

## **303 Common Findings of IRB Non-Compliance and Their Solutions**

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### **Objective**

- Understand the major compliance problems seen in IRBs, their risks, and their solutions

## Source of this information

- Results of the review of the policies, procedures, and practices of over 150 institutions in the AAHRPP accreditation process
- These were institutions that considered themselves ready for accreditation.
- There are compliance problems consistently noted in over 80% of these institutions.

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## Common compliance problems

- Use of the regulatory criteria for approval to approve research
- Recognizing the when research is FDA-regulated, requires an IND, or requires an IDE
- Managing non-compliance and unanticipated problems involving risks to subjects or others

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## **Use of the regulatory criteria for approval**

### **All approvals at a meeting require that the entire IRB determine that the criteria for approval are met**

- 45 CFR §46.111/21 CFR §56.111 Criteria for IRB approval of research.
  - (a) In order to approve research covered by this policy/these regulations the IRB shall determine that all of the following requirements are satisfied: ...
- 45 CFR §46.103/21 CFR §56. 102 Definitions
  - (g) *IRB* means any board, committee, or other group formally designated by an institution to review, to approve the initiation of, and to conduct periodic review of, biomedical research involving human subjects.
  - (g) *IRB* means an Institutional Review Board established in accord with and for the purposes expressed in this policy.

## Criteria for the Approval of Research

### Overview of Regulatory Criteria

#### Main Criteria

(45 CFR §46.111/ 21 CFR §56.111)

- (a)(1) – Minimization of risks
- (a)(2) – Risk-benefit relationship
- (a)(3) – Equitable selection
- (a)(4) – Consent process**
- (a)(5) – Consent documentation**
- (a)(6) – Data monitoring
- (a)(7) – Privacy/confidentiality
- (b) – Vulnerable subjects

The IRB must determine that criteria delineated in all three boxes are met.

#### Consent Process

(45 CFR §46.116, 21 CFR §50.20, §50.25)

Intro – Consent process

- (a)– Required disclosures
- (b)– Additional disclosures
- (c)– Waiver #1
- (d)– Waiver #2

#### Consent Documentation

(45 CFR §46.117, 21 CFR §50.27, § 56.109)

- (a) – General
- (b)(1) – Long form
- (b)(2) – Short form
- (c)(1) – Waiver #1
- (c)(2) – Waiver #2 (Not FDA)

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## The problem is that many IRBs do not use the regulatory criteria for approval

- Not expected
- Not taught
- IRB members don't know there are regulatory criteria
- IRB members think that the regulatory criteria require scientific expertise
- IRB members are voting to approve research based on the recommendation of one or two primary reviewers

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## To determine whether the criteria for approval are met all IRB members must review the relevant information

- Purpose
- Background
- Setting of the research
- Resources available to conduct the research
- Study design
  - Recruitment
  - Inclusion and exclusion criteria
  - Procedures involved in the research
  - Data management
  - Provisions to monitor the data collected to ensure the safety of participants
- Risks to participants
- Potential benefits to participants
- Provisions to protect the privacy interests of participants
- Provisions to maintain the confidentiality of the data
- Consent process
- Process to document consent
- Additional protections for vulnerable populations

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## Failure to use the regulatory criteria leads to inappropriate contingent approvals

- “Provide information regarding the validation, quality assurance, stability, sterility, and potency of the study drug.”
- “Please provide the justification for removal of the side effect “swelling of the legs.”
- “Explain what qualifies these individuals to obtain consent.”
- “Please provide general information about the success of rituximab as therapy.”
- “Add a data and safety monitoring committee.”
- “How will you maintain the confidentiality of the collected data?”
- “Will children be enrolled?”

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## **Failure to use the regulatory criteria leads to missed questions**

- Where and when will consent be obtained?
- Where are you doing this research?
- Who will be looking at the data to assess whether the aggregate data indicate that risks to subjects have changed.
- Would you allow adults unable to consent to take part in this study?

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## **Failure to use the regulatory criteria leads to mission creep**

- “Risks of research must be minimized to the extent possible.”
- “The risk/benefit ratio to subjects must be favorable.”
- “You cannot exclude non-English speaking subjects from research.”
- “All research must have a data and safety monitoring board.”
- “Audio tapes must be destroyed as soon as they are transcribed.”

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## **When IRBs have “mission creep” investigators go under the radar**

- IRB review becomes arbitrary and unpredictable.
- Investigators avoid submitting to the IRB.

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## **How can you assess this at your institution?**

- Talk to IRB members
- Look at review tools used by IRB members
- Look on departmental Web sites

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## Implementation Issues

- This always increases the IRB workload
- This always starts out greatly increasing the workload
- Consider smaller IRBs
- Consider more frequent meetings
- Consider maximizing use of expedited review and exemptions

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## Tools that may be useful

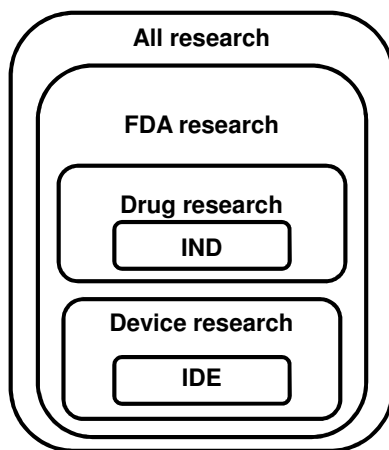
- FDA regulations:
  - <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm>
- DHHS regulations:
  - <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm>
- Huron HRPP Toolkit available for free at [www.besthrppsops.com](http://www.besthrppsops.com)
  - HRP-311 - WORKSHEET - Criteria for Approval and Additional Considerations
  - HRP-416 - CHECKLIST - Waiver of Written Documentation of the Consent Process
  - HRP-415 - CHECKLIST - Waiver or Alteration of the Consent Process

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## **Recognizing the when research is FDA-regulated, requires an IND, or requires an IDE**

### **Many institutions fail to recognize that research is FDA-regulated**



- Confusion about when research is FDA-regulated
- FDA research is more than drugs and devices
- IND/IDE represents a subset of FDA-regulated research

## **Common consequences of non-compliance**

- Reporting to OHRP without reporting to FDA
- Waiver of informed consent
- Failure to recognize that a study that is not research involving human subjects as defined by DHHS is research involving human subjects under FDA regulations
- No IND for drug studies that need an IND
- No IDE for device studies that need an IDE

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## **What is FDA-regulated research**

## What activities are FDA-regulated research”?

- 21 CFR §312.3(b): Any use of a drug except for the use of a marketed drug in the course of medical practice
  - Equivalent to: “... clinical investigations regulated by the FDA under section 505(i) of the FDC Act ...”
- 21 CFR §812.2(a): Any use of a device to evaluate the safety or effectiveness of that device
  - Equivalent to “... clinical investigations regulated by the FDA under section 505(i) of the FDC Act ...”
- 21 CFR §50.1: Any activity whose data will be submitted to or held for inspection by FDA in support of a marketing application

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## When is use of a device NOT a human research?

- When used in a research to measure physiology, monitor for a side effect, measure treatment progress, the device is not subject to FDA research regulations

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## Who are the human subjects?

- 21 CFR §56.102(e): Human subject means 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 individual or a patient.
- 21 CFR §812.3(p): Subject means a human who participates in an investigation, either as an individual on whom or on whose specimen an investigational device is used or as a control
- Be aware of:
  - Retrospective controls
  - Specimen collection
  - Deceased or anonymous subjects or their specimens

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## What is a drug?

- Articles recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and
- Articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and
- Articles (other than food) intended to affect the structure or any function of the body of man or other animals; and
- Articles intended for use as a component of any article specified in clause (A), (B), or (C).

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## What is a device?

- The term “device” means an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is -
- (1) recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them,
- (2) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or
- (3) intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes.

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## Regulatory applicability

- All FDA-regulated research involving human subjects requires compliance with 21 CFR §50 and §56
- Same as 45 CFR §46 (“Common Rule”) with some differences:
  - Different definitions of “research “ and “human subjects”
  - Different agency for reporting
  - No equivalent to DHHS exemption (including category #6)
  - Consent disclosure: A statement that notes the possibility that the Food and Drug Administration may inspect the records
  - Consent documents must be dated
  - No waiver of informed consent (except emergency research)
  - No waiver of written documentation for confidentiality issues

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## **“Off Label” Use of Drugs/Devices/Biologics**

- “Off label” refers to physicians using devices and approved drugs in a manner inconsistent with the package insert in order to treat patients.
- Only applies to medical practice
- There is no such thing as “off label” research
- What physician can freely do in the name of clinical care cannot be freely done as research

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## **IND’s when are they required?**

- Always unless the drug meets one of the exemption criteria

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## Exemption categories

- Approved drugs (within certain criteria)
- In-vitro serological tests (within certain criteria)
- Placebos

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## Clinical Investigation of FDA Approved Drugs (part 1)

- The clinical investigation of a drug product that is lawfully marketed in the United States is exempt from the requirements [for an IND] if ALL the following apply:
  - The investigation is not intended to be reported to FDA as a well controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug;
  - If the drug that is undergoing investigation is lawfully marketed as a prescription drug product, the investigation is not intended to support a significant change in the advertising for the product
  - **The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;**
  - The investigation is conducted in compliance with the requirements for institutional review set forth in Part 56 and with the requirements for informed consent set forth in Part 50; AND
  - The investigation is conducted in compliance with the requirements concerning the promotion and sale of drugs set forth in 21 CFR 312.7.

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## How to determine whether this criterion is met

- The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;
- **Practical Rule:** If, with the exception of the indication, the drug is not being used in accordance with the package insert, apply for an IND.

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## What if you are not sure?

- Have the investigator apply for an IND
- Fill out FDA Form 1571
- Follow directions on FDA Web site
- Takes experienced PIs 30 minutes
- FDA always responds in 30 days

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## **Devices**

**Devices used in research must fall into one of the following three categories**

- IDE issued by FDA
- Abbreviated IDE
- Exemption from IDE

## Most Common device exempt categories

- A device, other than a transitional device, in commercial distribution immediately before May 28, 1976, when used or investigated in accordance with the indications in labeling in effect at that time.
- A device, other than a transitional device, introduced into commercial distribution on or after May 28, 1976, that FDA has determined to be substantially equivalent to a device in commercial distribution immediately before May 28, 1976, and that is used or investigated in accordance with the indications in the labeling FDA reviewed under subpart E of part 807 in determining substantial equivalence.

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## What does that mean?

- Translation: Approved device being used in accordance with its labeling.
- How can you find out the labeling?
  - Look on the FDA Web site for the 510(k) or PMA approval notice. The marketed indication will be listed.
- What is a “transitional device”? A device regulated as a drug before the device laws were passed.

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## Next most common device exempt category

- A diagnostic device, if the sponsor complies with applicable requirements in §809.10(c) and if the testing: (i) Is noninvasive, (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.

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## Abbreviated IDE

- Devices that meet the abbreviated IDE requirements are considered to have an approved IDE without the approval of the FDA.

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## Abbreviated IDE requirements

- The device is not banned and :
- The sponsor\* labels the device in accordance with §812.5;
- The sponsor\* obtains IRB approval of the investigation after presenting the reviewing IRB with a brief explanation of why the device is not a significant risk device, and maintains such approval;
- The sponsor\* monitors the investigation in accordance with the §812.46;
- The sponsor\* maintains the records required under §812.140(b) (4) and (5) and makes the reports required under §812.150(b) (1) through (3) and (5) through (10);
- The sponsor\* ensures that participating investigators maintain the records required by §812.140(a)(3)(i) and make the reports required under §812.150(a) (1), (2), (5), and (7); and
- The sponsor\* complies with the prohibitions in §812.7 against promotion and other practices.

**\*For investigator initiated studies, the investigator is the sponsor**

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## Implement a new system

- Have all studies reviewed to ask:
  - Does it involve a drug? If yes:
    - Does it have a valid IND
    - Is it exempt from the IND requirements
  - Does it involve a device? If yes:
    - Does it have a valid IDE
    - Does it meet the abbreviated IDE requirements
    - Is it exempt from the IDE requirements
- Can be done by IRB staff or other knowledgeable people.
- If there is doubt regarding whether an IND or IDE is needed, apply to FDA.
- Does not need to be done by IRB members.

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## Tools that may be useful

- FDA Web site at [www.fda.gov](http://www.fda.gov):
  - Directions to apply for an IND:  
<http://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/investigationalnewdrugindapplication/default.htm>
  - Directions to apply for an IDE:  
<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/ucm046706.htm#idemod>
- Huron HRPP Toolkit available for free at [www.besthrppsops.com](http://www.besthrppsops.com)
  - HRP-316 - WORKSHEET - Devices
  - HRP-315 - WORKSHEET - Drugs

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**Managing non-compliance and  
unanticipated problems involving  
risks to subjects or others**

## Frequent conversation

- me: "The investigator told you about this new information. I have two questions. Would you consider this information unanticipated?"
- IRB manager: "Yes. Of course."
- me: "Would you consider this new information to indicate that subject are at increased risk?"
- IRB manager: "Yes. Of course."
- me: "So you consider this new information to be an unanticipated problem involving risks to subjects or others?"
- IRB manager: "Yes."
- me: "And you of course reported this to the convened IRB, regulatory agencies, and your institutional official?"
- IRB manager: "Um..."

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## Frequent conversation

- me: "It looks like you have been having a lot of problems with this investigator."
- IRB manager: "You bet. It has been a trying experience."
- me: "Now I can see nothing serious has been going on, but would you consider this to be continuing non-compliance?"
- IRB manager: "Yes. Of course."
- me: "And you of course reported this to the convened IRB, regulatory agencies, and your institutional official?"
- IRB manager: "Um..."

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**Many IRBs find unanticipated problems involving risks to subjects or others to be a confusing concept**

But is it really that mysterious?

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**The following information is provided to the IRB office:**

- A locally enrolled subject has died while on a bone marrow transplant study because of complications related to cancer relapse.
- Is this problem unanticipated?
- Does it involve risks to subjects or others?

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**The following information is provided to the IRB office:**

**Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes (N Engl J Med 356;24 June 14, 2007)**

- Rosiglitazone was associated with a significant increase in the risk of myocardial infarction and with an increase in the risk of death from cardiovascular causes.
- Your IRB is overseeing a rosiglitazone study.
- Is this problem unanticipated?
- Does it involve risks to subjects or others?

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**The following information is provided to the IRB office:**

- A blood sample for a drug level was obtained from a subject and sent to the lab as part of a research study on this drug. The blood sample tube broke in transit. A second blood level was obtained and the subject was found to have a critically low blood level.
- Is this problem unanticipated?
- Does it involve risks to subjects or others?

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**The following information is provided to the IRB office:**

- A modification for a protocol involving the smoking cessation drug Chantix is submitted to the IRB office with a request to add suicidal ideation to the consent form.
- What does your IRB do with these?

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**The following information is provided to the IRB office:**

- An investigator submits a revised investigator brochure.
- What does your IRB do with these?

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**The following information is provided to the IRB office:**

- An investigator submits a revised investigator brochure.
- The brochure cites a new study that demonstrates that the drug causes severe birth defects in several mammalian models.
  
- Is this problem unanticipated?
- Does it involve risks to subjects or others?

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**The following information is provided to the IRB office:**

- A research team member reports that a laptop containing subject information was stolen.
  
- Is this problem unanticipated?
- Does it involve risks to subjects or others?

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## **The following information is provided to the IRB office:**

- A research team member reports that a laptop containing subject information was stolen.
- This occurs in a multisite study at a site NOT under the jurisdiction of your IRB.
- Is this problem unanticipated?
- Does it involve risks to subjects or others?

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## **Example missed unanticipated problems involving risks to subjects or others**

- New England Journal of Medicine article showing that long-term Vioxx increases risk of heart attack and stroke
- FDA announces that Varenicline (smoking cessation drug) is associated with suicidal ideation
- Principle investigator is arrested on cocaine charges

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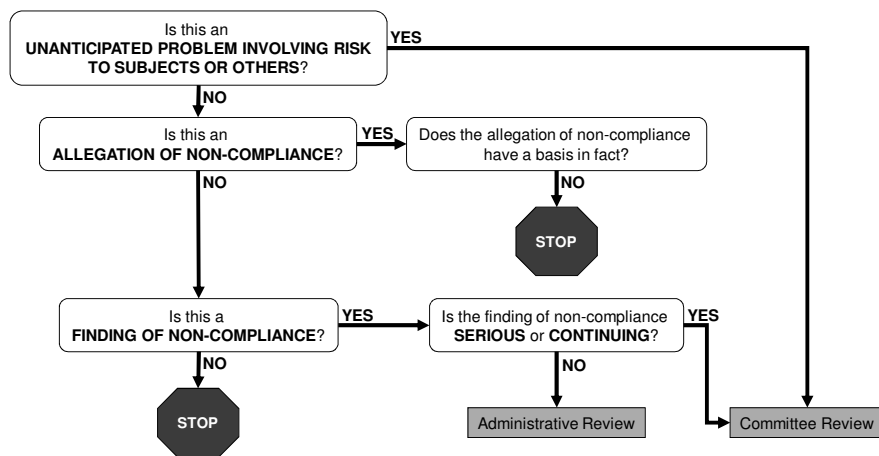
## Review of incoming information

- Triage of information that comes into the IRB
- Categories:
  - Request for approval
    - Initial review, continuing review, and modifications
    - Exemptions
    - Human subject research determinations
  - Modifications required to secure approval
    - Responsive material provided in request to a convened IRB
  - Emergency use notification
  - **Other information**
- Can be accomplished by IRB staff

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## Review of “other information”



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## Tools that may be useful

- Huron HRPP Toolkit available for free at [www.besthrppsops.com](http://www.besthrppsops.com)
  - HRP-024 - SOP - New Information
  - HRP-224 - FORM - Reportable New Information

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**Questions?**



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