



The Basics on Adverse Event Monitoring, Assessment and Reporting

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Overview of the Session

- Definitions
- Who regulates your study?
- Assessing AEs and UPs
- Reporting AEs and Ups
- The DSMP
- Case Examples (time permitting)

Why is this important?



The 111 Criteria

45 CFR 46.111 (OHRP) and 21 CFR 56.111 (FDA)

- Risks to subjects are minimized.
- Risks to subjects are reasonable in relation to benefits (i.e. favorable risk benefit ratio).
- Selection of subjects is equitable.
- Informed consent process.
- Informed consent documentation.
- Adequate provision for monitoring the safety and data.
- Provisions to protect privacy/maintain confidentiality.
- Safeguards for vulnerable populations.

Regulations Guiding Clinical Research

Subpart A: Protection of Human Subjects

45 CFR 46

OHRP

- Assurance
- Oversight
- Engagement

**Informed Consent
IRB Review/ Functions/
Operations**

21 CFR 312, 812, 50, 54, 56

FDA

- Sponsor/investigator roles and conduct
- Drug/device dev't & testing process

- Subpart B: Pregnant women, Fetuses, neonates
- Subpart C: Prisoners
- Subpart D: Children
- Subpart E: IRB Registration

45 CFR 160, 162, 164

HIPAA (Health Insurance Portability and Accountability Act of 1996)

- Privacy and Security of protected health information⁵



OHRP Regs Apply when....

- Research involving human subjects **conducted or supported by HHS** that is not otherwise exempt

-OR-

- Non-exempt human subject research **covered by Assurance of Compliance** (whether or not conducted or supported by HHS)

Does FDA regulate your study?

- “Clinical Investigation means **any experiment that involves a test article and one or more human subjects** that either is subject to requirements for prior submission to the FDA under section 505(i) or 520(g) of the act...or... the results are intended to be submitted to FDA... as part of an application for a research or marketing permit...” (21 CFR 50.3(c))
- *Soooo..... most studies testing drugs/devices, even if they are previously approved and currently marketed....*

FDA Regs

- IND: Investigational New Drug Application
 - 21 CFR 312
 - 21 CFR 312.2 – IND exemption
 - Investigator Responsibilities (312.50)
 - Sponsor Responsibilities (312.60)
- IDE: Investigational Device Exemption
 - 21 CFR 812
 - Investigator Responsibilities (812.100)
 - Sponsor Responsibilities (812.40)
- IRB and Consent
 - 21 CFR 50 (Protection of Human Subjects) and 21 CFR 56 (IRB)



New FDA Regulations re: AE Reporting for IND Studies

- Final Rule on IND Safety Reporting
 - Significant updates to IND regs published in Federal Register 9/29/10
 - New regs in effect 3/28/11
- Important implications for Sponsors and Investigators
 - See 2/2010 FDA guidance and read updated IND regs.



“Go-to” Regs and Guidance re: AEs

FDA

- FDA Regs (Drugs): 21 CFR 312.32 (IND reporting)
- FDA Regs (Devices): 21 CFR 812.150; 812.3 (definitions);
- *Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE studies, December, 2012*
- *Guidance for Clinical Investigators, Sponsors, and IRBs: AE Reporting to IRBs – Improving Human Subject Protection, Jan. 2009*

OHRP

- 45 CFR 46.103 (b) (5)
- *OHRP Guidance on UPs and AEs, Jan. 15, 2007*

ICH

GCP

- Definitions: 1.1, 1.2, 1.5
- Investigator: 4.11
- Sponsor: 5.17

AE Monitoring/Reporting

- Institutional policies
- Regs + Guidance under which your study is conducted
 - **OHRP** (45 CFR 46.103), **FDA** (drugs/biologics: 21 CFR 312; 600.80; marketed drugs: 21 CFR 310.305; 314.80; devices: 21 CFR 812.150), **ICH GCP** (3.3.8, 4.11, 5.17)
- Protocol (definitions of AEs, SAEs, etc.)
- Sponsor requirements
- Funding agency requirements (i.e. if different from “sponsor”)
- Requirements of the DSMB and/or Steering committee

What can cause an adverse event?



Adverse Events

- Adverse event (AE)
- Serious adverse event (SAE)
- Unanticipated problems (UP)



A few AE Definitions

- “Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject’s participation in the research, whether or not considered related to the subject’s participation in the research.” (*OHRP Guidance, Jan. 2007*)
- “Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.” (*21 CFR 312.32 (a)*)
- “Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment... any unfavorable or unintended sign... symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.” (*ICH E2A and E6*)

A few AE Definitions

- “Unanticipated Adverse Device Effect:

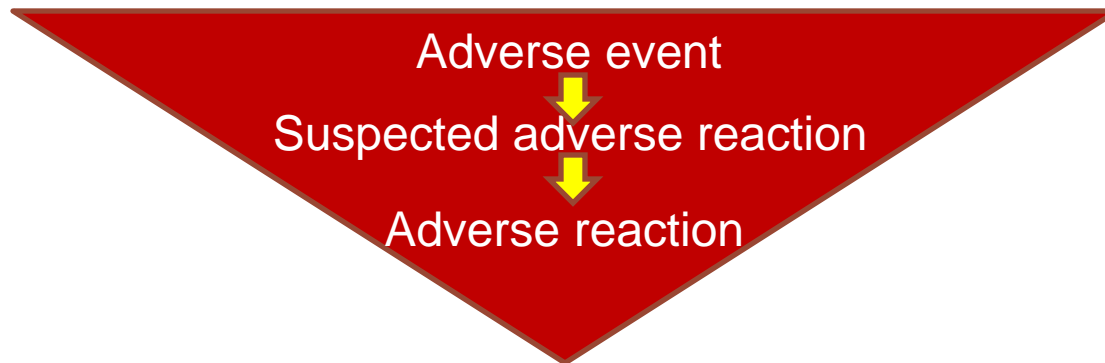
Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application) or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.” (21 CFR 812.3 (s))

AE Definitions: “Non-medical” studies

- Define AEs around known risks....
potential for:
 - Invasion of privacy
 - Breach of confidentiality
 - AEs related to study procedures
 - What’s *plausible* (considering procedures), but would be considered “unexpected” if it occurred?

A few AE Definitions (FDA IND)

- **Suspected adverse reaction:** “Any adverse event for which there is a reasonable possibility that the drug caused the adverse event.....”
 - ‘Reasonable possibility’: evidence to suggest a causal relationship between the drug and the adverse event.” (21 CFR 312.32)
- **Adverse reaction:** Subset of suspected adverse reactions
 - “Any adverse event caused by a drug.” (FDA Guidance, 12/12)



Serious Adverse Event Definition

Any adverse event that:

- results in death;
- is life-threatening (places the subject at immediate risk of death from the event as it occurred);
- results in inpatient hospitalization or prolongation of existing hospitalization;
- results in a persistent or significant disability/incapacity;
- results in a congenital anomaly/birth defect; or
- based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition."

(OHRP Guidance on UPs and AEs, Jan. 15, 2007)

Similar definitions:

FDA: 21 CFR 312.32; ICH: E6 1.5; E2A section II B

Life-threatening

- Places the subject at immediate risk of death.
- Does not include an AE that might cause death in a more severe form.

Expectedness (FDA)

- Unexpected:
 - **Not listed in Investigator Brochure** or is not listed at the specificity or severity that has been observed, or, if an investigator brochure is not required or available, is **not consistent with the risk information described in the general investigational plan** or elsewhere in the current application.

FDA Guidance Dec. 2012

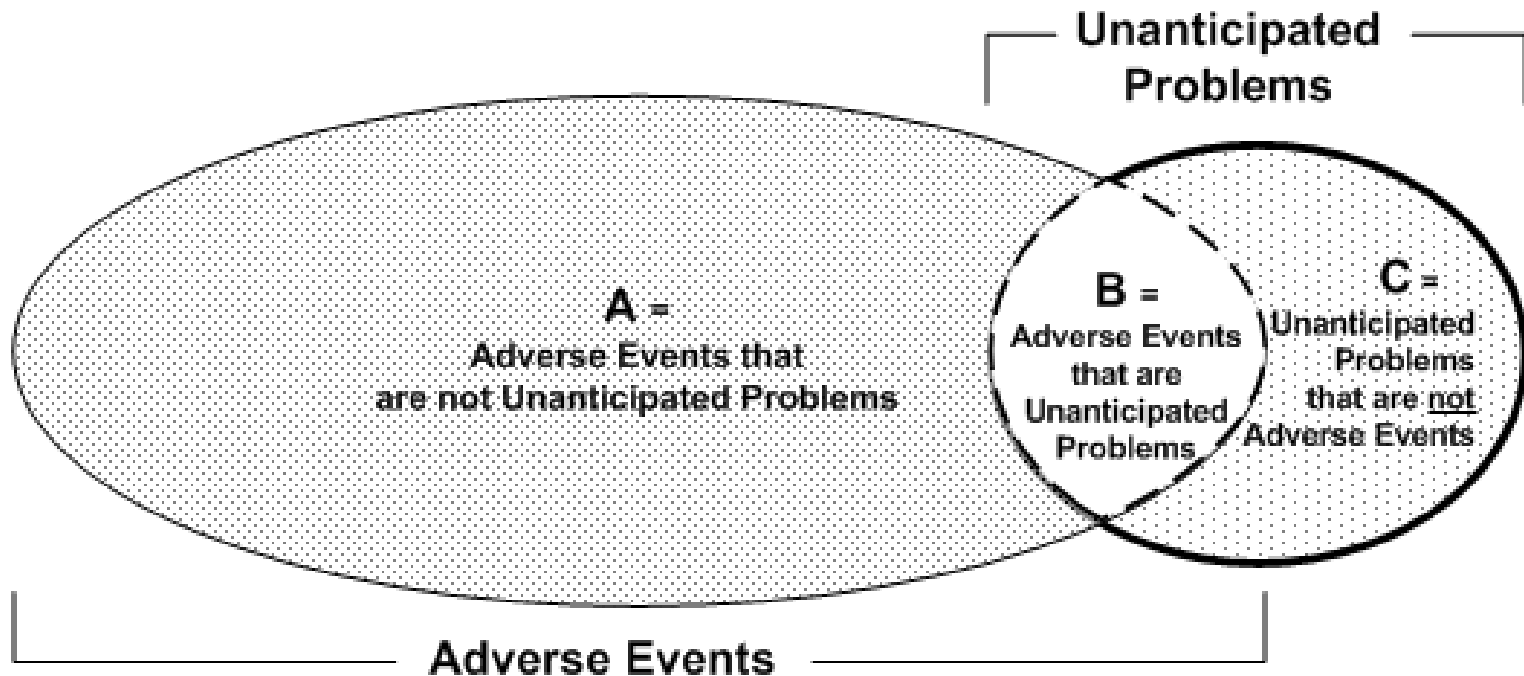
Unanticipated Problems (UPs)

“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
 - b) the characteristics of the subject population being studied;
- **Related or possibly related** to a subject’s participation 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) related to the research than was previously known or recognized.”

(OHRP Guidance on UPs and AEs, Jan. 15, 2007)

Unanticipated Problem



Under 45 CFR part 46: Do not report A, Do report (B+C)

(OHRP Guidance on UPs and AEs, Jan. 15, 2007)

- Most adverse events are not unanticipated problems
- Unanticipated problems include other incidents, experiences, and outcomes not considered adverse events

Unanticipated Problems (UPs)

An incident does not need to result in actual harm to a subject in order for the incident to be considered a UP involving risks to subjects or others.

- 10/30/09 OHRP Determination letter to Mt. Sinai Medical Center, Miami, FL
 - The Trial to Assess Chelation Therapy protocol specified that infusions should be completed in no less than 3 hours to allow for safe infusion rates
 - 440 instances involving 251 subjects across 63 sites where shorter infusion times occurred
 - “...some subset of the events associated with technician error or for which the cause was unknown may have represented unanticipated problems involving risks to subjects....”



Assessing AEs and Ups (FDA IND)

Investigator and Sponsor assess:

- **Seriousness:** Regulatory definition
- **Expectedness:** nature or severity is not consistent with information already known about the drug.
- **Severity:** intensity of a specific event

This is NOT about what's expected in the subject's disease process or what's expected in this population..

Grading scales based on:

- Common Terminology Criteria for Adverse Events
- Grading based on signs and symptoms
- Grading based on effect on usual daily activities

Investigator assesses causality but sends all SAEs to sponsor.
Sponsor assesses causality with benefit of all data from sites, etc.

- **Causality/relatedness (suspected adverse reaction?)**
 - Ex: Definite, Probable, Possible, Unlikely (or some rating scale)
 - Yes or No (Was there a reasonable possibility that the drug caused the event?)

Assessing AEs: Severity Scale example

Category	Toxicity	Gr 0	Gr 1	Gr 2	Gr 3	Gr 4
Cardiac	HTN	None	Asymp., transient inc. by > 20 mm Hg (D) or to > 150 / 100 if prev. WNL. No tx required.	recurrent or persistent inc. by > than 20 mm HG (D) or to > 150 / 100 if prev. WNL. No tx req.	Req. tx	Hyper-tensive crisis
GI	Vomiting	None	1 episode in 24 hrs	2-5 in 24 hrs	6-10 in 24 hrs	>10 in 24 hrs; req. parenteral support

Relatedness/Causality

Questions to ask in assessing causality are:

- Is the AE a known reaction of the intervention?
- Is the AE similar to other adverse events listed the investigator's brochure or consent documents?
- Has the AE occurred before in this study?
- Is the AE reasonably temporally related to the intervention?
- Does the AE improve or disappear when the intervention is discontinued? What happens on re-test?
- Was the AE present at the baseline assessment of the subject or in the subject's recent medical history?
- Can the AE be reasonably explained by the subject's clinical disease status?
- Are there any other potential causes for the AE?

Documentation of AEs

- What is the event?
 - Seriousness (this is a regulatory definition)
 - Expectedness (based on what is known about the intervention)
 - Severity (not same as “*seriousness*”)
 - Causality
- When did event occur?
- When was site aware of the event? **
- What (if any) clinical action taken?
- Duration?
- Outcome
- Reporting actions
 - Dates!



What needs to be reported – (IRB)?

Common Rule – 45 CFR part 46

FDA – 21 CFR 56.108(b)(1)

Requires Prompt Reporting to the IRB of:

- Any unanticipated problems involving new or increased risk to subjects or others
- Remember....
 - UPs may not necessarily meet your study's def of AE
 - UPs do not necessarily mean that participants have been harmed.

What needs to be reported?

BUMC IRB

- Events that meet the definition of UP:
 - **submit within 2 business days of becoming aware of the event**
- Summary of all AEs, including evaluation of the AEs by the monitor or investigator:
 - **submit at time of progress report (if no DSMB)**
- DSMB, DMC, or other data safety monitoring committee reports:
 - **submit when they become available.**

What needs to be reported (IND)?

FDA, Drugs (21 CFR 312)

Investigators are required to:

- **Report promptly to the IRB all unanticipated problems** involving risks to human subjects or others
 - **“Serious and Unexpected Suspected Adverse Reactions”**
[56.108(b)(1); 312.53(c)(1)(vii); 312.66]
- **Immediately report to the sponsor any serious adverse event**, whether or not considered drug related, including those listed in the protocol or investigator brochure....whether or not reasonable possibility that the drug caused the event. [312.64 (b)]
 - **Study endpoints that are SAEs** must be reported in accordance with the protocol (unless evidence suggests causal relationship between drug and event.... Then report “immediately” to sponsor.

What needs to be reported (IDE)?

FDA, Devices (21 CFR 812)

Investigators are required to:

- Submit to the reviewing IRB and the sponsor a report of any unanticipated adverse device effects (UADE) occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect [812.150(a)(I)]

What needs to be reported(IND)?

FDA, Drugs (21 CFR 312)

Sponsors are required to:

- **Promptly review** all info relevant to the safety of the drug
- **IND Safety Report:** Notify FDA and all participating investigators... under its INDs..., as soon as possible, but in no case later than 15 calendar days FDA Form 3500A, narrative, other
 - **Serious and Unexpected Suspected Adverse Reaction**
 - Findings from other studies
 - Findings from animal or in vitro studies

What needs to be reported (IDE)?

FDA, Devices (21 CFR 812)

Sponsors are required to:

- Immediately conduct an evaluation of a UADE ...report the results...to FDA, all reviewing IRBs, and participating investigators within 10 working days after the sponsor first receives notice of the effect. 812.46(b), 812.150 (b)(1).

A serious adverse event must be reported to the IRB within 2 business days.

1. True
2. False

Is a UP always a serious adverse event?

1. Yes
2. No

All Suspected Adverse Reactions must be reported to the FDA by the Sponsor in an IND Safety Report

1. Yes
2. No

Reporting AEs and UPs

- Based on assessment, there will be a “reporting cascade...”
 - Site (Investigator) makes judgment about:
 - Seriousness, Expectedness, Severity, (Causality)
 - Sponsor makes judgment about:
 - Seriousness, Expectedness, Severity, Causality
 - Reports to FDA and all investigators via IND Safety Report as necessary
- Factors to consider in determining reporting

Reporting Timeframe

- AE (non-serious)
- SAE
- Unanticipated Problem (related, unexpected, serious)
- DSMB Reports

AE Reporting example

Timeframe example for UP:

New drug under industry sponsor-IND; multi-center trial; PI of local site; serious, unexpected Suspected Adverse Effect

- PI report to BU IRB w/in 2 days
- PI reports to sponsor “immediately.” (21 CFR 312.64)
- Sponsor reports to FDA by ph/fax asap and in written safety report w/in 7 calendar days if life-threatening or death and w/in 15 calendar days if non-life-threatening.
- Sponsor reports to other study sites via safety report asap, no later than 15 calendar days.
- Sponsor reports to the DSMB as per protocol/DSMB Charter.

Common Problems

- Person(s) assessing event is not qualified to do so
 - not on study protocol, insufficient or no medical training, no licensing... etc.
- Events not appropriately documented
 - Ex: date of occurrence vs. date site aware
- Event meeting def of UP not reported to FDA and/or IRB
- Reporting timeframe requirements not met
- Protocol-specified study procedures not followed

FDA Warning letter: AE Reporting

- You failed to personally conduct or supervise the clinical investigation (Dov Linzer, 6/12/09)
- “...your clinical research coordinators were delegated responsibilities including but not limited to, affirmation of inclusion and exclusion criteria and **assessment of adverse events (AEs), serious adverse events (SAEs) and study endpoints**....In FDA’s review of the resumes...these individuals did **not appear to be qualified, certified, or significantly medically trained and licensed to be independently making judgments** related to determination of eligibility of subjects... and/or making the determination as to whether or not adverse events were related to the use of the investigational drug.
- “...your lack of supervision ...resulted in significant findings as detailed below, and raises significant concerns with respect to data integrity and how you protected rights, safety and welfare...”

FDA Warning letter: AE Reporting

- You failed to ensure that the investigation was conducted according to the investigational plan (Vaughn Mancha, 2/17/11)
- “Subject x had week 8 lab tests collected on 2/18/08 and the lab report faxed to your site on 2/20/08 showed that the subject’s creatinine level measured 3.2 mg/dL. A progress note dated 2/20/08 stated that the decision was made to terminate the subject from the study... and hold the drug until the termination visit. [There was no direct follow-up with the subject until 2/26...]
- You did not report the SAE of acute renal failure to the CRO until 2/27/08. This was not within the 24-hour reporting period required by the protocol. In addition, the report to the CRO stated that the onset of the SAE and the date your staff was notified of the SAE was 2/26/08. This is contradictory to your progress note, which stated that your site became aware of the SAE on 2/20/08. Your site did not report the SAE to the IRB until 2/27/08”

Content of a DSMP

- 1) Assessment of the level of risk/complexity in the particular study.
 - What monitoring is built into the study design? Think about side effects, risks of study procedures.... What kinds of testing or monitoring become part of the protocol to monitor for those risks and side effects?... frequent visits, lab testing, vital signs, etc.

- 2) Who is monitoring... what is being monitored... and at what frequency...
 - Description of what each individual or group will monitor.
 - Indication of the frequency of monitoring for each of the individuals and groups listed.
 - Description of stopping points, interim analysis (if applicable) and unblinding plan.

- 3) Reporting
 - AE Definitions, AE grading and attribution/causality scales.
 - Description of AE reporting mechanism(s): what gets reported, to whom, and in what timeframe.
 - Multicenter study?.... Is there a central entity that sees all AEs?

Thank you!

Any questions??

AE Assessment/Reporting Exercise

- For each of the following examples, determine:
 - Expectedness
 - Seriousness
 - Severity
 - Relatedness

 - Reporting

Example 1

65 yo ptp in a skin cancer prevention study who has been taking study drugs for 2 months comes to the ER with chest pain and is hospitalized overnight for observation. He is released the next day with diagnosis of gastric indigestion likely brought on by eating spicy shrimp at a SuperBowl party. His medications remain the same. He has a history of this condition. This is not a side effect noted in the Investigator Brochure.

Example 2

A two-year follow-up study of a behavioral intervention for smokers. A study coordinator was traveling to a home visit by train and on exiting the train realized that she left the study binder on the train. All efforts to retrieve the binder were futile. It was never recovered.

On subsequent review, it appeared that the subject's name, ss#, and medical history (including history of illicit drug use) were all contained in this binder on a page that was supposed to be filed elsewhere (per internal SOPs).

Example 3

32 year old female taking part in a yoga-dosing study stops coming to the yoga classes mid-way through the study. After three missed classes the staff calls but is unable to reach her.

Example 4

32 year old female is taking part in a domestic violence recovery study. The study provides services and counseling to assist women who are living in abusive relationships. One intervention is a once a week yoga class to lower stress and build confidence. Mid-way though the study she stops coming to her yoga class. After three missed classes the staff calls but is unable to reach her.

Example 4.5

32 year old female is taking part in a domestic violence recovery study. The study provides services and counseling to assist women who are living in abusive relationships. One intervention is a once a week yoga class to lower stress and build confidence. Mid-way though the study she stops coming to her yoga class. After three missed classes the staff calls but is unable to reach her.

She finally calls from the hospital saying that her partner abused her severely after hearing a phone message left by the study identifying the study by name, a violation of study procedures.

Example 5

Drug study subject experienced mild CHF (Congestive Heart Failure) and shortness of breath. He went to the ER where he was treated with diuretics and oxygen. Once stabilized, he returned home the same day.

From UPenn GCP Module example, 2003

Example 6

A 67 year old female is taking part in a study looking at the difference between yoga, walking, and meditation in effecting stress levels (both subjective and objective measures). During her yoga session she complains of shortness of breath and dizziness. She was taken to the ER where she was found to have irregular heart rhythm. She was admitted to the hospital. She has no cardiac history and generally in very good health.

Example 7

Subject in a hypertension study was noted at a follow-up visit to have severe vertigo and a BP of 80/60.

Example 8

A 72 year old female who recently underwent open heart surgery is participating in a 5 year study (beginning while still in-patient) looking at daily meditation sessions for 6 months to speed recovery and improve long term outcomes and quality of life (i.e. annual QOL measures and survival assessment for 5 years).

After 3 months of participation in the study the woman experienced an MI and died.

Example 9

55 yo healthy female taking part in a drug dosing study c/o chest pain at her baseline visit, prior to the 1st dose. Her EKG shows concerning changes and she is brought to the ER and admitted for observation.

Example 10

Research ptp in drug study was admitted to the hospital for elective surgery (planned prior to study participation).

During surgery he had an unexpected amount of bleeding and required multiple transfusions. The study intervention is not known to be associated with bleeding.

Example 11

A 52 year old female taking part in a yoga dosing study reports in her study diary that her back pain is increasing.

Example 12

A 52 year old female taking part in a yoga dosing study complains that the yoga teacher touched her inappropriately during a study yoga session.

Example 13

Research ptp in a yoga dosing study was admitted to the hospital for elective surgery (planned prior to study participation).

During surgery she had an unexpected amount of bleeding and required multiple transfusions.

Example 14

Research ptp has a history of behavioral problems. He received church-provided counseling for these problems after the study intervention.

Would this one single episode of this counseling while on the study constitute an AE?

Example 15

A 51 year old male was entered into a clinical study for the treatment of Chron's disease.

The study drug was administered on 12/10. On 12/16, he visited the study site and c/o a severe sore throat to the point where he had difficulty eating certain foods.

The investigational brochure lists severe sore throat as an occurrence reported by 1% of subjects receiving this drug.

Example 16

A 71 year old woman taking part in a yoga exercise trial complained of muscle pain, especially in her right calf.

Later that week the woman was hospitalized for a pulmonary embolism due to DVT.

Example 17

A 35 yo man is receiving injections of a Product X for asthma in a phase 2 clinical trial. Immediately following his second injection he experienced severe bronchospasm and angioedema of the throat and tongue. He was treated and released by the local ER. He recovered completely from the event.

The investigators' brochure for Product X states:
“Anaphylaxis, presenting as bronchospasm, hypotension, syncope, urticaria, and/or angioedema of the throat or tongue has been reported.

Thank you!

Any questions??