Human Research Protection Program

Post-Approval Event Reporting

July 14, 2015
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
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
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
So…

What is a Post Approval Event?

And which do we have to report to CHR?
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
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.
Don’t think of Post Approval Event Reporting as this:
Think of it like this:
Adverse Events (AEs) & Serious Adverse Events (SAEs)

Definitions and Determining What To Report and What NOT To Report
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...
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
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
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

*any study procedure, not just the main intervention
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
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
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
Internal Adverse Events:

- Adverse Event
  - Related to research? (definitely, probably, possibly)
    - No*
      - Is it Serious?
        - No
          - Is it Unexpected?
            - Yes
              - 5-day Reportable to CHR
            - No
          - Yes
        - Yes
      - Yes
    - Yes
  - Yes

*internal death, interventional trial
Expected AEs:

• Reasonably anticipated as result of study procedure or study participation

• Described in Application, Consent Form

• Part of normal disease progression

NOT REPORTABLE
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
External Adverse Events:

Adverse Event

Does it change the study risk? Does it result in modification?

Yes Yes

No No

10-day Reportable to CHR

Annual AE Summary Log
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”
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](http://www.research.ucsf.edu/chr/VA/chrVA.asp)
- Sponsors may require reporting even if CHR does not do what Sponsor says.
Reporting Adverse Events
Protocol Violations & Incidents

Definitions and Determining What To Report and What NOT To Report
Major Protocol Violations & Incidents

Report to the CHR within 10 working days of learning of it
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
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
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.
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)
Protocol Violations and Incidents
Other Safety Information

Definitions and Determining What To Report and What NOT To Report
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
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
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.
Submitting Other Safety Information
CHR Review Process of PAERs?
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
CHR Review Process

• QIU Review & acknowledgment
  – No letter sent

• Chair Review & acknowledgement
  – No letter sent

• Convened Committee Review
  – If necessary
  – Outcome Letter generated
Possible Outcomes

• SAEs
  – Unanticipated Problem

• Protocol Violations/Incidents
  – Serious Noncompliance
  – Continuing Noncompliance
  – Noncompliance
  – Serious and Continuing Noncompliance
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
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…
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
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.
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
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
CHR Review Process of Post-Approval Event Reports
Submitting
Post Approval Events
Submitting Post-Approval Events

- Submissions Dashboard
- Creating Post-Approval Event Reports
- Review by affiliated offices
  - Privacy Office
  - Research Risk Mgmt
  - SFVAMC
Top Tips for Submitting Post-Approval Event Reports
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
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
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
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
Using iRIS and Top Tips
“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
Where to go for help:

- **Reporting Post-Approval Events to CHR:**

- **QIU Section of HRPP Website:**
  - [http://www.research.ucsf.edu/chr/Qip/hsppQip.asp](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](http://www.research.ucsf.edu/chr/VA/chrVA.asp) (415) 221-4810 x6425
Where to go for help:

- **Clinical Research Coordinators Website:**

- **Subjects Injury Program:**
  - Bruce Flynn, Director, Risk Management
  - 476-2498

- **Privacy Office Contact Information**
  - 353-2750
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
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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Thank You