Clinical Trials - ~~Reporting~~ Informing Obligations for Investigators

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Agenda

- What Information Needs to be Shared
- Whom to Share
  - Institutional Review Boards (IRBs)
  - Human Subject Participants
  - Sponsors
  - Others
- When To Share
- How to Analyze Information for Reporting Purposes

Applicability

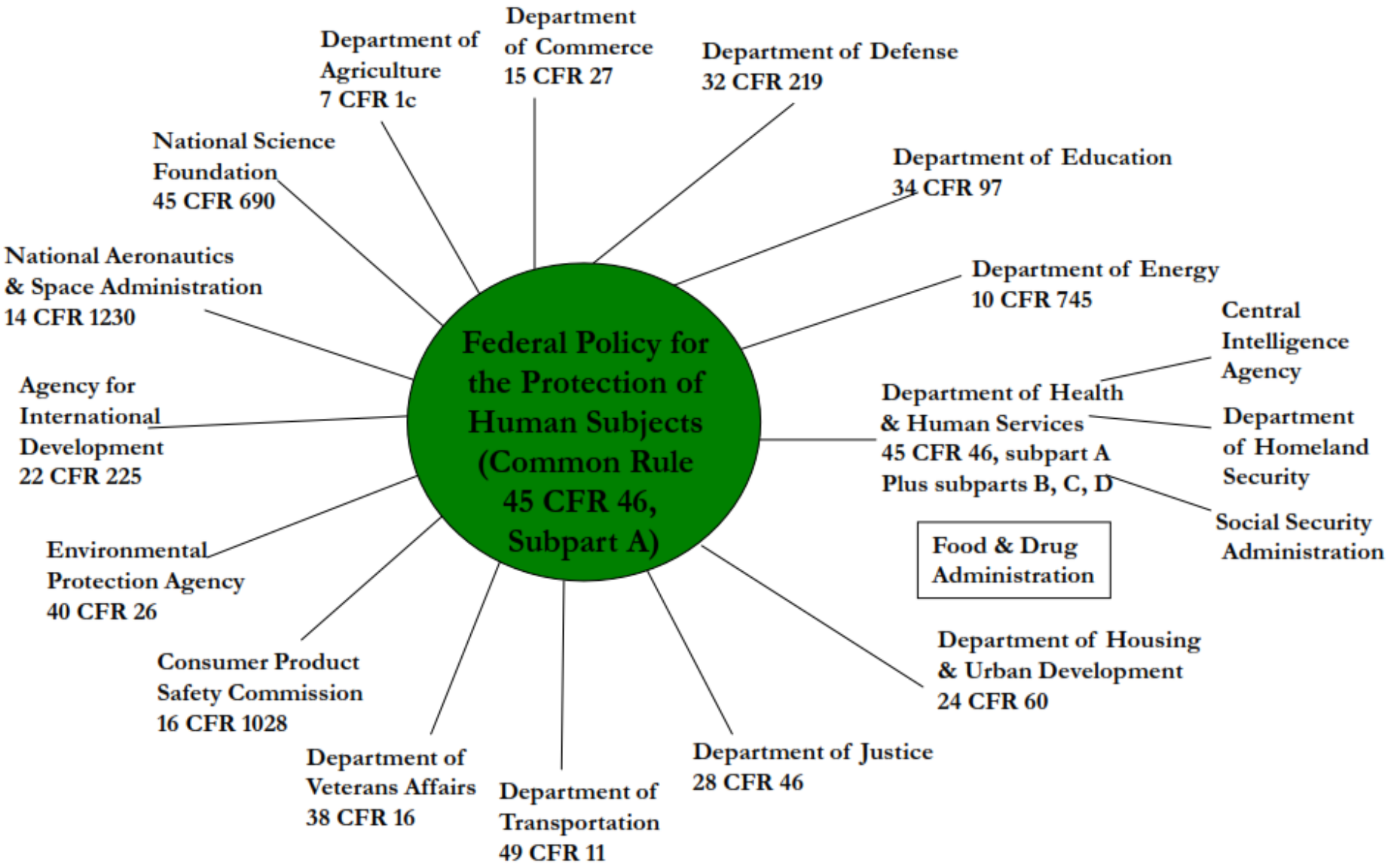
- Clinical trials that are:
  - Sponsored by someone other than investigator and
  - Involve Federalwide Assurance (FWA) covered research or FDA-regulated research.

As a result, this presentation is limited to investigator informing obligations only.

Applicability (cont'd)

- FWA covered clinical trial:
  - Conducted or supported by HHS;
  - Conducted or supported by a non-HHS federal department or agency that has adopted the Common Rule (Common Rule Department/Agency); or
  - Covered by a FWA, regardless of funding source.
    - ✓Check the box concept

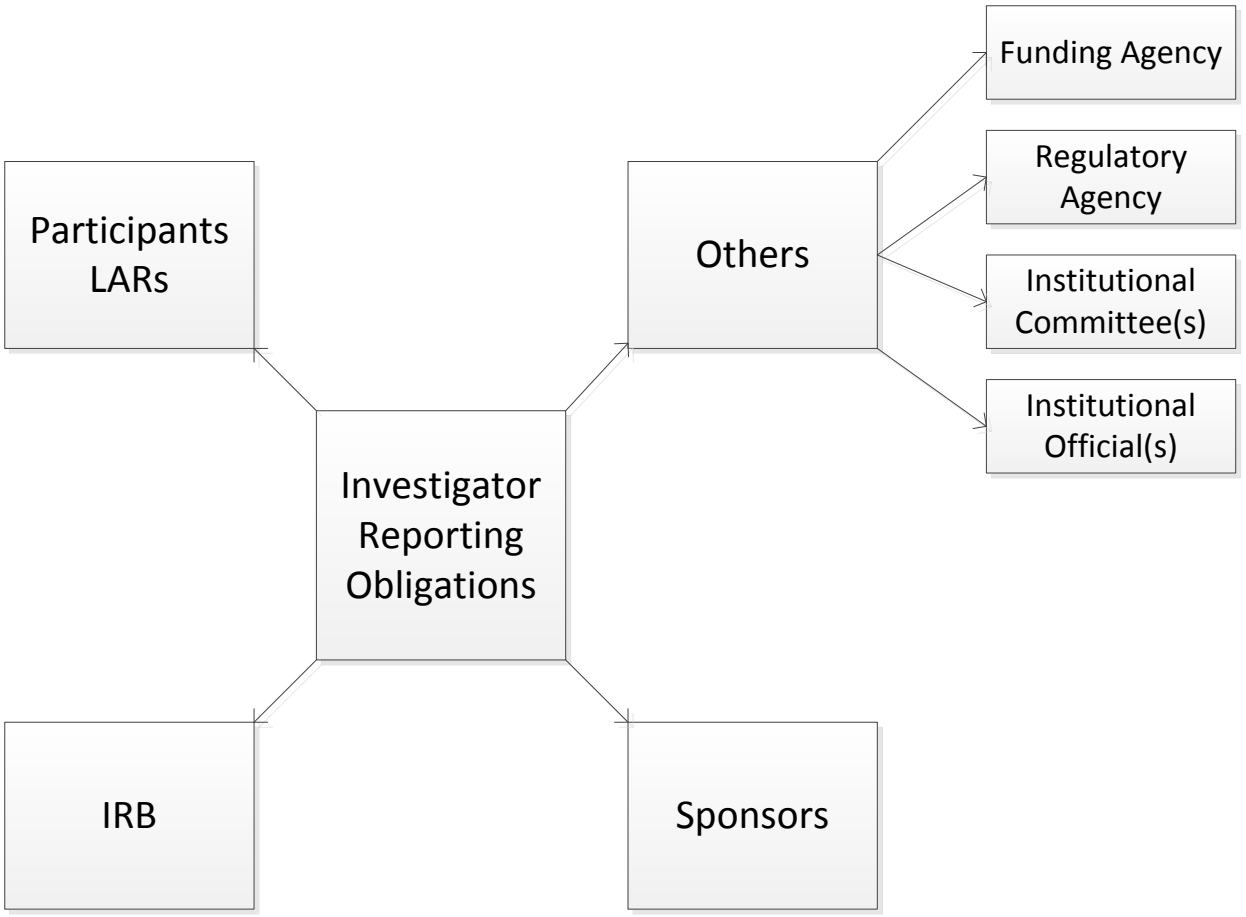
Common Rule Departments & Agencies



Applicability (cont'd)

- FDA covered clinical trial: An experiment that involves a test article and one or more human subjects and is either:
  - An IND or IDE regulated clinical trial or
  - Not an IND/IDE regulated clinical trial, but the results of which are to be submitted to, or held for inspection by, FDA to support research or marketing permits.

Investigator Informing Obligations



Initial Review
~~Reporting~~ Informing Obligations

Investigator Informing Obligations - What to Report, To Whom & When

Event	IRB	Participants LARs	Sponsor	Others
New Protocol	Before study begins	N/A	IRB approved protocol before study begins	Specialized Committees before study begins per regulations/ institutional policy
Citations	46.103(b)/46.109(a) 56.103(a) GCP 3.1.2	N/A	312 30(b) 812.35 GCP 4.5.1/5.11 Protocol	If protocol requires supplemental review

Investigator Informing Obligations - What to Report, To Whom & When

Event	IRB	Participants LARs	Sponsor	Others
Financial Interest(s)	Before study begins & as updated	During initial consenting process and as updated if IRB requires notification, i.e., additional information	Before study begins & promptly as updated for 1 year following study completion	To institutional conflicts committee if involves PHS or NSF funded research If investigator is responsible for reporting to funding entity … To PHS funding component - prior to expenditure of funds & w/in 60 days of any newly identified FCOI and annually. To NSF - When COI cannot be managed, reduced, or eliminated at institution
Citations	Before: 46.111(a)(4) 56.111(a)(4) Update: 46.109(b)/56.109(b)	46.109(b)/56.109(b)	54.4(b) For FDA covered studies	42 CFR 50.605(b)

Investigator Informing Obligations - What to Report, To Whom & When

Event	IRB	Participants LARs	Sponsor	Others
IBs/Device Manual	Before study begins, as updated either at CR (if update did not result in change to research) or at amendment review (if update results in change to research)	N/A	N/A	N/A
Citations	Before: 46.103(b)/56.103(a) GCP 3.1.2/4.4.2/7.1 CR: 46.109(e)/56.109(f) Update: 46.103(b)(4)(iii)/56.108(a)(4) GCP 4.4.2/7.1	N/A	N/A	N/A

Investigator Informing Obligations - What to Report, To Whom & When

Event	IRB	Participants LARs	Sponsor	Others
CVs Qualifications	Before study begins & as updated	N/A	Before study begins	N/A
Citations	Before: 46.107(a)/56.107(a) 46.111/56.111 GCP 3.1.2 Update: 46.111/56.111 GCP 4.1.1	N/A	312.53(c)(2) 812.43(c)(1) GCP 4.1.1 Protocol	N/A

Investigator Informing Obligations - What to Report, To Whom & When

Event	IRB	Participants LARs	Sponsor	Others
FDA 1572/ Investigator Agreement	Before study begins & as updated	N/A	Before study begins & as updated	N/A
Citations	Before: 46.103(b)/56.103(a) Update: 46.103(b)(4)(iii)/56.108(a)(4)	N/A	312.53(c) 812.43(c) 812.140(b)(3) GCP 4.5.1 Protocol	N/A

Investigator Informing Obligations - What to Report, To Whom & When

Event	IRB	Participants LARs	Sponsor	Others
Informed Consent Process & Form	Before study begins, at continuing review (CR) & as updated	Before participation & as additional information or significant new findings (SNF) become available	Before study begins, at CR & as updated	Treating Physician
Citations	Before: 46.117(a)/50.27(a) GCP 3.1.2 -3.1.9 CR: 46.109(e)/56.109(f) Update: 46.103(b)(5)/56.108(b) 46.115(a)(7) 56.115(a)(7)	Before: 46.116/50.20 312.53(c)(vi)(d) 812.100 GCP 4.8.10 Additional information: 46.109(b)/56.109(b) GCP 3.1.5/4.8.2 SNF: 46.116(b)(5)/50.25(b)(5) 4.8.2	Before: 312 30(b) 812.35 GCP 4.5.1/5.11 CR: 312.64(a) 812.150(a)(3) GCP 5.11.3 Update: GCP 4.5.2/4.5.4/ 5.11 Protocol	GCP 4.3.3

Amendment Review
~~Reporting~~ Informing Obligations

Investigator Informing Obligations - What to Report, To Whom & When

Events	IRB	Participants LARs	Sponsor	Others
Change to/Deviation from Research	Before changes implemented except when necessary to eliminate apparent immediate hazards to subject. If meets exception, then for non-GCP, in accordance with IRB procedures, or for GCP - promptly.	Within IRB timeframe if IRB says participants must be notified, i.e., additional information or SNF	After IRB approval, unless meets exception. If meets exception: promptly for GCP studies N/A for IND/IDE studies	N/A
Citations	46.103(b)(4)(iii)/56.108(a) GCP 3.3.7/3.3.8 GCP 4.5.2/4.5.4	46.109(b)/56.109(b) 46.116(b)(5)/56.115(a)(7) GCP 3.1.5/4.8.2	GCP 4.5.2/4.5.4/ 5.11 Protocol	N/A

Continuing Review
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Investigator Informing Obligations - What to Report, To Whom & When

Event	IRB	Participants LARs	Sponsor	Others
Continuing Review/Progress Report	Annually or more frequent	N/A	Annually or more frequent	Monitor
Citations	46.109(e)/56.109(f) GCP 4.10.1	N/A	312.64(a) 812.150(a)(3) GCP 5.11.3 Protocol	812.150(a)(3)

Continuing Review (CR) Overview

- In order to re-approve research at CR, IRB must find that all applicable IRB approval criteria continue to be satisfied.

- In order for the IRB to fulfill its CR mandate, investigators must provide the IRB with updated study information.

- IRB, in turn, will rely upon updated study information when deciding whether the study:

  - Continues to meet IRB approval criteria; or
  - Requires revisions in order for study to meet IRB approval criteria.

What To Report at Continuing Review (CR)

- Updated study information includes:
  - Number of subjects accrued;
  - Brief summary of any amendments to research approved by IRB since last IRB review;
  - New & relevant information, published or unpublished;
  - Summary of both UPs and available information about AEs;
  - Summary of any withdrawal of subjects from the research & reasons for withdrawal, if known;
  - Summary of any complaints about the research;
  - Latest version of IRB approved protocol and sample ICFs;
  - Any proposed modifications to research;
  - Current IB, if available, including any modifications; and
  - Any other significant information related to subject risk, e.g., most recent data safety monitoring report.

Investigator Informing Obligations - What to Report, To Whom & When

Event	IRB	Participants LARs	Sponsor	Others
Auditing Monitoring Reports	At CR (as new/relevant information)	Within IRB timeframe if IRB says participants must be notified , i.e., additional information or SNF	At CR	N/A
Citations	CR: 46.109(e)/56.109(f) GCP 4.10.1	46.109(b)/56.109(b) 46.116(b)(5)/56.115(a)(7) GCP 3.1.5/4.8.2	312.64(a) 812.150(a)(3) GCP 5.11.3 Protocol	N/A

Investigator Informing Obligations - What to Report, To Whom & When

Event	IRB	Participants LARs	Sponsor	Others
Participant Complaints	At CR	Within IRB timeframe if IRB says participants must be notified, i.e., additional information or SNF	At CR	N/A
Citations	CR: 46.109(e)/56.109(f) GCP 4.10.1	46.109(b)/56.109(b) 46.116(b)(5)/56.115(a)(7) GCP 3.1.5/4.8.2	312.64(a) 812.140(b)(5) 812.150(a)(3) GCP 5.11.3 Protocol	N/A

Investigator Informing Obligations - What to Report, To Whom & When

Event	IRB	Participants LARs	Sponsor	Others
Safety Reports (AEs/SAEs)	At CR	Within IRB timeframe if IRB says participants must be notified, i.e., additional information or SNF	As follows:	N/A
Citations	CR: 46.109(e)/ 56.109(f) GCP 4.10.1	46.109(b)/56.109(b) 46.116(b)(5)/ 56.115(a)(7) GCP 3.1.5/4.8.2	AEs – 312.64(b)/GCP 4.11.2 – In accordance with protocol SAEs – 312.64(b) – Immediately GCP 4.11.2 – Immediately except for SAEs noted as not requiring immediate reporting CR: 312.64(a) GCP 5.11.3 Protocol	N/A

Investigator Informing Obligations - What to Report, To Whom & When

Event	IRB	Participants LARs	Sponsor	Others
Unanticipated Adverse Device Effects (UADEs)	As soon as possible, but no later than 10 working days after investigator learns of event and at CR	Within IRB timeframe if IRB says participants must be notified. i.e., additional information or SNF	As soon as possible, but no later than 10 working days after investigator learns of event & at CR	N/A
Citations	812.150(a)(1) CR: 46.109(e)/ 56.109(f) GCP 4.10.1	46.109(b)/56.109(b) 46.116(b)(5)/56.115(a)(7) GCP 3.1.5/4.8.2	ASAP: 812.150(a)(1) GCP 4.11.1 CR: 812.150(a)(3) GCP 5.11.3 Protocol	N/A

Investigator Informing Obligations - What to Report, To Whom & When

Event	IRB	Participants LARs	Sponsor	Others
Significant New Finding	In accordance with IRB requirements (non-GCP) or promptly (GCP) and at CR (as significant information relating to subject risks)	Within IRB timeframe if investigator notifies IRB before participants	Non GCP – N/A, or GCP (promptly) and at CR.	N/A
Citations	46.115(a)(7)/50.25(b)(5) GCP 3.3.8/4.10.2 CR: 46.109(e)/56.109(f) GCP 4.10.1	46.116(b)(5)/56.115(a)(7) GCP 4.8.2	Promptly - GCP 4.10.2 CR: 312.64(a) 812.150(a)(3) GCP 5.11.3 Protocol	N/A

Investigator Informing Obligations – What to Report, To Whom & When

Event	IRB	Participants LARs	Sponsor	Others
Premature Termination or Suspension by entities other that IRB	Non GCP - at CR GCP - promptly	Non GCP - Within IRB timeframe if IRB says participants must be notified, i.e., additional information or SNF GCP - Promptly	Non GCP - as noted in protocol GCP - promptly	N/A
Citations	CR: 46.109(e)/56.109(f) GCP: 4.12.1/4.12.2	46.109(b)/56.109(b) 46.116(b)(5)/56.115(a)(7) GCP 4.12	GCP 4.12.1 4.12.2	N/A

Investigator Informing Obligations – What to Report, To Whom & When

Event	IRB	Participants LARs	Sponsor	Others
Final Report	As follows:	Within IRB timeframe if IRB says participants must be notified, i.e., additional information	As follows:	N/A
Citations	812.150(a)(6) - Within 3 months after completion of study GCP 4.13 – Upon completion of the trial	46.109(b)/56.109(b)	312.64(c) – Shortly after completion of investigator participation 812.150(a)(6) -Within 3 months after completion of study GCP 4.13 – Upon completion of the trial	N/A

Prompt ~~Reporting~~ Informing Obligations for Investigators

Prompt Informing Requirements

45 CFR 46.103(a) & (b)(5)

- Require institutions to have written procedures for **prompt** reporting to IRB, appropriate institutional officials (IOs), the funding agency and OHRP of any:
  - Unanticipated problems involving risks to subjects or others (UPs);
  - Serious or continuing noncompliance with 45 CFR 46/applicable subparts or the requirements or determinations of the IRB; and
  - Suspension or termination of IRB approval.

21 CFR 56.108(b)

- Requires IRBs to follow written procedures for **prompt** reporting to IRB, IOs & FDA of any:
  - UPs;
  - Serious or continuing noncompliance with 21 CFR 50/56/312/812 or the requirements of determinations of the IRB; and
  - Suspension or termination of IRB approval.

Prompt Informing

- Investigator must report events within certain timeframe of becoming aware of event regardless of:

  - How became aware of event
    - ✓Reports
    - ✓Observations;
    - ✓Literature or news accounts, etc.

  - When became aware of event
    - ✓Study status (opened vs. closed);
    - ✓Participants status (active, withdrew or completed study)

OHRP Guidance - Prompt Reporting

- Investigators should review and report UPs & AEs to IRBs as follows:
  - UPs that are SAEs – report to IRB within 1 week of becoming aware;
  - All other UPs – report to IRB within 2 weeks of becoming aware;
  - All UPs should be reported to IO, supporting agency head & OHRP within 1 month of IRB receiving report.
- Institutions should report incidents to OHRP as follows:
  - More serious incidents report to OHRP within a few days of IRB receiving report;
  - Less serious incidents, report to OHRP within a few weeks of IRB receiving report.

Why Report Promptly

- Required by regulations &
- May stop OHRP from opening a compliance oversight investigation with your institution
  - If a complainant notifies OHRP of an incident requiring prompt reporting after OHRP receives a report from the institution, OHRP will not open an investigation; rather will process the report via its reportable events procedures vs.
  - If a complainant notifies OHRP of an incident before OHRP receives a report, OHRP may open an investigation into the matter.

Investigator Informing Obligations – What to Report, To Whom & When

Event	IRB	Participants LARs	Sponsor	Others
Suspension or Termination of IRB Approval	Promptly	Within IRB timeframe if IRB says participants must be notified, i.e., additional information or SNF	Within 5 working days	If investigator is responsible for reporting, report promptly to IOs **and** If FWA covered clinical trial - Funding agency and OHRP **or** If FDA regulated clinical trial - FDA
Citations	46.103(b)(5) 56.108(b)	46.109(b)/56.109(b) 46.116(b)(5)/56.115(a)(7) GCP 3.1.5/4.8.2	812.150(a)(2) GCP 5.11.3 Protocol	46.103(b)(5) 56.108(b)

Suspension or Termination of IRB Approval

- Occurs whenever an IRB gives a directive to an investigator to:
  - Suspend (temporarily halt); or
  - Terminate (permanently stop);
  - Some or all activities being conducted under an IRB approved research protocol

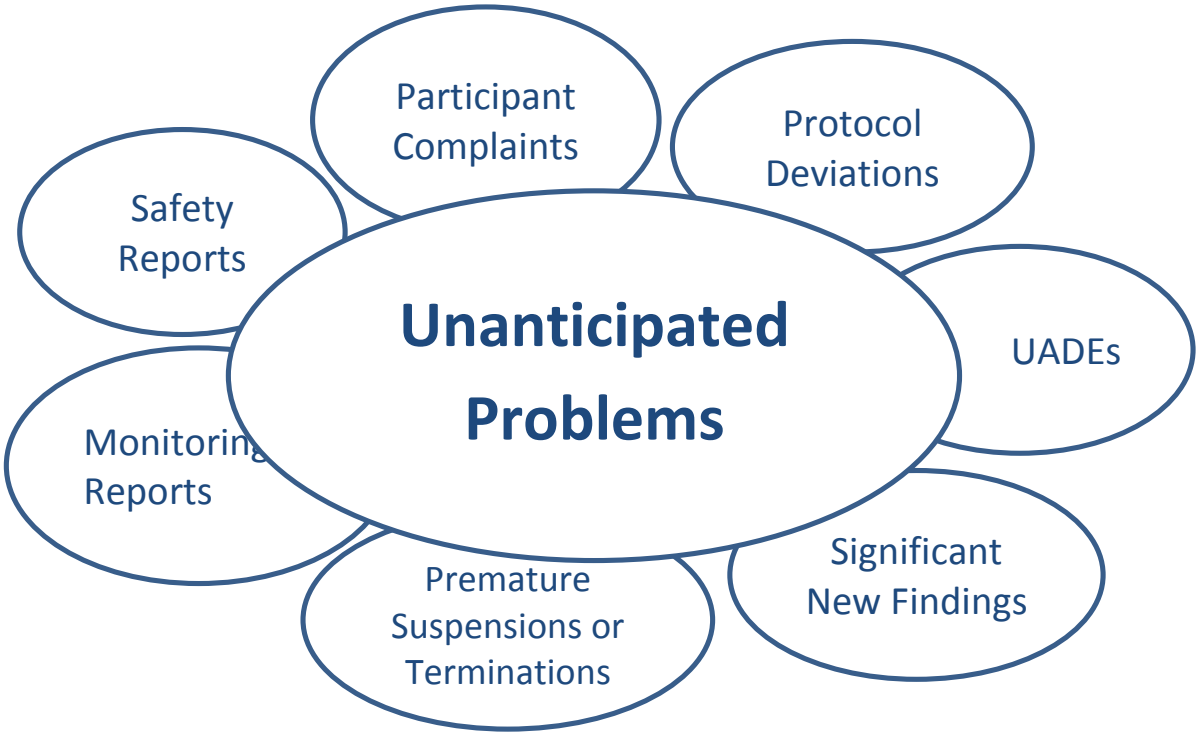
Suspension or Termination of IRB Approval (cont'd)

- What is NOT IRB suspension or termination:
  - Expiration of IRB approval;
  - Investigator decision to suspend or terminate even if prompted by IRB;
  - Directives by non-IRB entities, e.g., sponsors, cooperative groups, DSMBs
    - ✓Even though non-IRB directives are not reportable, any UPs or serious or continuing noncompliance that led to directives must be reported

Unanticipated Problems

- Any incident, experience, or outcome meeting the following criteria:
  - Unexpected (nature, severity, or frequency);
  - Related or possibly related to research procedures;
  - Suggests that the research places **subjects or others at a greater risk of harm** (including physical, psychological, economic, or social harm) than previously known or recognized; &
  - Usually requires some action to address the incident, experience or outcome.

Events Revealing Possible Unanticipated Problems



Investigator Informing Obligations - What to Report, To Whom & When

Events	IRB	Participants LARs	Sponsor	Others
Unanticipated Problem	Promptly and at CR	Within IRB timeframe if participants must be notified, i.e., additional new information or SNF	N/A	If investigator is responsible for reporting, report promptly to IOs **and** If FWA covered clinical trial - Funding agency and OHRP **or** If FDA regulated clinical trial - FDA
Citations	Prompt: 46.103(a)/(b)(5)/ 56.108(b) GCP 3.3.8 CR: 46.109(e)/56.109(f)	46.109(b)/56.109(b) 46.116(b)(5)/56.115(a)(7) GCP 3.1.5/4.8.2	Protocol	46.103(b)(5) 56.108(b)

Investigator Informing Obligations – What to Report, To Whom & When

Event	IRB	Participants LARs	Sponsor	Others
Serious or Continuing Noncompliance	Promptly	Within IRB timeframe if IRB says participants must be notified, i.e., additional information or SNF	N/A	If investigator is responsible for reporting, report promptly to IOs **and** If FWA covered clinical trial - Funding agency and OHRP **or** If FDA regulated clinical trial - FDA
Citations	46.103(b)(5)/ 56.108(b)	46.109(b)/56.109(b) 46.116(b)(5)/56.115(a)(7) GCP 3.1.5/4.8.2	Protocol	46.103(b)(5) 56.108(b)

Noncompliance

- Any accidental or intentional failure to follow:
  - 45 CFR part 46 (including applicable subparts)
  - FDA governing regulations (21 CFR 50, 56, 312 & 812); and
  - IRB requirements or determinations that go beyond the regulations.

- Failure to follow includes:
  - Performing acts that violate the above; and
  - Failing to act when required to do so.

- Failure on part of individuals involved in research:
  - Investigators/research team members;
  - IRB members/staff; and
  - Institutions.

Serious Noncompliance

- Not defined; refer to institutional procedures
  - Serious noncompliance involves acts or omissions that:
    - ✓Compromise the rights and welfare of subjects;
    - ✓Harm subjects or place subjects at increased risk of harm;
    - ✓Significantly decrease potential benefits to subjects/alter the risk benefit ratio;
    - ✓Adversely affect the scientific integrity of the study;
    - ✓Compromise the integrity or effectiveness of an institution's HRPP;
    - ✓Adversely impact ethical principles;
    - ✓Any other appropriate criteria, e.g. Common rule agency definitions, e.g., VA, DOD, etc.

OHRP Considers the Following to be Serious Noncompliance

- Implementing more than minor protocol changes without IRB approval, except when necessary to prevent immediate hazard(s) to subjects;
- Conducting non-exempt human subjects research without IRB review and approval;
- Failing to obtain the legally effective informed consent of subjects, when required by the IRB, prior to involvement of subjects in non-exempt human subjects research activities.

Continuing Noncompliance

- Not defined; refer to institutional procedures.
  - Continuing noncompliance involves:
    - ✓Repeated acts or omissions, e.g., same mistake being made repeatedly with one study/investigator or the same mistake is being made one or more times across multiple studies/investigators;
    - ✓Indicate an inability or unwillingness to comply with applicable regulations or the requirements or determinations of the IRB;
    - ✓Particularly after an individual has received notice that action must be taken to correct a similar or related noncompliance concern
      - Investigator repeatedly fails to obtain IRB approval prior to study expiration
      - Investigator repeatedly fails to notify IRB of UPs or serious or continuing noncompliance involving one or more of his/her studies

How to Analyze Events to Determine Whether To ~~Report~~ Inform Promptly

UP and Noncompliance Concepts

- Every event must be assessed as:
  - An isolated event; and
  - In the aggregate, if applicable;
  - To determine whether the isolated event or aggregate analysis of same or similar events, i.e., trend, meets:
    - ✓ UP Criteria;
    - ✓ Serious Noncompliance Criteria; or
    - ✓ Continuing Noncompliance Criteria.

Think Isolated Event Analysis
As Well As Trend Analysis!

Isolated Event & Trend Analysis Example 1

- AE Reports
  - Isolated AE report showing allergic reaction at higher frequency & severity; followed by multiple reports reflecting trend - higher frequency & severity than known

Reports	UP?	Serious NC?	Continuing NC?
First Report	No	No	No
Additional Reports Reflecting Trend	Yes	No	No

Isolated Event & Trend Analysis Example 2

- Protocol Violation (Modification) Reports
  - Isolated report of subject receiving a drug that is 5 x's higher than dose dictated by protocol resulting in temporal unfavorable medical outcome; followed by additional reports reflecting dosing error trend across a number of studies

Reports	UP?	Serious NC?	Continuing NC?
First Report	Yes	Maybe, depending on definition	No, given one time error
Additional Reports Reflecting Trend	Yes	Most likely yes	Yes

Isolated Event & Trend Analysis Example 3

- Monitoring Reports
  - A monitoring report revealing protocol changes in one protocol without IRB approval, followed by additional reports revealing trend of numerous protocol changes across many protocols without IRB approval

Reports	UP?	Serious NC?	Continuing NC?
First Report	Most likely no	Maybe, depending on changes & definition	No, given one time error
Additional Reports Reflecting Trend	Maybe, depending on changes	Most likely yes if more than minor change in research	Yes

Isolated Event & Trend Analysis Example 4

- Participant Complaints
  - Complaint revealing investigator's failure to pay subject in accordance with informed consent terms followed by additional complaints revealing trend of failing to pay subjects in accordance with informed consent terms.

Reports	UP?	Serious NC?	Continuing NC?
First Report	No	No	No
Additional Reports Reflecting Trend	No	Possibly, depending on definition	Yes

??? Questions ???

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