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Post-Approval Event Reporting

July 14, 2015

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What is Human Research Protection Program?

- **CHR- reviews and approves protocols**
- **QIU- monitoring, education, post-approval events**

- **Overall Mission:**

  Ensure the ethical and equitable treatment of research participants

  Work with PI improve research and overall compliance

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What is the Quality Improvement Unit?

- Routine on-site reviews and directed (for-cause) investigations of clinical research studies
- Indirect monitoring of clinical research activities through processing of adverse events, violations and incident reports submitted to the CHR
- Management of non-routine participant complaints and concerns

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Outline for Today

- Types of Post-Approval Events
- What and How to submit to CHR
- CHR/QIU role in review of Events
- Tips for Reporting
- Using iRIS to submit reports
- Q & A at the end of each section

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So…

What is a Post Approval Event?

And which do we have to report to CHR?

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Types of Post-Approval Event Reports

- **Serious and/or Unexpected Adverse Events**
- **Protocol Violations/Incidents**
- Safety Information:
  - Investigator Brochure/Package Insert updates
  - DSMB/DMC Report
  - Audit Reports
  - Study Holds
- Study Close-Out Reports

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Post Approval Event Reporting: Why?

- Federal regulations and HRPP policies require reporting of possible
  - Unanticipated Problems (Adverse Events)
  - Serious and/or Continuous Noncompliance (Violations/Incidents)
- The CHR determines whether these definitions apply when evaluating post-approval reports.

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Don’t think of Post Approval Event Reporting as this:

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Think of it like this:

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Adverse Events (AEs) & Serious Adverse Events (SAEs)

Definitions and Determining What To Report and What NOT To Report

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Definition of "Adverse Event"

An Adverse Event (AE) is:

any untoward medical occurrence in a participant administered a pharmaceutical product **and that does not necessarily have a causal relationship** with this treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal product.

~ICH E6 (1.2)

However…

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Not all AEs – or even SAEs – need to be reported to the CHR!

- The CHR has specific criteria describing and defining specifically which AEs should be reported.
- These criteria are available on the HRPP's website at

  http://www.research.ucsf.edu/chr/Guide/Adverse_Events_Guidelines.asp

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Adverse Events – Internal vs External

- "Internal" AEs
  - enrolled by a UCSF investigator or
  - at a UCSF-affiliated site
  - CHR serves as the IRB
- "External" AEs
  - enrolled in the same study but
  - at a site not under the control of a UCSF investigator or CHR

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Adverse Events – Internal

If …

The PI determines the event to be:

- Related to research*
- Definitely, Probably or Possibly

and

- Serious or Unexpected

Then…

Report the event to the CHR within **5 working days** of learning of it

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**any* study procedure, not just the main intervention

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Relatedness:

- ***Definitely:*** clear that the event was caused by study participation
- ***Probably Related:*** reasonable possibility that the event is **likely** to have been caused by study participation.
- ***Possibly Related:*** reasonable possibility that the event **might** have been caused by study participation. Possible relationship cannot reasonably be ruled out.
- ***Unrelated:*** The cause of the AE is **known** and the event is in no way related to any aspect of study participation

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Serious AEs:

- **Death**
- **Life-threatening** event
- Inpatient **hospitalization (>24 hrs)** or prolonged existing hospitalization
- Persistent or significant **disability/incapacity**
- Congenital anomaly/**birth defect**, or **cancer**
- Significant medical, surgical, or other **intervention/precaution required to prevent one of the outcomes listed above**
- **Event occurred in a gene therapy study**

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Unexpected AEs:

- **Not listed in the materials reviewed by the CHR**
- **More serious** than expected
- **More frequent** than expected
- **Due to overdose** of study medication
- **Due to a protocol violation**
- AE **results in participant's unexpected withdrawal** from study

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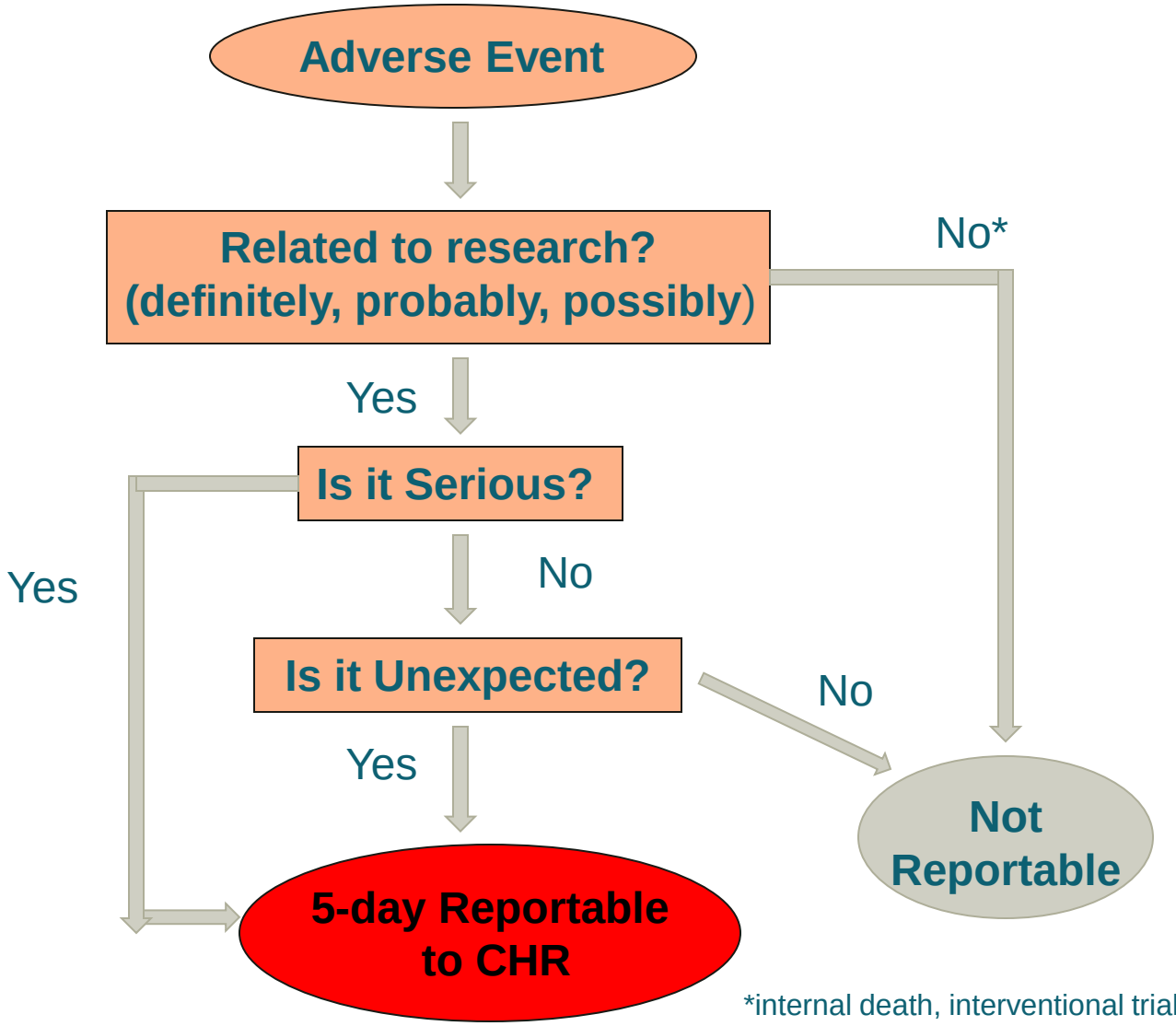
Internal Adverse Events:



*internal death, interventional trial

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Expected AEs:

- Reasonably anticipated as result of study procedure or study participation
- Described in Application, Consent Form
- Part of normal disease progression

NOT REPORTABLE

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Adverse Events – External

If…

- The UCSF PI determines that the event:
  - Changes the study risks or benefits

  And/Or

  - Requires a modification to the CHR Application or the Consent form

Then…

- Report event to CHR within 10 working days of learning of it

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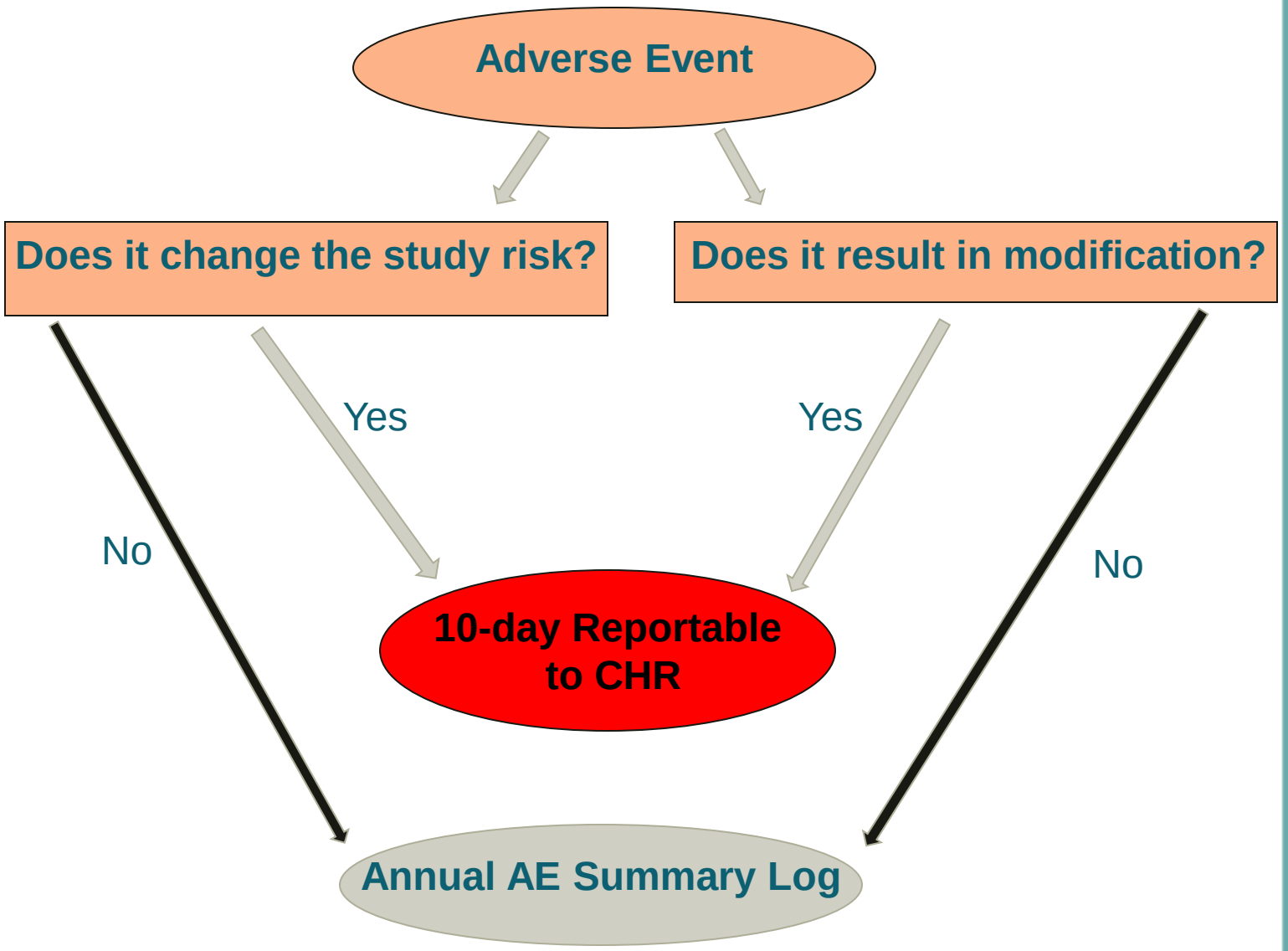
External Adverse Events:



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AE's that do not meet CHR 5-day reporting criteria

- Do **not** submit using AE Reporting Form
- For Internal Interventional Studies *only*, any ***unrelated death*** should be reported using the Adverse Event Summary Log
- If Sponsor requires reporting an event that does not meet CHR criteria, use the Adverse Event Summary Log
- Attach Log Adverse Event Summary Log as an "Other Study Document"

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Determining What to Report

Note:

- Study sponsors and the FDA have expanded reporting requirements.
- The VAMC has a shorter timeline (5 days) than UCSF for reporting certain categories of post-approval events
- http://www.research.ucsf.edu/chr/VA/chrVA.asp
- Sponsors may require reporting even if CHR does not- do what Sponsor says

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Reporting Adverse Events

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Protocol Violations & Incidents

Definitions and Determining What To Report and What NOT To Report

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Major
Protocol Violations & Incidents

Report to the CHR
within 10 working days of learning of it

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Major Protocol Violations Definition:

Unapproved changes in procedures

Within investigator's control that may effect:

1) Participant's rights, safety or well-being

or

2) Completeness, accuracy, and reliability of the study data

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Major Protocol Violations Examples:

- Incorrect research treatment or intervention given
  - Wrong drug or wrong dosage
- Enrollment of participant ineligible per CHR-approved protocol
  - Even if Sponsor approves
- Procedure/lab required not done
  - Primary safety lab regarding study drug
- Procedure/lab done outside study window
  - Window based on safety or consistency

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Major Incidents - Definition:

- **Problematic or unanticipated events involving the conduct of the study or an individual's participation**
- **Possibly involves significant potential to harm the participant(s) or others.**

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Major Incidents – Examples:

- Problem with the informed consent or recruitment process
  - Wrong version of CF, missing HIPAA
- Significant concern or complaint received
  - Maltreatment, inappropriate behavior
- Lapse in study approval (and study activities were conducted)
- Loss of adequate resources to conduct study
  - Impacts safety and compliance
- Unauthorized disclosure of private information
  - stolen or lost research data, privacy incident

Minor Protocol Violations and Incidents: Do **not** need to be reported to CHR

- Also known as Protocol Deviations
- Unapproved changes, deviations, or departures from study design that:
  - Have not been reviewed and approved by the CHR **but**
  - Do not affect participants' rights, safety, or well-being or the completeness of study data
- Document in study regulatory binder and develop a Corrective Action Plan (CAP)

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Protocol Violations and Incidents

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Other Safety Information

Definitions and Determining What To Report and What NOT To Report

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Other Safety Information

- Updated Investigator Brochure*
- DSMB/DMC Reports*
- Audit Reports with findings
- Hold on Study Activities
- Other Safety Information or Updates that suggests a **change to the risk** or benefit of the research

Report to the CHR within 10 working days of learning of new information

*even if no change is described

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Study Close-Out Report

- Updates the CHR on conduct of the study since the last renewal
- Required for **all** studies
- Report within 10 working days of receiving Sponsor's Close-Out letter or PI's decision to close study

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Study Close-Out Report

Do **not** close out a study with CHR if:

- Local enrollment to the study is ongoing
- Local research-related interventions are ongoing
- Local participant follow-up is ongoing
- Data analysis or manuscript preparation requiring use of or access to individually identifiable information is ongoing
- External sponsor has not given permission to close the study with the CHR.

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Submitting Other Safety Information

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CHR Review Process of PAERs?

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What is CHR trying to determine?

- Risk-benefit ratio continues to be acceptable
- Research protocol and informed consent document accurately and completely present risk information to research subjects
- Subjects already enrolled should be advised of newly identified risks
- Unanticipated Problem or Serious and/or Continuing Noncompliance

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CHR Review Process

- QIU Review & acknowledgment
  - No letter sent
- Chair Review & acknowledgement
  - No letter sent
- Convened Committee Review
  - If necessary
  - Outcome Letter generated

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Possible Outcomes

- **SAEs**
  - Unanticipated Problem
- **Protocol Violations/Incidents**
  - Serious Noncompliance
  - Continuing Noncompliance
  - Noncompliance
  - Serious and Continuing Noncompliance

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Adverse Events: Are they Unanticipated Problems?

- Involves risk to participants or others, and
- Is unexpected or exceeds the nature, severity, or frequency described study documents, and
- Related to research

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Protocol Violations/Incidents: Are they Serious Noncompliance?

1) Failure to follow:

- State or federal regulations
- University policies
- Determinations of the CHR

for protection of the rights and welfare of study participants,

AND…

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Protocol Violations/Incidents: Are they Serious Noncompliance?

2) Results in, or indicates a **potential** for:

- a significant risk to enrolled or potential participants or others

or

- compromises the effectiveness of the UCSF HRPP or the University

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Continuing Noncompliance

A pattern of noncompliance that continues to occur after a report of noncompliance and a corrective action plan have been reviewed and approved by the CHR.

- The pattern suggests the likelihood that instances of noncompliance will continue without intervention.

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After the Meeting

- **PI and Study Contacts receive an Outcome Letter**
  - Provides details regarding the Committee's decisions and any required follow-up by the PI
  - Provides directions to PI to acknowledge/appeal the Committee's determination
- **PI and Study Contacts receive a Submission Response Request Form**
  - Provides instructions to PI to acknowledge/appeal the Committee's determination
  - Other stipulations as per the Outcome Letter
  - Provides timeframe to respond
- **PI responds to Committee's Letter**
  - Chair acknowledges PI's response or returns to Committee for further review

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Regulatory Reporting Requirements

- Federal Agencies
  - Office for Human Research Protection (OHRP)
  - FDA
- Associate Vice-Chancellor for Ethics and Compliance
- UCSF Legal Affairs
- UCSF Privacy Office
- SF Veterans Affairs (if VA study)
- Other offices or groups as required by the nature of the study

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CHR Review Process of Post-Approval Event Reports

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Submitting
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Submitting Post- Approval Events

- Submissions Dashboard
- Creating Post-Approval Event Reports
- Review by affiliated offices
  - Privacy Office
  - Research Risk Mgmt
  - SFVAMC

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Top Tips for Submitting Post-Approval Event Reports

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Tips for Post-Approval Event Reporting (1)

- Determine it meets CHR reporting requirements
  - Refer to QuickGuide chart
- Ask your PI or mentor for guidance
- Submit using appropriate iRIS form
  - AE, Protocol Violation/Incident, Reporting Form
- Answer **all** questions on the form ***completely***

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Tips for Post-Approval Event Reporting (2)

- Include supporting documents, if relevant
  - Reports from Sponsors, DSMB, consultants
- Call QIU Analyst of Day and document your QIU consultation
- If a Privacy Breach, contact the Privacy Office and provide documentation of your consultation
  - Include in Report

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Tips for Post-Approval Event Reporting (3)

- Explain the **context**-what should have happened v. what actually happened
- Provide **details** - dates, lab values, what caused the event, how it was discovered
- Explain the **actual** or **potential** consequence
- Provide a ***comprehensive*** CAP
- **Do not** include PHI in reports

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Common Mistakes

- Including PHI on form
- Not describing root cause
- Not checking “Unauthorized disclosure” question
- Not addressing “possible” consequences
- Subject injury question
- Not answering “why report is late” question

- **Not consulting with PI for assistance**

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Using iRIS and Top Tips

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"Slide of Shame"

- All participants signed *the same* consent form
- Consent form for a different study used
- Study and consent form were not approved
- Signature page torn off, kept by study team
- Professor made participation mandatory for grade
- Participant/post-doc consented himself

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Where to go for help:

- **Reporting Post-Approval Events to CHR:**
  - http://www.research.ucsf.edu/chr/Guide/hsppGP.asp#Reporting
- **QIU Section of HRPP Website:**
  - http://www.research.ucsf.edu/chr/Qip/hsppQip.asp
- **Call QIU Analyst of the Day (415) 476-1814**
- **SF VAMC:**
  - http://www.research.ucsf.edu/chr/VA/chrVA.aspClinical Research Office (415) 221-4810 x6425

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Where to go for help:

- **Clinical Research Coordinators Website:**
  - http://www.research.ucsf.edu/chr/Train/CRC_Group.asp
- **Subjects Injury Program:**
  - Bruce Flynn, Director, Risk Management
  - 476- 2498
- **Privacy Office Contact Information**
  - 353-2750

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The Hub

http://hub.ucsf.edu/

- One stop shopping for many of your research questions
- Created by the Office of the AVC for Ethics and Compliance
- ***Excellent*** resource for Investigators, Coordinators/Research Staff, and Participants

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Next Available HRPP Classes

iRIS Training Classes

-Introduction to iRIS

- Thursday, August 20, 1:30-3:30 PM
- Tuesday, September 15, 10:00 AM-12:00 PM

-Advanced iRIS-Managing Approved Studies

- Wednesday, September 30, 1:30-3:00 PM
- Thursday, November 19, 1:30-3:00 PM

Recruitment: Ethics, Regulations and Practical Solutions

- Thursday, August 27, 10:30 AM – 12:00 PM

Full Training Calendar at:

www.research.ucsf.edu/chr

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