Case causality assessment
David Coulter

How close is the relationship between drug and event?
Did the drug cause the event?
The data elements 1

- Patient ID / National ID; Gender & DoB
- All drugs and dates of administration
- Doses
- Indications for use
- The event story and description
- Date of onset of the event
- Patient history eg hepatic disease
The data elements 2

From the report we derive:

• Duration to onset of the event
• Reaction terms
• Severity and seriousness
• Results of dechallenge & rechallenge
• Outcome information
### Adverse Reactions to Medicines, Vaccines and Devices

and all clinical events for IMMP

**Patient Details**

- **Surname:**
- **First Name(s):**
- **NHI No.:**
- **Address:**
- **Date of Birth:**
- **Sex:**
- **Ethnicity:**

**All Medicines in Use - *** Asterisk Suspect Medicine(s) *** Include OTCs and alternative medicines**

<table>
<thead>
<tr>
<th>Medicine(s) / Vaccine(s) batch no.</th>
<th>Daily Dose</th>
<th>Route</th>
<th>Date Started</th>
<th>Date Stopped</th>
<th>Reason for Use</th>
</tr>
</thead>
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**Description of Adverse Reaction or Incident**

- **Date of onset:**

- **Recovered:**
- **Not yet recovered:**
- **Unknown:**
- **Fatal:**
- **Date of Death:**

- **Severe:**
- **Yes:**
- **No:**
- **Rechallenge:**
- **Yes:**
- **No:**

**Other Factors:** Please note or specify as appropriate:

- **Renal:**
- **Hepatic:**
- **Allergy:**
- **Other Medical Conditions:**
- **Nutritional Supp:**
- **Chemical Exposure:**

**Reporting Doctor/Pharmacist/Dentist/Nurse/Other**

- **Name:**
- **Address:**
- **Signature:**
- **Phone:**
- **Date:**

**Danger / Warning**

- **Input by:**
- **Date:**

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26 March 2003
The data elements and more

• We use all the information available on the report, and
• Our pharmacological knowledge, and
• Our knowledge of previous reports received, and
• Our search of the WHO database, and
• Our knowledge of any literature reports
To assess causality
Case causality assessment 1

• What we are really doing is assessing the strength of the relationship between the drug and the event
• We can seldom say without any doubt that a specific drug caused a specific reaction
• We work with imperfect data and our conclusions are those of probability
Case causality assessment 2

• The accumulation of case reports at national and international level is immensely valuable in providing the means for determining real cause and effect

• Sometimes epidemiological studies are needed to confirm causality
Case causality assessment 3

Case causality assessment is an essential discipline. *It ensures:*

• careful review of report details
• standardised assessment
• an in-depth understanding of the data
• standardised data for later evaluation
• the ability to sort reports by quality
Case causality assessment 4

Definitions

• **Dechallenge:** withdrawing the drug(s) and recording the outcome - *improved or not improved*

• **Rechallenge:** giving **one** drug again under the same conditions as before and recording the outcome - *recurrence or no recurrence*
Case causality assessment 5

WHO categories

1. CERTAIN

- Event with plausible time relationship
- No other explanation - *disease or drugs*
- Response to withdrawal plausible
- Event definitive - *specific problem*
- Rechallenge
Case causality assessment 6

2. PROBABLE

- Event with reasonable time relationship to drug intake
- No other explanation
- Response to withdrawal clinically reasonable
- No rechallenge
3. POSSIBLE

- Event with reasonable time relationship to drug intake
- Could also be explained by disease or other drugs
- Information on drug withdrawal lacking or unclear
Case causality assessment 8

4. UNLIKELY

• Event with a duration to onset that makes a relationship improbable (but not impossible)

• Diseases or other drugs provide plausible explanations
Case causality assessment 9

5. Unclassified (conditional)

• An adverse event has occurred, but there is insufficient data for adequate assessment, or

• Additional data is awaited or under examination
Case causality assessment 10

6. Unclassifiable (unassessable)

- A report suggesting an ADR
- Cannot be judged because of insufficient or contradictory information
- Report cannot be supplemented or verified
The process 1

Objective evaluation

- Dates of use of drug(s)
- Date of onset of event
- Nature of event - apply ADR term
- Response to dechallenge
- Response to rechallenge
- Outcome
The process 2

Subjective assessment

• Is a reaction plausible?
• Consider
  – indication for use
  – background or past disease
  – pharmacology
  – prior knowledge of similar reports with the suspect drug or related drugs
The process 3

- Discuss and consult
- Decision on causality
- Be prepared to revise your decision
The process 4
Check your logic

• You should not have causality 1 if there has been no rechallenge
• You should not have causality 2 if there has been no dechallenge
• You should not have causality 2 if the outcome is unknown
• You should not have causality 2 if the outcome is unknown
<table>
<thead>
<tr>
<th>Event</th>
<th>Sev</th>
<th>Rel</th>
<th>Pnt</th>
<th>Onset</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haematemesis</td>
<td>1</td>
<td>2</td>
<td>21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypotension</td>
<td>1</td>
<td>2</td>
<td>21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastric ulcer</td>
<td>1</td>
<td>2</td>
<td>21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>URTI</td>
<td>2</td>
<td>4</td>
<td>16</td>
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**Outcome**
- **A**: recovered without seq
- **B**: recovered with seq
- **F**: not yet recovered
- **D**: died - due to AR
- **C**: died - med may be contributory
- **N**: died - unrelated to Med
- **O**: died - cause unknown
- **U**: unknown

**Seriousness**
- **H**:

**Category**
- **ALI**
- **CIR**
- **RES**

**Dose Reduced**
- **Withdrawn**: ☑
- **Died**: ✗
Other methods

- French imputation system
- Algorithms eg Naranjo