

## **RP4 Raising the Bar on Adequate Human Subject Protection**

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**Maximize human subject protection  
while minimizing workload and  
regulatory oversight**

## Comparison of HRPP programs

### Poor Understand of the Regulations

- Worried about decisions
- Mission creep
- Avoid regulatory flexibility
- Complicated workflows/policies
- Upset investigators
- Overworked

### Good Understanding of the Regulations

- Confidently follow the process
- Focus on protecting subjects
- Use regulatory flexibility
- Simple workflows/policies
- Respectful investigators
- Right sized

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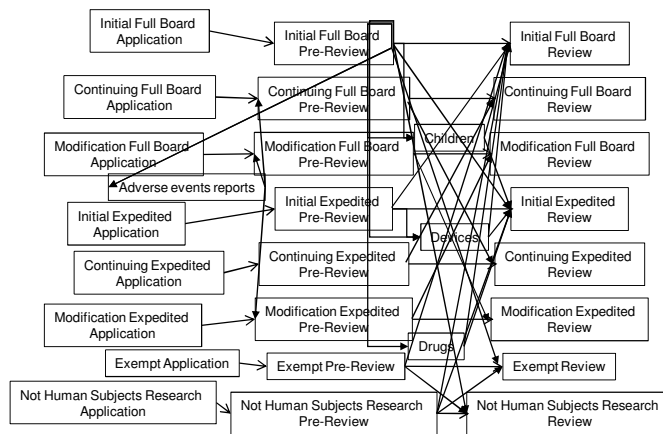
## Rules of Human Subject Protection

- Everything necessary to protect human subjects is embodied in the regulations.
- The regulations are much simpler than they are made out to be.
- Many IRBs are having problems because:
  - They are not following the regulations
  - They are making up unnecessary rules that do not protect subjects

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# The IRB Process According to the Regulations

## Typical workflows



## Regulatory facts

- The regulations describe one process for:
  - Initial review
  - Continuing Review
  - Review of modifications to previously approved research
- Expedited and full board procedures are identical except for:
  - Who does the review
  - The authority to disapprove research
- The regulations define one process to deal with new information, such as:
  - Adverse events
  - Protocol deviations
  - Non-compliance

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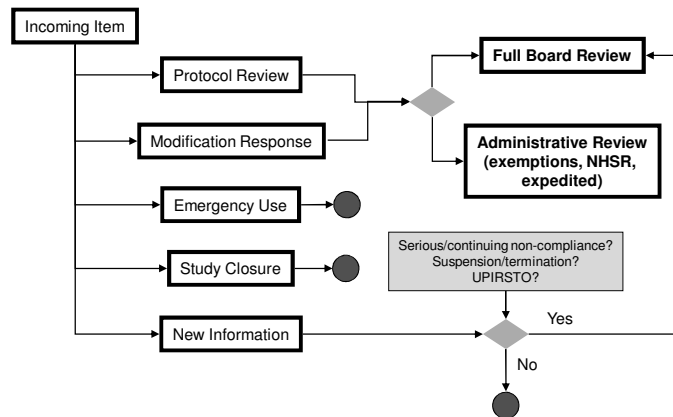
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## What are the key business processes of an IRB?

- Incoming items
- Non-committee review
- Committee review

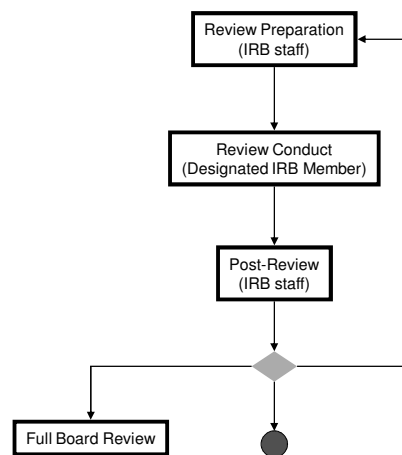
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## Incoming items



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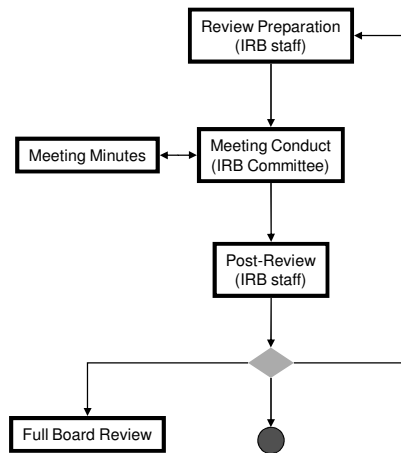
## Administrative review



- Each step handles all types of reviews:
  - Not HSR
  - Exempt
  - Expedited
  - Initial
  - Continuing
  - Modification
- Regulatory issues distributed among steps:
  - Waivers
  - Subparts
  - Devices
  - Drugs
- IRB member is instructed to select least regulatory restrictive category.
- If minor changes will result in a lesser restrictive category, offered to investigator

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## Full-board review



- Each step handles all types of reviews:
  - Initial
  - Continuing
  - Modification
  - Unanticipated problems involving risks to subjects or others
  - Serious/continuing non-compliance
  - Suspensions/terminations
- Regulatory issues distributed among steps:
  - Waivers
  - Subparts
  - Devices
  - Drugs

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## Review Procedures

## 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.

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## The only changes for expedited review are who does the review and that research cannot be disapproved

- 45 CFR §46.110/ 21 CFR §56.110 Expedited review procedures for certain kinds of research involving no more than minimal risk, and for minor changes in approved research.
  - Under an expedited review procedure, the review may be carried out by the IRB chairperson or by one or more experienced reviewers designated by the chairperson from among members of the IRB. In reviewing the research, the reviewers may exercise all of the authorities of the IRB except that the reviewers may not disapprove the research.

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## **Whenever the IRB grants an approval, it must follow the uniform regulatory process and criteria**

- Initial review
- Continuing review
- Review of modifications
- Convened IRB review
- Review using the expedited procedure

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## **What does not make sense:**

- Different applications for:
  - Convened
  - Expedited
  - Exempt review
- Different criteria/checklists for:
  - Initial review
  - Continuing review
  - Review of modifications
  - Convened IRB review
  - Review using the expedited procedure
- Different set of materials reviewed for:
  - Initial review
  - Continuing review
  - Review of modifications
  - Convened IRB review
  - Review using the expedited procedure

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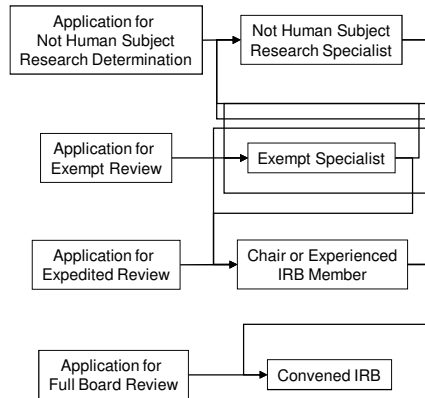
## Recommendations

- Use one common application process
  - One set of questions
  - Allow the answers to vary based on the type of research
    - Not the level of regulatory review
- Use one set of regulatory criteria for all approvals
- Use a common procedure for post-reviews

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## **Processes to determine the level of review**

## Determining the level of review

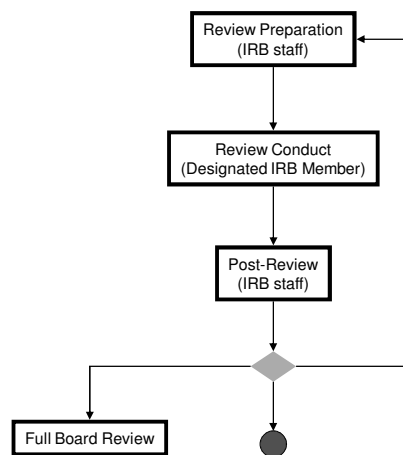


### Problems

- Investigator has to predict the level of review
- If you are a hammer every problem looks like a nail
- Cumbersome handoffs
- No attempt to modify research to level of least regulatory oversight

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## Administrative review



- Each step handles all types of reviews:
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## When there are multiple processes:

- Investigator has to predict the level of review
  - Investigator's decision becomes an assumption of the reviewer
  - Changing the level of review is work for investigator and reviewer
  - Discourages attempts to modify research to least regulatory oversight
- “If you are a hammer, every problem looks like a nail”
  - Reviews occur by rote
  - Key decisions are missed
  - Key information is not requested
  - Compliance with additional requirements becomes lax
    - Consent requirements
    - Waivers of informed consent
    - Subpart determinations

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## Why “least restrictive review” level

- If you can move a protocol to a lower level of review, subjects are better protected.
- Puts the onus back on reviews to consider the overall ethical issues, particularly with review of exemptions

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## But we follow a higher ethical standard by not using/restricting the exemption categories!

- Exemption ≠ No ethical review
  - “If I don’t apply the regulations, I have no oversight over this research.”
- No legal rules ≠ No IRB rules
- Add the protections that make sense:
  - Consent process
  - Consent documentation
  - Debriefing
  - Assent
  - Parental permission
  - Consent documentation
  - Continuing review
  - Protection of confidentiality
  - Monitoring of data
- Don’t add the protections that don’t make sense.
- In the end, the approved protocol should look the same regardless of level of review.

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## Recommendations

- Have expedited reviewers qualified to make exemption and not human research determinations
  - The level of analytical capability required for each is the same
- Put IRB staff on the IRB and designate them as expedited reviewers
  - Accepted by OHRP, FDA, and AAHRPP
  - Professional reviewers (people hired to do reviews full-time) do a better job than part-time reviewers.
  - More likely to get consultation when needed

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## Handling New Information

### What do the regulations require the IRB to review?

- Research requesting approval
  - Proposed research
  - Continuing reviews
  - Proposed modifications (with one exception)
- Other information
  - Unanticipated problems involving risk to subjects or others
  - Serious or continuing non-compliance with the regulations and the requirements of the IRB
  - Suspensions and terminations of IRB approval

**If in the above, IRB review is needed to protect subjects.**

**If not, IRB review has no subject protection value.**

**In order to protect subjects, when does the IRB have to pay attention to:**

- An adverse event?
- A protocol deviation?
- A subject complaint?
- A allegation of non-compliance?
- A breach of confidentiality?
- A DMSB report?
- A new publication?
- Correspondence from the sponsor?
- A revised investigator brochure?

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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 an study that includes rosiglitazone.
- Is this problem unanticipated?
- Does it involve risks to subjects or others?

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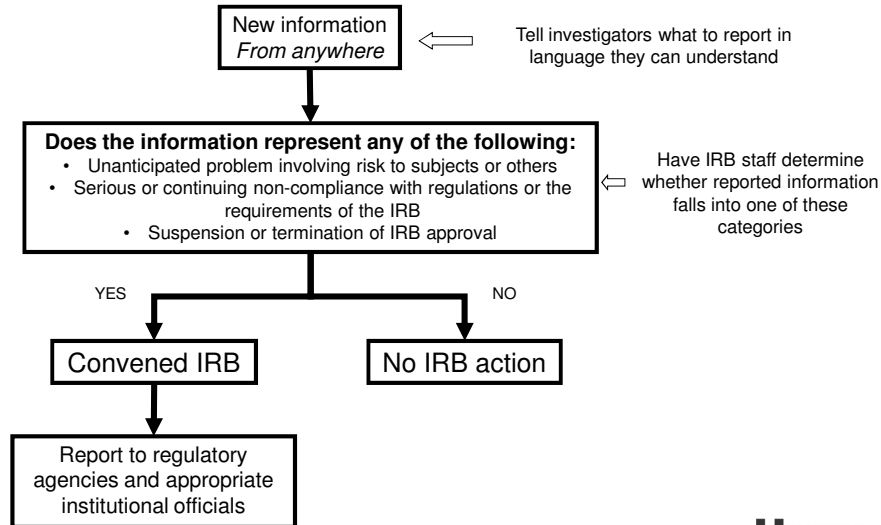
**The following information is provided to the IRB office:**

- 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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## IRB Workflow



## Tell investigators the problems they need to send to the IRB so that among those problems will be the important new information.

- Report all new or changed risks
- All failures to follow the regulations or IRB requirements
- Protocol violations that
  - Placed a subject at risk; or
  - Were caused by the action or inaction of the research team
- Unresolved subject complaint
- Audit, inspection, or inquiry by a federal agency
- Breach of confidentiality
- Change to the protocol taken without prior IRB review to eliminate an apparent immediate hazard to a participant
- Subject incarceration
- Unexpected and related adverse events
  - Regardless of local/external or serious/non-serious
  - Unanticipated adverse device effects

## Assessment

- Look through all of your IRB policies, procedures, guidance, training materials, forms, etc.
- If you were an investigator are you provided clear unambiguous instructions about what to promptly report to the IRB? Do you investigators understand them?
- Do the procedures describe a process where all new information is evaluated first to determine whether it is an unanticipated problem, and if so require IRB review and reporting to regulatory agencies and appropriate institutional officials?

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## Implementation

- HRP-024 - SOP - New Information
- HRP-224 - FORM - Reportable New Information
- HRP-306 - WORKSHEET - Review of Information Items

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## Smaller IRB sizes

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

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## Regulatory requirements of IRB review

- §46.107 IRB membership.
  - (a) Each IRB shall have at least five members, with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution.
- §46.109 IRB review of research.
  - (b) Except when an expedited review procedure is used (see §46.110), review proposed research at convened meetings at which a majority of the members of the IRB are present, including at least one member whose primary concerns are in nonscientific areas.
  - In order for the research to be approved, it shall receive the approval of a majority of those members present at the meeting

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## Regulatory requirements

- All IRB members are to make the regulatory criteria for approval determinations.
- All IRB members are to read the application information relevant to the regulatory criteria for approval:
  - Purpose
  - Resources
  - Selection criteria
  - Data monitoring
  - Privacy
  - Consent documentation
  - Background
  - Study design
  - Procedures
  - Risks
  - Confidentiality
  - Setting of the research
  - Recruitment
  - Data management
  - Potential benefits
  - Consent process
  - Protections for vulnerable populations
- Making the regulatory criteria determinations does not require scientific expertise.

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**If you want to have an effective meeting,  
how many people should be involved in the  
meeting?**

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## **Many busy IRBs**

- Have committees with way more than 7 members.
- Focus on “scientific ascertainment.”
- Contrary to the regulations
  - Only one or two primary reviewers make the regulatory criteria for approval determinations.
  - Only one or two primary reviewers read the application information relevant to the regulatory criteria for approval.
- Cooper’s Law: *No matter how many members attend an IRB meeting, only 5-7 people are present.*

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## Recommendation

- Have IRBs with 5-7 members.
  - Can consist of much larger pool of alternate members
- Liberally use consultation for scientific ascertainment
- Have all members read all relevant application materials.
- Have all IRB members determine as a group whether the regulatory criteria for approval are met.

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## Benefits to subject protections

- Better decision making
- Focus on ethical review rather than scientific ascertainment

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