescribe the investigational product prescribers.

Investigational products shall be dispensed according to established departmental policies and procedures, including documentation in each participant's medication profile and medication administration record. The identities of all personnel involved in the dispensing,[7] administration,[7] and follow-up monitoring of investigational products should be recorded.

Policies and procedures for handling partially or completely empty containers (e.g., vials) should be developed, to ensure that any quantity of the investigational product remaining after administration is handled safely, correctly, and in accordance with the study protocol.

Records of investigational products dispensed should be completed at the time when the drug is dispensed.

The pharmacy should be able to reconcile records of stock received from the study sponsor and records of investigational products administered to participants and the quantity of remaining stock on hand.

All dispensing of the investigational product shall cease when a clinical trial is suspended, discontinued, or terminated.

8.1.1 Labelling and packaging

To ensure safe handling and administration of the investigational product, the immediate packaging of the product should be labelled according to the institution's policies and procedures for non-investigational products, with the following additional information:

a) an indication that the product is an "investigational product" or an "investigational drug" or a "study drug"; and
b) the protocol code or identification.

When the study sponsor permits repackaging of an investigational product, the label affixed to the new package should provide the relevant information given on the original package and any additional information required to comply with the organization's drug-labelling procedures.

When the study sponsor does not permit repackaging of an investigational product, an additional label should be affixed to the package, displaying all necessary information according to the organization's drug-labelling procedures. Care must be taken to ensure that the additional label does not conceal any information on the original container.[10]

Care should also be taken to ensure that the code name given to the drug by the study sponsor is not altered, which could introduce the potential for confusion with codified names of other products from the same or a different sponsor.

To facilitate access to information about the study drug in an emergency situation, the pharmacy's telephone number should be provided on the label.[11]

Note: The Food and Drug Regulations[3] set forth labelling requirements for Canadian drug products, which the sponsor is expected to ensure are followed; investigational products that are radiopharmaceuticals have additional labelling requirements.

8.1.2 Blinded Labelling

In clinical trials where blinding must be maintained, the prescription label shall designate the possible identities and strengths of the product(s) that the participant could receive in the study, e.g., "drug name x mg or placebo".

8.2 Provision of Information about the Investigational Product

Pharmacy personnel involved in the study should collate information about the investigational product in a form that can be made readily accessible to the appropriate healthcare personnel if needed. This information should include a summary of the study protocol and any information about the investigational product that is provided in the investigator's brochure.

The first time that a product (e.g., investigational product, placebo) is dispensed in a study, pharmacy personnel or the principal investigator (or designate) shall provide, or make readily accessible, the following information in the area where the investigational product is to be administered and the participant monitored:

a) summary of the study protocol;
b) name, strength(s), dosage form(s), and therapeutic classification of the investigational product;
c) any synonyms for the name of the investigational product;
d) pharmacological action of the investigational product;
e) dosage range;
f) dosing regimen for the study (investigational product name, dose, route of administration, dose frequency);
g) expected therapeutic effects;
h) processes to correctly use and store the investigational product once it has been dispensed;[6]

i) exact method of administration, including diluent and rate for intravenously administered products;
j) stability and storage requirements, as well as method of disposal of unused investigational product;
k) all known or suspected side effects and contraindications;
l) clinical parameters to be monitored, including methods of reporting adverse events;
m) name and contact information of the principal investigator and authorized prescribers; and
n) repository for additional information (department, telephone number, location).

All of the foregoing information should be added to the participant's medical record, along with the participant's written consent to participate in the trial, and should be accessible by all persons responsible for administering the investigational product or monitoring the participant's response to the product.

8.3 Transfer of Investigational Product and Related Materials from Another Healthcare Organization

If a participant is admitted or transferred to a healthcare organization other than where the participant was enrolled in the trial (termed the receiving institution), the pharmacy staff of the receiving institution shall request the originating institution to send the following items to the receiving institution:

a) obtain a copy of the participant's consent form;[11]
b) a supply of the investigational product and related product information (if not provided in advance) such as:
    i) information on the product's stability, storage, and administration;
    ii) an information summary sheet for health professionals in the secondary institution who may be treating the patient, including the name, and phone number of the investigator; and
c) a copy of the IRB's approval letter.

The pharmacist should also ask the attending physician to contact the qualified investigator to decide if the investigational product should be continued and at what dose (the principal investigator will decide if the participant's admission to the receiving institution constitutes an adverse event to be reported to the sponsor).[11]

Pharmacy personnel in the receiving institution should assess whether any investigational product that the participant brings to the institution is suitable for use.[6]

9 Breaking the Randomization Code

The rules for breaking the randomization code shall be established before the trial begins. The pharmacy or the principal investigator should have rapid access to the code-breaks, which are provided in the study protocol, in the event that the identity of the dispensed treatment needs to be unblinded for the participant's safety (regardless of whether the investigational product or placebo was dispensed). These rules should help determine the conditions under which the code should be broken, who is authorized to break the code, how to break the code, and what follow-up procedures must be undertaken.

Where the pharmacy does not hold the code-break for a clinical trial, procedures should be in place to ensure that 24-hour coverage is available to access the code-break, if necessary.[6]

The date and time that the code was broken shall be noted in the participant's health record by the person who broke the code. The reason for breaking the code and the names of the authorizing person and the person doing so should also be included.

Pharmacy personnel should be aware of the steps to take, including whom to contact, if the code is unintentionally broken.[1]

10 Medication Incidents

The principal investigator shall be informed promptly following discovery of a medication incident involving an investigational product or when a participant is harmed by a medication incident that did not involve the investigational product. The study sponsor should also be notified when a medication incident involves the investigational product.

When a medication incident occurs, personnel shall follow the organization's procedures for reporting, investigating, and following up on such incidents.

Note: For more information, refer to the joint publication of CSHP and the Institute for Safe Medication Practices Canada entitled Medication Incidents: Guidelines for Reporting and Prevention.[15]

11 The End of a Clinical Trial

A clinical trial ends either as predetermined by the study protocol or when premature termination is justified. The study coordinator or sponsor should inform the pharmacy when a study ends.

At the end of a trial, all investigational products held outside the pharmacy shall be returned to pharmacy, and the pharmacy shall ensure that all unused or unusable investigational products are destroyed and disposed of or returned to the manufacturer, as specified in the study protocol.

Pharmacy personnel should expect to have a meeting with the study sponsor to resolve any outstanding issues.

12 Quality Management

An ongoing quality management program shall be in place to assess the quality of and improve the organization's procedures for managing investigational products. This program should include an assessment of risks, with the aim of minimizing potential risks to patients and staff.[7]

The completeness and accuracy of record-keeping should also be assessed. An audit of records may be performed by the healthcare organization's personnel, by clinical trial monitors (employed by the sponsor), by Health Canada, or by other regulatory bodies involved in the study (e.g., the United States Food and Drug Administration).

The pharmacy department should determine which measures (or end points) it should monitor to effectively assess the structure, process, and outcomes of its clinical trials program. Such measures of quality should take into account the satisfaction of the various stakeholders[1] with whom pharmacy personnel will be working (e.g., investigators, IRB, sponsors, nursing personnel, academics). Methods should be established to regularly collect and analyze the data for these measures. A plan should be developed to effect change when required, with the goal of improving the pharmacy's clinical trials service.

At least once a year, a report highlighting the accomplishments of the service over the past year should be compiled and submitted to the pharmacy manager to whom the clinical trials service reports. The report, which shall facilitate the documentation, review, and reporting of the performance of the service, should include the following elements:

a) list of clinical trials supported;
b) achievements, including a summary of workload activity and revenues;
c) performance compared with the prior reporting period;
d) unresolved issues affecting performance of the clinical trials program (e.g., instances of non-compliance); and
e) plans to continually improve performance of the clinical trials service.

A summary report on the use of investigational products within the institution should be presented annually or semi-annually to the pharmacy and therapeutics committee for informational purposes.

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Additional Resources

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