Review of the Investigational Drug and Device Regulations

Changes to the RSRB Online Submission System (ROSS) Application for Drugs and Devices

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What is an Investigational Drug?

21 CFR 312.3(b)

• a new drug or biological drug used in a clinical investigation
• Clinical Investigation:
  – Any experiment in which a drug is administered, dispensed, or used, involving one or more human subjects
  – EXCEPT: the use of a marketed drug in the course of medical practice
Investigational Drugs

- Is the investigational drug being used according to its FDA approved indication?
  - Indication
  - Dose
  - Route of Administration
  - Population

*NOT* how it is used in clinical care, but how it is labeled on the *package insert*
Investigational Drugs

• Example #1
  – Drug approved to treat colon cancer at 10 mg/day
  – Study using this drug in ovarian cancer at 20 mg/day
  – Answer = NO

• Example #2
  – Drug approved to treat asthma in children at 30 mg/day
  – Study using this drug in asthma in adults at 60 mg/day
  – Answer = No

Is this drug/biologic **exempt** from IND requirements?

21CFR.312.2(b)

**ALL MUST APPLY**

i. Not intended to change labeling;

ii. Not intended to support a change in advertising;

iii. Study will not significantly increase risk or decrease the acceptability of risk due to a change in the:
  • Route of administration
  • Dose
  • Population
  • Other factor

iv. Conducted in compliance with the requirements for institutional review and informed consent; **AND**

v. Conducted in compliance with the requirements of 312.7 (Promotion of investigational drugs)
If the use of the drug/biologic in the study doesn’t qualify for exemption….AN IND IS REQUIRED!!

Joan Adamo in the CTSI Office of Regulatory Support available to provide assistance in IND preparation:
www.urmc.rochester.edu/ctsi/regulatory-support/investigational-drugs.cfm

Changes to ROSS Rationale

• Improvements for obtaining required information within the application for purposes of adequately documenting FDA and/or RSRB determinations, as well as to ensure the convened board has sufficient information provided for review and approval of the protocol.
• Modifications to profile pages to better structure and highlight section topics within the page, as well as to improve the ‘decision-making’ flow.
  • Consulted with Joan Adamo, CTSI
  • Consulted with Steve Bean, IDS
ROSS - Section 49

49. Drugs, Biologics, Supplements, and Devices

49.1 * Will the study be using drugs, biologics, supplements, or devices?

Response should be "yes" if the drug/device/biologic/supplement itself is being investigated or is "under study", or if data is being collected on a drug/device/biologic/supplement not being used according to an approved indication. Response is generally "no" if a drug/device/biologic/supplement is being used as part of the study procedures, but itself is not under study and there is being used in an approved/routine manner (e.g., CAT scan, sedation drugs, dilation drops).

Contact the RSRB if you have questions regarding the appropriate response.

ROSS Section 50 – Main Page

Drugs, Supplements, Biologics, and Devices

Drugs/Supplements/Biologics - click Add button to enter study drug, supplement, or biologic

<table>
<thead>
<tr>
<th>Name</th>
<th>FDA Approved Indication</th>
<th>IND</th>
</tr>
</thead>
<tbody>
<tr>
<td>There are no items to display</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Devices - click Add button to enter study medical device

<table>
<thead>
<tr>
<th>Name</th>
<th>HUD</th>
<th>FDA Approved Indication</th>
<th>IDE</th>
</tr>
</thead>
<tbody>
<tr>
<td>There are no items to display</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

For information regarding drugs, biologics, devices, or humanitarian use devices refer to the policy below:

Research Using FDA Regulated Drugs or Biologics

Research Using FDA Regulated Devices

If a biologic is being used, UR IRB approval is required before RSRB approval may be obtained.

For additional information on Investigational Drugs, Biologics or Devices, consult the FDA website at www.fda.gov.
ROSS Section 50 – Main Page

*Indicate the phase of the study:
- Phase 1
- Phase 1/2
- Phase 2
- Phase 2/3
- Phase 3
- Phase 3/4
- Phase 4
- Phase N/A
- Feasibility/Pilot Phase (Device)
- Pivotal Phase (Device)
- Post-Marketing Phase (Device)

If placebo is used, refer to the guideline "Use of Placebo in Clinical Research".

* Will placebo be used in this study?

* Has the University of Rochester PI filed with the FDA for any IND or IDE used in this study?
If "Yes", list the drug(s), biologic(s), or device(s) used in this study to which the FDA application applies:

If the UR PI is the holder of the IND or IDE used in this study, upload a copy of the PI’s IND/IDE training certificate (required to obtain RSRB approval):

[ADD BUTTON]

If the UR PI is the holder of the IND or IDE and used in this study, contact Investigational Drug Services (IDS) at (275-6153) to ensure the required processes are completed to comply with New York State Laws.

“Controlled substance” is any that the FDA/DEA has classified as a Schedule 2, 3, 4, or 5 substance. Examples include narcotics, sedatives, amphetamines, etc. Additional products may apply per NYS law.

All requirements of IDS must be met prior to enrolling subjects.

ROSS Section 50 – Main Page

*Is the study using a drug/biologic/supplement that you intend to have managed by a University pharmacy?
If “Yes”, select the location:
- Investigational Drug Service (IDS)
- Cancer Center Pharmacy

If “No”, and a drug/biologic/supplement is listed in Section 50.1, indicate the section of this study’s protocol that describes the plans to manage the drug/supplement/biologic, OR, provide that description here: [open field]

ROSS Section 50 – Main Page

Refer to Section 8 of the Biomedical Protocol Template for guidance.
Refer to the OHSP QI Study Documentation Tool Box for documents pertaining to management of drugs/biologics.
ROSS Section 50 – Main Page

<table>
<thead>
<tr>
<th>*Does the study list a device in Section 50.1? Y/N</th>
<th>Refer to Section 8 of the Biomedical Protocol Template for guidance.</th>
</tr>
</thead>
<tbody>
<tr>
<td>If &quot;Yes&quot;, indicate the section of this study’s protocol that describes the plans to manage and account for the device, OR, provide that description here: [open field]</td>
<td>Refers to use of an investigational drug/device/biologic outside of a clinical trial to treat a patient with a serious disease or condition, who has no comparable or satisfactory alternative treatment options. Refer to the guideline on Expanded Access for Treatment Use in Research.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>*Is this a request for expanded access to an investigational drug, biologic or device for treatment use? Y/N</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>If &quot;Yes&quot;, indicate the section of this study’s protocol that describes the plans to manage and account for the device, OR, provide that description here: [open field]</td>
<td></td>
</tr>
</tbody>
</table>

Drug/Supplement/Biologic Profile Page

**USE OF DRUGS/SUPPLEMENTS/BIOLOGICS**

- If the drug or biological is being used or investigated according to an FDA approved indication (i.e., dose, route and population), or for supplements, used for evaluation of the effect on the structure or function of the body? Y/N
- If “Yes”, complete only the General Information section below.
- If “No”, complete remainder of the form.

**GENERAL INFORMATION**

<table>
<thead>
<tr>
<th>Name (Generic) of Drug/Biologic/Supplement: [open field]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturer: [open field]</td>
</tr>
<tr>
<td>Upload a copy of the Investigator Brochure and/or Package Insert for this drug/biologic/supplement. [Add button]</td>
</tr>
</tbody>
</table>

**IND INFORMATION**

- If this drug/biological/supplement is not being used or investigated according to an FDA-approved indication, is there an IND? Y/N
- Note: If the study is being conducted to investigate a supplement’s ability to diagnose, cure, mitigate, or prevent a disease, an IND may be required under 21 CFR 312. Contact the FDA to ask for a determination of whether an IND will be required.
- If “Yes”, there is an IND; complete the following information:
  1. Indicate the name of the holder of the IND (and affiliated institution): [open field]
  2. Indicate the IND number: [open field]
  3. Upload documentation from the FDA (or sponsor) verifying the IND number (e.g., FDA letter assigning the number/safe to proceed letter) [Add button]
- Note: Communication from FDA indicating the study may proceed is required prior to obtaining RSRB study approval (FDA letter or Investigator documentation of FDA communication is acceptable).
Drug/Supplement/Biologic Profile Page

If “No”, there is not an IND; upload a copy of FDA documentation to confirm exemption from FDA IND requirements, or complete the questions below for the RSB to make this determination.

1. This study is not intended to be reported to FDA in support of a new indication for use, or to support any other significant change in the labeling for the drug/biologic. Y/N
2. This study is not intended to support a significant change in the advertising for the product. Y/N
3. The use of this drug/biologic does not involve changes to the following three criteria, or other factors that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug/biologic.
   a. a route of administration Y/N
   b. a dosage level Y/N
   c. use in a subject population Y/N
4. This study is conducted in compliance with the requirements for IRB review and informed consent. Y/N
5. The Investigator must comply with 21 CFR 312.7 that prohibits promotional claims (i.e., for commercial purposes) of safety and effectiveness of drugs for unlabeled indications. As such, this study is conducted in compliance with those requirements concerning the promotion and sale of the drug/biologic. Y/N

If “Yes” to all criteria above, this study may be exempt from the FDA IND regulations. The RSB will make this determination during review of the study. If response to any criteria above is “No”, contact the FDA.

What is an Investigational Device?

21CFR812.3(g)

- A device, including a transitional device, that is the object of an investigation
  - Important to remember that the device must be “under study”
  - e.g. Determining effectiveness or safety

3 Classifications

*IDE* = *Investigational Device Exemptions*

Increasing level of FDA regulation and scrutiny

IDE

Abbreviated IDE

Exempt from IDE Regulations

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Exempt from IDE Regulations

21CFR812.2(c)

1. Device in commercial distribution and being used or investigated consistent with the labeling

2. Device in commercial distribution that FDA determined to be *substantially equivalent* to a device approved before 05/28/1976, used or investigated consistent with the labeling.

**Take Home:** Device is for sale and is being used **AS APPROVED in the study.**
Exempt from IDE Regulations
21CFR812.2(c)

3. A diagnostic device that is:
   
i. Non-invasive
   ii. Does not require an invasive sampling procedure that presents significant risk,
   iii. Does not by design or intention introduce energy into a subject, **AND**
   iv. Is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure.

Exempt from IDE Regulations
21CFR812.2(c)

4. A device undergoing:
   • consumer preference testing,
   • testing of a modification, or
   • testing of a combination of two or more devices in commercial distribution,

   If the testing is **NOT** for the purpose of determining safety or effectiveness **AND**
   does not put subjects at risk.
Exempt from IDE Regulations
21CFR812.2(c)

5. Device used in animals

6. Research for or with lab animals

Exempt from IDE Regulations
21CFR812.2(c)

7. Custom Device – unless used to determine safety or effectiveness for commercial distribution

Custom device 21CFR812.3(b):
• Deviates from devices commercially available in order to comply with the order of an individual physician or dentist;
• Not generally available to, or used by, other physicians or dentists;
• Not generally available in finished form for purchase or for dispensing upon prescription;
• Not commercially available; and
• INTENDED FOR AN INDIVIDUAL PATIENT, or to meet the special needs of the physician or dentist in the course of professional practice.
What is a Significant Risk Device?

21CFR812.3(m)

• Potential for **serious risk** to the health, safety, or welfare of a subject and is:
  - Implanted;
  - Used to support or sustain human life;
  - Substantially important in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health;
  - “Other”

Example #1

• The study of a change to a commercially available pacemaker, new leads and battery pack
• Previous research demonstrates that this pacemaker is an improvement on the previous model because the battery pack lasts longer and the leads are smaller and more durable
Significant Risk…Why???

- Device is used to support or sustain human life
- Presents a potential for serious harm to the subjects
- Even though the revision to the pacemaker may potentially pose less risk, or only slightly greater risk, in comparison to the commercially available model.

What is a Non-Significant Risk Device?

A device that DOES NOT meet the definition for a significant risk device.
Example #2

- An investigational study to determine the effectiveness of a sensor pad to be used during surgery to determine the electrical activity of the spinal cord

- What to consider?
  - How and when the sensor pad is used?
  - Is it implanted?
  - How will the data be used?

Non-Significant Risk…Why???

- How and when the sensor pad is placed?
  - Surgery would occur anyway
- Is it implanted?
  - Not implanted just used during the surgery, no serious risk of harm by the sensor pad
- How will the data be used?
  - The sensor pad will be used in addition to the standard method currently used to detect electrical activity
  - The data from the two mechanisms will be compared to determine research results
Who Decides Whether A Device Study is SR or NSR?

1\textsuperscript{st} – Sponsor/PI makes an assessment
2\textsuperscript{nd} – IRB reviews the Sponsor/PI assessment and can agree or disagree
3\textsuperscript{rd} – If necessary to adjudicate, the FDA will make final decision

If the FDA has already made the risk determination, the IRB is not required to make another risk determination.

IRB Review at a convened meeting

Determination of SR vs. NSR and document the decision

Risk Determination

Significant Risk
Non-Significant Risk

IDE required???

IDE (IDE must be submitted and approved by the FDA)
Abbreviated IDE (IRB application, no FDA involvement)
Requirements for a Non-Significant Risk Device

- IRB approval (FDA not involved)
  - IRB serves as the FDA’s surrogate for review, approval, and continuing review of the NSR device studies

- Must follow the abbreviated IDE regulations at 21CFR812.2(b): address labeling, IRB approval, informed consent, monitoring, records, reports, and prohibition against promotion

IRB Responsibilities

- Review information about the device:
  - description of the device
  - reports of prior investigations conducted with the device
  - the proposed investigational plan
  - subject selection criteria

The Sponsor/PI should provide the IRB with a risk assessment and the rationale used in making that SR or NSR determination.
What should the IRB consider when making the SR vs. NSR?

• Risk/Nature of the Harm that results
  – based on the proposed use of the device in the study, not on the device alone
  – Potential for serious risk to health, safety or welfare of the subject
• Other procedures required
  – Surgery to implant

What is the difference between Non-significant risk and Minimal risk??

• Non-Significant risk (NSR) = risk related to the device and the use of the device within the study
• Minimal risk (MR)= risk of the entire study
  – MR study with a NSR device = YES
  – GMR study with a NSR device = YES
  – MR study with a SR device = NO
If a Significant Risk Device…AN IDE IS REQUIRED!!!

Joan Adamo in the CTSI Office of Regulatory Support available to provide assistance in IDE preparation:

[www.urmc.rochester.edu/ctsi/regulatory-support/investigational-devices.cfm](http://www.urmc.rochester.edu/ctsi/regulatory-support/investigational-devices.cfm)

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### ROSS Changes to Device Profile Page

<table>
<thead>
<tr>
<th><strong>HUMANITARIAN USE DEVICES</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Is this study using a Humanitarian Use Device (HUD)? y/n</td>
</tr>
<tr>
<td>If “No”, go to the General Device Information section.</td>
</tr>
<tr>
<td>If “Yes”, is this device being used under an FDA approved humanitarian device exemption (HDE)? y/n</td>
</tr>
<tr>
<td>If “Yes”, complete the following information:</td>
</tr>
<tr>
<td>1. Indicate the name of the holder of the HDE:</td>
</tr>
<tr>
<td>2. Indicate the HDE number: [open field]:</td>
</tr>
</tbody>
</table>

Complete the General Device Information section and upload a copy of the device manufacturer brochure.

<table>
<thead>
<tr>
<th><strong>GENERAL DEVICE INFORMATION</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Device name: [open field]</td>
</tr>
<tr>
<td>Manufacturer: [open field]</td>
</tr>
<tr>
<td>Device class (I, II, or III):</td>
</tr>
<tr>
<td>For information on classification of devices, go to the FDA “Classify Your Medical Device” page.</td>
</tr>
</tbody>
</table>

Upload a copy of the manufacturer brochure for this device.

[Add button]
Device Profile Page

USE OF THE DEVICE
Is this device FDA approved and marketed? Y/N

If “Yes”, is this device being used or investigated according to an FDA approved indication (i.e., labeling and intended use)? y/n

If “Yes”, complete at least one of the items below and upload documentation of FDA approval:
• 510(k) not required per FDA
• Premarket notification/510(k) number: [ADD button]
• Premarket Approval (PMA) number: [ADD button]

FDA approval documentation of 510(k) or PMA may be obtained by searching the FDA medical device database.
For 510(k): http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm
For PMA: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm

If “No”, complete information under the Investigational Device Exemption section below.

Device Profile Page

INVESTIGATIONAL DEVICE EXEMPTIONS (IDE)
If this device is not being used or investigated according to the FDA approved indication, is there an IDE for this device? y/n

If “Yes”, there is an IDE, complete the following information:
1. Indicate the name of the holder of the IDE: [open field]
2. Indicate the IDE number: [open field]
3. Upload the FDA letter assigning the IDE number and documentation from the FDA indicating the study is safe to proceed: [ADD button]

If the PI is the holder of the IDE, documentation from FDA is required.
Research using devices of significant risk (SR) must be approved by both FDA and RSRB before the study may begin.
Research with devices of non-significant risk (NSR) must be approved by the RSRB before the study may begin.

If “No”, there is not an IDE, explain why the device should be considered as a non-significant risk (NSR) device: [open field] [ADD button]
Supporting documentation may include information provided by the Investigator, sponsor, or FDA.

If “No”, there is not an IDE, does this device meet the requirements for IDE exemption under 21 CFR 812.2(c)? y/n
If Yes, specify which category (1 – 7):
See 21 CFR 812.2 for a listing of the seven categories. Note in particular category (3) pertaining to a diagnostic device.
The RSRB may request that the Investigator consult with FDA to verify the study is exempt from IDE requirements.
Questions

Reference

- 21 CFR 812
Reference Slides

Examples of Non-Significant Risk Devices

- Contact Lens Solutions
- Conventional Hospital Catheters
- Conventional Implantable Vascular Access Devices (ports)
- Digital Mammography
- General Biliary Catheters
- General Urological Catheters
- Menstrual Pads/Tampons (Cotton or Rayon, only)

- Transcutaneous Electric Nerve Stimulation (TENS) Devices for treatment of pain (except for angina)
- Ureteral Stents
- Wound Dressings, excluding absorbable hemostatic devices/dressings and Interactive wound/burn dressings that aid in healing
Examples of Significant Risk Devices

- Surgical Lasers
- Intravascular Stents
- Tracheal/Bronchial Tubes
- Organ Storage/Transport Units
- Epidural and Spinal Needles
- Dental Implants
- Cardiac Assist Devices
- Cochlear Implants
- Cardiac Bypass Devices
- Sutures
- Intraocular Lenses (IOLs)
- Implantable Prostheses (ligament, tendon, hip, knee, finger)