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

the power of you

Disclosures

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

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IDS Policy & Procedure Development and CQI Strategies

Christine M. Formea, Pharm.D.
IDS Manager, Mayo Clinic
December 9, 2008

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.

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

http://www.businessdictionary.com/definition/policies-and-procedures.html

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

http://www.qaproject.org/methods/resglossary.html

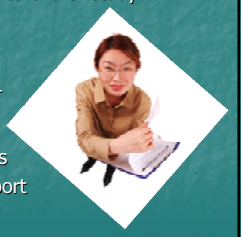
Health-System Pharmacy and IDS

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

http://www.gpo.gov/nara/cfr/waisidx_02/21cfr312_02.html

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

http://www.gpo.gov/nara/cfr/waisidx_02/21cfr312_02.html

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-approved authorized prescriber
  - CQI Opportunity
    - Use institutional resources to identify prescribers

http://www.gpo.gov/nara/cfr/waisidx_02/21cfr312_02.html

Dispensing

- 21 CFR 312.6
  - Labeling of an investigational new drug
    - "Caution: New Drug—Limited by Federal (or United States) law to investigational use."
    - Immediate packaging
  - Policy and Procedure
    - Labels: auxiliary label requirement
  - CQI Opportunity
    - √ sponsors' packaging
    - Add to dispensing instructions

http://www.gpo.gov/nara/cfr/waisidx_02/21cfr312_02.html

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

http://www.gpo.gov/nara/cfr/waisidx_02/21cfr312_02.html

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

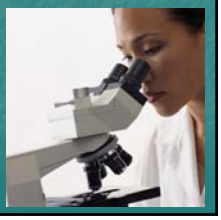
http://www.gpo.gov/nara/cfr/waisidx_02/21cfr312_02.html

Equipment Technology

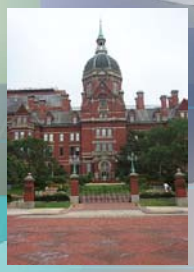
- Policy and Procedure
  - Identify equipment and temperature ranges
    - Pharmacy Services Devices: Dept Equipment Monitoring
      - Refrigerator 36 to 46°F (2 to 8°C)
      - Research freezer -13 to 14°F (-25 to -10°C)
      - Super cold freezer -103 to -85°F (-75 to -65°C)
- CQI Opportunities
  - 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



Hye Y. Kim, RPh
Investigational Drug Pharmacist
The Johns Hopkins Hospital

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**

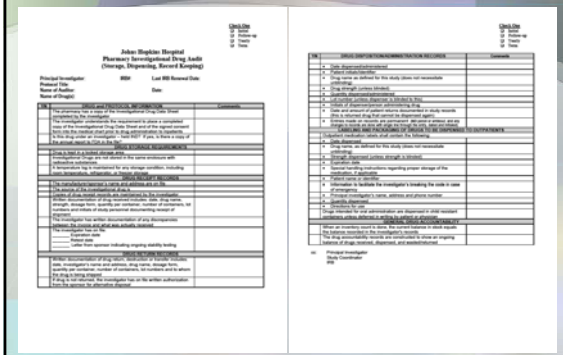
Investigator Recordkeeping

- **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**

Drug and Protocol Information

Johns Hopkins Hospital
Pharmacy Investigational Drug Audit
(Storage, Dispensing, Record Keeping)

Principal Investigator:
IRB#: Last IRB Renewal Date:
Protocol Title:
Name of Auditor: Date:
Name of Drug(s):

Y/N	DRUG and PROTOCOL INFORMATION	Comments
	The pharmacy has a copy of the Investigational Drug Data Sheet completed by the investigator	
	The investigator understands the requirement to place a completed copy of the Investigational Drug Data Sheet and of the signed consent form into the medical chart prior to drug administration to inpatients	
	Is this drug under an investigator-held IND? If yes, is there a copy of the annual report to FDA in the file?	

Drug Data Sheet

In accordance with the policy on investigational new drugs, a member of the study team must place a completed Investigational Drug Data Sheet in the inpatient medical chart each time a patient is admitted while participating in the study, including admissions for adverse events. (Form to be placed in front section of the inpatient medical chart.) For outpatient studies, a copy of the Drug Data Sheet as well as a copy of the consent form must be sent for inclusion in the main Hospital record.

** NOTE: Questions about the description or contents of this form or other matters regarding investigational drug use should be directed to the P&T representative to the assigned IRB**

Principal Investigator:
Office Phone:
Supply Emergency Contact Information
Pager or Cell Phone or Home Phone:
Co-Investigators:
Authorized Prescribers:
Protocol Title:
IRB #: APPROVED/RENEWED (date):

1. Drug Name (Name to be used in prescribing and labeling):

2. Drug Synonyms:

3. Dosage Form (e.g., tablets, capsules, injection) and Strength (e.g., mg content of each tablet) Administered to the Participants in This Study:

4. Dosing Regimen for This Study (drug, dose, route, frequency:

5. Directions for Administering Drug:

6. Indicate below Persons/Pharmacy Responsible for Storing and Dispensing Drug(s) for this Study *(include location and phone #):*
Person/Pharmacy: Research Pharmacy
Storage Location: Dispensing location:
Phone Number:

7. Expected Therapeutic Effects:

8. Possible Adverse Effects:

9. Describe, in detail, any special precautions required for the person(s) handling the drug according to the sponsor of the IND, based on teratogenicity, carcinogenicity, mutagenicity, and reproductive toxicity data:

10. Special Instructions for Managing the Drug after Dispensing: (e.g., storage requirements, disposal of used or unused medications and containers/bags):

Prepared by: Date:
Submission of this form implies endorsement of its contents by the Principal Investigator, even if Principal Investigator is not the one who prepared it.

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**

Drug Storage Requirements

	DRUG STORAGE REQUIREMENT	
	Drug is kept in a locked storage area	
	Investigational Drugs are not stored in the same enclosure with radioactive substances	
	A temperature log is maintained for any storage condition, including room temperature, refrigerator, or freezer storage	

Templates – Temperature Log

TEMPERATURE LOG
Location (Building, Room #): _____
Month/Year:_____
Acceptable Temperature Range:
_____°F or °C (circle one)

Date	Temp °F or °C (circle one)	Initials	Date	Temp °F or °C (circle one)	Initials
1			17		
2			18		
3			19		
4			20		
5			21		
6			22		
7			23		
8			24		
9			25		
10			26		
11			27		
12			28		
13			29		
14			30		
15			31		
16					

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

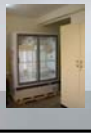
Out of Range Notification

- 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

DRUG RECEIPT RECORDS	
The manufacturer/sponsor's name and address are on file	
The source of the investigational drug is: _____	
Copies of drug receipt records are maintained by the investigator	
Written documentation of drug received includes: date, drug name, strength, dosage form, quantity per container, number of containers, lot numbers and initials of study personnel documenting receipt of shipment	
The investigator has written documentation of any discrepancies between the invoice and what was actually received	
The investigator has on file: _____ Expiration date; _____ Retest date _____ Letter from sponsor indicating ongoing stability testing	
DRUG RETURN RECORDS	
Written documentation of drug return, destruction or transfer includes: date, investigator's name and address, drug name, dosage form, quantity per container, number of containers, lot numbers and to whom the drug is being shipped	
If drug is not returned, the investigator has on file written authorization from the sponsor for alternative disposal	

Templates – Receipt record

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:

Drug Name	Drug Strength	Dosage Form	# per container	# of containers	Lot #	Exp. Date

Drug received by:

Condition of drug:

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

- **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 return or transfer

- **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 – Return/transfer record

RETURN RECORD (or TRANSFER RECORD)
OF INVESTIGATIONAL DRUG

Date of drug return: _____ **IRB #:** ____
Principal Investigator: _____
Address: _____

Returned to (Transferred to): _____
Address: _____

Drug Name	Drug Strength	Dosage Form	# per container	# of containers	Lot #

Drug returned by (transferred by): _____

Returns and Expired Drug

Drug destruction

- **Same information as return**
- **written authorization from the sponsor for alternative disposal - Type 1 deviation**

Templates – destruction record

RECORD OF DESTRUCTION OF INVESTIGATIONAL DRUG

Date Destroyed

RPN #:
Principal Investigator:

Investigator's Address:

Drug Name	Drug Strength	Dosage Form	# per container	# of containers	Lot #

Drug destroyed by: _____
Method of destruction: _____

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**

Labeling/packaging for outpatient dispensing

LABELING AND PACKAGING OF DRUGS TO BE DISPENSED TO OUTPATIENTS		
	Outpatient medication labels shall contain the following: Drug will not be dispensed for outpatient use.	
	• Date dispensed	
	• Drug name, as defined for this study (does not necessitate unblinding)	
	• Strength dispensed (unless strength is blinded)	
	• Expiration date	
	• Special handling instructions regarding proper storage of the medication, if applicable	
	• Patient name or identifier	
	• Information to facilitate the investigator's breaking the code in case of emergency	
	• Principal investigator's name, address and phone number	
	• Quantity dispensed	
	• Directions for use	
	Drugs intended for oral administration are dispensed in child resistant containers unless deferred in writing by patient or physician	

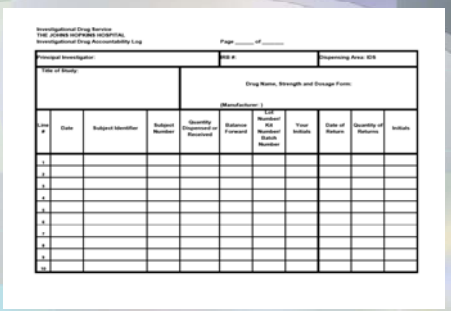
Drug Disposition/administration records

- **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**

Drug Disposition/administration records

DRUG DISPOSITION/ADMINISTRATION RECORDS	Comments
• Date dispensed/administered	
• Patient initials/Identifier	
• Drug name as defined for this study (does not necessitate unblinding)	
• Drug strength (unless blinded)	
• Quantity dispensed/administered	
• Lot number (unless dispenser is blinded to this)	
• Initials of dispenser/person administering drug	
• Date and amount of patient returns documented in study records (this is returned drug that cannot be dispensed again)	
• Entries made on records are permanent (NO pencil or whiteout, and any changes to records are done with single line through the entry, dated and initialed)	

Drug accountability log



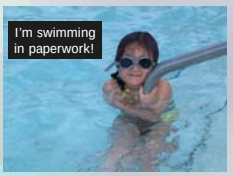
General Drug accountability

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

GENERAL DRUG ACCOUNTABILITY	
When an inventory count is done, the current balance in stock equals the balance recorded in the investigator's records	
The drug accountability records are constructed to show an ongoing balance of drugs received, dispensed, and wasted/returned	

DOCUMENT, DOCUMENT, DOCUMENT

- **If it's not documented, it didn't happen**



Failure to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects will result in a warning letter or 483!

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]

Investigational Drug Issues Relevant to Joint Commission Inspections

Darlette G Luke, RPh
University of Minnesota Medical Center, Fairview

Objective

- Delineate investigational drug issues relevant to Joint Commission inspections.

Be Prepared

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

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

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 a 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.

MM.7.40

- When a hospital operates a pharmacy, procedures specify that the pharmacy controls the storage, dispensing, labeling and distribution of the investigational medication.

RI.2.180

- 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.

RI.2.180

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

RI.2.180

- 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.

RI.2.180

- 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.

Consent Form

- The document must include the name of the person proving the information, and date.
- Address privacy, confidentiality and safety concerns.
- 21 CFR 50.25

RI.2.180

- 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.

Patient Admitted on Study Medication

- 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.

What is it?

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

But……What is it?

- 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.

FDA Guideline

- **Use of Investigational Products When Subjects Enter a Second Institution.**
- Outlines three scenarios of when a subject who is participating in a research study at one institution is admitted to another facility.

Hospitalization is unrelated to research

- If a subject is admitted into your hospital on an investigational drug prescribed by a physician outside your institution:
  - 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.


ASHP 2008
Darlette G. Luke
University of Minnesota Medical Center, Fairview
612-273-6212
dluke1@fairview.org

IDS and the IRB

Kathleen Truelove, BSPharm

Investigational Drug Pharmacist
The Johns Hopkins Hospital
IRB member
The Johns Hopkins University School of Medicine
Baltimore, Maryland

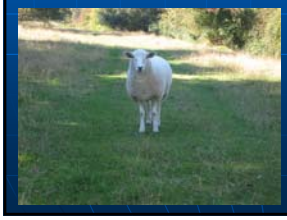
IDS and the IRB

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.

Expertise of some IRB members in:

- Knowledge of institutional regulations, applicable law, and professional conduct & practice.

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!

ktruelo@jhmi.edu