Goals

• Review:
  – Human Subject Protection Regulations
  – Good Clinical Practice Guidelines
  – OHSP Policies

• Provide resources for future use

• Think about topics for future seminars
If you want candy...

• You have to play by the rules:
  – Raise hand rather than shouting out answers
  – Speak loudly & clearly and we won’t make you use a microphone
  – Don’t be shy!!
Fill in the Blank:

_____________________ are original documents, data and records (e.g., hospital records) whose purpose is to validate the existence of a subject and the integrity of the data collected.
Source Documents

Good Clinical Practice Definitions:

Source Documents (GCP 1.52): “Original documents, data and records (e.g., hospital records, clinical & office charts, laboratory notes, memoranda, subject diaries or evaluation checklists, pharmacy dispensing records...)

Source Data (GCP 1.51): “All information in original records and certified copies of original records of clinical findings, observations or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents...”

Good Clinical Practice Guidelines: [http://ichgcp.net/](http://ichgcp.net/)
• Validates existence of subject & integrity of the data
• 21 CFR 312.62(b) & 21 CFR 812.140(a) → maintain case histories that include evidence of informed consent, relevant observations & other data pertinent to investigation
• Best practice → make maximum use of indigenous site records/standard medical records
• All data reported on CRFs should be consistent with source documents
• CRF becomes the source document when is data entered directly into CRF
• Copies of source documents maintained for study files should be certified copies

Good Clinical Practice Guidelines: [http://ichgcp.net/](http://ichgcp.net/)
(Mathieu, 2010)
The leader of a support group for single parents plans to inform group participants of a study being conducted at the University of Rochester that they may be eligible for. The leader will only provide interested participants an information sheet with contact information. Is this leader engaged in the research and does he/she need IRB approval?
OHRP’s Guidance on Engagement provides the following example of an institution who is NOT engaged in human subject research: “Institutions whose employees or agents:

A. inform prospective subjects about the availability of the research;
B. provide prospective subjects with information about the research (which may include a copy of the relevant informed consent document and other IRB approved materials) but do not obtain subjects’ consent for the research or act as representatives of the investigators;
C. provide prospective subjects with information about contacting investigators for information or enrollment; and/or
D. seek or obtain the prospective subjects’ permission for investigators to contact them.”

But...the investigator at the UR must have this method of recruitment approved by the RSRB prior to implementation.

Part One:
An investigator plans to conduct research on pre-existing blood samples and a corresponding data set that he/she will receive from an outside entity. These samples were collected & stored as part of a separate study and will be provided to the investigator in a coded manner (no HIPAA identifiers are included in the data set). The investigator will not have access to the link that identifies the subject. Is this human subject research?
While the samples & data are coded, the investigator does not have access to the link that identifies the subjects. As such, neither the samples nor the data are individually identifiable and the research is not considered human subject research.

OHRP Human Subject Regulations Decision Charts:  
http://www.hhs.gov/ohrp/policy/checklists/decisioncharts.html#c1

RSRB Guideline for Determining Human Subject Research:  
Part Two:
If the data set includes vaccination dates would this research still be considered “not human subject” research?
“All elements of a date (except the year) for dates related to an individual” are considered HIPAA identifiers.

Part Three:
What does the investigator need to obtain prior to conducting their research (on the samples/data set that include vaccination dates) to comply with HIPAA?
Data Use Agreement (DUA): An agreement into which URMC enters with the intended recipient of a limited data set that establishes the ways in which the information in the limited data set may be used and how it will be protected.

Limited Data Set (LDS): PHI that excludes direct identifiers or any other unique items that would reveal the identity of an individual. LDS may include town/city/state/zip & dates.

# Sending & Receiving Data/Specimens

## Procedures for Sending and Receiving Data/Specimens to/from Outside Institutions

<table>
<thead>
<tr>
<th>Procedures</th>
<th>RSRB Responsibilities</th>
<th>ORPA Responsibilities</th>
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<tbody>
<tr>
<td><strong>Sending Data</strong>&lt;br&gt;Is the data/specimen that is being shared de-identified to the individual(s) receiving the data/specimen?&lt;br&gt;&quot;Data/Specimens being shared do not contain any of the 18 HIPAA identifiers. OR The data/specimen may be labeled with a code by the sending institution as long as the individual(s) receiving the data/specimen do not have access to the linking mechanism.&quot;</td>
<td>- No action required; this study (or portion of a larger study) does not meet definition of “human subject”&lt;br&gt;- Recommend that the study team submit to the RSRB for exemption (or include in larger study protocol) but not required.</td>
<td>- Confirm RSRB approval has been obtained on agreement checklist&lt;br&gt;- ORPA will use Data Use Agreement for a Limited Data Set (LDS) (HIPAA form 25.6.2 if under covered entity)</td>
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<tr>
<td>YES</td>
<td>• Ensure that the RSRB application and protocol identifies who will be receiving the data/specimens and notes that a Data Use Agreement (DUA) has been/will be obtained for HIPAA compliance (if this information was not previously included, an amendment must be submitted).</td>
<td>• ORPA to review the DUA received from the other party</td>
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<tr>
<td>NO</td>
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<td>• ORPA to review the DUA received from the other party</td>
</tr>
<tr>
<td>Are the identifiers that will be shared with the data/specimens limited to dates and/or town, city, state and zip code (i.e., a limited data set)?&lt;br&gt;NO (sending more than LDS)</td>
<td></td>
<td>• Confirm RSRB approval has been obtained on agreement checklist&lt;br&gt;- ORPA will use Data Use Agreement for a Limited Data Set (LDS) (HIPAA form 25.6.2 if under covered entity)</td>
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<td>NO</td>
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<td>• Refer to Grants Administrator to review CTA and revise accordingly&lt;br&gt;- Notify RSRB of the discrepancy.</td>
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<tr>
<td>Are the identifiers that will be shared with the data/specimens limited to dates and/or town, city, state and zip code (i.e., a limited data set)?&lt;br&gt;YES</td>
<td></td>
<td>• Confirm RSRB approval has been obtained on agreement checklist&lt;br&gt;- ORPA will use Data Use Agreement for a Limited Data Set (LDS) (HIPAA form 25.6.2 if under covered entity)</td>
</tr>
<tr>
<td>NO</td>
<td></td>
<td>• ORPA to review the DTA received from other party</td>
</tr>
</tbody>
</table>

After the administration of an investigational drug, a study subject at the UR had to be hospitalized overnight for a fever spike. Both the IRB and consent identifies this as a potential risk. The investigator feels that the fever was related to the administration of the drug. How should this be reported to the RSRB?

a) Within 5 days as a local SAE (Type 1)
b) Within 10 days as a UPIRTSO (Type 4)
c) Within 3 days as “New Information” (Type 6)
d) In aggregate at the time of continuing review
D) In Aggregate at Time of CR

- Report within 10 calendar days if serious, unexpected & related to study participation
- If not...submit in summary at time of continuing review (Questions 5.7, 5.7.1 or 7.5 or in Progress Report)

Fever spike was not unexpected

RSRB Guidance for Reporting Reportable Events to the RSRB:  

OHRP Guidance on Reviewing and Reporting UPIRTSOs and Adverse Events:  http://www.hhs.gov/ohrp/policy/advevntguid.html

FDA Guidance for Clinical Investigators, Sponsors & IRBs: Adverse Event Reporting to IRBs – Improving Human Subject Protection:  

Study Documentation Tool Box (Adverse Event Logs):  http://www.rochester.edu/ohsp/quality/studydocumentationtoolBox.html
True or False:
Certificates of Confidentiality (COC) prevent voluntary disclosures and provide permanent protection of information collected about research subjects while the certificate is in effect.
False

• COCs help protect the privacy of subjects by protecting against compulsory legal demands (e.g., court orders and subpoenas)

• Protection is permanent

• BUT does not protect against voluntary disclosure

RSRB Investigator Guidance:  

Certificates of Confidentiality Kiosk:  http://grants.nih.gov/grants/policy/coc/
What is the correct method for changing information documented in a consent form, case report form or any other study document?
CRF Corrections

Good Clinical Practice Guideline 4.9.3:
“Any change or correction to a CRF [or any other record/report] should be dated, initialed and explained (if necessary) and should not obscure the original entry (i.e., an audit trail should be maintained)”

** Do not use white-out, scribbles or other methods of redaction!**

Good Clinical Practice Guidelines: [http://ichgcp.net/](http://ichgcp.net/)
True or False:
An individual who is receiving non-residential, court-ordered substance abuse treatment and is residing in the community is considered a “prisoner” per the federal regulations.
False

Prisoner = “any individual involuntarily confined or detained in a penal institution”

→ Individuals who are not detained in a residential facility are not considered prisoners

→ Regulations apply to individuals who are prisoners at outset or who become incarcerated after enrollment

Federal Regulations: 45 CFR 46
True or False:
The RSRB approval on your study has lapsed. Even though the study is complete, you still need to submit a final progress report.
Investigators whose studies are suspended/terminated due to failure to submit a progress report will not have new studies reviewed by the RSRB until a progress report is submitted and the continuing review is completed or the study is formally closed.

RSRB Investigator Guidance:
What does HRPP stand for?
Human Research Protections Program

Not just the IRB...includes all aspects of an institution’s human subjects protection program

OHSP Policy 102 (University of Rochester’s Human Research Protection Program):

OHSP Policy 103 (Organizational Structure of the Human Research Protection Program):
Part One:
Section 8 of the GCP guidelines state “Essential documents are those documents which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. These documents serve to demonstrate the compliance of the investigator, sponsor and monitor with the standards of [GCP] and with all applicable regulatory requirements.” How many “essential documents” are identified in section 8 of the GCP guideline?
### 8.2 Before the Clinical Phase of the Trial Commences

During this planning stage the following documents should be generated and should be on file before the trial formally starts.

<table>
<thead>
<tr>
<th>Title of Document</th>
<th>Purpose</th>
<th>Located in Files of</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Investigator/Institution</td>
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</tbody>
</table>

#### 8.2.1 INVESTIGATOR’S BROCHURE
- To document that relevant and current scientific information about the investigational product has been provided to the investigator
  - X for Investigator/Institution
  - X for Sponsor

#### 8.2.2 SIGNED PROTOCOL AND AMENDMENTS, IF ANY, AND SAMPLE CASE REPORT FORM (CRF)
- To document investigator and sponsor agreement to the protocol/amendment(s) and CRF
  - X for Investigator/Institution
  - X for Sponsor

#### 8.2.3 INFORMATION GIVEN TO TRIAL SUBJECT
  - INFORMED CONSENT FORM (including all applicable translations)
    - To document the informed consent
      - X for Investigator/Institution
      - X for Sponsor
  - ANY OTHER WRITTEN INFORMATION
    - To document that subjects will be given appropriate written information (content and wording) to support their ability to give fully informed consent
      - X for Investigator/Institution
      - X for Sponsor
  - ADVERTISEMENT FOR SUBJECT RECRUITMENT (if used)
    - To document that recruitment measures are appropriate and not coercive
      - X for Investigator/Institution

#### 8.2.4 FINANCIAL ASPECTS OF THE TRIAL
- To document the financial agreement between the investigator/institution and the sponsor for the trial
  - X for Investigator/Institution
  - X for Sponsor

Good Clinical Practice Guidelines: [http://ichgcp.net/](http://ichgcp.net/)
Essential Docs - Regulatory Files

• Not just GCP... federal regulations & RSRB requirements also require maintenance

• Tips:
  – Can be maintained electronically or in hard-copy (or both)
  – Should be systematically organized (e.g., use standard naming conventions) & accessible to entire study team
  – Don’t...rely on ROSS to be your regulatory file


Study Documentation Tool Box (Regulatory File Contents Description):
http://www.rochester.edu/ohsp/quality/studyDocumentationToolbox.html

RSRB Initial Application, Amendment & Continuing Review Approval Letters
Essential Docs - Regulatory Files

How to Build an Electronic Regulatory File

- **FOLDER: Name of Study or Study ID**
  - **FOLDER: Regulatory File**
    - **Initial Approval (date)**
      - Approved Documents
        - IRB Approval Letter
        - Watermarked Consent(s)
        - Protocol
        - Recruitment Flyer(s)
      - Drafts
    - **Continuing Review 1 (date)**
      - Approved Documents
        - IRB Approval Letter
        - Watermarked Consent(s)
        - Recruitment Flyer(s)
      - Drafts
    - **Amendment 1 (date)**
      - Approved Documents
        - IRB Approval Letter
        - Watermarked Consent(s)
        - Protocol
        - Recruitment Flyer(s)
      - Drafts
    - **Reportable Event 1 (date)**
      - Approved Documents
      - Drafts
      - ROSS Submission Form
    - **Other Study Related Documents**
      - Contract(s), Sponsor Documents, Data Analysis, etc.
Part Two:

Why is it important to maintain copies of study team member CVs, medical licenses, human subjects training, GCP training, etc?
Essential Docs – CVs, etc.

• Maintaining CVs, etc. documents qualifications and eligibility to conduct the study and/or provide supervision of subjects

• Ensuring investigators/study team members have adequate qualifications = responsibility of IRB, Investigator & Sponsor

Copies of UR & HH FWAs: www.rochester.edu/ohsp/index.html
Federal Regulations: 21 CFR 312 & 21 CFR 812
Good Clinical Practice Guidelines: http://ichgcp.net/
True or False:
A PI is initiating a new study sponsored by Pfizer. One of your sub-investigators receives ~$4000/yr from Pfizer for consulting. As this investigator is involved in another Pfizer-sponsored study at the UR and he/she already has a COI Management Plan in place, no additional actions are required for the new study.
False

• Report new study to COI committee → Review/Update management strategy
• Report conflict to RSRB/WIRB with application (including a copy of the management plan)
• Ensure that any/all measures included in the management strategy are appropriately addressed (e.g., disclosure in the consent form)

UR Financial Conflict of Interest Policies: http://www.rochester.edu/orpa/compliance/#fcoi
Put your RSRB Specialist hat on...
The following is an image of the last page of a last signed consent document submitted at the time of continuing review:

1) Identify the errors and/or questions you may have in reviewing this consent.

2) What additional information do you need to verify whether RSRB expectations regarding consent documentation have been met?
Please mark an X in the boxes below to indicate if you want to donate your leftover tissue for future research (as described above on page 4).

☐ Yes, I give my permission to store leftover tissue for future research.
☐ No, I do not want my leftover tissue stored for future research.

**Subject Consent**

I have read (or have had read to me) the contents of this consent form and have been encouraged to ask questions. I have received answers to my questions. I agree to participate in this study. I have received (or will receive) a signed copy of this form for my records and future reference.

Date

1/10/2014

**Person Obtaining Consent**

I have read this form to the subject and/or the subject has read this form. I will provide the subject with a signed copy of this consent form. An explanation of the research was given and questions from the subject were solicited and answered to the subject’s satisfaction. In my judgment, the subject has demonstrated comprehension of the information. I have given the subject adequate opportunity to read the consent before signing.

Kelly Unsworth, Study Coordinator

Name and Title (Print)

Signature of Person Obtaining Consent

Date

1/18/2014

RSRB No. 54321
Expires January 7, 2014
- mac 11/4/13 -
Last Signed Consent Review

• The expiration date has passed... Content consistent?
• The signature dates differ... Why?
• The checkboxes were not completed... What happened to the leftover tissue?
• The handwriting of the dates look similar... Did the POC date both?
• Things we don’t know:
  – Is the person who obtained consent approved?
  – Was the first page of the consent printed on letterhead?
RSRB Expectations Include:

– Obtaining/Documenting consent in a manner approved by RSRB (i.e., comply with protocol)
– Consent materials must bear the RSRB watermark
– Only the most recently approved version may be used
– Must be printed on letterhead

RSRB Guidance on Recruitment & Informed Consent:
http://www.rochester.edu/ohsp/documents/rsrb/pdf/Informed_Consent_Guidance.pdf#page=30&zoom=auto,0,11

RSRB Initial Application, Amendment & Continuing Review Approval Letters
Fill in the Blank:
____________ is a pattern of non-compliance that continues despite identification by the RSRB, notice to the investigator or prior submission of a corrective action plan. This pattern may or may not result in increased risk to subject. Although it may be due to a variety of factors, continuing non-compliance implies that an investigator is either unwilling or unable to develop and apply successful corrective measures.
• **Example:**
  – Issues with PI oversight identified during routine QI review
  – Board reviews incident and approves CAPA
  – 1-2 years later same issues arise
  – Incident returns to the board for review

• Reportable to Dept Chair, Institutional Officials, OHRP/FDA & Sponsor

Federal regulations identify specific criteria that studies must meet in order for an IRB to approve the research. How many criteria are there?
1) Risks to subjects are minimized
2) Risks to subjects are reasonable compared to benefits
3) Selection of subjects is equitable
4) Informed consent obtained
5) Informed consent appropriately documented
6) Adequate provisions for monitoring data to ensure safety
7) Adequate provisions for protecting privacy & maintaining confidentiality
8) Adequate safeguards included to protect vulnerable populations

Federal Regulations: 45 CFR 46 & 21 CFR 56
RSRB Policy 404 (Criteria for RSRB Approval of Research):
What is the purpose of a Delegation of Authority Log?
Delegation of Authority

Provides a list of study personnel and identifies the personnel to whom the investigator has delegated study-specific tasks

Study Documentation Tool Box (Adverse Event Logs): [http://www.rochester.edu/ohsp/quality/studyDocumentationToolBox.html](http://www.rochester.edu/ohsp/quality/studyDocumentationToolBox.html)

<table>
<thead>
<tr>
<th>Study Title:</th>
<th>Protocol No:</th>
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<tr>
<td>Principal Investigator:</td>
<td>Sponsor:</td>
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<tr>
<th>Printed Name</th>
<th>Study Role</th>
<th>Key Delegated study Task(s)*</th>
<th>Duration From:</th>
<th>To:</th>
<th>Signature</th>
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*Key for list of delegated study task(s)

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<td>Obtain informed consent</td>
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<td>Reviewing and Reporting Adverse Events</td>
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Delegation of Authority

• Remember... Investigator is still ultimately responsible for conduct of study

• When delegating, consider:
  – Are individuals who were delegated tasks qualified to perform such tasks?
  – Has the study team received adequate training to perform delegated tasks?
  – Is there adequate supervision and ongoing involvement?

Identify 4 elements that should be included in a Note to File
Components of a Notes to File

- Description of the problem/error
- Root cause
- Corrective/Preventative action
- Resolution
- Date
- RSRB/WIRB #
- Signature of person writing NTF
- Printed on department letterhead

(Mathieu, 2010)
Study Documentation Tool Box (Adverse Event Logs): [http://www.rochester.edu/ohsp/quality/studyDocumentationToolBox.html](http://www.rochester.edu/ohsp/quality/studyDocumentationToolBox.html)
What is this....
9. COMMITMENTS

I agree to conduct the study(ies) in accordance with the relevant, current protocol(s) and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of subjects.

I agree to personally conduct or supervise the described investigation(s).

I agree to inform any patients, or any persons used as controls, that the drugs are being used for investigational purposes and I will ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and institutional review board (IRB) review and approval in 21 CFR Part 56 are met.

I agree to report to the sponsor adverse experiences that occur in the course of the investigation(s) in accordance with 21 CFR 312.64. I have read and understand the information in the investigator’s brochure, including the potential risks and side effects of the drug.

I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments.

I agree to maintain adequate and accurate records in accordance with 21 CFR 312.62 and to make those records available for inspection in accordance with 21 CFR 312.68.

I will ensure that an IRB that complies with the requirements of 21 CFR Part 56 will be responsible for the initial and continuing review and approval of the clinical investigation. I also agree to promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

I agree to comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 CFR Part 312.
By signing form, the investigator agrees to:

- Conduct/Supervise the study in accordance with the protocol
- Ensure that requirements related to informed consent & IRB review are met
- Inform patients that drugs are investigational
- Report adverse experiences to the sponsor
- Ensure all study personnel are properly trained
- Maintain adequate & accurate records (and to make these records available for inspection)
- Ensure that an IRB complies with 21 CFR 56
- Comply with 21 CFR 312

CTSI Office of Regulatory Support - Guidance for FDA IND: http://www.urmc.rochester.edu/ctsi/regulatory-support/
Form FDA 1572: http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM072728.pdf
When do the federal regulations require a witness when obtaining documenting informed consent?
Oral Presentation/Short Form

- Only when obtaining consent through oral presentation & a short form
- All other cases, if witness included → Protocol should address if optional/mandatory & if optional, circumstances for use

Federal Regulations: 45 CFR 46 & 21 CFR 50
RSRB Guidance on Recruitment & Informed Consent:
http://www.rochester.edu/ohsp/documents/rsrb/pdf/Informed_Consent_Guidance.pdf#page=30&zoom=auto,0,11
What does UPIRTSO stand for?
UPIRTSO

• Unanticipated Problem Involving Risks to Subjects or Others

• “Unanticipated Problem” – 3 criteria:
  1) Unexpected (in terms of nature, severity or frequency);
  2) Related or possibly related to participation in research; **AND**
  3) Suggests that the research places subjects or others at a greater risk of harm

RSRB Guidance for Reporting Reportable Events to the RSRB:  

OHRP Guidance on Reviewing and Reporting UPIRTSOs and Adverse Events:  http://www.hhs.gov/ohrp/policy/aveventaud.html

FDA Guidance for Clinical Investigators, Sponsors & IRBs: Adverse Event Reporting to IRBs – Improving Human Subject Protection:  
Match the ethical principle described in the *Belmont Report* with their respective application in human subjects research:

A) Respect for Persons
B) Beneficence
C) Justice

1) Selection of Subjects
2) Informed Consent
3) Risk/Benefit Assessment
Match the ethical principle described in the *Belmont Report* with their respective application in human subjects research

A) Respect for Persons

B) Beneficence

C) Justice

1) Selection of Subjects

2) Informed Consent

3) Risk/Benefit Assessment

What is a sponsor-investigator?
Sponsor-Investigator

“An individual who both initiates and conducts, alone or with others, a clinical trial, and under whose immediate direction the investigational product is administered to, dispensed to or used by a subject.”
(GCP 1.54)

→ Assume the responsibilities of both the sponsor & the investigator

Good Clinical Practice Guidelines: http://ichgcp.net/
Which ethical guideline (first issued in 1964) was recently revised?
Declaration of Helsinki

• Adopted by the World Medical Association in 1964
• Enforces the principles of the Nuremberg Code
• 9 revisions; most recently October 2013
  – Increased protections for vulnerable populations, comp for injury, post-trial provisions, etc.

References

• DHHS Regulations:
  – 45 CRF 46: Protection of Human Subjects
• OHRP Human Subject Regulations Decision Charts: http://www.hhs.gov/ohrp/policy/checklists决策charts.html#c1
• OHRP Guidance on Reviewing and Reporting UPIRTSOs and Adverse Events: http://www.hhs.gov/ohrp/policy/advevntguid.html
• FDA Regulations:
  – 21 CFR 50: Protection of Human Subjects
  – 21 CFR 56: Institutional Review Boards
  – 21 CFR 312: Investigational New Drugs Applications
  – 21 CFR 812: Investigational Device Exemptions
References

- Form FDA 1572: http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM074728.pdf
- Good Clinical Practice Guidelines: http://ichgcp.net/
UR-Specific References

- OHSP Homepage: http://www.rochester.edu/ohsp/index.html
- RSRB Homepage: http://www.rochester.edu/ohsp/rsrb/index.html
- OHSP/RSRB Policies & Guidelines: http://www.rochester.edu/ohsp/policies/guidanceDocuments.html
- OHSP Study Documentation Tool Box: http://www.rochester.edu/ohsp/quality/studyDocumentationToolBox.html
- UR Financial Conflict of Interest Policies: http://www.rochester.edu/orpa/compliance/#fcoi
- CTSI Office of Regulatory Support: http://www.urmc.rochester.edu/ctsi/regulatory-support/