Adverse Events in Clinical Trials: Recognition and Reporting — Case studies

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Ben

- Ben has active Crohn’s disease
- He has completed screening for a clinical trial for novel immune-suppressive therapy
- He is coming in today for his first day of treatment
- However, in the past 2 days he has developed a fever, rhinitis, and congestion
  - Is this an adverse event?
  - Should he still enroll?
What defines an adverse event?

- Per the International Conference on Harmonization (ICH) – Good Clinical Practice (GCP):

An AE is any **untoward medical occurrence** in a patient or clinical investigation subject 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 (investigational) product.
What defines an adverse event?

- Basically…
  - Unwanted/unexpected event
  - Occurs after use of a medical product
  - May have no relation to medical product

- Examples?
  - Rash, fever, weight gain
  - Falling down the stairs
  - Animal bite
  - Increase in current disease symptoms (GI or other)
Are Ben’s symptoms an Adverse Event?

- It depends!
- Per ICH-GCP
  - No, this is not considered an adverse event
  - He has not taken study med yet
- Per Protocol
  - It can vary!
  - Always check… sometimes the study protocol will want you to report everything that occurs after signing the informed consent.
What happens after AE determined?

- Should Ben be enrolled today?
  - Check with protocol, PI, and medical monitor if needed
- Study med is an immune-suppressive medication
  - Sounds like Ben currently has an infection
  - Study med could affect his ability to fight off this infection
  - Most likely need to reschedule appointment!
Adverse Events Can Be Tricky to Spot

- Often a research patient may not report an adverse event
  - They forget to mention at study visits
  - They do not feel as though it was important enough to mention
Adverse Events Can Be Tricky to Spot

- Sometimes the study coordinator can be confused as to what qualifies as an “event”
- Some events seem insignificant / unrelated
- Need to consider all labs, exam notes, or outside records
Sarah

- Sarah is participating in a clinical trial
- Has a small patch of rash on her leg
  - Thinks its from dog allergy
  - Does not report at study visit
- Rash is noted on physical exam
  - Coordinator notes this in the subject’s chart
  - Coordinator doesn’t think to add as an adverse event
- Adverse event was missed twice!
How to Get All of the Details

- Ask subjects to carefully track all new signs/symptoms
  - Even if unrelated!

- Ask subjects to call or email you promptly if any new event arises between scheduled study visits

- Any contact with healthcare should be reported
How to Get All of the Details

- Request outside records from your subjects
- Check internal medical records before your subject’s next visit
- Set up automatic alerts
  - MiChart (EPIC EMR) alerts me if subject goes to ED
How to Get All of the Details

- Throughout the trial:
  - Check in with subject at EACH study visit
  - Ask before any other procedure
  - Review adverse event log and previous notes
How to Get All of the Details

- Give a few examples of adverse events
  - Ex. Common cold/ rash
  - Help subjects remember the past month

- If they are taking a new medication
  - Ask why they are taking it

- Casually talk to subjects about their life
  - Sometimes an adverse event will come to mind
Mary

- Arrived for her study appointment
- Immediately informed the study coordinator that she had a sore throat yesterday
- Study coordinator learned that Mary had also fallen off of her bicycle last week
  - She had a bruise on her left arm
  - Mary had forgotten to mention this before!
- The study coordinator also noticed that Mary had seen her PCP a few weeks ago
  - Mary’s PCP diagnosed Mary with anemia
Mary’s Adverse Events

- The study coordinator recorded:
  - Mary’s sore throat
  - Mary’s bruise
  - Mary’s diagnosis of anemia
What about an increase in IBD symptoms?

- Could an increase in daily bowel movements be an adverse event?
- How do you differentiate an AE from one’s baseline medical history?
Phillip

- Has active ulcerative colitis

At start of study:
- 4 BMs/daily
- Blood in his stool
- Hemoglobin = 10
- Mild acne

Week 8 in the study:
- 7 BMs/daily
- Still having blood in stool
- Hemoglobin = 7
- Moderate acne

Are these considered AEs or part of baseline disease?
These need to be reported as Adverse Events
- Compare to baseline
- If objectively worse = AE

Can be missed since related to disease
- Be careful!

Same with other ongoing diseases on medical Hx
- If event is worse than baseline = AE
- Example: Phillip’s acne
Other Adverse Events to Look Out For

- Abnormal lab results and findings on physical examination:
  - PI or Sub-I to indicate clinical significance
  - If significant, report as adverse event and confirm if follow up is needed

- To ensure patient safety, always remember to check for adverse events and new symptoms **BEFORE** drug administration
Things to Document with Each AE

- Need to determine:
  - Severity
  - Causality
  - Relation to study medication
    - aka Investigational Product (IP)
  - Expectedness
  - AE vs. SAE
    - (Serious Adverse Event)
  - AE of Special Interest (AEOSI)
# Things to Document with Each AE

<table>
<thead>
<tr>
<th>Event/Diagnosis</th>
<th>Onset Date</th>
<th>Severity</th>
<th>Action to IP</th>
<th>Action to Subject</th>
<th>SAE or AEoSI?</th>
<th>Outcome Date</th>
<th>Relation to IP?</th>
<th>PI initials</th>
<th>Cause</th>
<th>Med Error?</th>
<th>Sign &amp; Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phillip: Increase in acne</td>
<td>4JUN2016</td>
<td>1</td>
<td>1</td>
<td>4</td>
<td>No</td>
<td>On going</td>
<td>Possible</td>
<td>PH 4JUN2016</td>
<td>2</td>
<td>No</td>
<td>Start: KS 4JUN2016 Stop:</td>
</tr>
</tbody>
</table>

### Severity

- **1= Mild**
  - 1= No action taken
  - 2= Increased
  - 3= Reduced
  - 4= Stopped Temporarily
  - 5= Permanently discontinued
  - 6= Not Applicable

- **2= Moderate**
  - 1= No action taken
  - 2= Increased
  - 3= Reduced
  - 4= Stopped Temporarily
  - 5= Permanently discontinued
  - 6= Not Applicable

- **3= Severe**
  - 1= No action taken
  - 2= Increased
  - 3= Reduced
  - 4= Stopped Temporarily
  - 5= Permanently discontinued
  - 6= Not Applicable

- **4 = Not Applicable**
  - 1= No action taken
  - 2= Increased
  - 3= Reduced
  - 4= Stopped Temporarily
  - 5= Permanently discontinued
  - 6= Not Applicable

### Action to Subject

- **1.** Withdrawn from the study
- **2.** Treatment given
- **3.** Other
- **4.** No action

### Serious Criteria Apply?

- **Yes**
- **No**

### Relation

- **Possible**
- **Unlikely**

### Cause

- **1.** Disease under study
- **2.** Other illness (specify)
- **3.** Concomitant treatment (specify)
- **4.** Other (specify)**
When does an AE become an SAE?

- Sometimes an AE will worsen and be considered a **Serious Adverse Event (SAE)** …
Matthew

- Came in for study visit, feeling fine
- He mentioned that he had a weird bump on his arm
- He was in a hurry to receive study medication and leave
- Physical exam was not scheduled for the visit, but the study coordinator insisted that the PI or Sub-I needed to evaluate the new finding first prior to medication administration
- The Sub-I requested the subject have the bump biopsied and the visit rescheduled
- The bump was cancerous! This is now a Serious Adverse Event!
What is an SAE defined as?

- Per the International Conference on Harmonization (ICH) – Good Clinical Practice (GCP):

  An untoward medical occurrence that at any dose:
  - results in death,
  - is life threatening,
  - requires inpatient hospitalization or prolongation of existing hospitalization,
  - results in persistent or significant disability/incapacity, or
  - is a congenital anomaly/birth defect
Examples of an AE vs. SAE

**Adverse Event**
- Abnormal mole
- Visit to the ED
- Jaundice
- Car accident (minor injuries)
- Increase in diarrhea

**Serious Adverse Event**
- Basil cell carcinoma
- Admission to the hospital
- Liver cancer
- Car accident (significant injuries)
- Dysentery and dehydration
Reporting an **AE** vs. an **SAE**

- To report an AE
  - Check the protocol
    - Is it an AE of Special Interest?
    - Does the protocol require specific timing?
  - Check your IRB standards
    - UMHS IRBMED wants to see a list of all Adverse Events only once per year
  - Ensure PI or Sub-I determines the
    - Causality
    - Severity
    - Relation to study medication
Reporting an AE vs. an SAE

- **To report an SAE**
  - **Report to Sponsor within 24 hours of awareness!**
    - You can always add more detail later
    - Know how to report SAE prior to one happening – in case monitor is unavailable!
  - Check your IRB standards
    - UMHS IRBMED wants certain related and unexpected SAEs to be reported within 7 calendar days of awareness
  - Ensure PI or Sub-I determines the
    - Causality
    - Severity
    - Relation to study medication
Matthew’s biopsy confirmed to be cancer

The AE “unknown bump on arm” became an SAE

SAE was submitted to the sponsor by the end of the day

Per IRB standards, SAE was reported within 7 calendar days

PI determined that this SAE was severe, had an unknown cause, and was possibly related to the study medication

Matthew did not receive another dose of study medication

Is he done with the study?
Matthew

- Matthew withdrew from study treatment but..
  - He can’t just disappear!
  - Still need continuous safety follow-up!
  - Need to determine plan for data collection
    - Reach out to sponsor/medical monitor

- Need to inform other study participants
  - Change in risk section of the informed consent
  - Event could change other subjects’ interest in continuing
  - Note: the consent is an ongoing process!
    - It does not end after the screening visit
Why does this matter?

- Why is the accurate and prompt reporting of AEs and SAEs so important?
- How do your reports contribute to the big picture?
The Big Picture

Research patient discusses S/Sx with the Study Team

Reported AE and SAEs

Study team discusses new AE/SAE with other subjects

This may affect subject’s decision to continue trial
Consent is an Ongoing Process

- Subjects should always be aware of new information learned throughout the study
  - They may not want to continue participating in the trial
  - They need the option to make this decision
  - The consent process does not end have after the screening visit
Now Imagine…

- **You** go to see your IBD specialist and are excited to hear there is a new medication on the market that could help you!
- However… what about the risks?
- What is known about this new medication?
- Where did this information come from?
The Bigger Picture

- Research patient discusses S/Sx with the Study Team
- Physician in clinic discusses possible risks with patient
- Medication becomes FDA approved
Side Effects Can Surprise You

- Bimatoprost was approved in 2001 as a treatment for Glaucoma
- Patients noticed an increase in eyelash growth
- Developed into Latisse!

https://www.verywell.com/latisse-treatment-for-longer-eyelashes-3422098
Side Effects Can Surprise You

- Aspirin is used to reduce fever and pain
- Young children that take Aspirin after having a viral infection can develop Reye syndrome
  - This serious condition can cause swelling of the liver and brain and can be fatal!

http://www.mayoclinic.org/diseases-conditions/reyes-syndrome/basics/definition/CON-20020083
You’re a **Key Part** of Drug Safety!

- The AEs and SAEs that you report are very important!
- You identify unknown risks/ side effects
- You inform current and future patients of possible side effects
Remember

- Communicate often with your study participants
- Report ANY and EVERY medical occurrence
- Refer to protocol, sponsor, and IRB for reporting guidelines
- Have PI/Sub-I determine severity, causality, and relation to research study
- Our efforts help to keep current and future patients informed and safe!
Questions?