Adverse Events, Unanticipated Problems, and Protocol Deviations

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Learning Objectives: Adverse Events

- Understand the importance of adverse event reporting to clinical investigation and patient safety
- Define and identify adverse events (AEs)
- Define and identify serious adverse events (SAEs)
- Define unanticipated problems (UAPs)
- Understand Investigator, Clinical Research Coordinator (CRC) and Sponsor responsibilities with regards to identifying, documenting and reporting AEs
Why do we collect Adverse Event data?

• To determine the safety profile of a drug or device
• To evaluate the risks and benefits of a product
• To provide information for the package insert, if approved for marketing

Determination of safety is often one of the primary protocol objectives when evaluating new therapies

Lui and Davis, 2013
Protecting **subject safety** is one of the most important responsibilities of an investigator

- Federal mandate (21CFR 312.64) = the law!
- and commitment (FDA form 1572)
Institutional Review Boards (IRBs) also share the responsibility

• Ensure studies do not expose subjects to undue harm
• Ensure the risk-benefit ratio falls within an acceptable range

45CFR 46.103(b)(5) and 21CFR 56.108 (b)(1)
Adverse Event Definition:

- any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related

21 CFR 312.32 (a)

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 not identified in the device brochure, protocol, or consent form

21 CFR 812.3(s)
Synonyms of Adverse “Event” include:

- Effect
- Experience
- Health consequence
- Occurrence
- Outcome
- Reaction (to a drug)

Goldfarb, 2012, pg. 3,15
Examples of AEs:

• Abnormal lab value
• Worsening of pre-existing condition
• Physical sign or symptom
• Abnormal exam, test or procedure result
• Concurrent illness
• Subjective report
• Change in vital signs or physical exam
Examples of AEs:

- Complication from surgery or procedure
- Psychological symptoms or harm
- Device malfunction/failure
- Device user error
- Incorrect dose or overdose
- Drug dependence

*Important to know the subject’s baseline conditions and concomitant medications (time of enrollment)!
Examples of what AEs are not:

- A procedure or surgery
  - The medical condition that caused the need for the procedure or surgery is the AE
- Pre-existing condition that remains unchanged during the study

**A thorough history and physical at baseline is a must, to discern what is and is not an AE**
Serious Adverse Event definition (SAE):

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- Life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

21 CFR 312.32
Where are you going to identify AEs?

• Medical Records
  • Lab reports, radiology reports, progress notes, surgical reports
• Subject questionnaires
• Subject diaries
• Medication reconciliation
Where are you going to identify AEs?

- Observation
- Specific information for Case Report Forms (CRFs)
- Open ended questions to subject and family
  - “How have you been feeling since I saw you last?”
  - “Can you describe any changes since you started the study medication?”
How are you going to identify AEs?

- Develop a **systematic method** for collecting information
  - Use tools to ensure thoroughness
  - Practice open ended questions
  - Avoid leading questions:
    - “Are you experiencing nausea?”
  - Remain objective
  - Take time to reassure the patient and listen
Documenting AEs:

Adverse Event Form

STUDY NAME

Site Name: ____________________________
Pt_ID: ____________________________

This form is cumulative and captures adverse events of a single participant throughout the study.

<table>
<thead>
<tr>
<th>Severity</th>
<th>Study Intervention Relationship</th>
<th>Action Taken Regarding Study Intervention</th>
<th>Outcome of AE</th>
<th>Expected</th>
<th>Serious Adverse Event (SAE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 = Mild</td>
<td>0 = Not related</td>
<td>0 = None</td>
<td>1 = Resolved</td>
<td>1 = Yes</td>
<td></td>
</tr>
<tr>
<td>2 = Moderate</td>
<td>1 = Unlikely related</td>
<td>1 = Dose modification</td>
<td>2 = Recovered with minor sequelae</td>
<td>2 = Yes</td>
<td></td>
</tr>
<tr>
<td>3 = Severe</td>
<td>2 = Possibly related</td>
<td>2 = Medical Intervention</td>
<td>3 = Recovered with major sequelae</td>
<td>2 = No (if yes, complete SAE form)</td>
<td></td>
</tr>
<tr>
<td>4 = Life-Threatening</td>
<td>3 = Probably related</td>
<td>3 = Hospitalization</td>
<td>4 = Ongoing/Continuing treatment</td>
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<td></td>
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<tr>
<td></td>
<td>4 = Definitely related</td>
<td>4 = Intervention discontinued</td>
<td>5 = Condition worsening</td>
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<td></td>
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<td></td>
<td></td>
<td>5 = Other</td>
<td>6 = Death</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>7 = Unknown</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

At end of study only: Check this box if participant had no adverse events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Start Date</th>
<th>Stop Date</th>
<th>Severity</th>
<th>Relationship</th>
<th>Action Taken</th>
<th>Outcome of AE</th>
<th>Expected?</th>
<th>SAE?</th>
</tr>
</thead>
<tbody>
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</tr>
</tbody>
</table>


Documenting AEs:

- **Event** (nomenclature/description)
- **Grading** (Severity/Intensity)
- **Relationship** (Causality)
- **Expected?**
- **Serious?**
- **Action taken** (Treatment?)
- **Duration**
- **Outcome**
Event:

- **Terminology** used to describe event is very important
  - “Preferred terms” often defined in the protocol or by the sponsor
- Inaccurate or inconsistent coding of events may lead to missed safety signals

Examples:

- Wheezing vs. Bronchospasm vs. Asthma
- Hypertension vs. high blood pressure

A **coding dictionary** may be used: MedDRA (Medical Dictionary for Regulatory Activities)
Event:

Understanding documentation requirements in advance prevents queries, additional work and possible erroneous data.
Grading (Severity):

Common Terminology Criteria for Adverse Events (CTCAE) created by the Health and Human Services, National Institutes of Health, National Cancer Institute

Grading (Severity):

- **Grade 1 Mild**: asymptomatic or mild symptoms; intervention not indicated
- **Grade 2 Moderate**: minimal intervention indicated; may limit ADLs
- **Grade 3 Severe**: medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL
- **Grade 4 Life-threatening**: consequences; urgent intervention indicated
- **Grade 5 Death**: related to AE
Severe ≠ Serious!

*Severity* refers to the **intensity** of an event

*Seriousness* is a guide for defining regulatory reporting obligations
  * based on patient/event **outcome** or action
  * usually associated with events that threaten a patient's life or functioning
Severe ≠ Serious!

Example:
New onset migraine; lasting two days, causing subject to stay in bed and miss work, unable to care for children

• Not life threatening, No hospitalization, No persistent disability, *Not Serious*

• But, intensity is *Severe*
**Relationship (Causality):**

Is there a reasonable possibility that the event was related to, or caused by the investigational intervention?

**Study Intervention Relationship**

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Not related</td>
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</tr>
<tr>
<td>4</td>
<td>Definitely related</td>
</tr>
</tbody>
</table>

**Relationship terms and descriptions are often defined in the protocol, by the sponsor**
Relationship (Causality):

OF COURSE THE DEATH WAS STUDY-RELATED. HE WAS READING THE PATIENT INFORMATION SHEET WHEN THE BUS HIT HIM.
Expected versus Unexpected:

- **Expected AEs** will be described in the following:
  - Investigator’s Brochure (IB); contains information regarding all AEs reported in all trials of the test article, to date
  - Package Insert; safety and dosing information on all approved products
  - Protocol and Informed Consent
  - Safety profile of other drugs in the same class
Expected versus Unexpected:

**Unexpected adverse event:**

- not listed in the 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)
- not consistent with the risk information described in the general investigational plan

21 CFR 312.32 (a)

** There are often specific and/or expedited timelines and reporting requirements for Unexpected AEs
- Know your Institutional and Sponsor requirements
**Expected versus Unexpected:**

**Examples: (provided in the CFR)**

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

- if the investigator brochure listed only cerebral vascular accidents cerebral thromboembolism and cerebral vasculitis would be unexpected (*by virtue of greater specificity*).
Serious?:

- Death
- a life-threatening adverse event
- inpatient hospitalization or prolongation of existing hospitalization
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- a congenital anomaly/birth defect
- Important medical events

** There are often specific and/or expedited timelines and reporting requirements for SAEs

-Know your Institutional and Sponsor requirements
**Action Taken** (treatment):

- Specific information collected is defined in protocol, by sponsor.
- Often, all treatments will need to be documented in the CRF or follow-up reports.

<table>
<thead>
<tr>
<th>Action Taken Regarding Study Intervention</th>
</tr>
</thead>
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<tr>
<td>0 = None</td>
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<tr>
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<td>3 = Hospitalization</td>
</tr>
<tr>
<td>4 = Intervention discontinued</td>
</tr>
<tr>
<td>5 = Other</td>
</tr>
</tbody>
</table>
Duration and Outcome:

- **Duration**: Start and Stop date (and sometimes time)
  - this may be unknown or ongoing

- **Outcome**:
  - Resolved
  - Ongoing
  - Resolved with sequelae
Reporting AEs: All about safety!

[Diagram showing the flow of information between Subject, Sponsor, FDA, CRC, Study Staff, IRB, and Principal Investigator]
Reporting Responsibility:

**Investigators** and **IRBs** must *promptly* report information regarding AEs or unanticipated problems that involve **risks to subjects** or others

21 CFR 312.53 (c)(1)(vii), 21 CFR 56.108 (b)(1)
Reporting Responsibility:

• *All AEs should be reviewed by and signed by a qualified clinician/investigator

• **Know the reporting requirements and timelines for your institution and study!
Appendix: Decision Tree for reporting adverse events

1. **Adverse Event**
   - **Is the adverse event SERIOUS?**
     - **YES**
       - **Is the adverse event **EXPECTED?**
         - **YES**
           - **Is the adverse event related/possibly related to the study treatment or procedure?**
             - **YES**
               - The event must be reported to the IRB within 48 hours (working days) **24 hours if it is a grade 5** from the time of notification or knowledge using the eSAEy system:
                 - http://www.jefferson.edu/human_research/irb/index.cfm
             - **NO**
               - PI judgment: The adverse event must be included in the AE log and reported at continuing review. Please keep in mind ultimately it is the responsibility of the PI to determine relationship to the treatment or procedure and provide a viable justification.
         - **NO**
           - Adverse Event must be included in AE log along with CTC grade (if applicable), attribution, action, length and outcome and submitted at continuing review.
     - **NO**
   - **NO**
Expected versus Unexpected:

• **Expected AEs** will be described in the following:
  • Investigator’s Brochure (IB); contains information regarding all AEs reported in all trials of the test article, to date
  • Package Insert; safety and dosing information on all approved products
  • Protocol and Informed Consent
  • Safety profile of other drugs in the same class
Reporting Guidelines: Quorum Review IRB

Must meet **all three** criteria

1. Serious
2. Unanticipated
3. Related - “a reasonable possibility that the adverse event may have been caused by the study product or study procedures (e.g. possibly, probably and definitely related)"

Must be reported within **10** business days
Internal versus External AEs

In the context of a multi-center trial

• **Internal AE** is an event that is experienced by subjects enrolled at your institution
  • Also known as *On-Site*

• **External AE** in an event experienced by subjects enrolled at other institutions that are participating in the same multi-center trial
  • Also known as *Off-Site*
Related terms:

- **IND Safety Reports** (Investigational New Drug):
  - A report issued by the sponsor of an investigational product when a safety issue arises
  - Submitted to the FDA, investigators and IRBs
  - Required by regulations 21CFR 312.32 (c)(1)

*PI and IRB must review these reports*
THOMAS JEFFERSON UNIVERSITY ADVERSE REACTION REPORT FORM

TO BE COMPLETED BY PRINCIPAL INVESTIGATOR WHEN AN ADVERSE REACTION (AE) OCCURS IN STUDIES CONDUCTED OFF-SITE.

This Form Must Be Typewritten

POLICY: Any serious and/or unexpected (not in consent form) off-site adverse event (AE) that is deemed by the principal investigator to be probably or definitely related to the study drug, and that necessitates a change to the protocol and/or consent form, must be reported within five days of receipt of report. AEs judged to be unrelated to the drug, the result of progressive disease, or other factors such as accidents or unrelated medical procedures, need not be reported. (Consult IRB Policy & Procedures Handbook or website for more information.)

Principal Investigator/Department: ____________________________ IRB Control #________________________

Title of Project: ____________________________________________

Sponsor (if applicable): ______________________________________ Study Drug(s)/Device: __________________________

Provide a brief and concise description of adverse reaction (no narrative, please):

<table>
<thead>
<tr>
<th>Is this:</th>
<th>A new report?</th>
<th>Yes □ No □</th>
<th>A follow-up report?</th>
<th>Yes □ No □</th>
<th>Have you previously reported this adverse reaction to the IRB?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>For this study? Yes □ No □</td>
</tr>
<tr>
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<td></td>
<td>For this patient? Yes □ No □</td>
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<td></td>
<td></td>
<td>Date Reported: ___________</td>
</tr>
</tbody>
</table>

How many times has this reaction occurred in individual patients participating in this study?: _____ (usually in the company narrative)

What is the total national/international enrollment for the study?: ______

In the Principal Investigator’s opinion, was the event drug-related or caused by the procedures associated with this protocol?

(Circle One): UNRELATED PROBABLY RELATED DEFINITELY RELATED

If UNRELATED, DO NOT SUBMIT TO IRB. Keep report for your records.

Is the risk of this adverse reaction described in the consent form?: Yes □ No □

If Yes, DO NOT SUBMIT TO IRB. Keep report for your records.

If No, should this risk be described in the consent form?: Yes □ No □

If Yes, submit revision to consent form. (Provide 33 collated, stapled copies of: OHR-12, revised consent form with changes highlighted, current stamped consent form, and adverse event report(s).)

If No, provide justification for not including this reaction as a risk in the consent form:

Has this AE changed the risk to benefit ratio of the study in any way?: Yes □ No □

Explain:
Related terms:

- **DSMB or DSMC**: Data Safety Monitoring Board/Committee
  - An *independent committee* of clinicians, statisticians, ethicists, and other specialists who assess the progress of a trial, its safety and/or its efficacy at specified intervals
  - The committee can make recommendations that a study be continued, modified, or stopped based on the data reviewed

  (Lui)
Unanticipated Problems (UAPs) involving risks to subjects or others:

Must meet all of the following criteria:

1. **unexpected** (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol and informed consent document; and (b) the characteristics of the subject population being studied;

2. **related or possibly related** to participation in the research

3. suggests that the research places subjects or others at **greater risk of harm** (including physical, psychological, economic, or social harm) than was previously known or recognized

http://www.hhs.gov/ohrp/policy/advevntguid.html
Unanticipated Problems:

- A = Adverse Events that are not Unanticipated Problems
- B = Adverse Events that are Unanticipated Problems
- Unanticipated Problems that are not Adverse Events

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

An adverse event occurs in one or more subjects.

1. Is the adverse event unexpected in nature, severity, or frequency?
   - NO
   - YES

2. Is the adverse event related or possibly related to participation in the research?
   - NO
   - YES

3. Does the adverse event suggest that the research places subjects or others at a greater risk of physical or psychological harm than was previously known or recognized? NOTE: If the adverse event is serious, the answer is always YES.
   - NO
   - YES

Report the adverse event as an unanticipated problem under 45 CFR part 46

The adverse event is not an unanticipated problem and need not be reported under 45 CFR part 46

http://www.hhs.gov/ohrp/policy/advevntguid.html#AA
Examples of UAPs involving risks to subjects or others: include but are not limited to:

- An interim analysis (DSMB) suggesting additional risk
- A report (journal article or abstract, etc.) that reveals a change in risks/benefits
- A breach of confidentiality
- Change in FDA labeling or withdrawal from marketing of a drug, device, or biological used in a research protocol
- Incarceration of a subject in a protocol not approved to enroll prisoners
- Sponsor imposed suspension for risk
- Protocol violation that may harm subjects or increase risk of harm
Unanticipated Problems:

- AEs that are **serious and UAPs** are considered the most important subset of adverse events
  - suggests that the research places subjects or others at a greater risk of harm
  - warrants consideration of significant changes in the research protocol or informed consent or other corrective actions in order to protect the safety, welfare, or rights of subjects

**IRBs have authority to suspend or terminate approval of research that has been associated with unexpected serious harm to subjects (45 CFR 46.113)**
Helpful Hints for Reporting UAPs to OHR at TJU

- Reported via eazUP Electronic Reporting System
  - Unanticipated Problems (OHR-20) paper form still exists on OHR website; Forms

- If the event poses increased risk, should be reported within 10 working days of learning of the event
Really? Is she ever going to stop talking?
Learning Objectives: Protocol Violations/Deviations

- Understand current definitions of protocol deviation versus protocol violation
- Describe documentation and reporting of protocol deviations
Protocol Violations/Deviations: **Definition**

An unplanned or unintentional departure from an IRB approved protocol, without prior sponsor or IRB approval.

*There is currently no consensus (or definition in CFR or ICH) on how to differentiate between deviation versus violation!*

NIH IRB Professional Administrators Committee Regulatory Process Workgroup
Protocol Violations/Deviations:

- **Protocol Violation** is a deviation from the IRB approved protocol that may:
  - Reduce the completeness, accuracy and reliability of study data
  - Contradict or invalidate the Informed Consent
  - Impact the subject’s safety, rights or well-being

NIH IRB Professional Administrators Committee
Regulatory Process Workgroup
Protocol Violations/Deviations:

- **Protocol Deviation:**
  - Has no significant consequence to the subject or protocol integrity and is considered **minor**
  - A frequently accepted delineation is that a deviation does not expose the subject to increased risk, whereas a violation does.
  - Often deviation/violation is considered a joint term, with the only difference being reporting guidelines after the event has been assessed.
Protocol Violations/Deviations:

• May result from the actions of:
  • Subject
  • Investigator
  • Study Staff
Protocol Violations/Deviations:

- May be unavoidable or unintentional
- May be purposeful
  - If so, explore the possibility of a waiver, in advance

Prospective Protocol Waiver: “Any prospective request for an intentional deviation from the IRB approved protocol except when necessary to eliminate an apparent immediate hazard to a participant”

Quorum Review IRB
Examples of Protocol Deviations:

• Subject follow-up visit occurs out of window (provided this does not affect subject well-being or integrity of study data)
• Schedule of events is not followed
  • Questionnaire administered out of order
• Number of subject enrolled exceeds the IRB approved number
Examples of Protocol Violations:

**Significant risk of harm to the research subject**
- Subject received the wrong treatment or incorrect dose
- Subject met withdrawal criteria during the study but was not withdrawn
- Subject received an excluded concomitant medication
Examples of Protocol Violations:

**Compromise to the scientific integrity of the data collected**

- Subject was enrolled but does not meet the protocol's eligibility criteria
- Changing the protocol without prior IRB approval
- Inadvertent loss of samples or data
Examples of Protocol Violations:

Breach of human subject protection regulations, policies, or procedures on the part of the investigator(s)

- Failure to obtain informed consent prior to initiation of study-related procedures
- Inadequate or improper informed consent procedure
- Falsifying research or medical records
Examples of Protocol Violations:

Noncompliance with federal, state, local or institutional human subject protection regulations, policies, or procedures

• Working under an expired professional license or certification
• Performing tests or procedures beyond the individual's professional scope or privilege status (credentialing)
• Repeated minor deviations
• A breach of confidentiality
Reporting Violations/Deviations:

The investigator shall also assure that he or she will *promptly* report to the IRB all changes in the research activity and all unanticipated problems involving risk to human subjects or others, and that he or she will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

21CFR312.66

**reporting requirements are defined by individual IRBs and sponsors.**
Reporting Violations/Deviations:

**In general:**

**Deviations:** Keep a log
- The Investigator should review and sign in real time
- Submit to the IRB with the annual review
- The sponsor will review during routine monitoring visit

**Violations:**
- Need to be reported to the IRB and sponsor as they occur
- Aka: **Unanticipated Problem** posing risk to subject or others (UAP)
Reporting Violations/Deviations at TJU:

Protocol deviations/violations not posing risks to subjects or others are not considered unanticipated problems involving risk and should not be reported to the IRB at the time they occur. It is recommended that you keep a log of protocol deviations/violations in the study file for inclusion in the continuing review submission or final report.

Policy GA 120: Reporting and Reviewing Unanticipated Problems Involving Risks to Subjects or Others
Reporting Violations/Deviations to Quorum:

The following events/information must be reported to Quorum within 10 business days.

<table>
<thead>
<tr>
<th>Reportable Events That Occur at the PI's Research Site or are Associated with the PI</th>
<th>Examples (not all-inclusive)</th>
<th>Reporting Criteria (What to report)</th>
<th>How to Report</th>
</tr>
</thead>
</table>
| **Serious Adverse Event (SAE)** | - Pneumonia resulting from study drug administration  
- Significant allergic reaction resulting from study drug(s)  
- Cardiovascular event induced by study drug(s) or device | An adverse event that is:  
- Serious  
- Unanticipated, and  
- Related | SAE Report |
| **Major Protocol Deviation/Violation** | - Failure to obtain informed consent  
- Omitting study procedure(s) required by approved protocol  
- Drug dispensing/dosing error  
- Failure to securely control the study product  
- Deviation necessary to eliminate an apparent immediate hazard to a participant | Any change from Board-approved protocol that adversely affects the:  
- Risk/benefit ratio of the study, or  
- Rights, safety, or welfare of the participants or others, or  
- Integrity of the study | Major Protocol Deviation/Violation Report |
| **Prospective Protocol Waiver/Exception** | - Intentional deviation from the inclusion/exclusion criteria set forth in the protocol | Any prospective request for an intentional deviation from the IRB approved protocol except when necessary to eliminate an apparent immediate hazard to a participant. | Copy of Sponsor approval  
Prospective Waiver/Exception Request Form |
References:

The Code of Federal Regulations, Title 21—Food and Drugs and Title 45, Part 46 Protection of Human Subjects.


KEEP CALM
The presentation is over
AND
Any
Questions???