Handling Investigational Drugs 101: Tips of the Trade from Experienced Investigational Drug Service Practitioners

IDS Policy & Procedure Development and CQI Strategies

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Learning Objectives

1. Describe the purpose of policies and procedures.
2. Discuss the importance of continuous quality improvement.
3. Describe the labeling requirement for investigational new drugs.

Disclosures

✓ The presenters for this continuing pharmacy education activity report no relevant financial relationships.

Health-System Pharmacy: Policy and Procedures

- Policies
  - Organization’s rules, principles and guidelines
- Procedures
  - Day-to-day expression of policies
- Policies + Procedures
  - Organization’s viewpoint reflected into outcomes

Health-System Pharmacy: Continuous Quality Improvement

- CQI: an approach to improve and maintain quality
- Internally-driven
- Continuous assessments of causes of quality defects
- Act to correct or avoid defects in quality
Health-System Pharmacy and IDS

Similarities
- FDA-approved drugs
- Drug inventory and storage
- Dispensing
- Recordkeeping
- Drug destruction
- Billing

Dissimilarities
- INDs
- Sponsor requirements for inventory and storage
- Rigorous documentation
- Grant billing

What Sponsors Look For

Demonstrate Accountability
- Drug handling from beginning to end of study
- Policies and procedures
- Inventory control
- Investigational drug dispensing
- Destruction or return to sponsor

Show Value
- Equipment monitoring systems
- Health-system pharmacy support

FDA Requirements under CFR Section 21

Part 312 of Section 21
- 312.6 Investigational new drug labeling
- 312.59 Unused investigational drug disposition
- 312.60 General responsibility of investigator
- 312.61 Control of investigational drug
- 312.62 Investigator recordkeeping
- 312.68 Inspection of records and reports

Real Life

Documentation

21 CFR 312.62
- Investigator recordkeeping & record retention
  - Drug disposition
    - Maintain adequate drug disposition records
    - Dates, quantity, subject use
  - Record retention
    - If approved, maintain records for 2 years
    - If not approved, maintain 2 years after study closure

21 CFR 312.68
- Inspection of investigator’s records & reports

Real Life

Documentation

Policy and Procedure
- Inventory logs
- Patient dispensing logs
- Preparation instructions
- Door-to-door documentation of chain-of-custody
- Retention procedure
  - State BOP requirements
  - Perpetuity
Documentation

- CQI Opportunities
  - Detailed dose preparation instructions
  - Double checks
  - Delivery slips for receipt of investigational drug
  - Placebo inventory
  - Verify sponsor’s shipping/packing slip indicates for “Investigational Use”

Dispensing

21 CFR 312.61

- Control of the investigational drug
  - Investigational drug administered only to subjects under the investigator’s or sub-investigator’s personal supervision

Policy and Procedure

- Verify order/prescription written by an institutional IRB-authorized and approved investigator

CQI Opportunity

- Use institutional resources to identify prescribers

Dispensing

21 CFR 312.59

- Disposition of unused supply of investigational drug
  - Sponsor assures return of all unused supplies
  - Sponsor may authorize alternative disposition

Policy and Procedure

- Disposal and Destruction forms for documentation
- CQI Opportunity

- Handling of partial or empty vials

Equipment Technology

21 CFR 312.62

- Investigator recordkeeping & record retention

Monitoring Equipment

- “secure refrigerator 2°C to 8°C”
- Continuous monitoring and alarms
- Ambient temperatures
- Cold chain management
- Changing industry standards

Policy and Procedure

- Identify equipment and temperature ranges
  - Pharmacy Services Devices: Dept Equipment Monitoring
    - Refrigerator 36 to 46°F (2 to 8°C)
    - Research freezer -12 to -14°F (-25 to -26°C)
    - Super cold freezer -103 to -13°F (-75 to -85°C)

CQI Opportunities

- Create response and recovery plan
- Define roles and expectations
Conclusion

- Policies and Procedures create structure and support
- CQI constantly seeks quality improvement in the system
  - Completion of clinical trials
  - Advancement of health science
  - Optimization of patient care
Inventory Management and Infrastructure

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Role of Pharmacist

- Under direction of IRB
- Audit recordkeeping documents
- Provide document templates to facilitate recordkeeping
- Guidance for resolving discrepancies or deviations
- Be present at FDA audits for studies audited by IDS – not required

Investigator Recordkeeping

- Disposition of drug. An investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects. If the investigation is terminated, suspended, discontinued, or completed, the investigator shall return the unused supplies of the drug to the sponsor, or otherwise provide for disposition of the unused supplies of the drug under 312.59. [21CFR312.62]

Types of pharmacy audits

- Initial audit – occurs prior to start of study, during irb approval process
- Follow up – after first few subjects enroll
- Yearly – at study renewal
- Termination audit – When all study drug dispensing is over

Drug Audit Form

Audit Deviation Rating Scale

- TYPE 1: SERIOUS: REQUIRES FOLLOWUP WITHIN ONE MONTH– EMAIL COPY OF AUDIT TO RESPONSIBLE IRB
- TYPE 2: REQUIRES FOLLOWUP WITHIN 2 MONTHS
- TYPE 3: REQUIRES FOLLOW UP AT NEXT REGULARLY SCHEDULED AUDIT
Drug and Protocol Information

- **Drug Data Sheet – Type 2 Deviation**
  - for IND studies only
  - provides information about study drug for clinicians
  - pertains only to the current study

- **Investigator-held IND?**
  - Annual report to FDA

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Drug Data Sheet

- Principal Investigator
- Other PI
- Principal Investigator’s Contact Information
- Co-Investigators
- Authorized Personnel
- Federal Title

1. Use of the drug
2. Drug Form
3. Formulation
4. Routes of Administration
5. Storage and Handling

**NOTICE:** The information in this Drug Data Sheet may be subject to change without notice. It is the responsibility of the investigator to ensure that the most current version is used.

Temperature Monitoring:

- For all storage conditions, temperature monitoring is required.
- Incubator, refrigerator, freezer storage.

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Drug Storage Requirements

- **Locked storage area – Type 1 deviation**
- **Radioactive material – type 1 deviation**
- **Temperature monitoring for ALL storage conditions**
  [inc. room temperature] - Type 2 deviation

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Templates – Temperature Log

- Temperature Log Table
- Date
- Time
- Temperature (°C)
- Initial
- Final
- Acceptable Temperature Range (°C)
Temperature Monitoring Technology

- All Drug Storage Locations:
  - Clinic
  - Inpatient Unit
  - During Transport

- Notification of out of range conditions

Data Logger

- Monitor conditions over time
- Temperature
- Humidity
- Download data to computer to store
- Print paper copy to file

Out of Range Notification

- Local Alarm
- Telephone notification
- E-mail notification
- Pager notification

Shipment

- Device included to monitor temperature during shipment
- Follow instructions
- Quarantine stock if out of range

Temperature Controlled Storage

Drug Receipt

- Manufacturer's information on file – Type 3 deviation
- Source of investigational product
- Copies of invoices are maintained by investigator – Type 2 deviation
- Discrepancies?
Drug Receipt and return

**RECEIPT RECORD OF INVESTIGATIONAL DRUG**

- Date of drug receipt:
- IRB #: __________
- Principal Investigator: __________
- Drug Received from: __________
- Investigator’s address: __________
- Expiration or retest date for drug received:

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Drug Strength</th>
<th>Dosage Form</th>
<th># per container</th>
<th># of containers</th>
<th>Lot #</th>
<th>Exp. Date</th>
</tr>
</thead>
</table>

Drug received by: __________
Condition of drug: __________

The sponsor shall assure the return of all unused supplies of the investigational drug from each individual investigator whose participation in the investigation is discontinued or terminated. The sponsor may authorize alternative disposition of unused supplies of the investigational drug provided this alternative disposition does not expose humans to risks from the drug. The sponsor shall maintain written records of any disposition of the drug in accordance with 312.57. [21cfr312.59]

Drug Receipt - documentation

- Type 2 deviation
- Date
- Name of investigational agent
- Strength
- Dosage Form
- Quantity per container
- Number of containers
- Lot number, batch number, Kit number
- Expiration Date, Re-test Date, On-going Stability

Drug return documentation

- Type 3 deviation
- Date
- Investigator’s name/address
- Drug name, dosage form
- Quantity per container
- Number of containers
- Lot numbers and to whom the drug is being shipped

Templates – Receipt record

Templates – Return/transfer record
Returns and Expired Drug

Drug destruction
- Same information as return
- Written authorization from the sponsor for alternative disposal - Type 1 deviation

Templates – destruction record

Labeling/packaging for outpatient dispensing
- Type 3 deviation
- Date dispensed
- Subject identifier
- Drug name
- Quantity dispensed
- Directions for use
- Expiration Date
- PI name, address, phone number
- Information to reveal the assignment, if applicable

Drug Disposition/administration records
- Type 2 Deviation
- Who: subject identifier
- What: Drug name, strength (unless blinded)
- When: date dispensed
- How much: quantity
- Study subject returns
- Sponsor Logs often inadequate

Labeling/packaging for outpatient dispensing
- Type 2 Deviation
- Who: subject identifier
- What: Drug name, strength (unless blinded)
- When: date dispensed
- How much: quantity
- Study subject returns
- Sponsor Logs often inadequate
Drug Disposition/administration records

Drug accountability log

General Drug accountability

• Type 1 Deviation
• Actual Count of current inventory must correspond to what is what is recorded in the logs
• Analogous to a checkbook

DOCUMENT, DOCUMENT, DOCUMENT

• If it’s not documented, it didn’t happen

How Long Are Records Kept?

• Record retention. An investigator shall retain records required to be maintained under this part for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified. [21cfr312.62]
Objective

- Delineate investigational drug issues relevant to Joint Commission inspections.

Medication Management Standards

- All of the Medication Management (MM) must be met for investigational medications as well as commercial drugs.
  - MM.1.10 – Access to medication information
  - MM.2.20 – Storage of medications
  - MM.2.40 – Meds brought in by patient/family
  - MM.3.20 – Medication orders

Note: All TJC standard numbers change in 2009

Be Prepared

- Important to have a plan in place, even if your institution is not participating in any clinical trials.

MM.3.20

- A well established plan must be in place identifying the:
  - Study medications;
  - Different active protocols;
  - Locations of subjects and medication;
  - Authorization to prescribe;
  - Documentation of staff training;
  - Dispensing and administration of clinical trial material.

MM.3.20

- Important for medications that are being studied within the institution as well as for clinical trial material brought into the institution by a patient.
MM.3.20

- Pharmacy must establish a mechanism to ensure orders are written by only physicians authorized to prescribe the investigational agent.
- Require a signed copy of FDA Form 1572, Statement of Investigator, on file in the Research Pharmacy. Pharmacy staff screen orders for authorization.

FDA Form 1572

- Statement of Investigator
- Includes the names of Sub-Investigators that will be assisting the Investigator with the conduct of the investigation.

MM.7.40

- Investigational medications are safely controlled and administered
  - Gone are the days when Dr. Do-It-Myself shows up at the bedside and administers an investigational agent that has been stored in her office cabinet.

MM.7.40

- Process is in place for the use of investigational medications; including
  - Reviewing investigational medication use;
  - Approving the use of these drugs;
  - Supervising use of drug;
  - And monitoring investigational medication use.

Collaboration & Communication

- Institutional Review Board
- Pharmacy and Therapeutics Committee
- Risk Management
- Institutional Biologics Committee
- Investigational Drug Service/Inpatient Pharmacy
- Nursing staff
- Research Administration

Communication Process

- Establish a mechanism to ensure that protocol has been approved by all of the players prior to dispensing and administration.
When a hospital operates a pharmacy, procedures specify that the pharmacy controls the storage, dispensing, labeling and distribution of the investigational medication.

Patient Rights section of the JC expectations. Includes elements of consent that must be met. Same information as required by IRB, FDA, Good Clinical Practice.

The hospital protects research subjects and respects their rights during research investigation, and clinical trials involving human subjects.

The Elements of Performance include:
- The agent of the hospital must review all research protocols in relation to its mission.
- The Institutional Review Board or Pharmacy and Therapeutics committee may serve this role.

Subject must be provided with adequate information in order to be able to make an informed decision regarding participation. The written Consent Form is the paper document supporting the discussion process.

The document must include the name of the person proving the information, and date. Address privacy, confidentiality and safety concerns.

21 CFR 50.25
The patient is informed that if they decide not to participate, their decision will not compromise their access to care, treatment and services.

HIPAA authorization to use and disclose individual health information for research purposed.

Scenario – patient is admitted to your hospital for a routine elective surgery.

At admission – it is noted that she is currently taking an investigational study medication.

The physician writes an order to continue taking “Study medication.”

This order is not acceptable.

Pharmacy can play an active role in providing valuable safety information to the physician writing the order to either continue the “study medication” or in deciding to hold the drug, or discontinue.

Outlines three scenarios of when a subject who is participating in a research study at one institution is admitted to another facility.

Must identify what COULD be in the bottle.

Do not need to unblind the study, but need knowledge to best be able to determine whether or not to have the now patient continue the drug.
Hospitalization is unrelated to research

- If the patient brought the bottle in – call the phone number on the bottle.
- Explain situation.
- Ask for copy of Consent Form: it explains the research study, including risks and potential side effects of the study drug, including interactions.

Hospitalization is unrelated to research

- Have your physician speak directly to the study principal investigator (PI).
- This serves two purposes:
  - Local MD: information to help decide if the drug should be continued and at what dose.
  - PI may need to report the hospitalization as an Adverse Event to the study sponsor.

Hospitalization is unrelated to research

- This scenario does not require IRB approval.
- Your site is providing incidental medical care and is not participating as a research site.

Policy

- Prepare a policy identifying what department is responsible for the information.
- We have shared responsibility.
  - IDS Pharmacy
  - Main Pharmacy
  - Physician

Other scenarios

- The guideline discusses
  - When the subject is expected to be seen at another hospital for routine care
  - When a subject is expected to be admitted into another hospital for research monitoring.

Conclusion

- Be knowledgeable of all aspects of the clinical trial process.
- Have a process in place to ensure the use of investigational medications meets all of the standards.
- Be prepared for change.
IDS and the IRB
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What is an Institutional Review Board?
DEFINITION:
"Any Board, committee, or other group formally designated by an institution to review, and to approve the initiation of, and to conduct periodic review of, biomedical research involving human subjects."
21 CFR 56.102

HUMAN SUBJECTS RESEARCH

WHY HAVE AN IRB?
"The primary purpose of such review is to assure the protection of the rights and welfare of the human subjects."
21 CFR 56.102

BASIC PROTECTION FOR HUMAN SUBJECTS
- Institutional assurances
- IRB review
- Informed consent
- Has 3 components:
  - Information
  - Comprehension
  - Voluntariness

IRB RESPONSIBILITIES
- Review all covered research at least yearly.
- Require that informed consent meets regulations.
- Require or waive documentation of informed consent.
- Notify investigators in writing of decisions.
IRB MEMBERSHIP

- Minimum membership is 5.
- Expertise of some members in:
  - Professional competence to review the specific research activities

Expertise of some IRB members in:

- Knowledge of “vulnerable” groups such as children, prisoners, pregnant women, or handicapped or mentally disabled people.

IRB MEMBERSHIP

- At least one member is unaffiliated with the institution
- At least one member has no scientific background.
- These can be the same person.

Outside consultants can be used when needed.

How does IDS fit in?

Liaison between investigators conducting IRB approved protocols and the pharmacists who dispense drug for the studies.
WHAT IS THE CONTRIBUTION OF THE PHARMACIST TO THE IRB?

- Understanding ADME for drugs
- Helps in reviewing investigator brochures
- Awareness of potential drug interactions
- Review of adverse events in drug studies

WHAT IS THE CONTRIBUTION OF THE PHARMACIST TO THE IRB?

- General knowledge of drugs
- Non study drugs in protocols
- Concomitant meds

WHAT IS THE CONTRIBUTION OF THE PHARMACIST TO THE IRB?

- Practical understanding of logistics
- It’s a long way from the lab bench to the pharmacy counter

WHEN AN IDS PHARMACIST IS AN IRB MEMBER

- Improved communication between pharmacy & IRB
- More awareness of pharmacy issues in protocol review
  - Pharmacist input part of review
  - Changes can be made before IRB approval

AND IN CONCLUSION

- QUESTIONS?
- COMMENTS?
- DISCUSSION!

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