Human Research Subjects' Safety & the IRB's Role, Part I

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THE UNIVERSITY
of NORTH CAROLINA
at CHAPEL HILL

Rights and Welfare

Rights and Welfare are equals as identified in:

- Nuremberg Code
- Declaration of Helsinki
- Belmont Report
- Common Rule
- FDA/OHRP Guidance

Why do we care?

- Belmont Principle: Respect for Persons
- Need subjects for studies
- Learning what doesn’t work is a valuable lesson
- IRB responsible to monitor risks

IRB's Mission:

OHRP:

The IRB shall be sufficiently qualified through the experience and expertise of its members to promote respect for its advice and counsel in safeguarding the **rights** and **welfare** of human subjects.

UNC:

Protects the **rights** and **welfare** of human subjects in research activities through independent review of proposed research.

Rights Categories

Rights are discussed in the following sections of the Common Rule:

1) §46.107 IRB membership
2) §46.109 IRB review of research.
3) §46.111 Criteria for IRB approval of research.
4) §46.116 General requirements for informed consent.

IRB Membership & Human Subjects' Welfare

1. Diverse membership

2. Unaffiliated members (good to have former subjects or parents of subjects)

3. Non-scientist members

4. Multiple years of experience, expertise, free to ask the "dumb/obvious questions

Rights of Vulnerable Subjects

§46.111 Criteria for IRB approval of research.

- (b) When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons, **additional safeguards have been included in the study to protect the rights and welfare of these subjects**

What are a subject's rights

Informed Consent Process

1. To have enough time to decide whether or not to be in the research study and to make that decision without any pressure from the people who are conducting the research.
2. To refuse to be in the study at all, and to stop participating at any time after you begin the study.
3. To be told what the study is trying to find out, what will happen to you, and what you will be asked to do if you are in the study.
4. To be told about the reasonably foreseeable risks of being in the study.
5. To be told about the possible benefits of being in the study.

What are a subject's rights

Informed Consent Process

6. To be told whether there are any costs associated with being in the study and whether you will be compensated for participating in the study.

7. To be told who will have access to information collected about you, and how your confidentiality will be protected.

8. To be told whom to contact with questions about the research, about research-related injury, and about your rights as a research subject. If the study involves treatment or therapy.

9. To be told about the other non-research treatment choices you have.

10. To be told where treatment is available should you have a research-related injury, and who will pay for research-related treatment.

Risk/Benefit Ratio

"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."

Institutional Review Board Guidebook, 1993

What is risk?

Risk is not harm:

it is the *possibility of harm*, and an analysis of the risks must take into account including both the *magnitude* of the possible harm and the *probability* that the harm may occur.

(The National Commission 1979 and Common Rule)

Risks

In order to approve research conducted or supported by HHS, the IRB must determine, among other things, that:

- 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 subject for diagnostic or treatment purposes (45 CFR 46.111(a)(1)).

- Risks to subjects are reasonable in relation to anticipated benefits, if any, to the subjects, and the importance of the knowledge that may reasonably be expected to result (45 CFR 46.111(a)(2)).

- When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects (45 CFR 46.111(a)(6)).

Formula for Perfect Study Protocol

- All IRB submissions would be complete & perfect
- No stips, no deferrals, no amendments
- Shorter IRB meetings

Research Protocols would be perfect, if only we had.....

There are No Crystal Balls for Research Study Designs, so……

- There are annual reviews of active studies,
- Amendments are submitted to the IRB for review when changes are found to be necessary,
- Safety events are reported to the IRB for review & determination of next steps.

In an Imperfect World

We do have stips, deferrals, amendments, and

Adverse Events

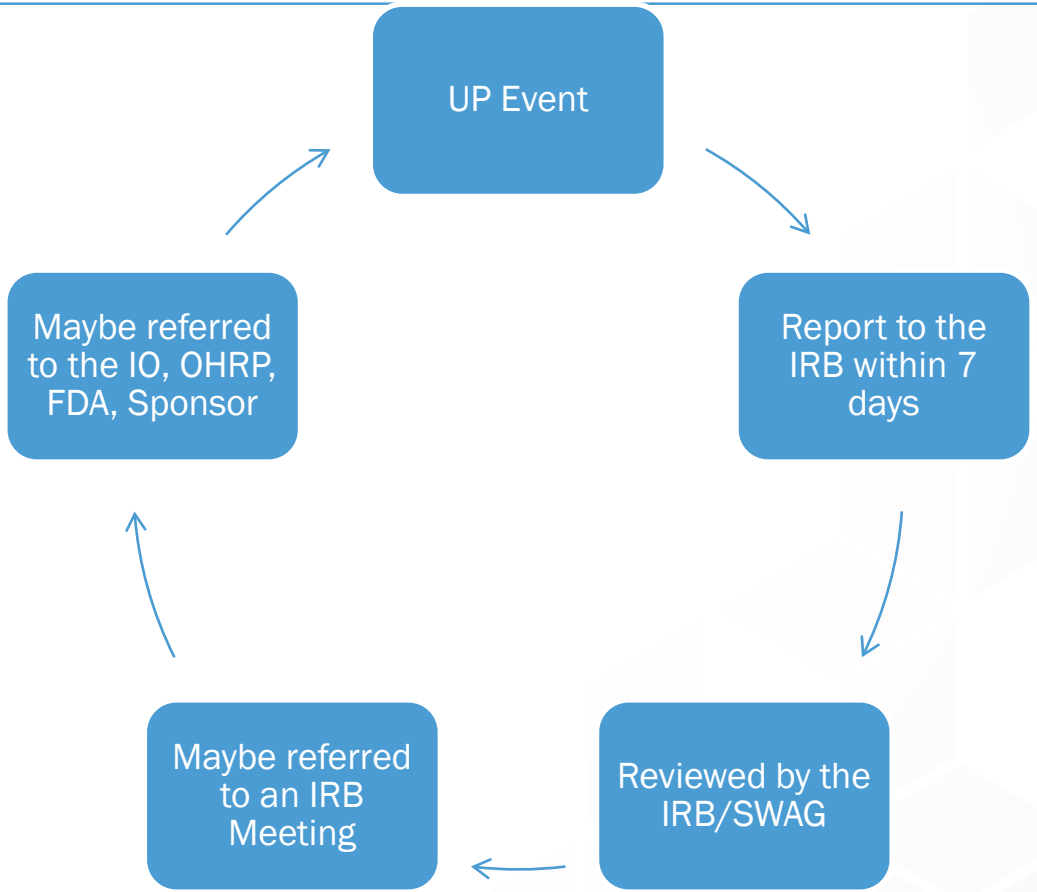
Serious Adverse Events

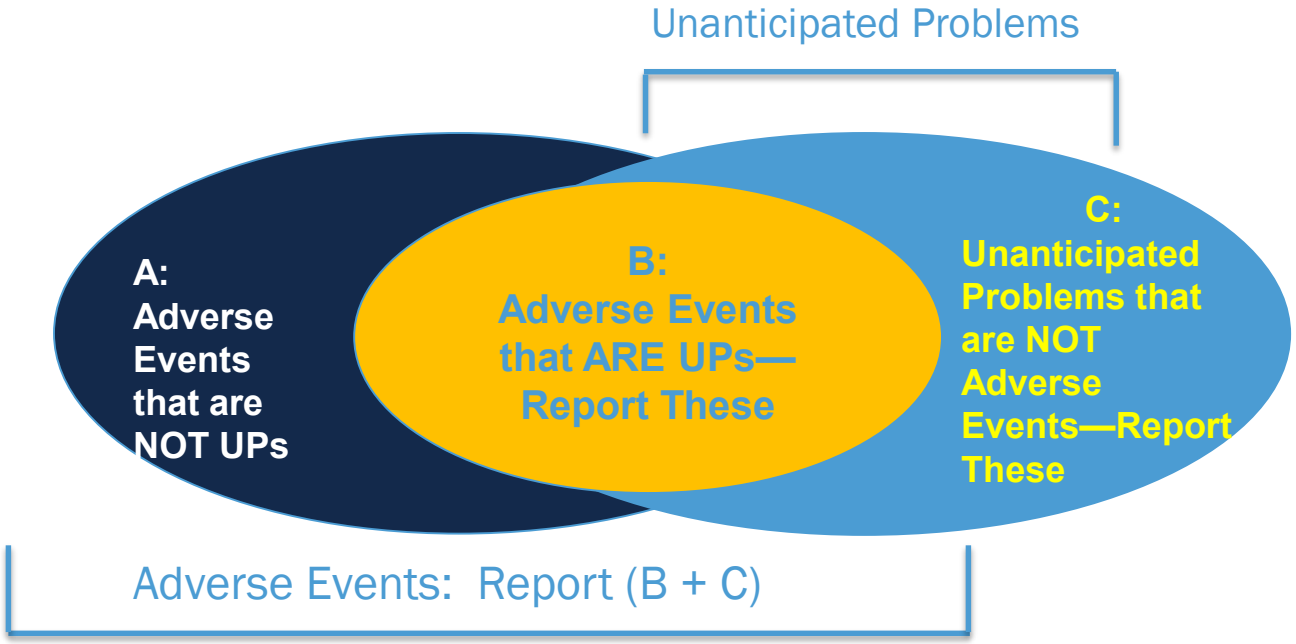
Unanticipated Problems.

It is the IRBs responsibility to review these events reported to it by the PI and determine next steps.

UPIRTSO/UPIRSO Human Subject Rights & Welfare

UP Cycle of Events




Unanticipated Problems
A:
Adverse
Events
that are
NOT UPs
B:
Adverse Events
that ARE UPs—
Report These
C:
Unanticipated
Problems that
are NOT
Adverse
Events—Report
These
Adverse Events: Report (B + C)

What is a UPIRTSO/UPIRSO

- The phrase “unanticipated problems involving risks to subjects or others” is found but not defined in the HHS regulations at 45 CFR part 46. OHRP considers *unanticipated problems*, in general, to include any incident, experience, or outcome that meets **all** of the following criteria:
  - *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;
  - *related or possibly related to participation in the research* (in this guidance document, *possibly related* means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
  - *suggests that the research places subjects or others at a greater risk of harm* (including physical, psychological, economic, or social harm) *than was previously known or recognized.*

OHRP Guidance on Rights and UPIRTSO's/UPIRSO

OHRP recognizes that it may be difficult to determine whether a particular incident, experience, or outcome is unexpected and whether it is related or possibly related to participation in the research.

OHRP notes that an incident, experience, or outcome that meets the three criteria generally will warrant changes in the research protocol or informed consent process/document or other corrective actions in order to protect the safety, welfare, or rights of subjects or others

Furthermore, there are other types of incidents, experiences, and outcomes that occur during the conduct of human subjects research that represent unanticipated problems but are not considered adverse events. For example, some unanticipated problems involve social or economic harm instead of the physical or psychological harm associated with adverse events. In other cases, unanticipated problems place subjects or others at increased *risk* of harm, but no harm occurs

When is a UPIRSO determination reported to OHRP/FDA/Other Reporting Agencies

OHRP

- Study is federally funded.

FDA

- Study is FDA regulated.

FDA

- Other federal agencies, when the research is overseen by those agencies and they require reporting separate from OHRP.

Example 1

An investigator conducting behavioral research collects individually identifiable sensitive information about illicit drug use and other illegal behaviors by surveying college students. The data are stored on a laptop computer without encryption, and the laptop computer is stolen from the investigator's car on the way home from work.

Example 1- OHRP's Response

This is an unanticipated problem that must be reported because the incident was

- (a) unexpected (i.e., the investigators did not anticipate the theft);
- (b) related to participation in the research; and
- (c) placed the subjects at a greater risk of psychological and social harm from the breach in confidentiality of the study data than was previously known or recognized.

this event may not have caused any detectable harm or adverse effect to subjects or others, it nevertheless represent unanticipated problems and should be promptly reported to the IRB, appropriate institutional officials, the supporting agency head and OHRP in accordance with HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5).

Example 2

A behavioral researcher conducts a study in college students that involves completion of a detailed survey asking questions about early childhood experiences. The research was judged to involve no more than minimal risk and was approved by the IRB chairperson under an expedited review procedure. During the completion of the survey, one student subject has a transient psychological reaction manifested by intense sadness and depressed mood that resolved without intervention after a few hours. The protocol and informed consent document for the research did not describe any risk of such negative psychological reactions.

Example 2- OHRP's Response

This is an example of an unanticipated problem that must be reported in the context of social and behavioral research because, although not serious, the adverse event was

- (a) unexpected;
- (b) related to participation in the research; and
- (c) suggested that the research places subjects at a greater risk of psychological harm than was previously known or recognized.

**the adverse events warranted consideration of substantive changes in the research protocol or informed consent process/document or other corrective actions in order to protect the safety, welfare, or rights of subjects.

Other Examples of UPIRTSO/UPIRSO's (AUDIT FINDINGS)

- University of Louisville (2016)
  - Failure to obtain IRB approval prior to initiating certain protocol changes
    - Billing Issues
      - Financial Risk/Right to be informed of costs
    - Eligibility Verification Missed
      - Safety Risk/Right to know what will happen
- Columbia (2019)
  - Breach in Confidentiality
    - The (cc) section of the email contained email addresses of other participants
      - Psychological Harm/Right to know who and how your information will be used
- https://www.hhs.gov/ohrp/compliance-and-reporting/types-of-determinations/index.html