Adverse Events- Love them, hate them, report them!

Billi Tatum, RN, CCRC
Regional Vascular Center
Harborview Medical Center and the University of Washington Medical Center

Objectives

- Define and identify an Adverse Event
- Define and identify a Serious Adverse Event
- Samples of AE collection tools
- Questions/ participant samples of AE/SAE

What is an Adverse Event (AE)?

21CFR312.32 *Adverse event* means: "Any untoward medical occurrence associated with the use of a drug/device in humans, whether or not considered drug/device related."

Elective hospitalizations for pre-existing conditions (e.g., elective cosmetic procedures) are not adverse events.

What is an Adverse Event (AE)?

Adverse Events may include, but are not limited to the following:

- Worsening of conditions present at the onset of the study i.e. Hypertension requiring an increase or addition of medications
- Concurrent illness i.e. new diagnosis of pneumonia

Why do I have to report AEs?????

- To Monitor the safety of the study
- To inform regulators , investigators and others of the risk(s) associated with certain events
- To make changes to the study if the risks to the subjects changes
- To inform the subjects of any new or additional risks

Why report AEs?

- Detect problem products, manufacturers, and ingredients
- Identify common injuries among product types
- Determine if warning statements are needed to prevent injuries or other action
- Discover common misuses of products

Black Box Warnings

- A black box warning, also known as a "black label warning" or "boxed warning," is named for the black border surrounding the text of the warning that appears on the package insert, label, and other literature describing the medication (e.g., magazine advertising).
- It is the most serious medication warning required by the FDA.

Black Box Warning Medications

Fluoroquinolone Antibiotics

According to the FDA, people taking a fluoroquinolone antibiotic have an increased risk of tendinitis and tendon rupture, a serious injury that could cause permanent disability. The FDA warning includes Cipro (ciprofloxacin), Levaquin (levofloxacin), Avelox (moxifloxacin) and other medications containing fluoroquinolone. (Warning issued July 2008.)

Diabetes Medications

According to the FDA, people with diabetes taking Avandia (rosiglitazone) have an increased risk of heart failure or heart attack if they already have heart disease or are at high risk of suffering a heart attack. (Warning issued November 2007.)

Additional Black Box Medications

Antidepressant Medications

According to the FDA, all antidepressant medications have an increased risk of suicidal thinking and behavior, known as suicidality, in young adults ages 18 to 24 during initial treatment (generally the first one to two months). The FDA warning includes Zoloft (sertraline), Paxil (paroxetine), Lexapro (escitalopram), and other antidepressant medication. (Warning issued May 2007

More can be found at ***blackboxrx.com*** ***or*** ***http://www.fda.gov/drugs/drugsafety/informationbydrugclass***

Black Box Warnings

The FDA announced in March 2005 that two topical eczema drugs -- Elidel cream and Protopic ointment -- would get a "black box" warning about a possible cancer risk. The warning states that there have been rare reports of cancer (for example, skin and lymphoma) in patients who had been receiving the two drugs; however, the drugs haven't been proven to cause cancer.

Unanticipated Uses for Products or Drugs

- Proscar- originally marketed to treat benign prostatic hypertrophy. After 5 years of testing, an interesting side effect was discovered- hair growth! (1990s)

- Viagra- originally was to be used to treat hypertension, angina and other symptoms of heart disease. It did not work very well at treating those diseases but it did have an interesting side effect- erections!

Other commonly found terms

Expected Adverse Events

Those experiences that have been identified in nature, severity or frequency in the current investigator plan or protocol and in the current Informed Consent.

Examples:
Nausea following surgery
Pain following surgery
Dark colored stools (when taking iron supplements)

Unexpected Adverse Events

Any adverse event, the specificity or severity of which is not consistent with the current investigator brochure or with the risk information described in the investigational plan or Informed Consent.

Examples:

- Hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure referred only to elevated hepatic enzymes or hepatitis.
- Cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure listed only cerebral vascular accidents.

http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=312.32CF

Unanticipated Problems

- Unexpected in terms of nature, severity or frequency given (a) the research procedures that are described in the protocol related documents such as the research protocol, investigators brochure and the informed consent and (b) characteristics of the study population

- Related or possibly related to participation in the research . 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

- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic or social harm) than was previously know or recognized.

45 CFR part 46

Relatedness of Drug/device to Product/procedure

- Not related- the adverse event is CLEARLY not related to the product /device
- Unlikely related- the adverse event is DOUBTFULLY related to the product/device
- Possibly related- the adverse event MAY be related to the product/device

Severity of Event

Mild: an experience that is usually transient and requires no special treatment or intervention

Moderate: an experience that is alleviated with simple therapeutic measures

Severe: an experience that requires therapeutic intervention

Sample of AE Tracking Log for a Device Study

Event #	Subject ID	Event Description	SAE (Y/N)	Start Date	End Date	Outcome: Continuing Resolved Unknown Death	Actions Taken: 0 = no action 1 = medication 2 = surgery/procedure 3 = hospital 4 = other	Device Relationship Not related Unlikely Possibly Definitely	Procedure Relationship Not related Unlikely Possibly Definitely	Device Malfunction? Not related Unlikely Possibly Definitely	Date IRB Notified	Other
1												
2												
3												
4												
5												
6												
7												
8												
9												
10												
11												

Definition of an SAE

A serious adverse event (SAE) is defined as one that suggests a significant hazard or side effect, regardless of the investigator's opinion on the relationship to the investigation product or device.

Definition of an SAE

This includes, but may not be limited to, any event that:

- Is fatal
- Is life-threatening
- Requires or prolongs inpatient hospitalization
- Is a persistent or significant disability or incapacity
- Congenital Anomaly/Birth Defect

Definition of an SAE

- Is considered an important medical event.

Important medical events may be considered serious by the investigator although they may not be immediately life threatening or result in death or prolong hospitalization. Such important medical events are those that may jeopardize the patient, require intervention to prevent one of the outcomes listed above, or result in urgent investigation.

SAE Important Medical Event Examples

Examples include, but are not limited to:

- allergic bronchospasm
- convulsions
- blood dyscrasias

Serious Adverse Events

- Death - needs no further definition

- Life threatening: in the view of *either* the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

SAE Examples

- Mild bronchospasm treated with epinephrine with complete recovery of subject.
- Bleeding following removal of a femoral artery sheath that is quickly controlled.

Serious Adverse Events

- Inpatient hospitalization or prolongation of existing hospitalization. Example: Subject in hospital for pneumonia and has a heart attack. The heart attack causes the subject to stay in the hospital longer.

- Is a persistent or significant disability or incapacity. Example: Person has a renal stent placed that failed and person now on dialysis

Serious Adverse Events

- Congenital Anomaly/Birth Defect.

Remember Thalidomide? Used in the late 1950s early 1960s to treat nausea in pregnant women with resultant limb malformations. The drug *was* approved in 1998 for the treatment of leprosy and multiple myeloma.

Accutane, a medication used to treat cystic acne was found to cause life threatening birth defects.

Serious Adverse Events

- Is considered an important medical event.

Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Source:
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=312.32

Unanticipated Adverse Device Effects

Any serious adverse effect on the health or safety caused by or associated with a device, if the event was not previously identified in nature, severity or degree of incidence in the investigational plan

Any unanticipated serious problem associated with a device that relates to the rights, safety or welfare of subjects

CFRPart812

http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm? CFRPart=812

UADE Examples

- Stent fractures occurring at higher than anticipated numbers in an IDE study.

- Hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure only referred to elevated hepatic enzymes or hepatitis.

Unanticipated Adverse Device Effects

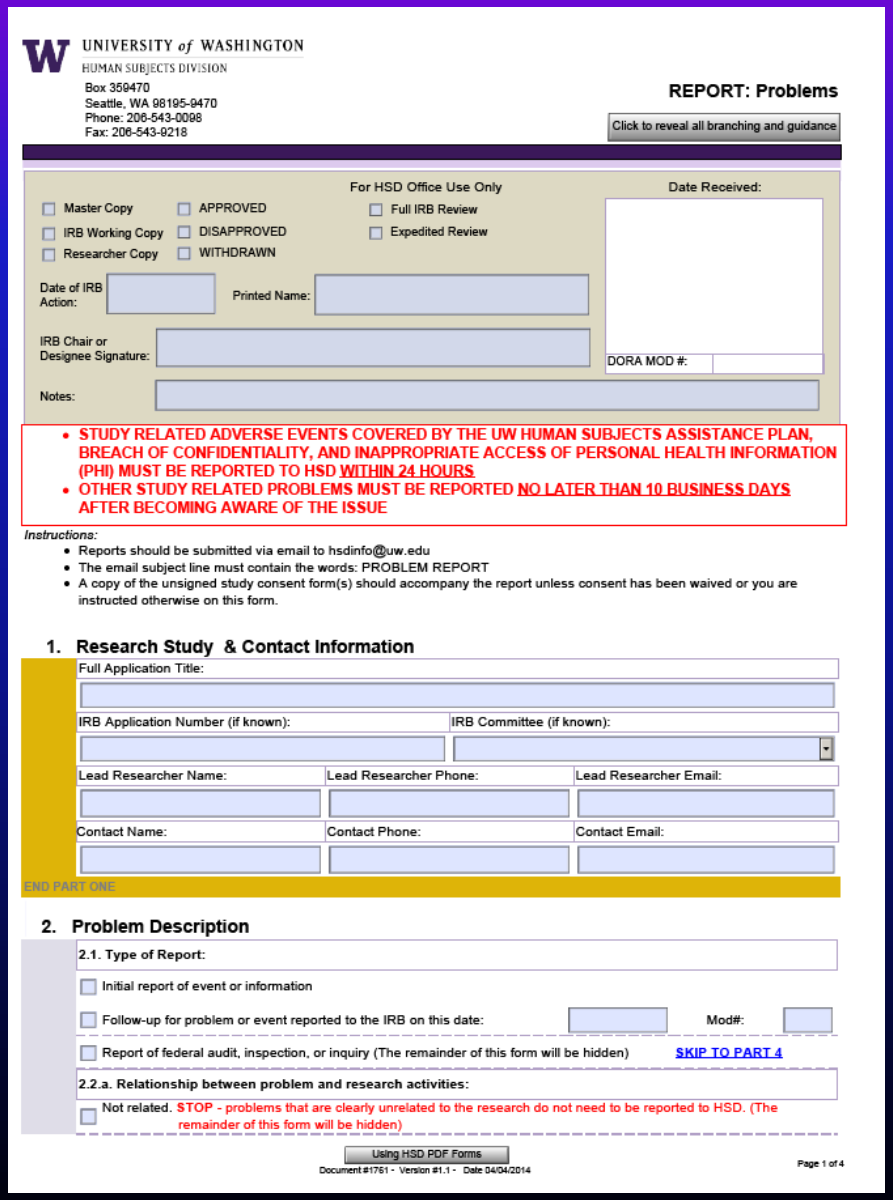
- Must report the event within 10 business days to the following:
  - FDA
  - Local IRB
  - Sponsor
  - Any other participating investigators

Reporting Adverse Events

Use the following form to report study related adverse events covered by the UW Human Subjects Assistance Plan, breach of confidentiality and inappropriate access of personal health information (PHI) to the Human Subjects Division **within 24 hours**.

Use the form to report other study related problems no later than **10 business days** after becoming aware of the issue.

Problem Reporting Form



UNIVERSITY of WASHINGTON
HUMAN SUBJECTS DIVISION
Box 359470
Seattle, WA 98195-9470
Phone: 206-543-0098
Fax: 206-543-9218

REPORT: Problems

Click to reveal all branching and guidance

For HSD Office Use Only

- ☐ Master Copy
- ☐ IRB Working Copy
- ☐ Researcher Copy
- ☐ APPROVED
- ☐ DISAPPROVED
- ☐ WITHDRAWN
- ☐ Full IRB Review
- ☐ Expedited Review

Date Received:

Date of IRB Action:

Printed Name:

IRB Chair or Designee Signature:

DORA MOD #:

Notes:

- STUDY RELATED ADVERSE EVENTS COVERED BY THE UW HUMAN SUBJECTS ASSISTANCE PLAN, BREACH OF CONFIDENTIALITY, AND INAPPROPRIATE ACCESS OF PERSONAL HEALTH INFORMATION (PHI) MUST BE REPORTED TO HSD WITHIN 24 HOURS
- OTHER STUDY RELATED PROBLEMS MUST BE REPORTED NO LATER THAN 10 BUSINESS DAYS AFTER BECOMING AWARE OF THE ISSUE

Instructions:

- Reports should be submitted via email to hsdinfo@uw.edu
- The email subject line must contain the words: PROBLEM REPORT
- A copy of the unsigned study consent form(s) should accompany the report unless consent has been waived or you are instructed otherwise on this form.

1. Research Study & Contact Information

Full Application Title:

IRB Application Number (if known):

IRB Committee (if known):

Lead Researcher Name:

Lead Researcher Phone:

Lead Researcher Email:

Contact Name:

Contact Phone:

Contact Email:

END PART ONE

2. Problem Description

2.1. Type of Report:

- ☐ Initial report of event or information
- ☐ Follow-up for problem or event reported to the IRB on this date:
- ☐ Report of federal audit, inspection, or inquiry (The remainder of this form will be hidden) SKIP TO PART 4

Mod#:

2.2.a. Relationship between problem and research activities:

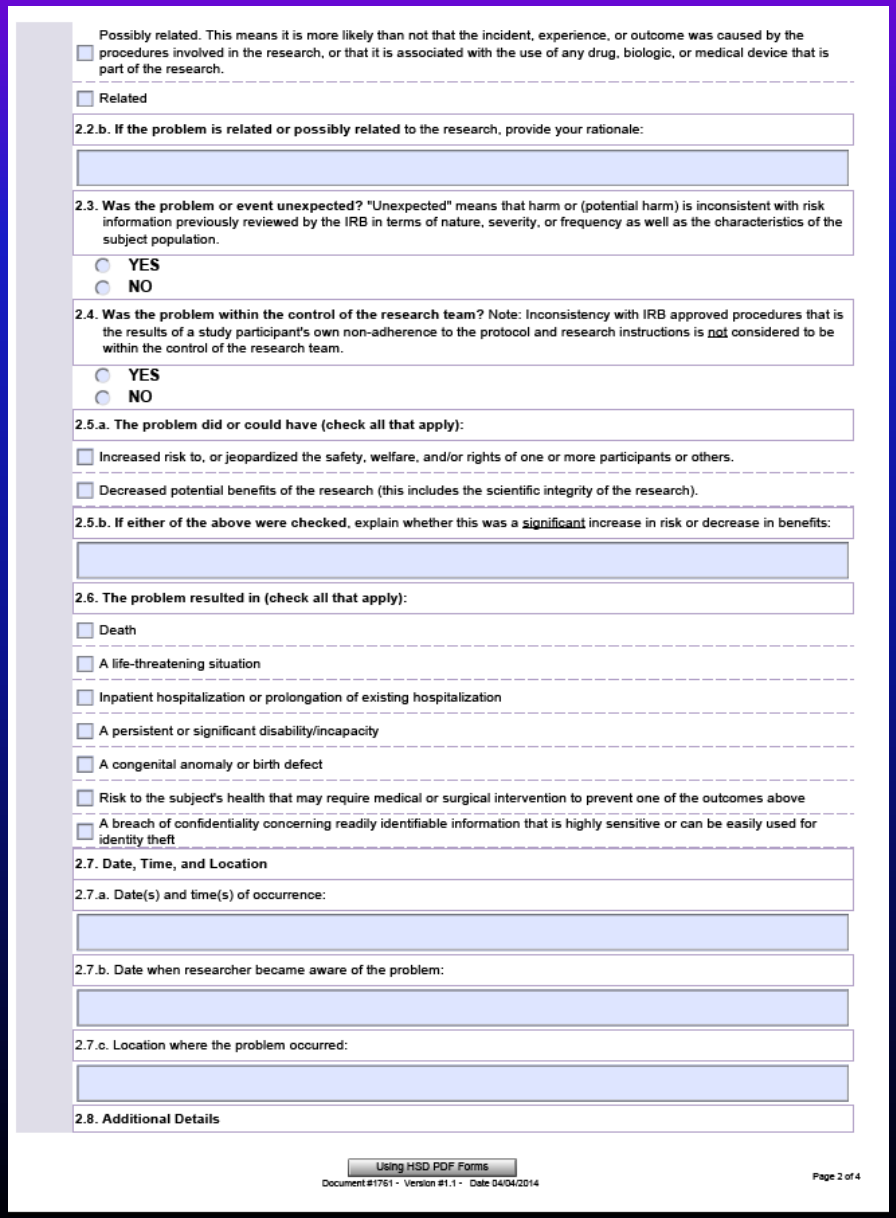
- ☐ Not related. STOP - problems that are clearly unrelated to the research do not need to be reported to HSD. (The remainder of this form will be hidden)

Using HSD PDF Forms

Document #1761 - Version #1.1 - Date 04/04/2014

Page 1 of 4

Problem Reporting Form



☐ Possibly related. This means it is more likely than not that the incident, experience, or outcome was caused by the procedures involved in the research, or that it is associated with the use of any drug, biologic, or medical device that is part of the research.

☐ Related

2.2.b. If the problem is related or possibly related to the research, provide your rationale:

2.3. Was the problem or event unexpected? "Unexpected" means that harm or (potential harm) is inconsistent with risk information previously reviewed by the IRB in terms of nature, severity, or frequency as well as the characteristics of the subject population.

○ **YES**
○ **NO**

2.4. Was the problem within the control of the research team? Note: Inconsistency with IRB approved procedures that is the results of a study participant's own non-adherence to the protocol and research instructions is not considered to be within the control of the research team.

○ **YES**
○ **NO**

2.5.a. The problem did or could have (check all that apply):

☐ Increased risk to, or jeopardized the safety, welfare, and/or rights of one or more participants or others.

☐ Decreased potential benefits of the research (this includes the scientific integrity of the research).

2.5.b. If either of the above were checked, explain whether this was a significant increase in risk or decrease in benefits:

2.6. The problem resulted in (check all that apply):

☐ Death

☐ A life-threatening situation

☐ Inpatient hospitalization or prolongation of existing hospitalization

☐ A persistent or significant disability/incapacity

☐ A congenital anomaly or birth defect

☐ Risk to the subject's health that may require medical or surgical intervention to prevent one of the outcomes above

☐ A breach of confidentiality concerning readily identifiable information that is highly sensitive or can be easily used for identity theft

2.7. Date, Time, and Location

2.7.a. Date(s) and time(s) of occurrence:

2.7.b. Date when researcher became aware of the problem:

2.7.c. Location where the problem occurred:

2.8. Additional Details

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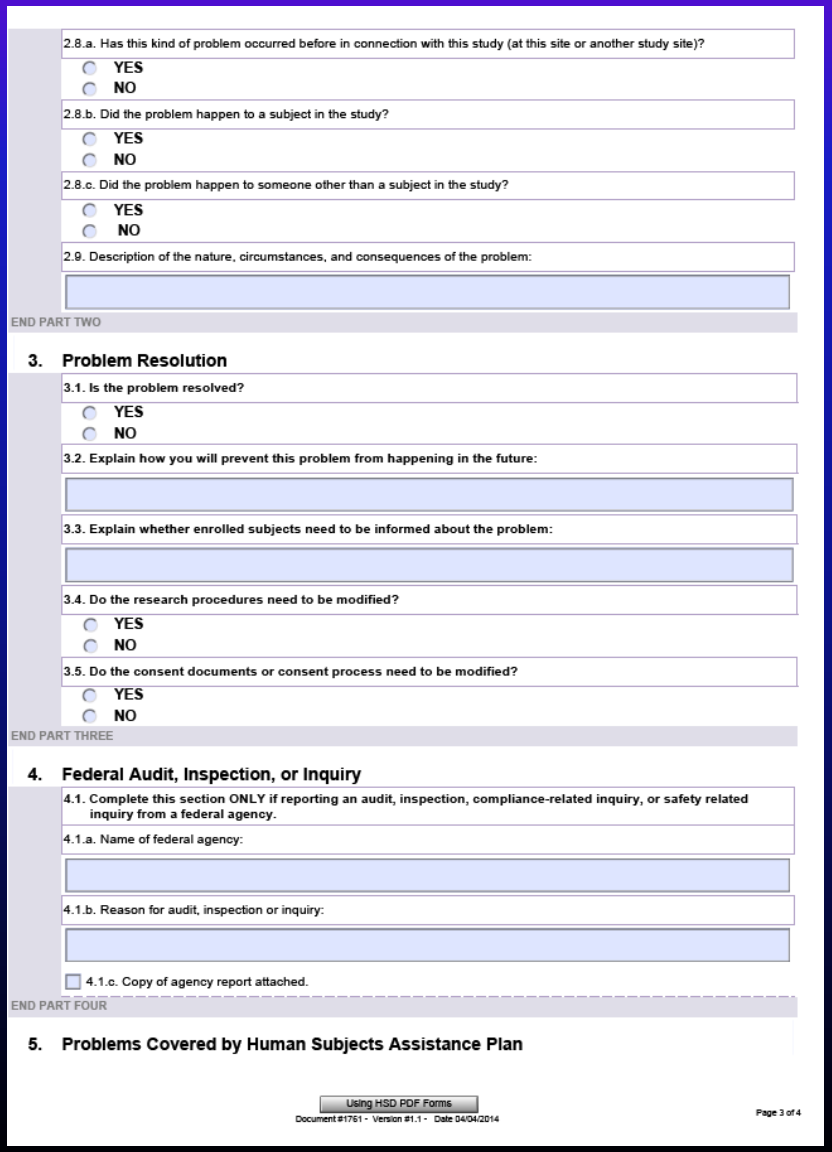
Problem Reporting Form



2.8.a. Has this kind of problem occurred before in connection with this study (at this site or another study site)?

- YES
- NO

2.8.b. Did the problem happen to a subject in the study?

- YES
- NO

2.8.c. Did the problem happen to someone other than a subject in the study?

- YES
- NO

2.9. Description of the nature, circumstances, and consequences of the problem:

END PART TWO

3. Problem Resolution

3.1. Is the problem resolved?

- YES
- NO

3.2. Explain how you will prevent this problem from happening in the future:

3.3. Explain whether enrolled subjects need to be informed about the problem:

3.4. Do the research procedures need to be modified?

- YES
- NO

3.5. Do the consent documents or consent process need to be modified?

- YES
- NO

END PART THREE

4. Federal Audit, Inspection, or Inquiry

4.1. Complete this section ONLY if reporting an audit, inspection, compliance-related inquiry, or safety related inquiry from a federal agency.

4.1.a. Name of federal agency:

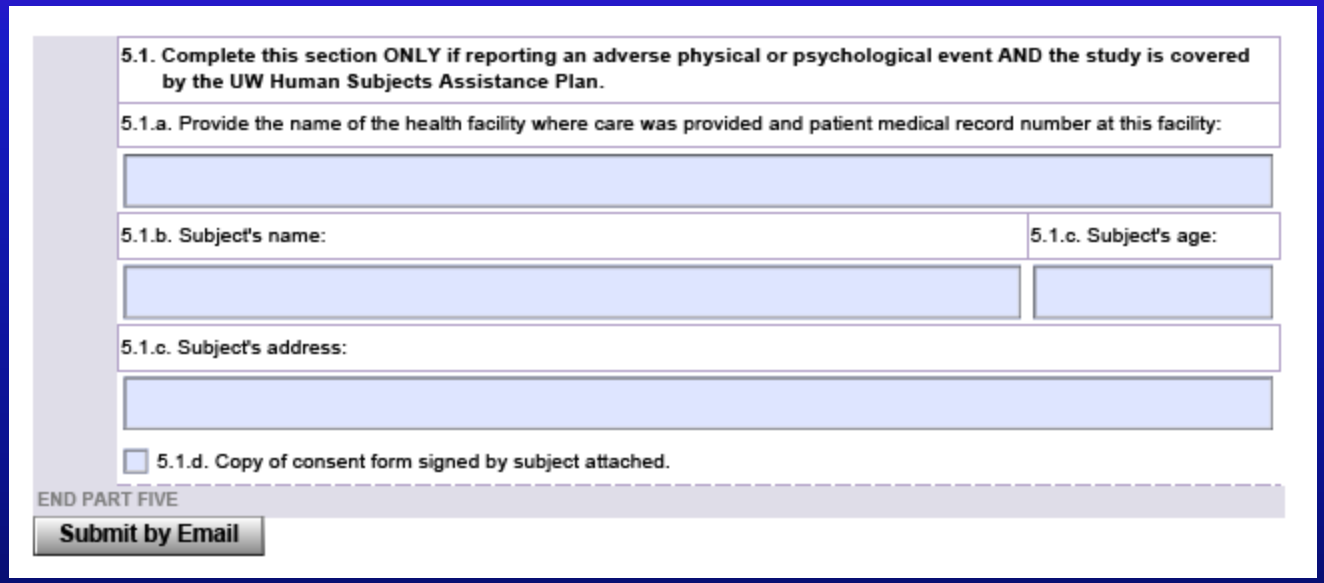
4.1.b. Reason for audit, inspection or inquiry:

☐ 4.1.c. Copy of agency report attached.

END PART FOUR

5. Problems Covered by Human Subjects Assistance Plan

Problem Reporting Form



5.1. Complete this section ONLY if reporting an adverse physical or psychological event AND the study is covered by the UW Human Subjects Assistance Plan.

5.1.a. Provide the name of the health facility where care was provided and patient medical record number at this facility:

5.1.b. Subject's name:

5.1.c. Subject's age:

5.1.c. Subject's address:

5.1.d. Copy of consent form signed by subject attached.

END PART FIVE

Submit by Email

Last Updated 04/04/2014

Version 1.10

IND Safety Reporting

Sponsor must submit an IND safety report if the event is:

- A suspected adverse reaction
- Serious AND
- Unexpected

- Report must be filed with the FDA within 15 calendar days of notification

- If the AE is fatal or life threatening, a report must be filed with the FDA within 7 days of notification

Relatedness of drug/device to product/procedure

- Probably related- the adverse event *is LIKELY* related to the product/device

- Definitely related- the adverse event *is CLEARLY RELATED* to the product/device

Adverse Events forms

- Date of onset
- Description of event – Death is not an event but an outcome
- Relatedness
- Action taken
- Severity (and /or Grade)
- Outcome
- Stop date

Med Watch Reporting Form

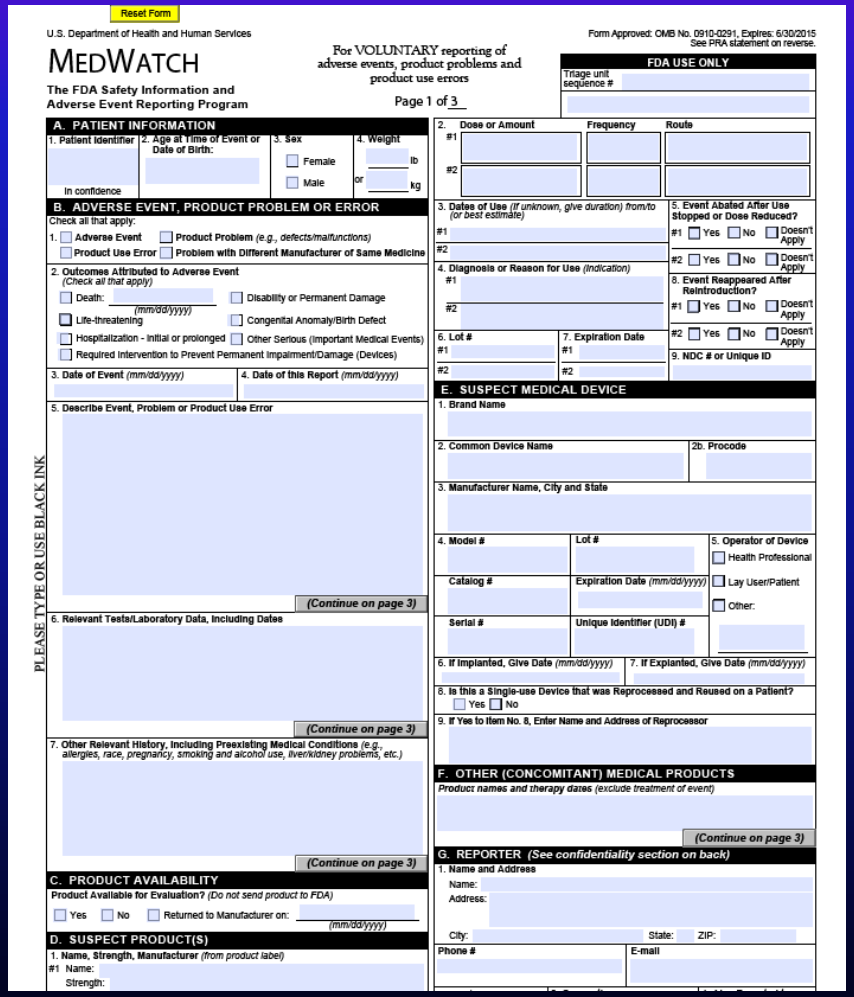
Mandatory Medical Device Reporting:

The Medical Device Reporting (MDR) regulation (21 CFR 803[1]) contains mandatory requirements for manufacturers, importers, and device user facilities to report certain device-related adverse events and product problems to the FDA. The FDA published a final rule[2] on Feb. 14, 2014, requiring manufacturers and importers to submit MDRs to the FDA in an electronic format that the FDA can process, review, and archive. This rule will be effective as of Aug.14, 2015.

Information on the requirements for each mandatory reporting group follows:

Manufacturers: Manufacturers are required to report to the FDA when they learn that any of their devices may have caused or contributed to a death or serious injury. (Key terms are defined in 21 CFR 803.3[3].) Instructions[4] are available for completing the required 3500A form[5]. Manufacturers must also report to the FDA when they become aware that their device has malfunctioned and would be likely to cause or contribute to a death or serious injury if the malfunction were to recur. For more information please see the draft guidance for manufacturers on medical device reporting[6].

Med Watch Form 3500



Reset Form

U.S. Department of Health and Human Services

MEDWATCH

The FDA Safety Information and Adverse Event Reporting Program

For VOLUNTARY reporting of adverse events, product problems and product use errors

Page 1 of 3

Form Approved: OMB No. 0910-0291, Expires: 6/30/2015
See PRA statement on reverse.

FDA USE ONLY

Triage unit sequence #

PLEASE TYPE OR USE BLACK INK

A. PATIENT INFORMATION

1. Patient Identifier (In confidence)
2. Age at Time of Event or Date of Birth:
3. Sex: Female / Male
4. Weight: lb or kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. Adverse Event / Product Problem (e.g., defects/malfunctions) / Product Use Error / Problem with Different Manufacturer of Same Medicine

2. Outcomes Attributed to Adverse Event (Check all that apply)
Death: (mm/dd/yyyy) / Disability or Permanent Damage / Life-threatening / Congenital Anomaly/Birth Defect / Hospitalization - Initial or prolonged / Other Serious (Important Medical Events) / Required Intervention to Prevent Permanent Impairment/Damage (Devices)

3. Date of Event (mm/dd/yyyy)
4. Date of this Report (mm/dd/yyyy)

5. Describe Event, Problem or Product Use Error
(Continue on page 3)

6. Relevant Tests/Laboratory Data, Including Dates
(Continue on page 3)

7. Other Relevant History, Including Preexisting Medical Conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)
(Continue on page 3)

C. PRODUCT AVAILABILITY

Product Available for Evaluation? (Do not send product to FDA)
Yes / No / Returned to Manufacturer on: (mm/dd/yyyy)

D. SUSPECT PRODUCT(S)

1. Name, Strength, Manufacturer (from product label)
#1 Name:
Strength:

2. Dose or Amount / Frequency / Route
#1
#2

3. Dates of Use (If unknown, give duration) from/to (or best estimate)
#1
#2

4. Diagnosis or Reason for Use (Indication)
#1
#2

5. Event Abated After Use Stopped or Dose Reduced?
#1 Yes / No / Doesn't Apply
#2 Yes / No / Doesn't Apply

6. Lot #
#1
#2

7. Expiration Date
#1
#2

8. Event Reappeared After Reintroduction?
#1 Yes / No / Doesn't Apply
#2 Yes / No / Doesn't Apply

9. NDC # or Unique ID

E. SUSPECT MEDICAL DEVICE

1. Brand Name
2. Common Device Name
2b. Procode
3. Manufacturer Name, City and State
4. Model #
Lot #
Catalog #
Expiration Date (mm/dd/yyyy)
Serial #
Unique Identifier (UDI) #
5. Operator of Device: Health Professional / Lay User/Patient / Other:
6. If Implanted, Give Date (mm/dd/yyyy)
7. If Explanted, Give Date (mm/dd/yyyy)
8. Is this a Single-use Device that was Reprocessed and Reused on a Patient? Yes / No
9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

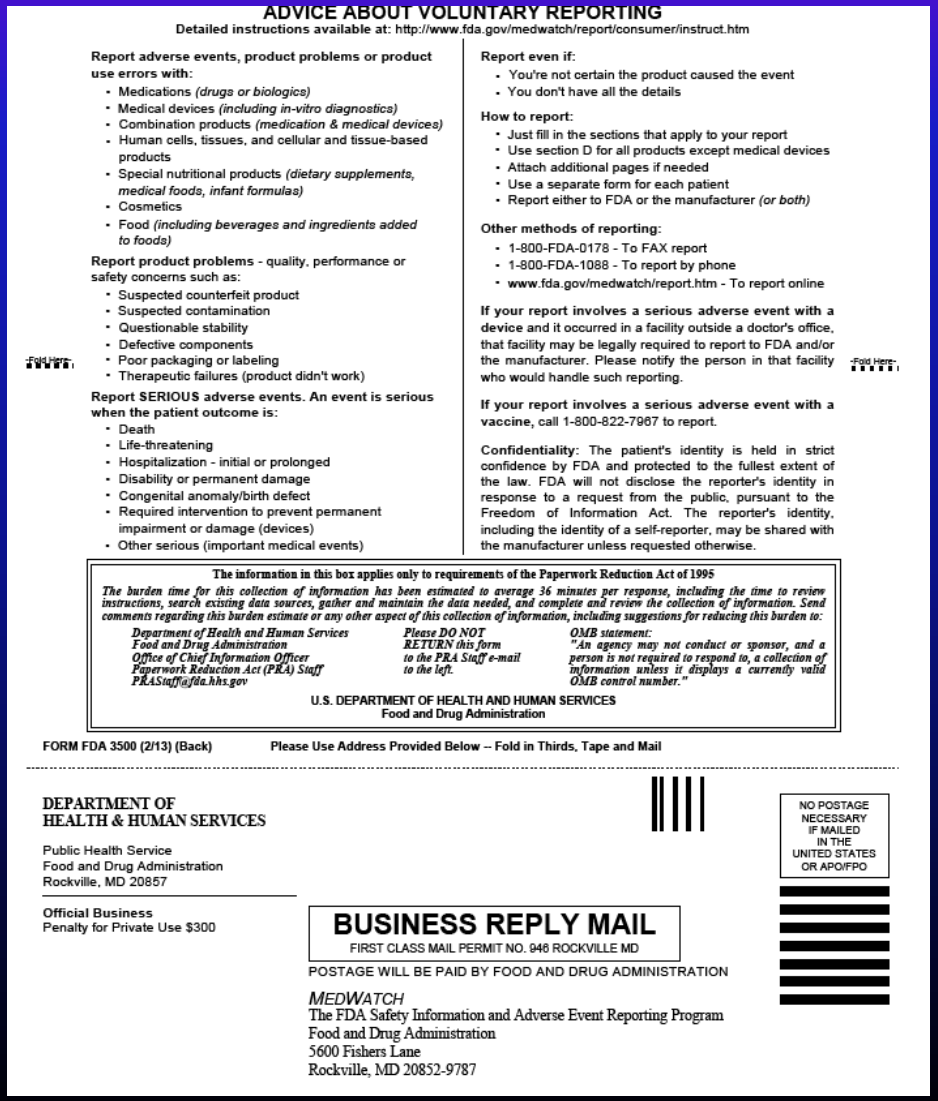
F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates (exclude treatment of event)
(Continue on page 3)

G. REPORTER (See confidentiality section on back)

1. Name and Address
Name:
Address:
City: State: ZIP:
Phone #
E-mail

Med Watch Form 3500



ADVICE ABOUT VOLUNTARY REPORTING

Detailed instructions available at: http://www.fda.gov/medwatch/report/consumer/instruct.htm

Report adverse events, product problems or product use errors with:

- Medications *(drugs or biologics)*
- Medical devices *(including in-vitro diagnostics)*
- Combination products *(medication & medical devices)*
- Human cells, tissues, and cellular and tissue-based products
- Special nutritional products *(dietary supplements, medical foods, infant formulas)*
- Cosmetics
- Food *(including beverages and ingredients added to foods)*

Report product problems - quality, performance or safety concerns such as:

- Suspected counterfeit product
- Suspected contamination
- Questionable stability
- Defective components
- Poor packaging or labeling
- Therapeutic failures (product didn't work)

Report SERIOUS adverse events. An event is serious when the patient outcome is:

- Death
- Life-threatening
- Hospitalization - initial or prolonged
- Disability or permanent damage
- Congenital anomaly/birth defect
- Required intervention to prevent permanent impairment or damage (devices)
- Other serious (important medical events)

Report even if:

- You're not certain the product caused the event
- You don't have all the details

How to report:

- Just fill in the sections that apply to your report
- Use section D for all products except medical devices
- Attach additional pages if needed
- Use a separate form for each patient
- Report either to FDA or the manufacturer *(or both)*

Other methods of reporting:

- 1-800-FDA-0178 - To FAX report
- 1-800-FDA-1088 - To report by phone
- www.fda.gov/medwatch/report.htm - To report online

If your report involves a serious adverse event with a device and it occurred in a facility outside a doctor's office, that facility may be legally required to report to FDA and/or the manufacturer. Please notify the person in that facility who would handle such reporting.

If your report involves a serious adverse event with a vaccine, call 1-800-822-7967 to report.

Confidentiality: The patient's identity is held in strict confidence by FDA and protected to the fullest extent of the law. FDA will not disclose the reporter's identity in response to a request from the public, pursuant to the Freedom of Information Act. The reporter's identity, including the identity of a self-reporter, may be shared with the manufacturer unless requested otherwise.

Fold Here

Fold Here

The information in this box applies only to requirements of the Paperwork Reduction Act of 1995

The burden time for this collection of information has been estimated to average 36 minutes per response, including the time to review instructions, search existing data sources, gather and maintain the data needed, and complete and review the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
Paperwork Reduction Act (PRA) Staff
PRAStaff@fda.hhs.gov

Please DO NOT RETURN this form to the PRA Staff e-mail to the left.

OMB statement:
"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number."

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

FORM FDA 3500 (2/13) (Back) **Please Use Address Provided Below -- Fold in Thirds, Tape and Mail**

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

Official Business
Penalty for Private Use $300

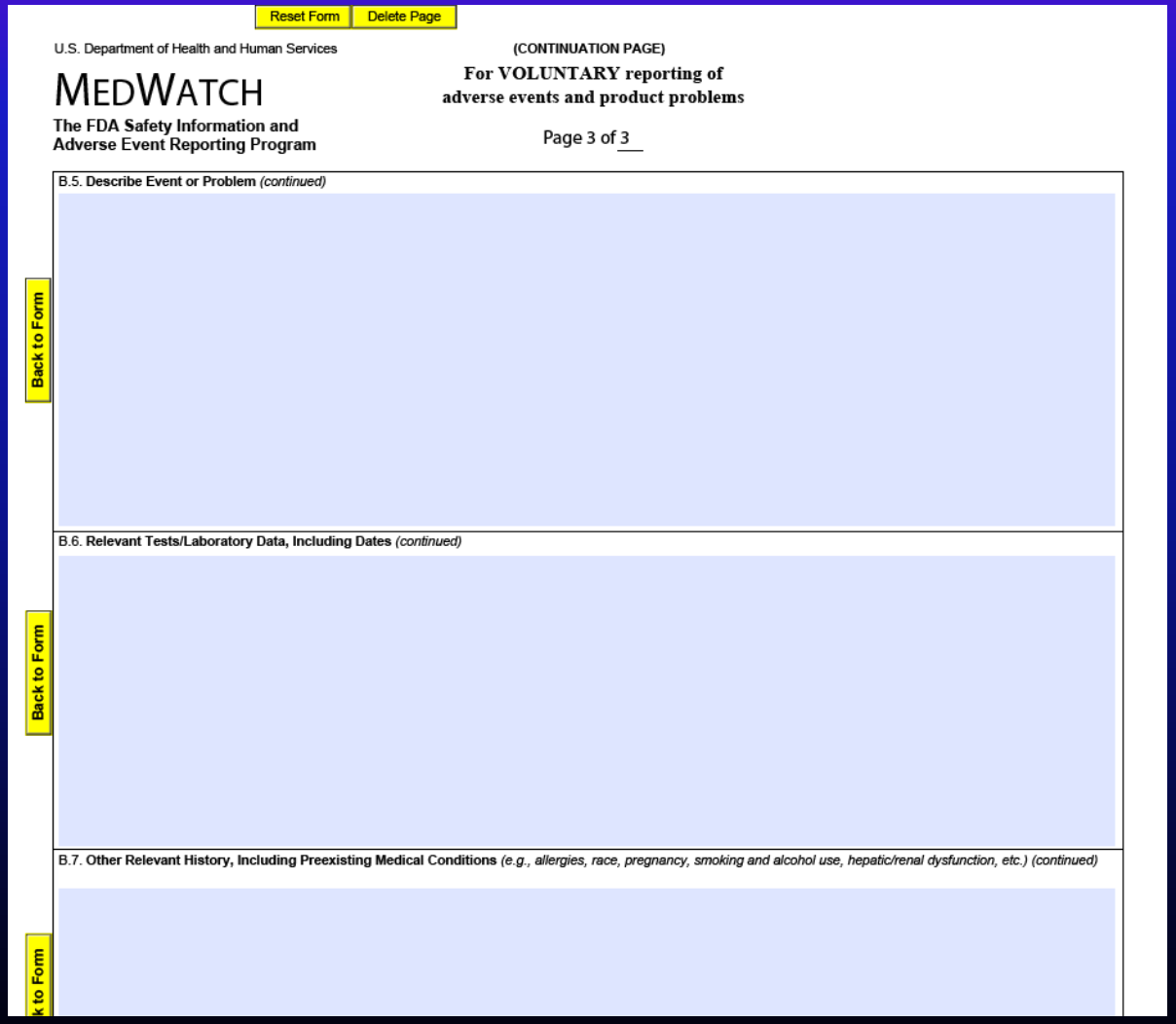
NO POSTAGE NECESSARY IF MAILED IN THE UNITED STATES OR APO/FPO

BUSINESS REPLY MAIL
FIRST CLASS MAIL PERMIT NO. 946 ROCKVILLE MD

POSTAGE WILL BE PAID BY FOOD AND DRUG ADMINISTRATION

MEDWATCH
The FDA Safety Information and Adverse Event Reporting Program
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20852-9787

Med Watch Form 3500



Reset Form Delete Page

U.S. Department of Health and Human Services

MEDWATCH

The FDA Safety Information and Adverse Event Reporting Program

(CONTINUATION PAGE)

For VOLUNTARY reporting of adverse events and product problems

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Back to Form

B.5. **Describe Event or Problem** *(continued)*

Back to Form

B.6. **Relevant Tests/Laboratory Data, Including Dates** *(continued)*

Back to Form

B.7. **Other Relevant History, Including Preexisting Medical Conditions** *(e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.) (continued)*

Conclusion

Any questions?

Thank you!