Adverse Events and Attribution 101 – A Casual Discussion

- What are the terms used in assessing adverse events?
- What is “attribution?”
- Why, when and how do we make attributions?
Attribute *(verb)*

-- to explain by indicating a cause

An attribution is an assessment of whether an adverse event is likely caused by the agent(s) we are testing
Definitions

• AE – Adverse Event
• EAE – Expedited Adverse Event
• SAE – Serious Adverse Event
• ADR – Adverse Drug Reaction
• SADR – Suspected Adverse Drug Reaction
• Toxicity Grades – a systemic way of grading the severity of adverse events
Adverse Event

“Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.”

ICH E2A
ADVERSE DRUG REACTION

“...a response to a drug which is noxious and unintended, and which occurs at dose normally used in humans for the prophylaxis, diagnosis or therapy of disease, or for a modification of physiological function.”

W.H.O 1972
ASSESSMENT OF ADVERSE EVENTS

- Seriousness
- Severity
- Relatedness
- Expectedness
SERIOUS ADVERSE EVENT

• An untoward medical occurrence that at any dose
  – Results in death
  – Results in significant disability/incapacity
  – Is a congenital anomaly/birth defect (or unintentional fetal loss, per DAIDS)
  – Requires inpatient hospitalization or prolongation of hospitalization
  – Is life-threatening

[ICH E6]
SEVERITY

• Assessed in terms of toxicity Grades 1-5, using the “DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events”
Toxicity Grades

• In our protocols, the severity of a toxicity is defined by the DAIDS toxicity tables:
  – Grade 1 = mild
  – Grade 2 = moderate
  – Grade 3 = severe
  – Grade 4 = life-threatening
  – Grade 5 = death
RELATEDNESS

• A crucial assessment made by a study physician and Medical Officer of whether or not the event is:
  – Definitely related …
  – Probably related …
  – Possibly related …
  – Probably not related …
  – Not related …

… to the study agent
RELATEDNESS

• **Definitely**: Direct association with study agent
• **Probably**: More likely explained by study agent
• **Possibly**: Study agent and other cause explained equally well
• **Probable Not**: More likely explained by other cause
• **Not**: Clearly explained by other cause*

*Requires documentation of other cause
Case # 1

• An 8 year-old with HIV is seen by her provider and is clinically well, but her CD4 count has dropped significantly
• She is started on a study with Lopinavir as the study drug (also on ZDV/3TC)
• Two days later, she develops abdominal pain and vomiting severe enough to be grade 3
• Her brother, not on the study, also has abdominal pain, vomiting and diarrhea
Is this?

• Definitely related
• Probably related
• Possibly related
• Probably not related
• Not related
Suspected Adverse Drug Reaction

• ICH definition
  – A noxious and unintended response to any dose of a drug product for which a causal relationship between the product and the event … cannot be ruled out.”
Suspected Adverse Drug Reaction

• If the adverse event falls into one of these categories of relatedness:
  – Definitely related …
  – Probably related …
  – Possibly related …
  – Probably not related …

… it is a SADR
EXPECTEDEDNESS

• An adverse event may be expected, i.e., an event related to the use of the study agent that has been previously observed (according to the package insert)
EXPECTEDEDNESS

• An unexpected adverse event is an event that is not consistent in nature and/or severity with those included in the package insert

Note: The concept of expected and unexpected is relevant when using the Targeted level of adverse event reporting (discussion to come)
EXPEDITED ADVERSE EVENT (EAE)

- An adverse event that meets the criteria for expedited reporting to DAIDS
- “Expedited” is in contrast to reporting adverse events by study CRFs
- The EAE Manual recognizes the differences between events requiring expedited reporting to DAIDS and SAEs as defined by ICH
Why so much Attention to Attribution?

- Preserve safety of our volunteers
- Safety is a primary endpoint and deserves comparable rigor as our laboratory endpoints
- AEs contribute to safety profile
  - Affect licensing of the medication
  - Affect future study design
  - Included in package insert when licensed
Why so much Attention to Attribution?

• It is essential to have the best assessment possible as to whether adverse events that occurred are related to study agents or not.
RELATEDNESS

- **Definitely:** Direct association with study agent
- **Probably:** More likely explained by study agent
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- **Probably Not:** More likely explained by other cause
- **Not:** Clearly explained by other cause*

*Requires documentation of other cause
When and by whom do we make attributions made?

- EAE reporting
- Study monitoring
- Patient management, both in clinical trials and in the clinic
EAE Reporting/Patient Management

- When an EAE occurs, the site investigator must report the EAE to the DAIDS which then evaluates it for submission to the FDA.
  - The site investigator makes an attribution determining the likelihood of relationship of the event to the study drug
  - The DAIDS medical officer makes an independent attribution of the relationship
EAE Reporting/Patient Management

Based on the attributions made by the site investigator and the DAIDS medical officer, and the seriousness and expectedness of the event, the DAIDS Safety Team determines whether a safety report needs to be filed to the FDA.
EAE Reporting/Patient Management

• Each protocol has criteria for management of a subject with defined toxicity grades

• The management of these subjects may be dependent on the attribution of the toxicity
EAE Reporting/Patient Management

For example, the protocol may state “if a subject has a Grade 3 toxicity that is probably or definitely related to study drug, the study drug should be stopped. The investigator should contact the study team to consider restarting study drug when the toxicity grade is Grade 2 or less.”
Study Monitoring

• As the protocol is being written, the study team determines what the criteria for pausing or stopping the study will be:
• This depends on the phase of the trial, the agents involved, and the population enrolled in the trial
• The study team also determines what level of AEs will be monitored
Study Monitoring

• For example, if a study team may determine that all Grade 3 and above AEs should be monitored

• If a drug is known to cause liver disease, the team may decide to review all Grade 3 and up AEs plus Grade 2 transaminase increases
Study Monitoring

• The protocol safety team will then make an attribution for each AE they have reviewed
• This can be in addition to the attributions made by the site investigator and the medical officer
• These attributions may affect whether the study continues
Pause Rules

• For example, the protocol may state that if 3 out of 8 patients have a Grade 3 EAE that is “possibly, probably or definitely related to study drug, the protocol will stop enrollment until it is reviewed by an independent safety review committee.”
How do we make an attribution?

1) Global Introspection: best “guess” based on the gestalt
   • Subjective
   • Poor reproducibility – inter- and intra-rater disagreements

2) Structured operational algorithms
   • More than 20 published over the last 25 years; widely variable
   • Weighting of criteria somewhat arbitrary
RELATEDNESS

- **Definitely**: Direct association with study agent
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- **Not**: Clearly explained by other cause

*Requires documentation of other cause*
Case # 2

- A highly-experienced adolescent goes onto a protocol using a new integrase inhibitor called **viraviroc**, with d4T/3TC
- After 8 months, she develops tingling in her feet diagnosed as peripheral neuropathy
- The investigator’s brochure says that in adults trials of 200 patients, 3 complained of peripheral neuropathy
Is this?

- Definitely related
- Probably related
- Possibly related
- Probably not related
- Not related
Attribution

• How do we assess if one thing is caused (attributed) by another thing?
  – Temporal relationship
  – Plausibility
  – Likelihood of other causes
  – Historical information: other similar events are known to have happened
Bradford Hill’s criteria

- Strength of association
- Consistency
- Specificity
- Temporality
- Dose-response
- Plausibility
- Experimental evidence

AB Hill: The environment and disease: association or causation
Pharmacovigilance Criteria

1. Temporality
2. Rechallenge
3. Dechallenge
4. Bibliographic Description
5. Etiologic Alternatives

French System
Chronological criteria
Semiological Criteria
Causality assessment of serious AEFI

Temporal relation
Association (time, place)

Clinical characteristics
Laboratory findings
- Concomitant or preceding conditions
- Confident diagnosis of lesion
- Laboratory results favour causation

Data quality
- Consistency
- Reproducibility
- Reliability

Biological plausibility
Previous knowledge
- Previously known reaction

Likelihood/exclusion of other causes
- Specificity and strength of association
- Treatment, risk factors, susceptibility, programme error
Attribution Criteria

1. Temporal Association
2. Search for Other Causes
3. Plausibility
   • Biological plausibility
   • Known pattern of response
4. Re-challenge
Temporal Association

Is the adverse event and exposure to the agent reasonably related in time?

- Arguably the most important criteria
- Cause precedes effect in time:
  - AE occurs after the child received the agent
- Time to onset: from last dose to AE
  - Important to consider nature of reaction
    - Long latency: cancer, autoimmune processes
    - Short latency: hypersensitivity reactions
Search for Other Causes

*Is there another likely cause for the AE?*

- **Clinical state**
  - Emphasizing the diversity of populations enrolled
    - Malaria would need to be considered in the differential for anemia in a Malawi PrEP trial
    - Anemia workup in menstruating women vs. men, etc.

- **Preexisting conditions**

- **Environmental factors**
  - New medication
  - Study related procedures
Plausibility

How reasonable is the assumption that the intervention caused this AE?

• History of association or known pattern of response:
  – Is the AE consistent with the agent profile?
  – Refer to the Investigator’s Brochure/Package Insert and the study protocol

• Biological Plausibility:
  – Is there a reasonable biological mechanism for this agent to cause this AE?

  Often difficult to know when human data is limited or not available
Challenge or consistency of response

• Re-Challenge
  – Does the AE occur when the agent is re-administered?

• Dose Response (a type of challenge)
  – Does the AE get worse at a higher exposure?
Attribution Literature

We know what works and what doesn’t work
Global introspection is not reliable

- About 50% overall agreement ($\kappa = 0.21-0.37$)
  Naranjo et al. 1981
- Disagreement among 5 senior experts in France
  Arimone et al. 2005
  - 41% overall agreement ($\kappa = 0.20$)
  - Agreement better at the extreme levels of causality
  - Very poor for the intermediate levels (some no different than chance)
Operational Algorithms

• Transparent

• Reproducible

• Systematic

• Facilitates Communication
**I - Chronological criteria**

<table>
<thead>
<tr>
<th>Event Onset</th>
<th>Very Suggestive</th>
<th>Compatible</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rechallenge</td>
<td>R(+) R(0) R(-)</td>
<td>R(+) R(0) R(-)</td>
</tr>
<tr>
<td>Dechallenge</td>
<td>C_3 C_2 C_1</td>
<td>C_2 C_1 C_0</td>
</tr>
<tr>
<td>Inclusive (suggestive with drug withdrawn)</td>
<td>C_4 C_3 C_2</td>
<td>C_1 C_0</td>
</tr>
<tr>
<td>Unsuggestive (no regression)</td>
<td>C_1 C_1 C_1</td>
<td>C_1 C_1 C_1</td>
</tr>
</tbody>
</table>

Classification: C_3 = suggestive, C_2 = possible, C_1 = dubious, C_0 = incompatible.

**II - Semiological Criteria**

<table>
<thead>
<tr>
<th>Specific Lab. Test</th>
<th>Suggestive of the drug (and/or very favoring factor)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>L(+) L(0) L(-)</td>
</tr>
<tr>
<td>Alternate non-drug</td>
<td></td>
</tr>
<tr>
<td>Related explanation</td>
<td></td>
</tr>
<tr>
<td>None (after appropriate search)</td>
<td>S_1 S_2 S_3 S_4 S_5 S_6</td>
</tr>
<tr>
<td>Possible (present or not reached)</td>
<td>S_1 S_2 S_3 S_4 S_5 S_6</td>
</tr>
</tbody>
</table>

Classification: S_1 = suggestive, S_2 = possible, S_3 = dubious.

Intrinsic imputability is obtained from the score of the chronological and semiological imputabilities.

<table>
<thead>
<tr>
<th>Chronology</th>
<th>S_1</th>
<th>S_2</th>
<th>S_3</th>
</tr>
</thead>
<tbody>
<tr>
<td>C_6</td>
<td>l_6</td>
<td>l_6</td>
<td>l_6</td>
</tr>
<tr>
<td>C_5</td>
<td>l_5</td>
<td>l_5</td>
<td>l_5</td>
</tr>
<tr>
<td>C_4</td>
<td>l_4</td>
<td>l_4</td>
<td>l_4</td>
</tr>
<tr>
<td>C_3</td>
<td>l_3</td>
<td>l_3</td>
<td>l_3</td>
</tr>
</tbody>
</table>

The drug-effect relation can be: UNLIKELY (l_0), DUBIOUS (l_1), POSSIBLE (l_2), PROBABLE (l_3), VERY LIKELY (l_4).

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The French System
Dangoumau et al. 1985
Does event have a reasonable temporal association with use of the drug?

Yes →

Was there a dechallenge from the drug?

Yes →

Did the observed event abate upon dechallenge?

Yes →

Was there a rechallenge?

Yes →

Did the reaction or event reappear upon rechallenge?

Yes →

Causal relationship considered highly probable.

No →

Causal relationship considered possible.

No →

Causal relationship considered possible.

No →

Could the event be due to an existing clinical condition?

Yes →

Causal relationship considered probable.

No →

Causal relationship considered possible.

No →

Causal relationship considered remote.

Jones et al. 1982
<table>
<thead>
<tr>
<th>Question</th>
<th>YES</th>
<th>NO</th>
<th>DO NOT KNOW</th>
<th>SCORE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Are there previous <strong>conclusive reports</strong> on this reaction?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>2. Did the adverse event <strong>appear after</strong> the suspected drug was administered?</td>
<td>+2</td>
<td>-1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>3. Did the adverse reaction <strong>improve</strong> when the drug was <strong>discontinued</strong> or a <strong>specific antagonist</strong> was administered?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>4. Did the adverse reaction <strong>reappear</strong> when the drug was <strong>readministered</strong>?</td>
<td>+2</td>
<td>-1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>5. Are there <strong>alternative causes</strong> (other than the drug) that could on their own have caused the reaction?</td>
<td>-1</td>
<td>+2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>6. Did the reaction appear when a <strong>placebo</strong> was given?</td>
<td>-1</td>
<td>+1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>7. Was the <strong>drug detected</strong> in the blood (or other fluids) in concentrations known to be <strong>toxic</strong>?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>8. Was the reaction <strong>more severe</strong> when the <strong>dose</strong> was <strong>increased</strong> or <strong>less severe</strong> when the <strong>dose</strong> was <strong>decreased</strong>?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>9. Did the patient have a similar reaction to the same or similar drugs in any <strong>previous exposure</strong>?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>10. Was the adverse event confirmed by any <strong>objective evidence</strong>?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

**Total Score**

Naranjo et al. 1981
Naranjo Criteria most cited and best validated

- High interrater agreement (83-92%)
- High intrarater agreement (80-97%)
- High validity when compared with consensus agreement of 3 experts (79-95%)
### Kim Criteria for Adverse Events

<table>
<thead>
<tr>
<th>Other Causes</th>
<th>Difficult to explain by other causes</th>
<th>Can be explained equally well by other causes</th>
<th>More likely explained by other causes</th>
<th>Clearly due to other cause</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other Causes</td>
<td>+2</td>
<td>0</td>
<td>-1</td>
<td>-5</td>
<td></td>
</tr>
</tbody>
</table>

Other Causes include **pre-existing conditions**, participant’s **clinical state**, and **environmental factors** or **other interventions**.

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>Unlikely but possible</th>
<th>No</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Did the adverse event occur within a reasonable interval after the (intervention) ?</td>
<td>+2</td>
<td>-1</td>
<td>-5</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Question</th>
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<th>Do Not know</th>
<th>No</th>
<th>Score</th>
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<tr>
<td>Is there a reasonable biological mechanism for the (intervention) to cause this event?</td>
<td>+1</td>
<td>0</td>
<td>-1</td>
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</thead>
<tbody>
<tr>
<td>Are there previous reports of similar events caused by related (interventions) ?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

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</thead>
<tbody>
<tr>
<td>Did the adverse reaction reappear when the (intervention) was readministered?</td>
<td>+1</td>
<td>0</td>
<td>-1</td>
<td></td>
</tr>
</tbody>
</table>

**Not Related:** $\leq -4$

**Probably Not Related:** -3 to -1

**Possibly Related:** 0 to 3

**Probably Related:** 4 to 5

**Definitely Related:** 6 to 7
There are systematic methods to assist in the Attribution of Adverse Events

• It would be ideal to utilize them as much as possible
• But these algorithms are extremely complex and can be difficult to use
Case # 3

• An HIV-infected woman is on AZT since week 14 and during labor and is on a protocol studying intrapartum tenofovir
• She receives the tenofovir 4 hours prior to delivery
• On day 3, the infant’s hemoglobin is 9.5
Is this?

- Definitely related
- Probably related
- Possibly related
- Probably not related
- Not related
The Use of Clinical Judgment

• Sometimes tendency to move towards
  – categories of uncertainty (possibly related) because “we can never be sure,“
  – or greater relationship (probably related) because “we don’t want to miss anything.”

• It is more important to make the best assessment with the information available.

• Assessments can (and do) change as we gather more information and as the safety profile of product is updated.
All scientific work is incomplete – whether it be observational or experimental. All scientific work is liable to be upset or modified by advancing knowledge…

Who knows, asked Robert Browning, but the world may end tonight? True, but on available evidence most of us make ready to commute on 8:30 the next day.

Bradford Hill
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