BROWN

GUIDANCE FOR INVESTIGATORS:
Management of Human Research Studies Involving Drugs and Medications

I. **PURPOSE**: The purpose of this document is to provide guidance to Principal Investigators (PIs) and licensed practitioners responsible for the medication management component of Brown University research studies with human subjects which include the use of prescription drugs for investigational purposes. This guidance is applicable to all studies where drugs are administered to human participants for research purposes. The "Prescription/Drug Medication Management Addendum" form must be completed by the PI and included with the IRB submission packet for all new protocols that involve drugs/medications or existing protocols that add a new drug/medication.

II. **SCOPE**: This guidance covers the use of investigational drugs, FDA-approved drugs being researched for new indications or in new populations, and Schedule I-V drugs that may be regulated by the Drug Enforcement Agency (DEA) as well as or instead of the Food and Drug Administration (FDA). In cases of drugs that are regulated by the DEA, there may be additional requirements included in the license that go above and beyond what is described in this document.

III. **APPLICABLE REGULATIONS & REQUIRED PROCEDURES**: There are both state and federal regulations regarding the distribution, dispensing and administration of drugs which are applicable to research studies involving drugs and medications. Federal law establishes the requirements with which all facilities and individuals must comply. However, similar to most other states, RI State Law legislates and promulgates more restrictive requirements that establish the minimum standard of practice with which compliance is required. Any licensed practitioner, including those involved in research studies, and/or PIs who handle drugs either by distribution, dispensing or administration must comply with these minimum standards.

In accordance with federal and state regulations (*see* **Appendix I**), study investigators must establish procedures for drug management that include the following elements:

1. Process for the procurement and transfer of drugs to and from a pharmacy or manufacturer to the authorized research laboratory that will conduct the study;
2. Storage and security requirements for the drugs;
3. Packaging and labeling requirements of the drugs;
4. A method to ensure that only an authorized practitioner prescribes the investigational drug;
5. A method to ensure that dispensing is limited to pharmacists;

6. A method to ensure that a drug utilization review takes place prior to the study providing study medication(s) to study participants. Documentation records that includes information on the description, amounts, and dates of drugs received, transferred, dispensed, wasted, destroyed or returned; and
7. A defined procedure to break the blinding code and reveal the identity of the study drug to other health care professionals, when there is a concern or indication relevant to the best interest of the participant regarding a decision of withdrawal from the study and/or possible subsequent treatment.

IV. GUIDANCE:

A. Drug Procurement

Any authorized licensed person or entity – physician, nurse practitioner, pharmacy -- may order study drugs from the manufacturer or wholesaler.

If study personnel are responsible for ordering the drug, best practice is to arrange for the drug to be drop shipped to the contracted pharmacy. Alternatively, study personnel may transport the study drug to the pharmacy or the pharmacy may utilize a courier to pick up the drug from the study site. To maintain proper chain of custody, transfer documentation should include:

a. name of the PI and institution, IRB protocol number, name of drug, quantity; and
b. name and address of pharmacy or authorized research laboratory receiving the drug; and
c. signatures of both parties

If the pharmacy is procuring the study drug, the invoice shall be for the study drug exclusively, and shall indicate the IRB protocol number and institution/PI conducting the study. Copies of the signed transfer document shall be maintained by the PI and the pharmacy.

The pharmacy and investigator shall ensure that the following information is available from the manufacturer or wholesaler:

a. Storage conditions required before and after preparation
b. Amounts and types of diluents for reconstitution and administration and the resulting final concentration of active drug
c. Stability of the prepared product
d. Known compatibility or incompatibility with other products
e. Light sensitivity
f. Filtration needs
g. Expiration dates
h. Special instructions for preparation and administration
i. Known adverse effects
j. Usual dosage regiments
k. Contraindications
l. Drug interactions
m. Special precautions for storage and handling (cytotoxic, hazardous drugs)
n. Pharmacology, including mechanism of action

o. Pharmacokinetic characteristics
p. Pharmacogenetics if available

A complete current copy of the research protocol should be supplied to the pharmacy.

B. Drug Storage and Security

Storage requirements for drugs is referenced in the United States Pharmacopeia. Individuals responsible for handling drugs are required to maintain environmental controls during the transport and storage of the drugs. Study drugs that are to be shipped offsite for a protocol must be packaged in containers that maintain the proper storage conditions during transport. Chain of custody and maintenance of proper storage conditions during transport should be documented. Study drugs should be stored in a limited-access location. Proper storage conditions should address the temperature, light, moisture, ventilation and sanitation needs of the product. Documentation of systematic recording of key environmental conditions should be maintained during the entire storage timeframe.

If the drug is a controlled substance, the item shall be stored in a securely locked, substantially constructed cabinet to which access is limited to individuals with dispensing or administration responsibilities. ***Any facility that stores controlled substances on site must obtain a federal DEA registration and Rhode Island Controlled Substance Registration.*** PIs planning to obtain controlled substances for their research for the first time are encouraged to contact Brown's Human Research Protection Program (HRPP) for further guidance and assistance related to DEA registration and licensing.

C. Control of Drugs

The PI is responsible for establishing and implementing procedures for the control of drugs. A copy of the IRB-approved research protocol, study procedure manual, and all amendments should be maintained at the institution and/or pharmacy. The research study is also responsible for creating and maintaining an adequate drug information/reference sheet. This sheet should be prepared for all study staff and pharmacy staff with responsibility for study drug dispensing and should contain, at minimum:

a. Drug designation and common synonyms
b. Dosage forms and strengths
c. Usual dosage range, including dosage schedule and route of administration
d. Indications pursued in the study
e. Expected therapeutic effect to be studied
f. Expected and potential adverse effects
g. Drug-drug, drug-alcohol and drug-food interactions
h. Contraindications
i. Storage requirements
j. Instructions for dosage preparation and administration, including stability and handling guidelines

k. Instructions for disposition of unused doses
l. Names and telephone numbers of PI and study coordinator(s)

The PI shall maintain a system of a detailed inventory record for all study drugs including those transferred and/or received by the study, dispensed to participants, stored at the study site, provided/administered to participants, and wasted or disposed of. Inventories and all other records may be stored electronically. Pharmacies participating in the dispensing process shall ensure that all documentation will be provided to the study PI at the conclusion of the study and at any other time upon request.

If administration is to occur at the study site, the PI shall maintain a log of participant-specific drugs received from the pharmacy and a separate log for administration of the drug to the study subject. Storage and security of investigational drugs shall comply with Section B above.

D. Dispensing

Only an authorized practitioner (Physician, Physician Assistant, or Nurse Practitioner) shall prescribe the study drug. Pursuant to RIGL 5-19.1 section 8.4, the prescription must include the following elements:

a. Full name and street address of the patient/participant;
b. Name, address, and if required by law or rules of the Board of Pharmacy, DEA registration number of the prescribing practitioner;
c. Date of issuance;
d. Name, strength, dosage form and quantity of drug prescribed and when applicable, the word placebo (e.g., “Acetaminophen or placebo”);
e. Directions for use; and
f. Refills authorized, if any.

The study drug will be dispensed by a licensed pharmacist. (Medication obtained directly from the manufacturer or wholesaler in prepackaged unit of use containers may be administered on site by a licensed practitioner or his/her delegate, without the pharmacist intermediary.) A delegate may be another person associated with the study who has received appropriate in-study training and guidance from the licensed practitioner.

Prior to dispensing, it is expected that the pharmacy will have been provided with:

a. The study protocol
b. Drug information is available in the pharmacy
c. A valid and complete physician’s order/prescription for each study participant
d. A list of all medications that the participant is taking, so that the pharmacist may check for drug-drug interactions.

Study drugs shall be labeled by the pharmacy, consistent with RI Board of Pharmacy Regulations, as follows:

a. "For Investigational Use Only"
b. "Caution: Drug Limited by Federal Law to Investigational Use Only"
c. Warning Labels, such as those indicated by the manufacturer
d. Subject research identification number OR name
e. Administration instructions
f. Accepted name of drug and dose
g. Number of units or total volume
h. Date prepared and expiration date
i. IRB protocol number
j. Ordering physician name and pharmacist name
k. Name, address and phone number of dispensing pharmacy

Pharmacists may fill the prescription with required labeling and deliver the filled prescription to the Brown study site for direct administration by authorized individuals. The pharmacy shall maintain a log for all medications delivered to the study site that includes:

a. Subject research identification number OR name
b. Name of drug
c. Protocol – IRB number
d. Date of delivery
e. Pharmacist signature

A copy of the log shall be provided to the study site with the drug. The log shall be signed by the PI, physician, or delegate who has received the drug and maintained at the study site and at the pharmacy.

E. Drug Administration

Administration of study drugs directly to patients at the study site shall be done by duly licensed individuals or a designated delegate. A physician, physician assistant, nurse practitioner, nurse or authorized delegate shall administer the drug from appropriately labeled containers provided by the pharmacy, or unit of use containers labeled by the manufacturer. An administration log for each research protocol shall be maintained at the study site. The log shall contain the study participant's name, drug administered, quantity administered, date and name of person who administered the drug.

F. Destruction or Return of Drugs:

Study drugs and supplies returned by subjects may not be re-dispensed to other study subjects and must be discarded/disposed of in the manner described in the approved IRB protocol. Containers returned by subjects are to be stored separately from study supplies that have not been dispensed

Controlled Drugs and Medications (Schedule I – V)

Controlled drugs and medications must be managed in accordance with all DEA procedures either for reverse distribution or witnessed destruction. The proper disposal process for the specific drugs and medications used in the research shall be coordinated with the responsible DEA Licensee and documented in your IRB protocol. Disposal of excess and/or unused controlled drugs and medications that are returned to the study site shall be done in accordance with Title 21 CFR Section 1300.

Whether the DEA Licensee or other study personnel arranges for witnessed destruction or utilizes a reverse distributor, the destruction or transfer must always be documented by the responsible registrant using a Form DEA-41

If the drugs and medications cannot be reverse distributed or witness destroyed due to the type of experimental process or the final condition of the drugs (e.g., contamination, dilution, spills, etc.), the DEA requires them to be rendered "non-retrievable"[1] at the initial point of waste generation (e.g., by chemical oxidation, thermal treatment, chemical dissociation, etc.). If you anticipate generating waste containing controlled drugs or medications that cannot be managed through the standard DEA procedures, contact Brown's EHS Environmental Compliance Specialist at x3-1610 for assistance determining appropriate methods of rendering materials non-retrievable. The agreed upon methodology should be included in your IRB protocol. This type of treatment for rendering drugs and medications non-retrievable must also be documented by the registered researcher using a Form DEA-41

Once the drug is made non-retrievable by the DEA Licensee, the resulting waste must be managed through the existing Brown University routine hazardous waste disposal procedures.

Non-Controlled Drugs and Medications

When non-controlled drugs and medications have been obtained through a pharmacy, that same pharmacy may have a procedure in place for accepting the return of the unused supply of drugs and medications for appropriate disposal. If this is the case, the typical procedure is that the pharmacy will receive the returns and arrange for pick-up by a reverse distributer. If this is the procedure to be used, this information must be included in your IRB protocol.

If a pharmacy return system, as described above, is not in place, non-controlled drugs and medications may require disposal as either hazardous waste or regulated medical waste depending on the drug being used. Contact the EHS Environmental Compliance Specialist x3-1610 for assistance determining the proper waste disposal procedures for your non-controlled drug. The agreed upon waste disposal procedure should be included in your IRB protocol.

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[1] "Non-retrievable" means the condition or state to which a controlled substance shall be rendered following a process that permanently alters that controlled substance's physical or chemical condition or state through irreversible means and thereby renders the controlled substance unavailable and unusable for all practical purposes. A controlled substance is considered "non-retrievable" when it cannot be transformed to a physical or chemical condition or state as a controlled substance or controlled substance analogue.

1. **Hazardous Waste Disposal**
   Some non-controlled drugs may meet the definition of a hazardous waste (e.g., nicotine patches, chemotherapeutics, etc.) and must be managed through existing Brown University hazardous waste disposal procedures. For assistance with hazardous waste determinations contact the EHS Environmental Compliance Specialist at x3-1610.
2. **Regulated Medical Waste Disposal**
   If drugs do not meet the definition of a hazardous waste and do not pose a risk to human health or the environment, then they may be disposed of with the Regulated Medical Waste (otherwise known as the Red Bag Lined Box [RBLB]). Contact Brown's EHS Biological Safety Officer at x3-3087 to request an RBLB pick-up or supply delivery.

G. Emergency Breaking of Blind in an Investigational Study

During a randomized and blinded research study, a situation may arise that requires breaking the blinding code to reveal the identity of the study drug when in the best interest of the study participant. A protocol for this situation must be established by the PI and described in the IRB protocol, addressing the following points:

- Procedure for retaining the blind (including specific procedures for protecting the blind should data collected in the study offer evidence of a participant's assignment to a particular study arm).
- Circumstances for breaking the blind. In general, the code should only be broken in the case of an adverse event where it is necessary for the PI to know which treatment the patient is receiving before the participant can be treated. The code may also have to be broken if someone not in the study uses the investigational drug (e.g., accidental ingestion by a child) to determine treatment.
- Individual(s) authorized to break the blind.
- Procedure for breaking the blind.

The IRB must be notified if the blind is broken and any sponsor notification requirements must also be followed.

In the case of emergency treatment, or if a patient's treating practitioner questions the pharmacy regarding the identification of the study drug, the pharmacy may break the blinding code. If this occurs, the pharmacy shall notify the PI as soon as possible. As referenced above, the PI will provide the pharmacy with a list of medications the subject is taking.

Pharmacies utilize a computer software program that provides a system for screening for drug interactions. If a significant drug interaction is detected, the pharmacy will notify the PI prior to dispensing the product.

APPENDIX I

Federal and Rhode Island state laws that are applicable to activities related to drug procurement, distribution, and dispensing include, but are not limited to:

- Title 21 Federal Food Drug and Cosmetic Act
- RIGL Title 21-31 State Food Drug and Cosmetic Act
- Title 21 Federal Controlled Substance Act
- RIGL Title 21-28 State Uniform Controlled Substance Act
- RIGL Title 5
    - Chapter 19.1 Rules and Regulations Pertaining to Pharmacists, Pharmacies and Manufacturers, Wholesalers and Distributors
    - Chapter 37 Board of Medical Licensure and Discipline
    - Chapter 54 Physician Assistants
    - Chapter 34 Nurse Practitioners, Nurses