



**RISK = a probability statement about the chance a harm occurring. RISKS can be described in terms of**

- The nature of the harm**
- Its probability or frequency**
- Its severity or magnitude and its duration**

(e.g., The probability that a venipuncture might cause a harm could note that it might have a 2% chance of causing a large, nasty, black, hematoma taking two weeks to resolve.)

The risk concept is defined (or refined) in multiple different ways within the regulations and, with each iteration, it is used differently:

|         |  |        |                               |
|---------|--|--------|-------------------------------|
| 56.111a | Risks should be minimized  | 812.3m | Significant Risk Device       |
| 56.111b | Risks should be < Benefits   | Guide  | Significant Risk Device Study |
| 56.111b | Risks of future harm   |        |                               |
| 56.102i | Minimal risk   |        |                               |
| 56.25.2 | Reasonably foreseeable risk  |        |                               |
| 56.108b | UPI RHSO Unanticipated problems involving risk to human subjects or others |        |                               |

Applicants should present all possible risks of harm together with their possible frequency, severity and duration and the source of the potential harm. The application should include plans made to minimize the risk of the harms occurring and their consequences should the harm actually occur. Several variables can alter the risk statement.

- Appropriate subject selection.
- Skill and training of the investigator and staff,
- Influences designed to encourage rapid recruitment.

In writing or evaluating a study, consider the variety of harms other than physical ones.

**1. Physical risks and discomforts**

- What are the known and theoretical physical harms from this test article?
- What are the known and theoretical harms from the various procedures?
- Are the risks being minimized through selection of appropriate and trained personnel both at the level of the principal investigators and the staff?
- Are there procedures that require special training? (e.g., cultural interviews)

- Are there harms from taking commonly used drugs?
- Are there any procedures that might cause physical discomforts or fears such as from claustrophobia or isolation?

**2. Inflicted knowledge – unintended consequences**

Information returned to a subject can cause the recipient to take further action. Certainly, information from standard diagnostic tests should be returned but there are many questions in other areas.

Educational testing can be just as diagnostic and just as questionable as medical testing.

- What is the potential for a false positive or negative?
- Is the information accompanied by counseling?
- If the results are unclear, what might be the emotional and financial consequences?
- What is the role of the primary physician?
- What are the considerations for and against reporting the individual results?

### **3. Financial risks**

Subjects should not be out-of-pocket for the benefit of the sponsor. Subject costs may be direct, as in being expected to pay for added follow-up visits, or may be hidden as in covering the time off work or the baby-sitter. Costs may also be unanticipated as when a third-party insurer rejects a claim on the basis that experimental procedures are involved.

- What costs are involved for the subjects or their third-party payer? For additional visits? For transportation? For payment for tests or the test article? How much time off work (or need for baby-sitting) might be involved?
- Will the insurer be involved?
- What is the maximum amount a subject might be asked to assume?
- Is there any way to minimize costs such as by providing child care or lab tests?
- Are there arrangements to provide free or low-cost care if the experimental arm is not effective?

### **4. Privacy risks (see also HIPAA)**

Loss of privacy is a risk of participation and it is one that is growing in importance. Despite the best safeguards and best training, briefcases have been lost and gossip has occurred in elevators. If data is to be submitted in a marketing permit,

FDA and sponsors have the right to audit all subject files and to review source documentation. *Confidentiality cannot be promised.*

- Is there any possibility of harm if participation or any of the results become known? How will confidentiality issues be handled? Will any records of the investigator or the sponsor contain individual subject identifiers? Is it possible to code the information so identities are not transmitted beyond the investigator?
- What source documents will be needed. How will they be accessed?
- Where will the individual subject records and consent forms be stored? Will such records be identifiable or coded? How long will they be retained?
- What will happen to the records at the end of the retention period. How will they be destroyed?

Database information poses special problems since there is a wealth of data available to anyone with access. Similarly pharmacoeconomic studies are of concern since a wealth of additional, non-study related data illustrating other forms of treatment will be available. Protocols should address the means used to protect data.

- Are there passwords for the computer? How often are they changed? Who has access to restricted areas of the database?
- What identifiers will be used on case report forms, and on the database? If there is no extremely good reason for use of the social security number or medical chart number, those numbers should not be considered.

- If outside reports are gained (bills, insurance statements, etc.) how are identifiers hidden?
- Receiving a false positive result may initiate more testing with related costs.

A **Certificate of Confidentiality** protects an investigator from forced release of information. It is available for some studies involving subjects who might be at legal risk should it become known that they even participated, such as studies of child abuse, or illegal activities. Call IRC for more information.

HIPAA must be considered in every application.

#### 5. Emotional or social risk

Subjects who feel they have been treated as means to an end or whose concerns have not been adequately addressed are not only unhappy, they also sue more often and they tell others of their experiences.

- Early termination of a patient/subject from a protocol providing care can cause substantial distress unless there is orderly transition to other care.
- Failure to pay compensation or reimbursement on time causes anger.
- Being identified as being in a group may cause social stigma. Gene identification and pedigree studies have particular stigmatization risks.
- Children can be shunned by other children just as can adults.

#### **Treatment and compensation for injury**

Occasionally a subject is injured during the course of research. An element of informed consent requires there to be a policy regarding treatment of injury and compensation for costs and that it be clearly stated.

A complete application reflects arrangements made to attend to anticipated injuries and financial arrangements made to cover their costs. The costs of treatment, later ancillary care, and, perhaps, time off work, child care, etc. should be considered. Simply indicating that the sponsor will not pay or has no program is to ignore the possibility and to wait for possible suit.

- Is there a clear policy on how injuries are to be handled and who will pay for such injuries?
- Is the policy clear and acceptable to the investigators?

The IRB does not need to know all financial arrangements between sponsor and investigator; it does need to know that those arrangements will result in appropriate arrangements to treat injuries and to compensate subjects.

