Adverse Event (AE)

• ICH definition:

• “Any untoward medical occurrence in a study participant who has been administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.”
Adverse Drug Reaction

All noxious and unintended responses to a medicinal product, related to any dose should be considered adverse drug reactions. It means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility – i.e. the relationship cannot be ruled out.

e.g.: subject who fell did so because he/she was dizzy as a result of taking study medication – the event would be an ADR
‘Side effects’
Can be used to describe unfavourable but also favourable effects

Advised that this term should no longer be used

Adverse Drug Reaction
Serious Adverse Event

Remember!!

- “Serious” and “Severe” are not synonymous
- “Severe” used to describe the intensity – as in mild, moderate, severe
- *(The event itself may be relatively minor medical significance)*
  Term “Serious” is based on event outcome/action
- Criteria usually associated with events that pose a threat to a patients life or functioning
Serious Adverse Event (SAE)

Any untoward medical occurrence that at any dose results in the following:

- Death
- Life-threatening
- Hospitalisation / prolongation of existing hosp.
- Persistent/significant disability/incapacity
- Congenital anomaly / birth defect
- Or Any other medically important event
Serious Adverse Event (SAE)

Life threatening refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Safety Reporting

• All SAE’s should be reported immediately (within 24 hrs) to the sponsor – except for those SAE’s that a protocol identifies as not needing immediate reporting

• The immediate and follow up reports should identify the subject by unique code numbers assigned to trial subject rather than by subjects name or address
Safety Reporting

• The sponsor is responsible for the ongoing safety evaluation of the Investigational Product(s)
• The sponsor should promptly notify ALL concerned Investigators and the regulatory authorities of findings that could adversely affect all subjects, all impact on the conduct of the trial, or alter the ethics approval/favorable opinion to continue the trial
Safety Reporting

- All SAE’s reported at the site **MUST** be reported to the ethics committee within 15 working days of the sponsor becoming aware of the SAE.
- Death must be reported within 1 working day, whether an outcome of a previous SAE or not.
- All local SAE’s will be entered into a data base.
- International Safety reports MUST be submitted to the ethics committee upon receipt from the sponsor (CIOMS).
What Info

- Subject Number / Initials / D.O.B.
- Protocol Number / Protocol Title
- Investigators Name
- Administrative and Sponsor / Company details
- Event onset date / time
- Diagnosis / Description of Event
- Suspected Medicinal Products
- Other treatments
- Event Outcome / Treatment
- Casualty / Action taken to study Product
SAE Reconciliation

...you're right, morphing into a hideous monster is not listed as a possible adverse reaction.
Overview of the process

SAE reconciliation is the process of reconciling the Data Management (DM) database (ie. Data collected on the CRF) with the Pharmacovigilance database (ie. SAE forms) to ensure the data is consistent and not contradictory.
Overview of the process

- Two separate entities are involved
  - Sponsor - Drug Safety and Pharmacovigilance
  - CRO - Data Management Department
Overview of the process

• Sponsor - Drug Safety and Pharmacovigilance
  - Database amassed from site submitted SAE forms

• CRO – Data Management Department
  - Database amassed from AE forms and other data completed in the CRF
    - Conmed pages
    - IP dispensing / Randomisation pages
    - Demographic pages
Data cleaning is first performed

- Query handling process
- MedDRA coding of event
- Medical review
DM-Overview of the process

• SAE data is collected in the Clinical Database
  ➢ Via CRF and double data entry
  ➢ Or Directly via EDC

OR

• SAE data received from sponsor
  ➢ Listing format
  ➢ SAE forms
SAE Reconciliation is performed (with support of Sponsor PV)

- For this we need a SAE Reconciliation Plan

Process should be described in a SAE recon SOP

- Data Management Plan to describe the study specific SAE Reconciliation process
  - List of items to be reconciled
  - Items identified requiring recon will either be Exact match, Consistent match
SOP-Reconciliation Plan

SAE Reconciliation list of items to be reconciled

- Any field that can be reconciled, must be
- i.e. if the data exists in both databases, it must be checked and compared

SAE Reconciliation to include:

- Actions to be taken to correct the databases
- Actions taken to capture potential unreported events (in CRF database but no SAE report sent)
- Actions taken to add event to CRF database (note the monitor would need to monitor this)
Recon Plan Examples

<table>
<thead>
<tr>
<th>Adverse Event Item</th>
<th>REMARK</th>
<th>TYPE OF MATCH</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRF data</td>
<td>SAE report</td>
<td></td>
</tr>
<tr>
<td>Study number</td>
<td>Study ID</td>
<td>Exact</td>
</tr>
<tr>
<td>Patient number</td>
<td>Patient ID</td>
<td>Exact</td>
</tr>
<tr>
<td>Adverse Event (as reported)</td>
<td>Event ID</td>
<td>Consistent</td>
</tr>
<tr>
<td>Should match on level of &quot;preferred term&quot;.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Start of event</td>
<td>Onset date</td>
<td>Consistent</td>
</tr>
<tr>
<td>AE and SAE are not reported separately in the CRF, therefore the start date in the CRF can be before the start date of the SAE report.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>End of event</td>
<td>Stop date</td>
<td>Consistent</td>
</tr>
<tr>
<td>AE and SAE are not reported separately in the CRF, therefore the stop date in the CRF can be after the stop date of the SAE report.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severity</td>
<td>Intensity</td>
<td>Exact</td>
</tr>
<tr>
<td>Seriousness criterion</td>
<td>AE serious</td>
<td>Consistent</td>
</tr>
<tr>
<td>Relationship to Study Drug</td>
<td>Investigator causality</td>
<td>Consistent</td>
</tr>
<tr>
<td>The relationship in the CRF refers to the combination of Study Medications, as in DSP only to Tacrolimus.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outcome / Date of Death on Mortality Report</td>
<td>Outcome of event/Death (seriousness criteria)</td>
<td>Consistent</td>
</tr>
<tr>
<td>Outcome may differ.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>If the outcome is ‘fatal’ a date of death must be provided and consistent.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(DSP may follow up for safety reasons after a patient has left the study).</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Concomitant Medication item</th>
<th>REMARK</th>
<th>TYPE OF MATCH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medication Name</td>
<td>All drugs present in the DSP database (suspect product, concomitant product) must be present in the CRF database but not vice versa.</td>
<td>Consistent</td>
</tr>
<tr>
<td>(DSP only collects information on drugs taken by the subject 1 month before onset event)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Start and stop dates, dosage and frequency</td>
<td></td>
<td>Exact</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medical History item</th>
<th>REMARK</th>
<th>TYPE OF MATCH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical Condition</td>
<td>All conditions present in the CRF database must be present in the safety database but not vice versa.</td>
<td>Consistent</td>
</tr>
<tr>
<td>Vertain term should match exact. Reconciliation of other information is not necessary.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study drug item</th>
<th>REMARK</th>
<th>TYPE OF MATCH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Start and stop date</td>
<td></td>
<td>Exact</td>
</tr>
<tr>
<td>Dosage and frequency</td>
<td>Only if data available in the CRF.</td>
<td></td>
</tr>
</tbody>
</table>
The SAE Reconciliation process can start

- The data in the Clinical and Safety databases are available
- We have an approved SAE Reconciliation Plan
- MedDRA coding of both databases has been performed
SAE recon process

Databases are compared for consistency/exact
Matches by:
- Manual process or
- Electronic process
SAE recon process

Step by Step:
- Check Number of events in each database are the same
- Verify each entry in the SAE database is flagged as an SAE in the DM database and visa versa
- Compare Key data defined in plan
- Query inconsistencies as per plan
- Retrieve signed/dated responses and updated relevant databases
Food for thought

- Perform MedDRA Coding first
- Agree upon a standard set of variables to reconcile at study start
- System interface to identify changes to databases immediately
- Make clear agreements between DM and PV
  - Responsibility for follow-up actions (like missing data)
  - Timelines (focus for PV is reporting; for DM database lock)