Research risk assessments: what must be considered and why.

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This session will

- **Discuss the importance of research risks for compliance officers.**
- **Delve into how research risks affect approval, IRB review, consent, and indemnifications.**
- **Describe how risk can be minimized using preliminary risk assessments.**

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Premise

- All researchers want their studies to be reviewed and approved quickly.
- Risk level assigned a study affects several factors.
- Understanding how risk levels are assigned can assist compliance officers identify risk areas.
- Making preliminary risk determinations can assist compliance officers in identifying research risk.

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Premise

- Risk assessments explain why there may/may not be flexibility.
- Knowing how risk assessments are made in research can help avoid compliance issues.

The importance of research risks

What is risk assessment in research?

- Determining whether a study is minimal or greater than minimal
  - **Minimal Risk:**
    - **HHS Definition from 45 CFR 46.102**
    - *Minimal Risk* means that the probability and magnitude of harm or discomfort anticipated 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 examinations or tests

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Risk Assessment

- Is normally done for the entire study but can also be done:
  - For a component of the study.
    - For example:
      - Modification of written consent for one population in the study
      - Minors (child) determination
      - Revision and whether it can be reviewed expedited

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Risk Assessment for Devices

- This is a different risk assessment for investigational devices that are not considered EXEMPT from the investigational device exemption (IDE) requirement.
- This is different from the risk rating given to an overall study.

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Devices and Risk

- A device is deemed non-significant risk but the overall study is still deemed greater than minimal risk.
  - Non-significant risk for a device means that an IDE is not needed.
  - Significant risk for a device means an IDE is needed.
- Overall study risk ≠ Device Classification

Why is risk assessment important?

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Risk Assessment is determining:

- the overall risk of a study.
- the risk of a change to a study.
- a device risk classification that is different from an overall study risk determination.

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What are research risks?

- **Physical** - drug toxicities, exposure to radiation, research injuries
- **Psychological** – emotional distress, anxiety in making choice
- **Social** – one's reputation, social standing, retaliation
- **Legal** – risk of criminal or civil liability
- **Economic** – impact on employment, insurance, research costs

How research risks affect approval, IRB review, consent, and indemnifications

The level of risk assigned a research protocol affects:

- Mode of review
  - Expedited vs Full Board
- Need for additional approvals
  - IRB alone or DHHS secretary needed
- Types of protections/additional protections
  - Certificate of Confidentiality
  - Data Safety Monitoring
- Frequency of review
  - Annual or more frequent
- Consent requirements
  - Written, modification, waiver
- Indemnification language negotiations
  - Needed?
- Etc.

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Assessing risk

- Is required in 45 CFR 46 and 21 CFR 50
- Is listed in the criteria for review

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Criteria for approval 45CFR 46.111 and 21 CFR 56.111
Risks to subjects are minimized
Risks to subjects are reasonable in relation to anticipated benefits
Selection of subjects is equitable and additional protections for vulnerable populations
Informed consent will be sought from each prospective subject or the subject's legally authorized representative.
Informed consent will be appropriately documented.
When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.

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Mode of Review: Expedited Review

The regulations allow for an expedited review (45 CFR 46.110 and 21 CFR 56.110):

(b) An IRB may use the expedited review procedure to review either or both of the following:

(1) some or all of the research appearing on the list and found by the reviewer(s) to involve no more than minimal risk,

(2) minor changes in previously approved research during the period (of one year or less) for which approval is authorized.

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. A research activity may be disapproved only after review in accordance with the non-expedited procedure set forth in §46.108(b).

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Examples of Minor Changes

- Changing most research team members
- Adding a recruitment method such as a flyer
- Adding a funding source
- Adding a performance site

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Expedited and Exempt Categories

- Both HHS and FDA define certain categories of research that may be reviewed using an "expedited reviewer" system.
- Research that falls exactly within the boundaries of these categories is considered *minimal risk*.

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What does "Exempt" Mean?

- Currently it is considered human subjects research.
  - It must be reviewed by an IRB or IRB designated reviewer.
- The study is "exempt" from the federal regulations but not pertinent ethical codes.
- Once approved, it does not have to be renewed annually however:
  - Any modifications must be submitted to and approved by the IRB.
  - Any events that increase risks to participants must be reported to the IRB along with any other reportable events.

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Exempt categories cannot be applied to:

- Research with prisoners
- Deception studies

45 CFR 46.101(b) and 21 CFR 56.104

If a study does not meet Expedited or Exempt Category criteria…..

It has to go to a full board to review…more than one reviewer.

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Full Board Reviews

- Investigational drugs, devices, biologics, supplements
- Investigational uses of FDA approved drugs and devices, biologics and supplements
- Radiation-emitting products such as X-Ray and PET
- Gene Therapy
- Any new study that does not fit exactly into one or more of the HHS Exempt or Expedited Categories

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Certificate of Confidentiality

- Issued by the National Institutes of Health (NIH) or the Food Drug Administration (FDA)
- Protects identifiable research information from forced disclosure (subpoena).
  - Allows refusal to access research records or disclose identifying information on research participants in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level.
  - Protects information that if disclosed could damage financial standing, employability, insurability, or reputation.
- May help achieve research objectives and promote participation in studies
- May be requested by the funding source

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Are there times when a Certificate of Confidentiality is ineffective?

1. The information is already in the medical record.
2. No sensitive information is being collected.
3. When disclosure is mandated by state or federal law. Examples include: suspected child abuse, threat of harm to self or others, reportable communicable diseases, FDA or DHHS audit or program evaluation.
4. the participant discloses the information to his/her insurance company, primary care provider or other clinician, or any other voluntary disclosure, etc.
5. Data maintained outside the U.S.

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All human subjects research needs some type of monitoring

- NIH now requires a Data Safety and Monitoring plan for all studies with human subjects
- FDA requires collection of safety and effectiveness data
- Monitoring should be commensurate with risks, nature, size and complexity of the trial

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Frequency of Review

- Studies deemed "exempt" do not undergo annual review.
- Studies deemed "minimal risk" must renew every 365 days.
- Studies deemed "greater than minimal" must renew no less than 365 days but may be put on a 3 or 6 month renewal due to risks.

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Consent Requirements

- Minimal risk studies that are FDA funded could qualify for a Waiver of Written Consent.
- Minimal risk studies that are not funded or HHS funded may qualify for a Waiver of Consent, Waiver of Written Consent, or Waiver of one of the eight elements of Consent.

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Risk Classifications for Minors

- 46.404; 50.51: Minimal Risk means that the probability and magnitude of harm or discomfort anticipated 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 examinations or tests.
  - **One parent signature**
- 46.405; 50.52: The research risk is greater than minimal and it presents the prospect of direct benefit to the participant.
  - **One parent signature**
- 46.406; 50.53: Minor increment over minimal risk: The research is greater than minimal with no direct benefit to the minors but is it likely to yield generalizable knowledge about the subject's disorder or condition.
  - **Two parent signature**
- 46.407; 50.54: The research uses minors that do not have the disease being studied and is greater than minimal risk.
  - **Two parent signature**

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Indemnification Language

- Injury language is required in greater than minimal risk studies.
- Often this language is negotiated at the time of the contract.
  - Language is often vague in nature.

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What risks are considered?

- 45 CFR 46.111 (a)(2): In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research).
- Harms are distinguished from discomforts
  - Severe allergic reaction vs. body image issues
  - Renal failure vs requiring a SS# for payment

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What does this mean?	What does this NOT mean?
Known risks are considered –Listed in the investigator's brochure, consent, recent literature, etc.	If this study is conducted, then in 5 – 10 years public policy will be changed to reflect the findings of the study.
Foreseeable risks are considered –When looking at the list of risks, there is a likelihood that a given risk could occur during the study	If this study is approved, then all other studies like this one will have to be approved.

How risk can be minimized using preliminary risk assessments

Determine appropriate Oversight

- Ensure Patient Safety
  - Standard or investigational procedures
  - Proper oversight by PI
  - Trained, qualified research team members with needed experience, expertise, licensure
  - Proper consent procedures
  - Privacy provisions
- Ensure Data Validity and Integrity
  - Confidentiality and security measures

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Corrective and Preventative Action (CAPA) involves:

- Improvements to an organizations processes
- Elimination of causes of non-conformities or undesirable situations
- Part of Good Manufacturing Practices (GMP), it focuses on root causes of identified risks or problems to prevent recurrence or occurrence, in the first place.
  - Principles can be applied to research in general

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Corrective action or minimizing risks can be done in response to:

- Complaints
- Protocol non-conformance
- Issues identified in an external or internal audit of the study.
- Adverse event trends
- On-going monitoring (data safety monitoring) of the study
- Findings in progress reports, statistical analysis

How can you make a preliminary risk assessment?

1. Know the published exempt and expedited categories.
   - If your study fits into one or more categories exactly, it will probably be minimal risk.
2. Know the types of interventions that get sent to full board.
   - These are most often given a greater than minimal risk rating.
3. Know the risks
   - Of the study; the severity of the risks; the probability of the risks

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Magnitude of Risks vs. Risk Probability Example

		PROBABILITY		
		RARE (<2%)	LESS LIKELY	LIKELY (>30%)
MAGNITUDE	MILD	Minimal	Minimal	Minimal
	MODERATE	Minimal	Reviewer's Discretion	Greater than Minimal
	SEVERE	Reviewer's Discretion	Greater than Minimal	Greater than Minimal

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4. Know your population
   - Adults: minimal vs greater than minimal risk
   - Minors: 4 risk classifications
     - Healthy?
       - 46.404 or 21 CFR 50.51
       - 46.407 or 21 CFR 50.54
     - Condition under study?
       - 46.405 or 21 CFR 50.52
       - 46.406 or 21 CFR 50.53
5. What has been done in the study to minimize risks?
   - Do these minimize the risks enough to change the risk rating?

What risk rating would you assign?

Example 1

- Subjects will be randomized to one of two surgical procedures. Both procedures are considered standard clinical care for the subjects condition.
- Subjects are 18 – 45 years old, diagnosed with the condition requiring treatment, no complicating factors
- Procedure will be the same standard care, but follow-up visits will be more frequent and in depth than standard care.
- PI will be qualified to perform both surgical procedures. Subjects will be monitored closely and medical care will be given as needed.
- Randomization is to one of two surgical procedures.

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Example 1 Classification

- Greater than minimal risk
  - Randomization to two surgical procedures where the physician discretion has been eliminated.
- How were risks reduced?
  - Standard care procedures
  - Close monitoring
  - Medical care given as needed
  - More frequent follow-up visits
  - More in-depth follow-up visits
  - Surgeon qualified to conduct both procedures.
- But, this is still greater than minimal risk.

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Example 2

- A study proposes to use a FDA approved device off-label.
- All other procedures are standard but being done solely for the research.
- The PI and study team are properly trained and qualified.
- Written consent will be obtained.

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Example 2 Classification

- "Off-label" means "investigational" in research terms.
  - This makes the study automatically greater than minimal risk.
- Standard procedures being done for research will need to be included in the consent form as they now become research procedures.
  - Risks of these procedures will also need to be included in the consent document.
- Risks are reduced by consent, qualified personnel, and use of standardly accepted procedures.

Can anything happen to change a study's risk rating?

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Unanticipated problem involving risks to participants or others:

- a. Are unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied; and
- b. Are related or possibly related to participation in the research; and
- c. Suggest that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.
  - Lost laptop
  - Study coordinator quits
  - Participant does not show up for his/her scheduled visit

THANK YOU!

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ADDITIONAL REFERENCES

- Office of Human Research Protection's Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events
- Food and Drug Administration's Guidance on Adverse Event Reporting to IRBs-Improving Human Subject Protection

APPENDIX 1:
Criteria for approval
45CFR 46.111 and 21 CFR 56.111

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- **Criteria for approval 45CFR 46.111 and 21 CFR 56.111:**
  - Risks to subjects are minimized: (i) by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.
  - Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result.

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- **Criteria for approval 45CFR 46.111 and 21 CFR 56.1111:**
  - Selection of subjects is equitable.
    - IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.
    - When some or all of the participants are likely to be vulnerable to coercion or undue influence, such as children, prisoners or pregnant women, additional safeguards have been included in the study to protect the rights and welfare of these participants.

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- **Criteria for approval 45CFR 46.111 and 21 CFR 56.111:**
  - Informed consent will be sought from each prospective subject or the subject's legally authorized representative.
  - Informed consent will be appropriately documented.
  - When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.
  - When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

APPENDIX 2:
Brief Description of Expedited Categories

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Expedited Categories

- **CATEGORY 1**
  FDA approved Drugs and/or Devices used for their FDA approved indication
- **CATEGORY 2**
  Blood Samples. No more than 50 ml in a 8 week period with no more than 2 sticks per week for children.
- **CATEGORY 3**
  Prospective collection of biological specimens for research purposes by noninvasive means.

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Expedited Categories

CATEGORY 4
Routine Noninvasive Procedures. Does not include any radiation exposure, e.g. DEXA, X-ray, PET

CATEGORY 5
Data Collected: clinical or for another research study. Can keep all the identifiers needed for the study

CATEGORY 6
Voice, Video, Digital, Image Recordings

CATEGORY 7
Group or Behavior Characteristics like interviews, surveys, focus groups

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Expedited Categories
renewals deemed minimal risk by a full board

- CATEGORY 8 Previously Approved Research
  a.) where (i) permanently closed to enrollment of new subjects; (ii) all subjects have completed all research- related interventions; and (iii) the research remains active only for long-term follow-up of subjects b.) where no subjects have been enrolled and no additional risks have been identified c.) where the remaining research activities are limited to data analysis.
- Category 9 Previously Approved Research not using an IND or IDE
  Continuing review of research, not conducted under an investigational new drug application or investigational device exemption where categories two (2) through (8) do not apply but the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified.

APPENDIX 3:
Brief Description of Exempt Categories

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Only FDA Exempt Category

- Taste and food quality evaluations and consumer acceptance studies, if wholesome foods without additives are consumed or if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural, chemical, or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

21 CFR 56.104 45 CFR 46.101(b)

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HHS Exempt Categories

1. Research conducted in established or commonly accepted educational settings…
2. Research involving use of educational tests, survey procedures, interview procedures, or observation of public behavior

45 CFR 46.101(b)

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HHS Exempt Categories

3. Research not approvable under #2 but is conducted with elected or appointed public officials or candidates for public office or federal statue requires that confidentiality of Private identifiable information will be maintained.

45 CFR 46.101(b)

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HHS Exempt Categories

4. Research involving the collection of existing data, documents, records, pathological specimens, or diagnostic specimens if sources are publically available or if information is recorded in such a manner that subjects cannot be identified directly or through identifiers linked to subjects.

45 CFR 46.101(b)

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HHS Exempt Categories

5. Research and demonstration projects which are conducted by or subject to the approval of Department or Agency heads

45 CFR 46.101(b)

APPENDIX 4: OPTIONS FOR DATA SAFETY MONITORING

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Data and Safety Monitoring

- Can be defined as a planned, ongoing process of reviewing data collected in a clinical trial
  - Includes adverse event reporting
  - Other safety information
  - Changes to the protocol, consent, investigator's brochure, device pamphlet
  - Recent literature

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What types of individuals should you select to Monitor Data and Safety?

- Clinical expert in the field under study
- Methodological expertise (biostatistician)
- Clinical trial expertise /DMC experience

And for DSMBs you will also want:

- A non-scientist member
- Should have no conflict of interest
- Ideally, should not be affiliated with the study

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Options include:

- **PI and IRB**
  -to review unanticipated problems, AEs, SAEs and other study events
- **Independent Safety Monitor**
  -independent MD/expert/safety officer reviews unanticipated problems, AEs, and other study events and makes recommendations
- **Independent Monitoring Committee**
  -small group of independent investigators and biostatisticians review data and make recommendations
- **DSMB**
  -independent committee reviews interim safety and efficacy data and makes recommendations about continuation, modification or termination of the study

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What might be recommended?

- Continue study plan as designed
- Study continuation with major or minor changes
- Temporary suspension until some uncertainty is resolved
- Early termination of the study
  -(i.e.) patients receiving the investigational treatment are found to be at higher risk of death than those in the control arm –or-
  -Interim analysis shows that the investigational product is of no benefit –or-
  -Unexpected, unacceptable side effects