



IRBMED
New Member Workshops
SESSION TWO

Workshop Agenda

- Regulations, regulations, regulations
- eResearch Application—Introduction



Regulation Overview

- DHHS—Food and Drug Administration (FDA) Regulations
 - 21 CFR 50 Informed Consent Requirements
 - 21 CFR 56 IRB Responsibilities & Administrative Action for Noncompliance
 - *21 CFR 312 Investigator, Sponsor, IND responsibilities*
 - *21 CFR 812 Investigator, Sponsor, IDE responsibilities*



Regulation Overview

- DHHS—Office of Human Research Protections (OHRP) Regulations
 - 45 CFR 46 IRB Responsibilities and Informed Consent Requirements
 - Subpart A—“Common Rule”
 - Subpart B—Fetuses, Pregnant Women, In Vitro
 - Subpart C—Prisoners
 - Subpart D—Children



Regulation Overview

- DHHS—Office of Civil Rights (OCR)
Regulations
 - 45 CFR 164
 - HIPAA



Regulatory Details

- IRB approval required before initiating research involving human subjects 45 CFR 46.109, 21 CFR 56.103



Is this research?



- Standard treatment for a certain kind of benign tumor that's usually found in the femur is to remove the tumor, curette the area, then fill the hole in the bone with cement, or cement plus hardware
- An orthopedic surgeon plans to modify this last step with a significant change to the hardware on a patient he thinks might benefit from this innovative approach

Regulatory Details— Defining ‘research’

- **OHRP:** A *systematic* investigation, including research development, testing and evaluation, designed to develop or contribute to *generalizable* knowledge. 45 CFR 46.102 (d)
- **FDA:** [A]ny experiment that involves a test article and one or more human subjects . . . the results of which are intended to be submitted to . . . FDA . . . The terms research, clinical research, clinical study, study, and clinical investigation are deemed to be synonymous for this part. 21 CFR 56.102 (c)

Is this research?



- Comparison of the safety and complication rate of ipsilateral versus contralateral breast reconstruction through retrospective chart review. Abstracted data to include:

- | | |
|---|--|
| <ul style="list-style-type: none">■ general demographic data■ stage of breast disease■ type of cancer■ adjuvant therapies (i.e. radiation therapy, chemotherapy)body mass index | <ul style="list-style-type: none">■ tobacco use history■ other medical problems and surgical history.■ complications such as partial or total flap loss, hematoma, seroma, abdominal wall herniation |
|---|--|

- The results of this study will increase the safety of mastectomy reconstruction through a critical analysis of surgical technique.

Is this human subject research?

Regulatory Details— Defining a ‘human subject’

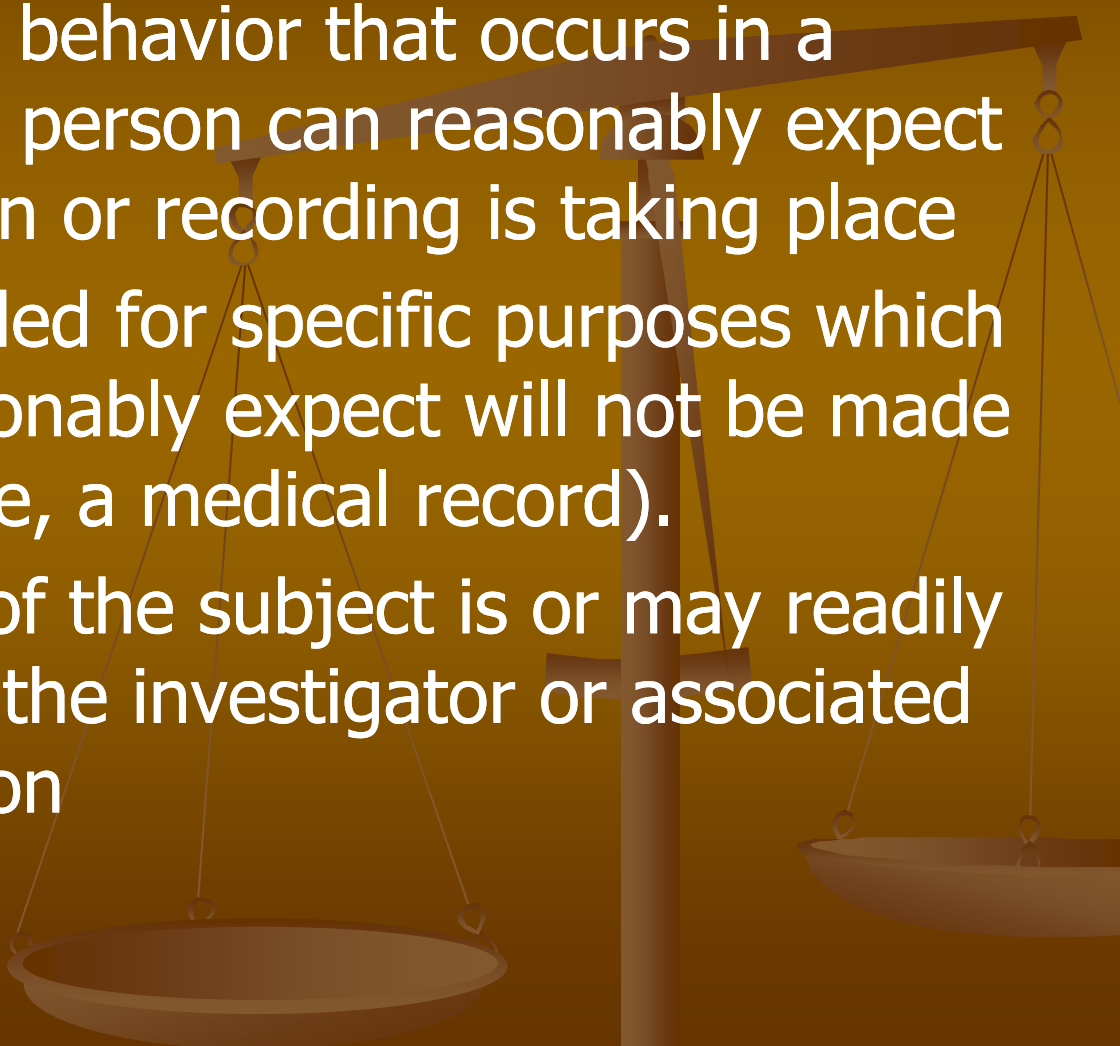
- **FDA:** A human . . . on whose specimen an investigational device is used OR An individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy human or a patient. 21 CFR

812.3(p), 21 CFR 50.3 (g) and 21 CFR 56.102 (e)

- **OHRP:** A living individual about whom an investigator conducting research obtains (1) Data through intervention or interaction with the individual, OR (2) Identifiable private information.

45 CFR 46.102 (f)

Regulatory Details— Defining a ‘identifiable private information’

- Information about behavior that occurs in a context in which a person can reasonably expect that no observation or recording is taking place
 - Information provided for specific purposes which a person can reasonably expect will not be made public (for example, a medical record).
 - **AND** the identity of the subject is or may readily be ascertained by the investigator or associated with the information
- 

Welcome to
the dark side.
It is your
destiny.



Regulatory Details— Criteria for Review

45 CFR 46.111 & 21 CFR 56.111

- Risks to subjects are minimized by using
 - procedures which are consistent with sound research design
 - procedures which do not unnecessarily expose subjects to risk
 - procedures (whenever appropriate) already being performed on the subjects for diagnostic or treatment purposes

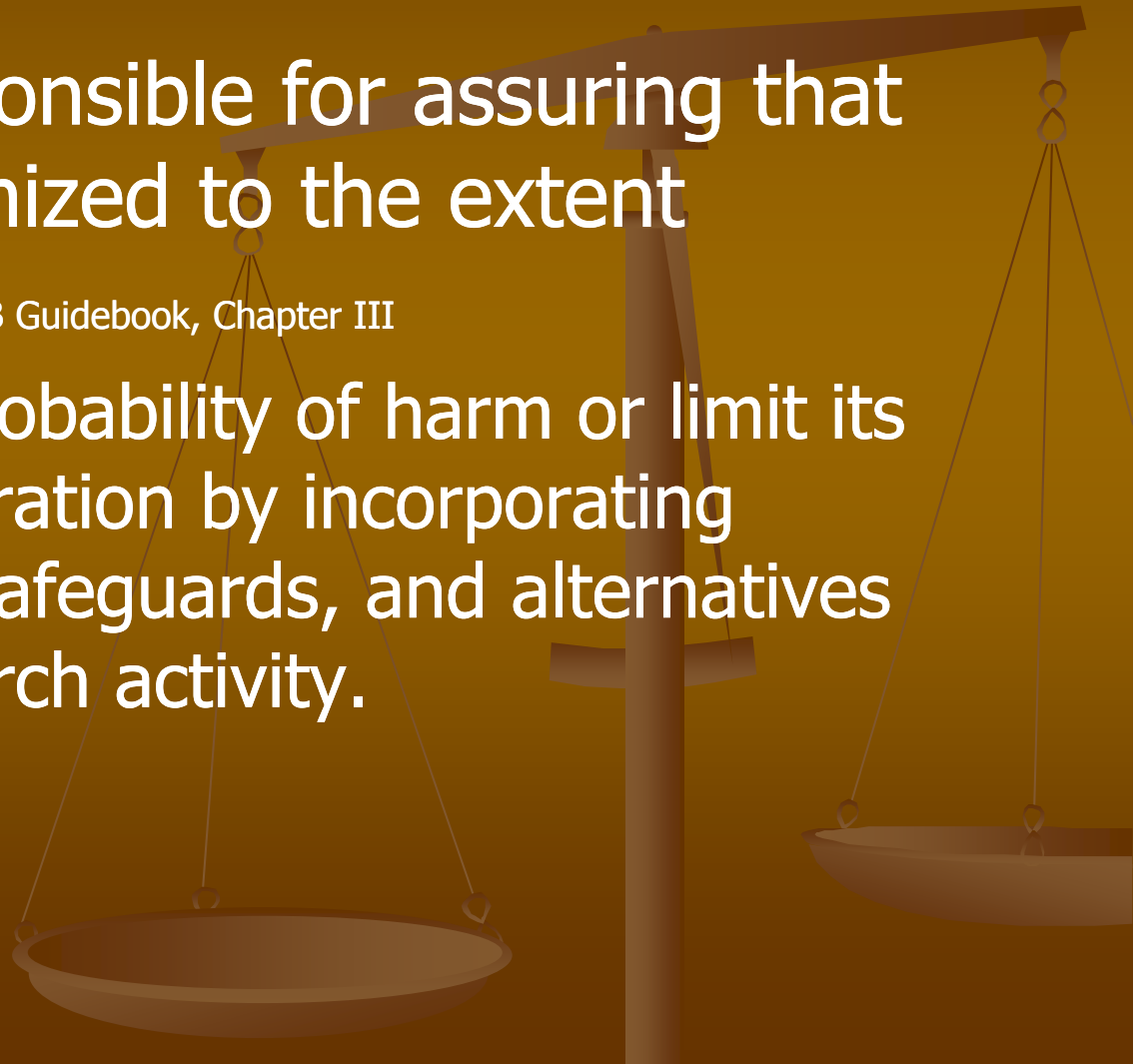
45 CFR 46.111 (a)(1)



Regulatory Details— Criteria for Review

45 CFR 46.111 & 21 CFR 56.111

- “IRBs are responsible for assuring that risks are minimized to the extent possible.” OHRP IRB Guidebook, Chapter III
 - Reduce the probability of harm or limit its severity or duration by incorporating precautions, safeguards, and alternatives into the research activity.



Regulatory Details— Criteria for Review

continued45 CFR 46.111 & 21 CFR 56.111

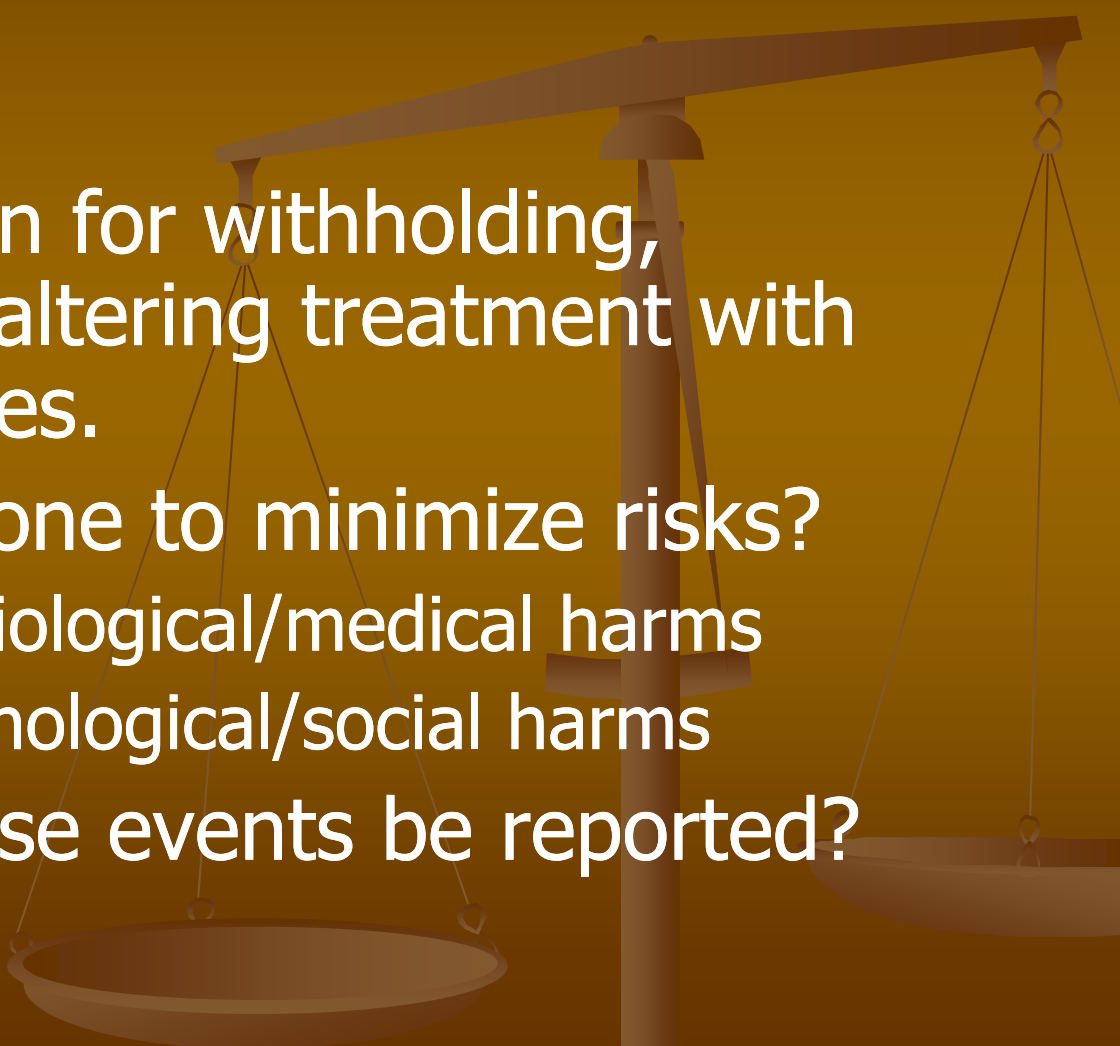
Once “risks to subjects are minimized”

“In order to approve research covered by this policy the IRB shall determine that all of the following requirements are satisfied”

- Risks are reasonable in relation to benefits
- Selection of subjects is equitable
- Informed consent will be sought and appropriately documented [unless waived]
- Subject safety is adequately monitored
- Plans to protect privacy of subjects and confidentiality data are adequate

Regulatory Details— Implementing .111 Criteria

CONSIDER:

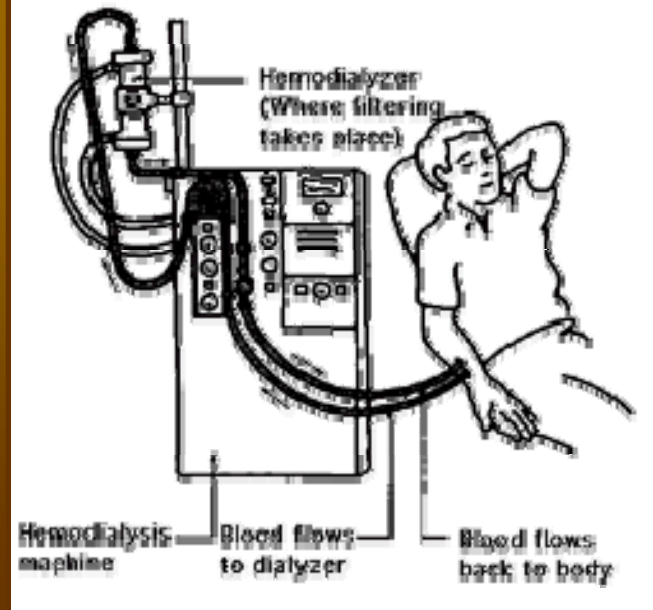
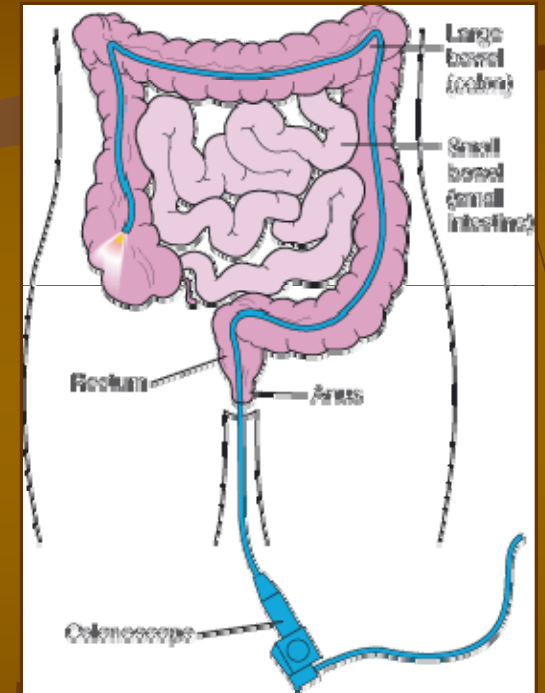
- The justification for withholding, postponing or altering treatment with proven therapies.
 - What will be done to minimize risks?
 - Potential physiological/medical harms
 - Potential psychological/social harms
 - How will adverse events be reported?
- 

Regulatory Details—Defining ‘Minimal Risk’

- The probability and magnitude of harm or discomfort anticipated as a result of participation in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examination or tests. 45 CFR 46.102 (i),
21 CFR 56.102 (i)

- “Encountered in daily life” means the daily life of the average, healthy, person or child.

Minimal risk?



Regulatory Details— Informed Consent 21 CFR 50 and 45 CFR 46.116

■ IRBMED Posted Template and Instructions

■ IRBMED Guidance <http://www.med.umich.edu/irbmed/guidance.htm>

- Questions about IRBMED IRB documents, applications, and
 - Informed Consent Guidance
 - [Additional Required Elements under HIPAA](#)
 - Children (see above, Children in Research, Assent)
 - [Non-English Speaking Subjects](#)
 - [Process](#)
 - [Simplification Guide to Medical Terms \(Glossary\)](#)
 - Telephone (see [Telephonic Consent](#))
 - [Template-What's New](#)
 - [Tips on Preparing Understandable Informed Consent Documents](#)
 - [Waiver under OHRP, FDA & HIPAA Regulations](#)
 - International Research

Regulatory Details—

*OHRP Informed Consent Waivers & Alterations**

Waiver of requirement to obtain informed consent	Request for <u>alteration</u> of informed consent requirement	Waiver of <u>documentation</u> of informed consent
Researcher will not be required to ask for informed consent from any subjects for all or part of the project	An informed consent process and documentation will be required but information that is otherwise required as part of the process may be excluded	An informed consent process will be required but subjects' signatures (or names) will not be required.

*The OHRP 'substitution' option will be discussed next week

Regulatory Details—

OHRP Criteria permitting an IRB to grant a waiver or alteration of informed consent 45 CFR 46.116 and .117

Waiver	Request for Alteration	Waiver of Documentation
<ul style="list-style-type: none">■ The research involves no more than minimal risk to the subjects■ The waiver or alteration will not adversely affect the rights and welfare of the subjects.■ Research could not practicably (i.e., feasibly) be carried out without the waiver or alteration.■ Whenever appropriate, the subjects will be provided with additional pertinent information after participation.		<ul style="list-style-type: none">■ The research presents no more than minimal risk of harm to the subject and involves no procedures for which written consent is normally required outside of the research context <p style="text-align: center;">OR</p> <ul style="list-style-type: none">■ The only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from breach of confidentiality

Regulatory Details—

FDA Informed Consent Exceptions/Waivers

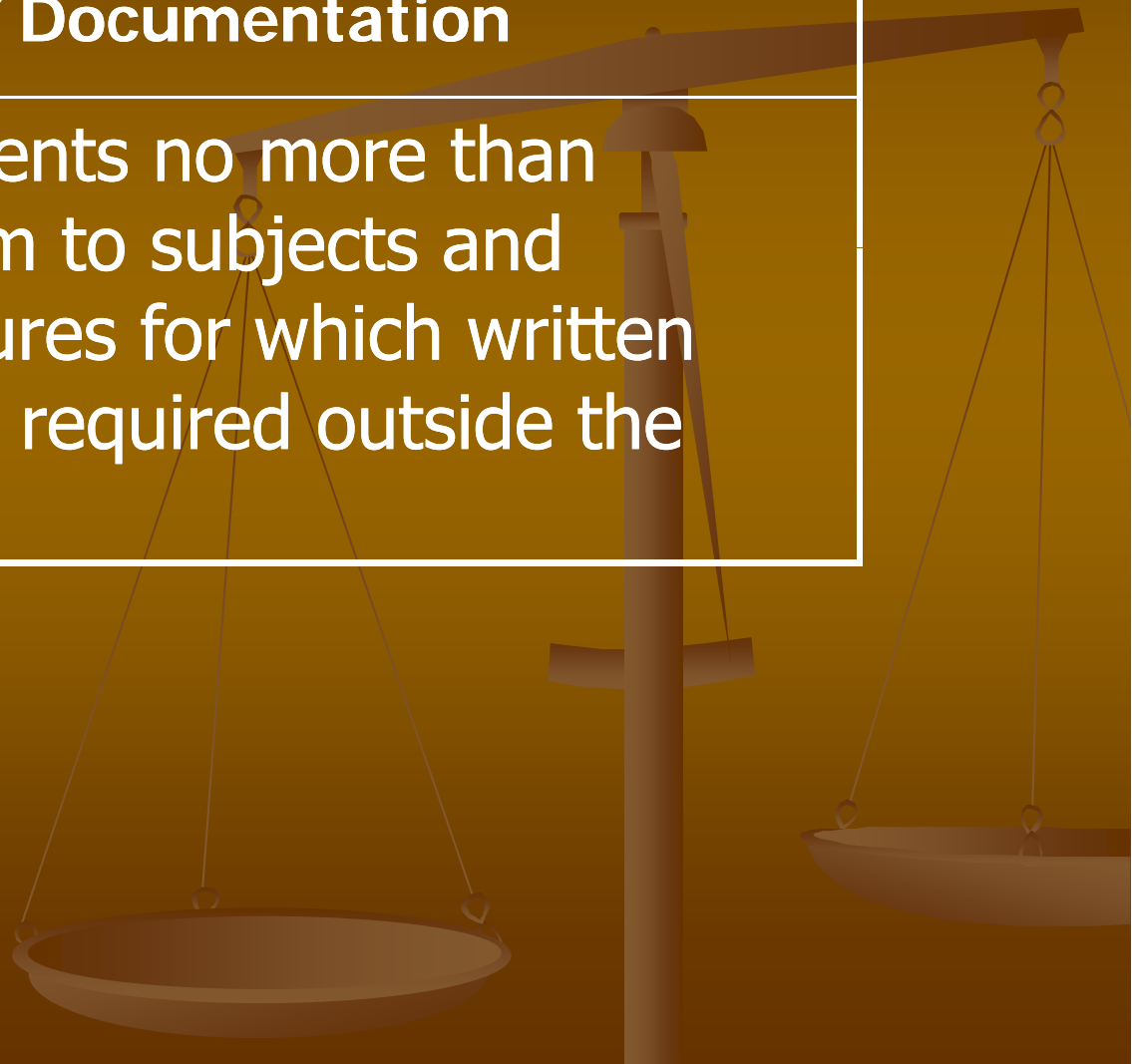
21 CFR 50.23 and .24

Exception from Informed Consent Requirement in Emergency Use	Exception from Informed Consent for Planned Emergency Research	Exception from Informed Consent for Terrorism/Public Health Emergency Testing	Presidential Waiver for Military
Investigational agent is administered for clinical care reasons in circumstances that don't allow IC to be obtained because of time constraints	Investigational agent is administered prior to obtaining IC because the research could not otherwise be conducted because of the delay the ICP would involve	An in vitro investigational diagnostic device is used to identify chemical, biological, radiological, or nuclear agents in life-threatening situation where IC is not feasible	The president may waive the requirement for IC when an investigational new drug can be administered to a member of the armed forces in connection with a military operation

*Regulatory Details—
FDA 21 CFR 56.109(c)(1)*

Waiver of Documentation

- The research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside the research context.



OHRP & FDA

Applying Both Regs at the Same Time

OHRP Waiver of requirement to obtain informed consent

OHRP Request for alteration of informed consent requirement

OHRP Waiver of documentation of informed consent

If the study is under FDA oversight OHRP waiver of informed or alteration are not allowed for the FDA component of the research. Waiver of documentation is allowed for minimal risk research for which consent would not otherwise be required.

FDA Emergency Use Exception

FDA Emergency Research Exception

**FDA Terrorism/
Public Health
Emergency
Exception**

**FDA/DOD
Presidential
Waiver for
Military**

Under OHRP, agent can be administered but data collected cannot be used for research

OHRP allows data to be collected and used for research if IC is obtained after the fact

OHRP allows research on data collected 46.116(d) applies (the waiver of consent regs above)

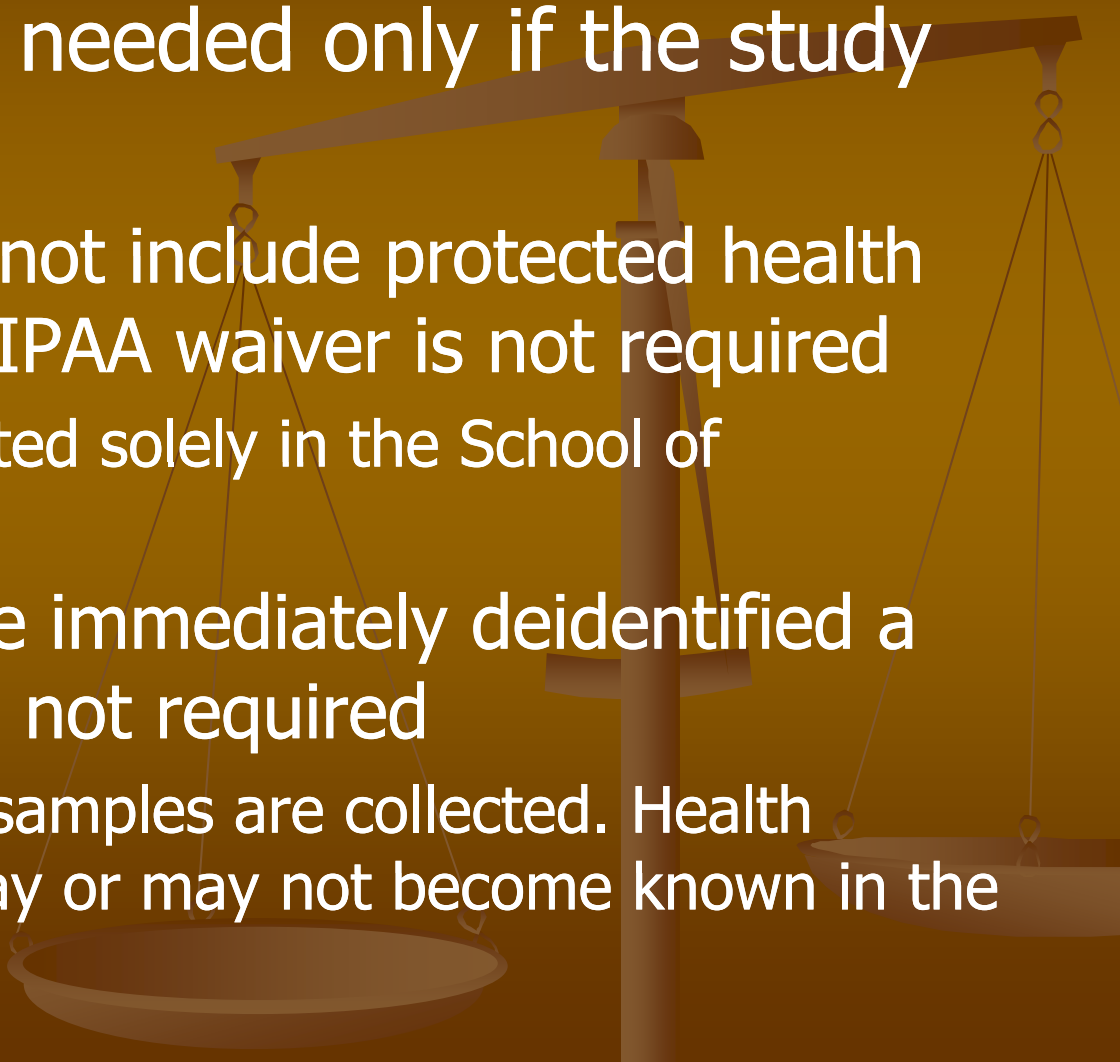
OHRP?

eResearch

Where in eResearch is the info?

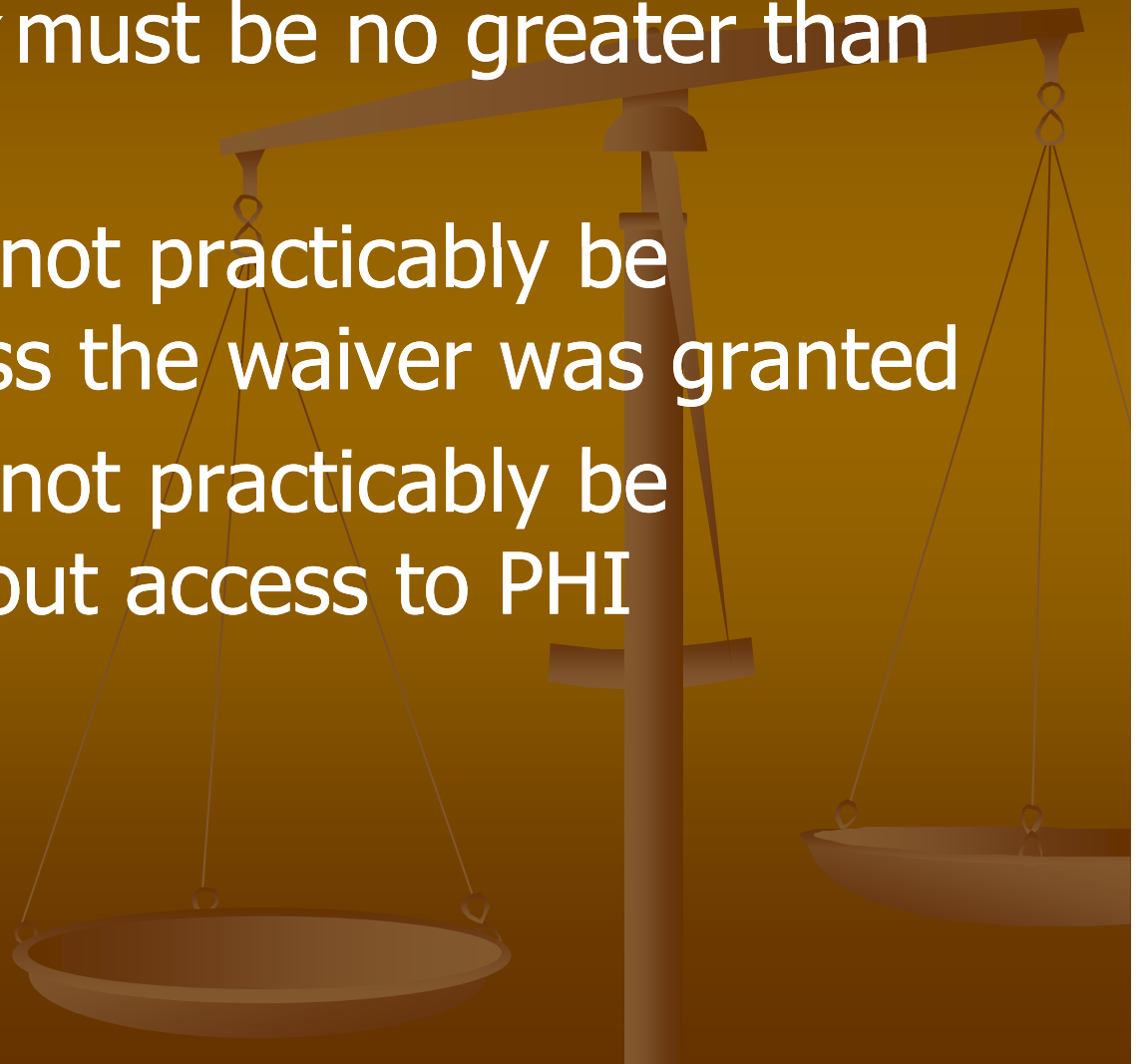
OHRP Waiver of requirement to obtain informed consent		OHRP Request for <u>alteration</u> of informed consent requirement	OHRP Waiver of <u>documentation</u> of informed consent	
Sections 10.1, 10-1, 10-3			Sections 10.1, 10-1, 10-4	
FDA Emergency Use Exception	FDA Emergency Research Exception	FDA Terrorism/ Public Health Emergency Exception	FDA/DOD Presidential Waiver for Military	
Drug or Biologic: Section 1-3 Device: Section 1-4	See protocol in Section 5 AND Sections 10.1, 10-1	Section 1-4 OR Sections 10.1, 10-3	Sections 10.1, 10-1, 10-3	

*Regulatory Details—
HIPAA criteria permitting an IRB to grant a
waiver of authorization*

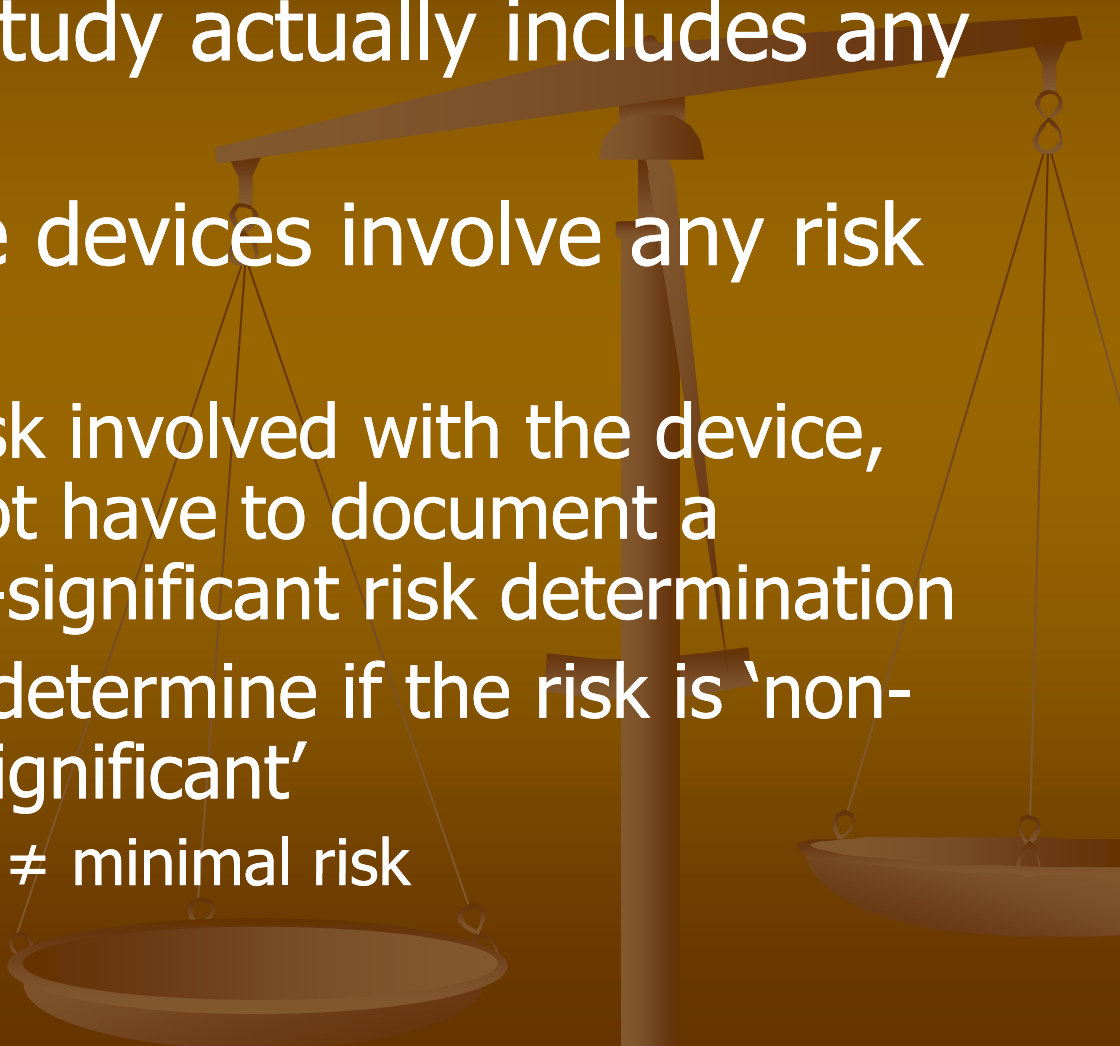
- HIPAA waiver is needed only if the study involves PHI.
 - If a study does not include protected health information a HIPAA waiver is not required
 - Studies conducted solely in the School of Engineering
 - If specimens are immediately deidentified a HIPAA waiver is not required
 - Urine or blood samples are collected. Health related data may or may not become known in the research tests
- 

*Regulatory Details—
HIPAA criteria permitting an IRB to grant a
waiver of authorization* 45 CFR 164.512

- Risks to *privacy* must be no greater than minimal
- Research could not practicably be conducted unless the waiver was granted
- Research could not practicably be conducted without access to PHI

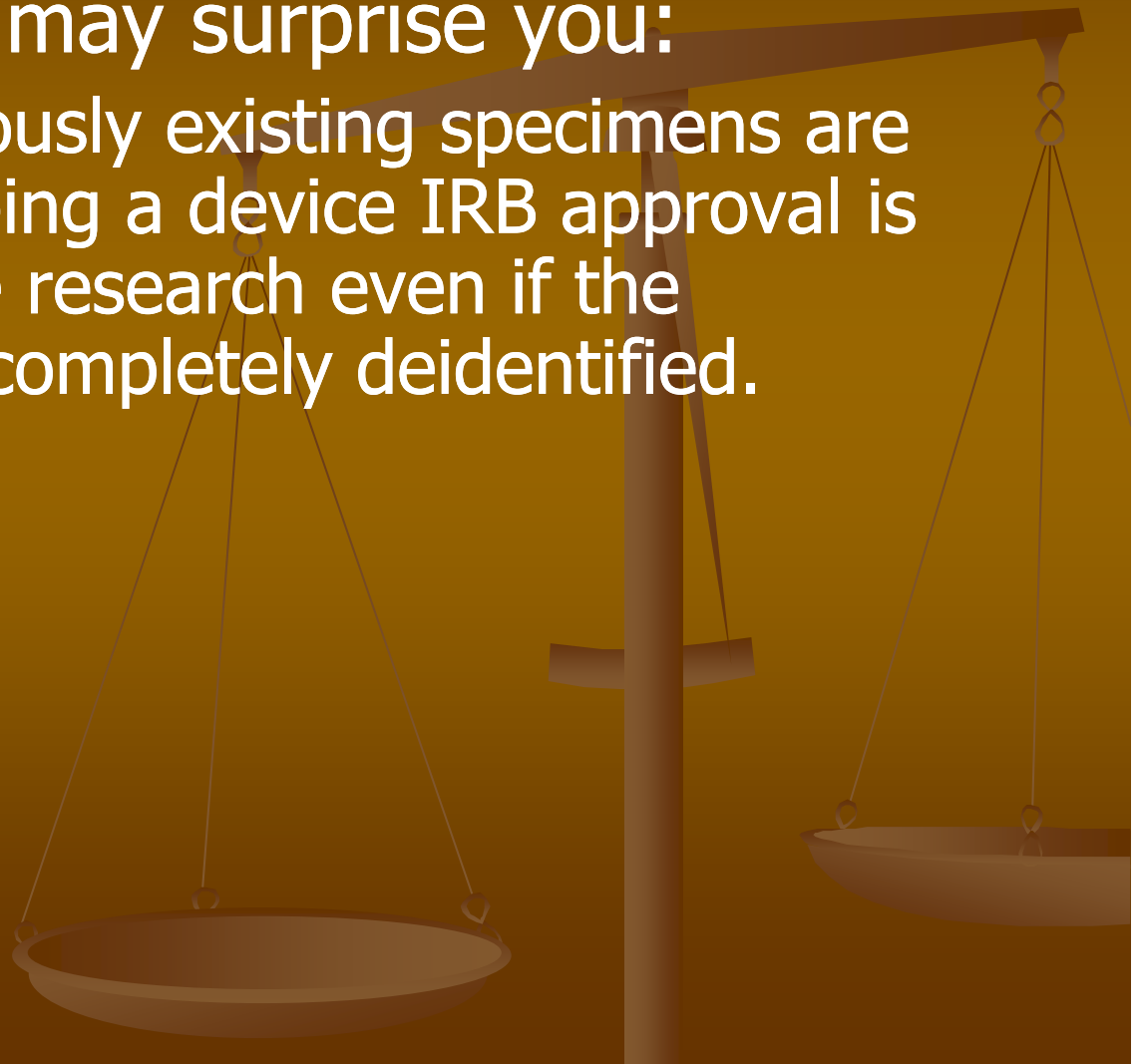


Regulatory Details— Studies that involve 'devices'

- Determine if a study actually includes any devices
 - Determine if the devices involve any risk to subjects
 - If there is no risk involved with the device, the IRB does not have to document a 'significant/non-significant risk determination'
 - If there is risk, determine if the risk is 'non-significant' or 'significant'
 - Non-significant ≠ minimal risk
- 

Regulatory Details— Studies that involve ‘devices’

- Something that may surprise you:
 - If human previously existing specimens are used in developing a device IRB approval is required for the research even if the specimens are completely deidentified.



Regulatory Details— Significant/Non-Significant Risk Assessment

16.2.1 Devices Not Approved by the FDA (including "510(k) devices"):

Note: For Dental School Applications, See H

Name	IDE	Nun
<input type="checkbox"/> Click here to see the SR/NSR sub-page		

16.2.6 * What is sponsor's risk designation for the device according to FDA definitions?

Select one:

Non-significant Risk (NSR)

Significant Risk (SR)

[Clear](#)

16.2.7 Non-significant Risk Device Detail: Complete the following two questions for devices that have a non-significant risk designation

16.2.7.1 Describe why this device and its use, as proposed in this study, constitute a non-significant risk to the subjects involved. *Include an evaluation of the safety risks to the subject in the event of a device failure.*

16.2.7.2 Upload documentation from the sponsor that supports the determination that the device does not pose a significant risk to subjects. *Include documentation of any prior investigations or other supporting materials.* [?](#)

name	version
There are no items to display	

Check here if the documentation is not available electronically.

Regulatory Details— Significant/Non-Significant Risk Assessment

eResearch **M** Edit: Applicati

Save | Exit | Hide/Show Errors | Print... | Jump

To: 07-1. Special Consideration - Continued

▶ **Note** (0 Notes Total)

7-1. Special Considerations (continued)

7-1.1 * Will any drugs, biologics, nutritional (e.g., herbal or alternative medication) supplements or other material be administered, implanted, or applied to the subjects as the object of the study? (Please note, a fee applies if using UMHS IDS services) [Require Section 15] ⓘ

Yes No [Clear](#)

7-1.2 * Will any devices be used, administered, implanted, or applied to the subjects? [Require Section 16]

Yes No [Clear](#)

7-1.3 * Will the study involve a placebo (drug, device, procedure, intervention, surgery, etc.) control group? [Require Section 17]

Yes No [Clear](#)

7-1.3.1 If yes, is the placebo for a drug? [Require Section 15]

Yes No [Clear](#)

Regulatory Details— Significant/Non-Significant Risk Assessment

21 CFR 812.2

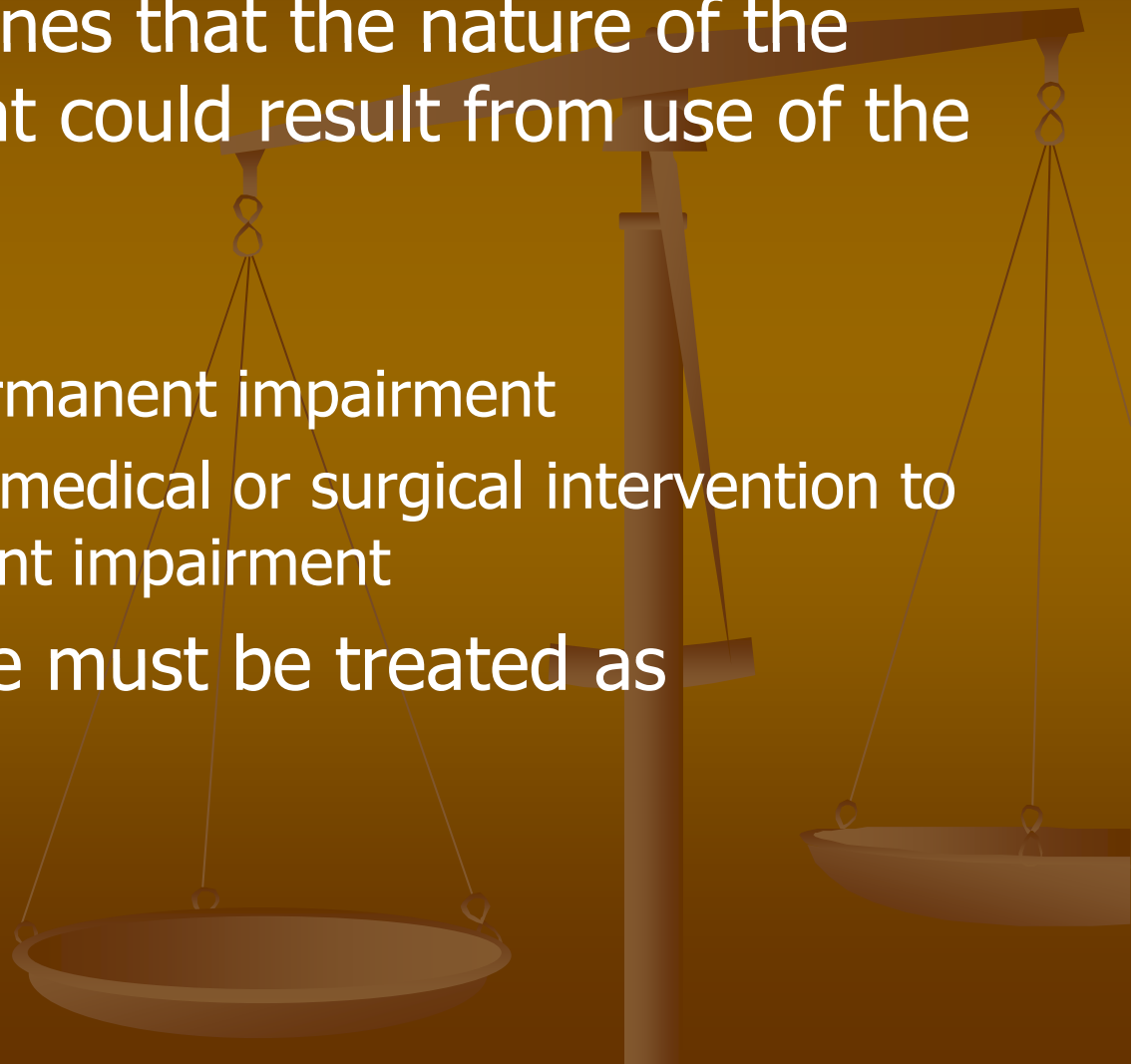
- Consider the proposed use of a device in an investigation, and not on the device alone.
 - Does the study present a potential for serious risk to the health, safety, or welfare of a subject?
 - Will the subject need to undergo an additional procedure as part of the study? Example: a surgical procedure
- IRBs should consider the potential harm the procedure could cause as well as the potential harm caused by the device.
- IRBs also make these judgments when an FDA approved device is used “off label”

Information Sheet Guidance For IRBs, Clinical Investigators, and Sponsors—Significant Risk and Nonsignificant Risk Medical Device Studies, January 2006

Regulatory Details— Significant/Non-Significant Risk Assessment

UM HRPPP Operations Manual

- If the IRB determines that the nature of the potential harm that could result from use of the device:
 - Is life-threatening
 - Could result in permanent impairment
 - Could necessitate medical or surgical intervention to preclude permanent impairment
- ... then the device must be treated as 'Significant Risk.'



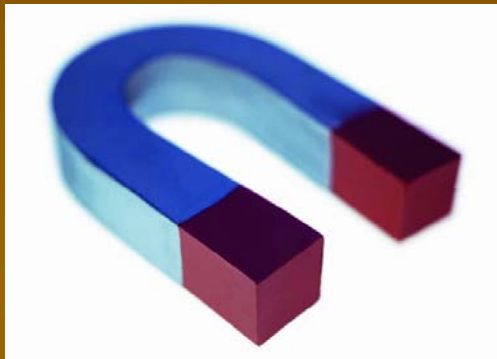
Regulatory Details—

Assessing Need for FDA Oversight

Devices

- If the study/device is 'Significant Risk'
 - The sponsor must contact the FDA for a determination and an Investigational Device Exemption (IDE).
 - If an IDE has been obtained prior to IRB approval or if being obtained, the study may be approved pending receipt of the IDE # or given a 'partial approval' to allow limited work on the study to begin
 - An amendment application providing the IDE would have to be submitted and approved prior to the device being used in the study.

Medical Device?



Regulatory Details— Assessing Need for FDA Oversight

What is a 'Device'?

- In 2004 research led to maggots and leeches receiving approval from the Food and Drug Administration to be marketed as medical device



Regulatory Details— Assessing Need for FDA Oversight



Drugs (or other non-device agents)

- 'New' agents not on the market
 - Sponsor usually submits an "Investigational New Drug" (IND) application to FDA prior to IRB Review
 - IRB approval requires receipt of the IND# or IRB may grant 'partial approval' to allow limited work on the study to begin
 - An amendment application providing the IND # would have to be submitted and approved prior to the agent being used in the study.



Regulatory Details— Assessing Need for FDA Oversight

Marketed Drugs—do they need an IND?

- **NO** if all of the following conditions are met (2 slides):
 - FDA approval will NOT be sought for the agent's use for a new indication
 - FDA approval will NOT be sought for a change in the labeling for the drug
 - Research is NOT intended to support a significant change in the advertising for the product

<http://www.fda.gov/oc/ohrt/irbs/offlabel.html>

Regulatory Details— Assessing Need for FDA Oversight

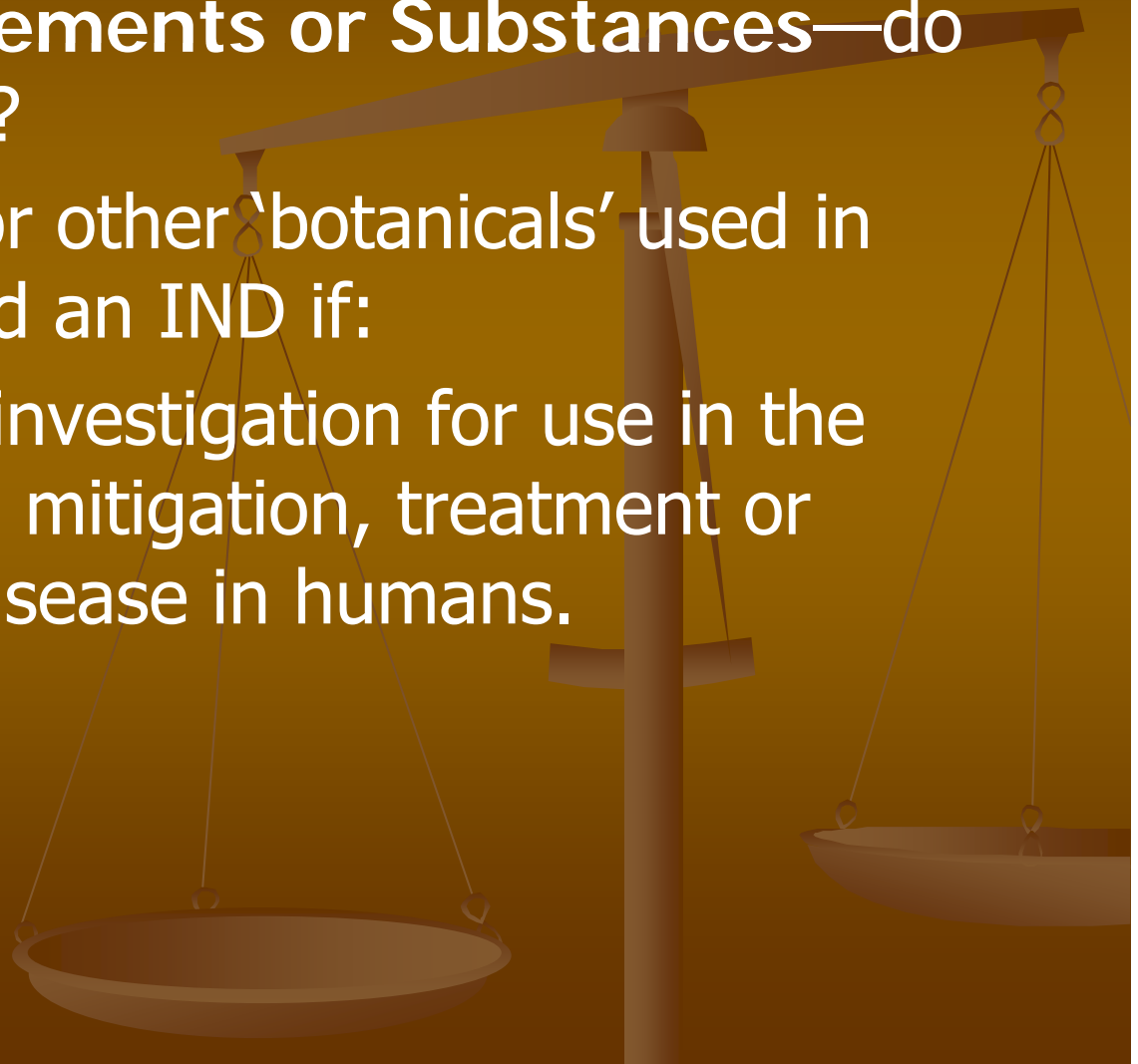
Continued . . . Conditions for not needing an IND

- Research does not involve a route of administration or dosage level, use in a subject population, or other factor **that significantly increases the risks (or decreases the acceptability of the risks)** associated with the use of the drug product
- Research will have IRB oversight
- Research does not intend to invoke 21 CFR 50.24 (it is not emergency research without informed consent)

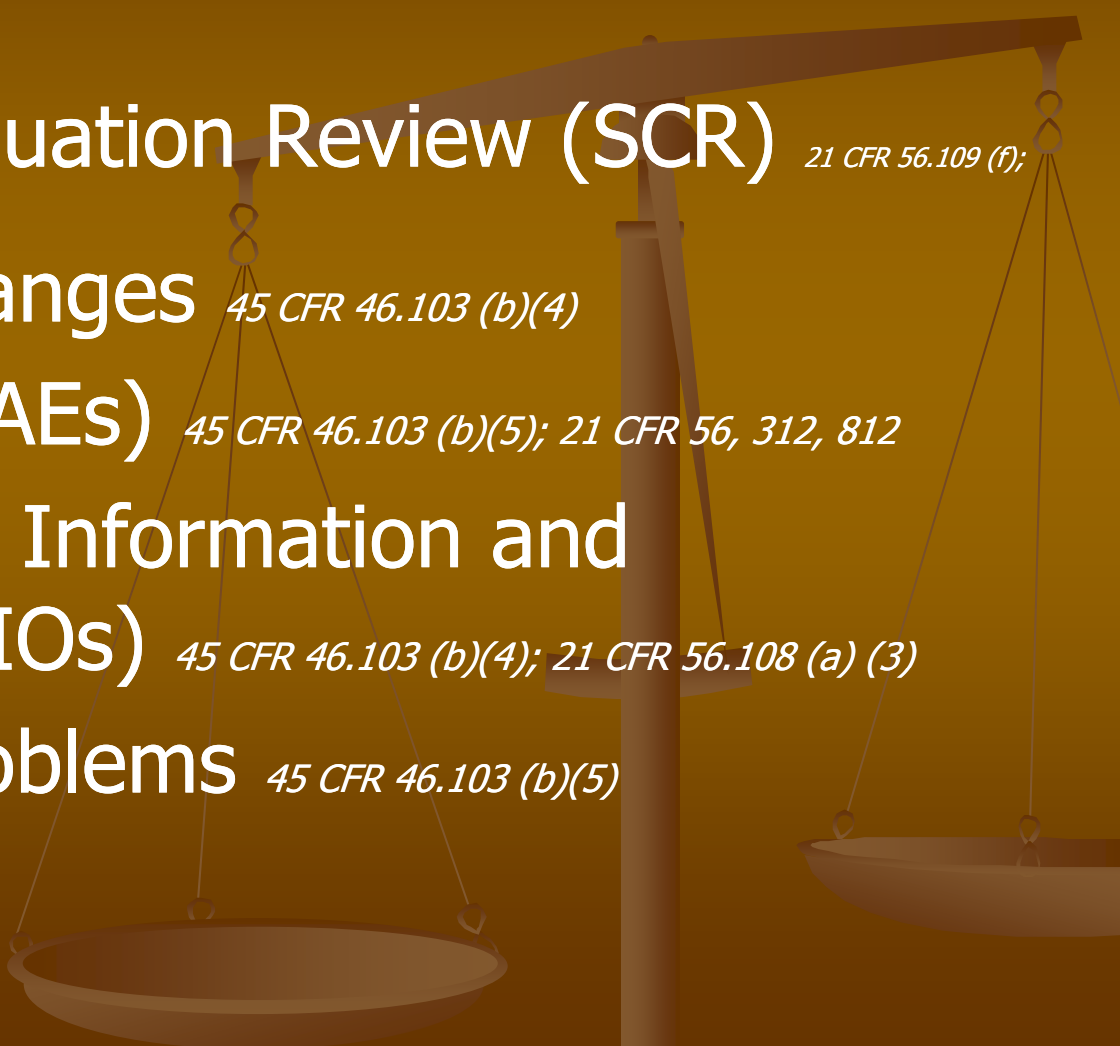
Regulatory Details—

Assessing Need for FDA Oversight

- **Marketed Supplements or Substances—do they need an IND?**
- **Vitamins, Herbs, or other 'botanicals' used in research may need an IND if:**
 - **Agent is under investigation for use in the diagnosis, cure, mitigation, treatment or prevention of disease in humans.**



Regulatory Details— IRB Review after Initial Approval

- **Scheduled Continuation Review (SCR)** *21 CFR 56.109 (f);
45 CFR 46.109 (e)*
 - **Amendments/Changes** *45 CFR 46.103 (b)(4)*
 - **Adverse Events (AEs)** *45 CFR 46.103 (b)(5); 21 CFR 56, 312, 812*
 - **Other Reportable Information and Occurrences (ORIOs)** *45 CFR 46.103 (b)(4); 21 CFR 56.108 (a) (3)*
 - **Unanticipated Problems** *45 CFR 46.103 (b)(5)*
- 

Regulatory Details— Scheduled Continuation Review


21 CFR 56.109 (f); 45 CFR 46.109 (e)

- Other terms used for “Scheduled Continuation Review”
 - SCR
 - Renewal
 - Continuation
 - Continuing Review
- Regulators expect significant review
 - The IRB must ensure that determinations regarding risks, potential benefits, informed consent, and safeguards for human subjects. “are satisfied at the time of both initial and continuing review.” OHRP Common

Findings

Regulatory Details— Scheduled Continuation Review

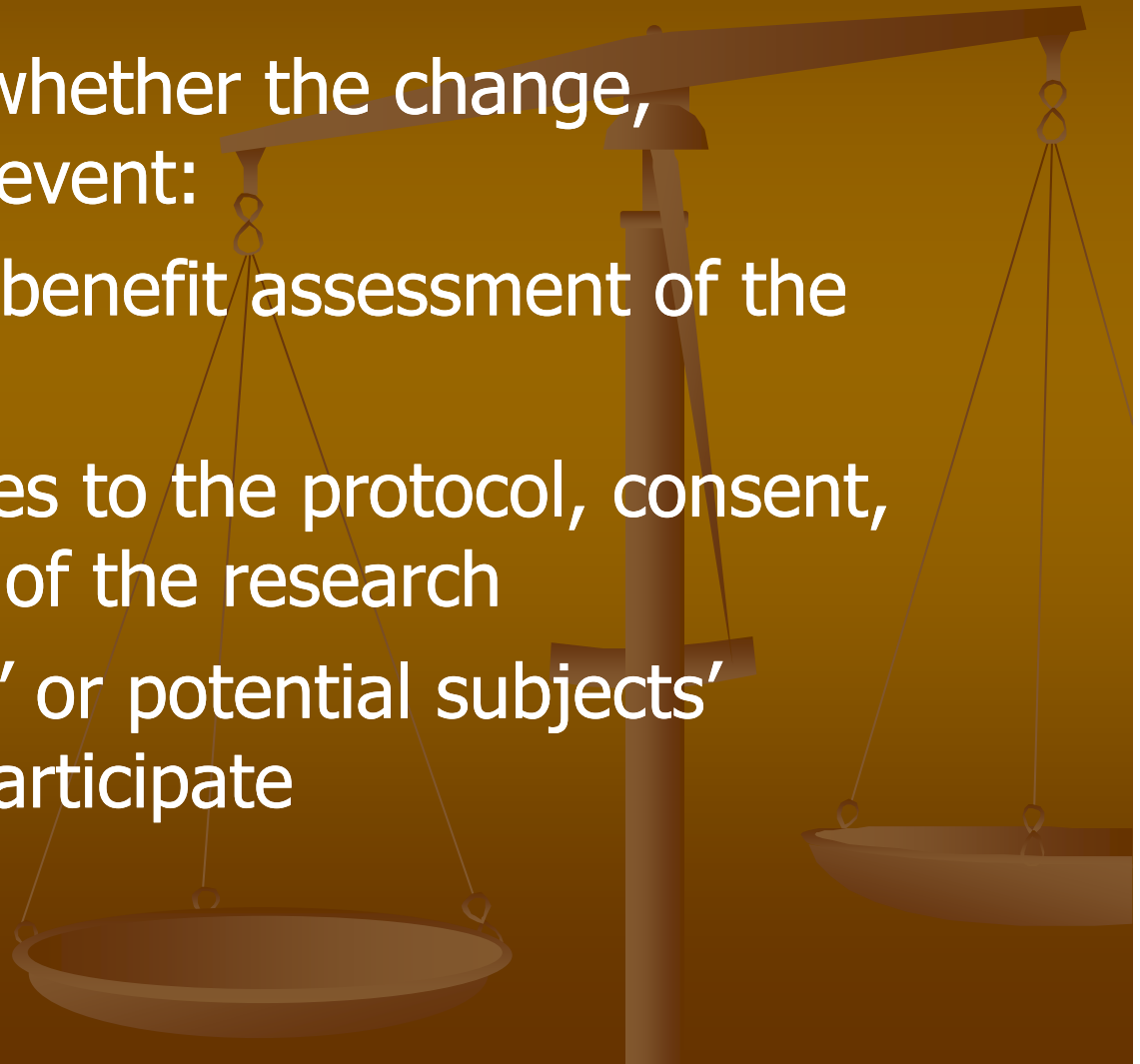
21 CFR 56.109 (f); 45 CFR 46.109 (e)

- Review protocol summary and status report on the progress of the research, including:
 - number of subjects accrued
 - summary of adverse events and
 - any unanticipated problems involving risks to subjects or others
 - withdrawal of subjects
 - complaints about the research since the last IRB review
 - summary of any relevant recent literature, interim findings
 - summary of amendments or modifications to the research
 - relevant multi-center trial reports or other information
 - copy of the current informed consent document and any newly proposed consent document.
- 

Regulatory Details— Amendment, AE, & ORIO Review

IRB must assess whether the change, information, or event:

- Affects the risk/benefit assessment of the study
- Requires changes to the protocol, consent, or other aspect of the research
- Affects subjects' or potential subjects' willingness to participate



Regulatory Details— Amendment, AE, & ORIO Review

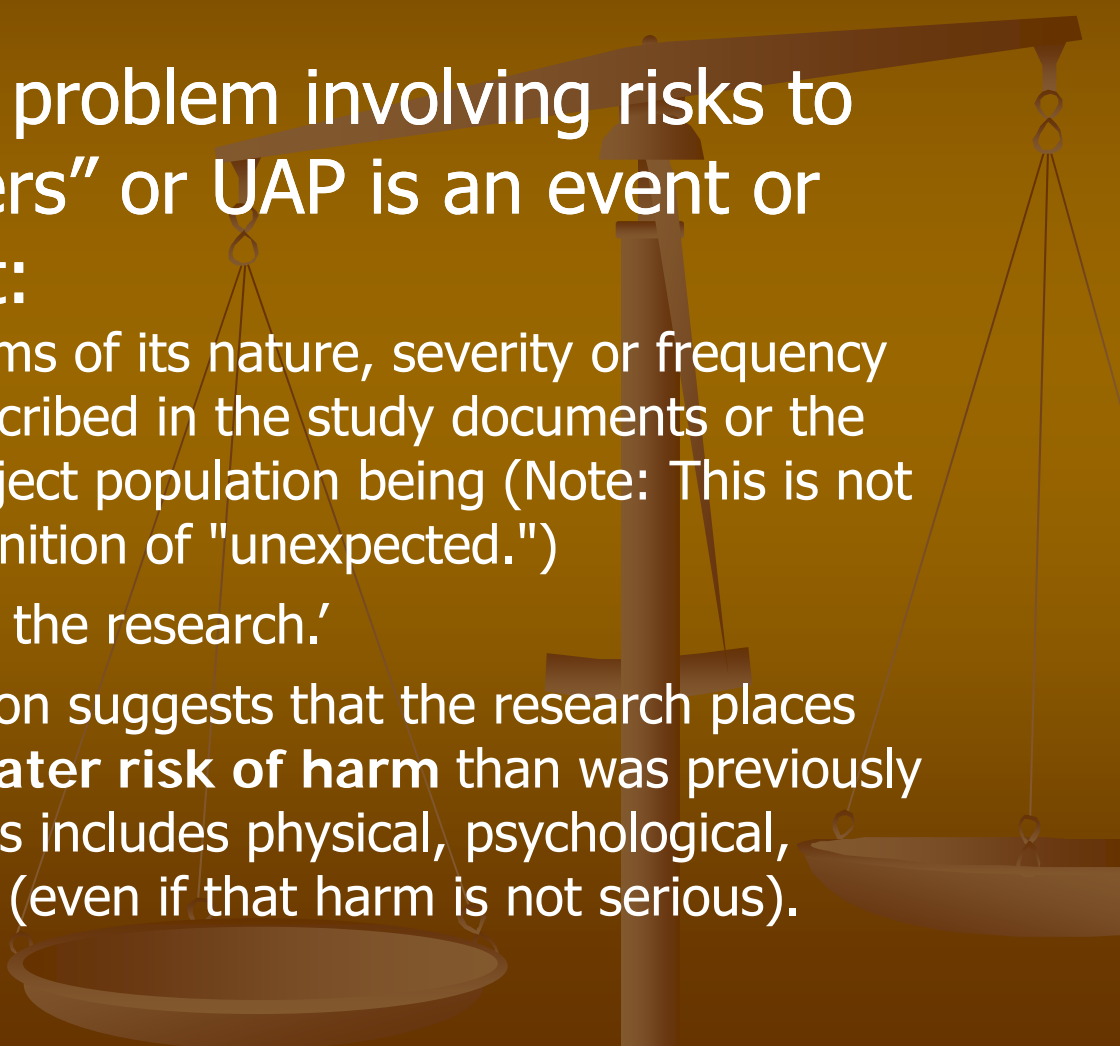
IRB must assess whether the change, information, or event represents an “unanticipated problem” or any of the following:

- Risks to subjects or others
- Serious non-compliance
- Continuing non-compliance



Regulatory Details— Amendment, AE, & ORIO Review

An “unanticipated problem involving risks to subjects or others” or UAP is an event or information that:

1. Is **not** expected in terms of its nature, severity or frequency given the procedures described in the study documents or the characteristics of the subject population being (Note: This is not the same as the FDA definition of “unexpected.”)
 2. It must be **‘related** to the research.’
 3. The event or information suggests that the research places subjects or others at **greater risk of harm** than was previously known or recognized. This includes physical, psychological, economic, or social harm (even if that harm is not serious).
- 

Regulatory Details—Defining ‘Expedited Review’

- It is a type of review that can be conducted “by the IRB chairperson or by one or more experienced reviewers designated by the chairperson from among members of the IRB” rather than going to the full board for presentation and vote 45 CFR 46.110
- ‘Expedited’ does not necessarily mean ‘fast’
- Conducted by experienced board members

Website of interest



- What OHRP finds IRBs do wrong most often:
<http://www.hhs.gov/ohrp/compliance/findings.pdf>
- OHRP Determination Letters:
<http://www.hhs.gov/ohrp/compliance/letters/index.html>
- FDA Warning Letters:
<http://www.fda.gov/foi/warning.htm>

A look at eResearch

