

Causality assessment Aide Memoire for Individual Case Safety Reports

This document aims at listing the relevant criteria to be evaluated when assessing the causal relationship between an Adverse Event (AE) and a suspected medicinal product or a combination of suspected medicinal products. **Medical judgment should always apply in allocating a final causality category to an 'AE-suspected drug' or an 'AE-suspected drug combination' pair.**

As a general rule, the following points should be considered in the evaluation of an 'AE-suspected drug' or an 'AE-suspected drug combination' pair:

Causality assessment Aide Memoire – Points to consider Bradford Hill criteria ⁽¹⁾			
Criteria	Questions	Answers	
		Yes	No
1. Strength of association	Is there a statistical association between the exposure and the AE, as reported in the literature or observed in MSF or other clinical trials?	<input type="checkbox"/>	<input type="checkbox"/>
2. Consistency	Is the same exposure-AE pair consistently observed across studies? Meaning by reproducing the exposure, do we observe a similar effect?	<input type="checkbox"/>	<input type="checkbox"/>
3. Specificity	Are there sub-groups in the exposed population (geographic, ethnic, age, disease severity, genetic variants, etc.) more prone to the development of the AE?	<input type="checkbox"/>	<input type="checkbox"/>
4. Temporality	Is the time-to-onset in favour of a causal association provided the nature of the event (e.g. anaphylaxis or solid malignancy)?	<input type="checkbox"/>	<input type="checkbox"/>
5. Biological gradient	Is there a dose-response relationship?	<input type="checkbox"/>	<input type="checkbox"/>
6. Plausibility, mechanism of action	Is there a potential biological mechanism that may explain the observed exposure-AE pair?	<input type="checkbox"/>	<input type="checkbox"/>
7. Coherence	Assuming the prior knowledge on the observed disease (i.e. the AE) is correct, is the observation in line with this knowledge (e.g. symptomatic lab data)?	<input type="checkbox"/>	<input type="checkbox"/>
8. Analogy	Is there knowledge of similar experiences in comparable setting/population or with an analogous active substance, a product with the same mechanism of action or similar drug combination?	<input type="checkbox"/>	<input type="checkbox"/>
9. Experiment (Dechallenge/Re-challenge)	Is there a positive dechallenge, i.e. by withdrawing or lowering the dose of the suspected product(s), symptoms are relieved? And/or a positive rechallenge (not possible in all setting), i.e. by reintroducing the suspected product(s) or the full dose, symptoms reappear?	<input type="checkbox"/>	<input type="checkbox"/>
INTERPRETATION	By answering 'yes' to one or more of these questions, you are providing evidences in the favour of a causal relationship between the exposure and the AE. The presence of confounding factors should also be carefully evaluated when answering (e.g. environment, medical history, concomitant treatments, or family history). In addition, the quality of data available for such evaluation should also be taken into account (e.g. controlled CT results, publications from peer-reviewed journals, postmarketing reports or animal studies).		

The scoring method presented below allows for the allocation of a causality category to an 'AE-suspected drug' or an 'AE-suspected drug combination' pair. Most "questions" should already have an answer if you previously used the Bradford Hill's method, but it is another way to brainstorm on causality. **The Naranjo score should be used as guidance only; medical judgment should always apply in allocating a final causality category.**

Causality assessment Aide Memoire – Naranjo ADR probability scale ⁽²⁾			
Questions	Answers		
	Yes	No	Not known
1. Are there previous conclusive reports on this reaction?	+1	0	0
2. Did the AE appear after the suspected drug/drugs' combination was administered?	+2	-1	0
3. Did the AE improve when the drug/combination was discontinued or a specific antagonist was administered?	+1	0	0

Causality assessment Aide Memoire – Naranjo ADR probability scale ⁽²⁾			
Questions	Answers		
	Yes	No	Not known
4. Did the AE reappear when drug/combination was readministered?	+2	-1	0
5. Are there alternative causes (other than the suspected drug(s)) that could solely have caused the AE?	-1	+2	0
6. Did the AE reappear when a placebo was given?	-1	+1	0
7. Was the suspected drug(s) detected in the blood (or other fluids) in a concentration known to be toxic?	+1	0	0
8. Was the AE more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0
9. Did the patient have a similar AE to same or similar drugs in any previous exposure?	+1	0	0
10. Was the AE confirmed by objective evidence (e.g. symptomatic lab data, specialist assessment)?	+1	0	0
Total score:	≥1	0 [I have ticked all 'not known']	≤0 [I have ticked ≥1 yes/no]
Corresponding MSF causality category (For info)	Related	Related by default in the absence of sufficient information to fully assess the case	Not related
INTERPRETATION	By obtaining a score ≥1, a reasonable causal relationship between the exposure and the AE is at least possible. The interpretation and definite conclusion on the causal relationship should take into account the presence of confounders/risk factors and the quality of the data used to answer the questions. A Naranjo score should not be the only criterion in the final decision of causality; medical judgment should always prevail.		

For the purpose of processing and reporting, a written comment on the evaluation of the causal association between the suspected drug(s) and the observed AE (possibly based on the answers to the Bradford Hill or Naranjo questionnaires) can be prepared. In addition, one of the following causality categories should be selected:

MSF Causal relationship between the adverse event and the suspected drug(s)		
MSF Category	Main characteristics	Naranjo score (for info)
Related	There is a reasonable possibility that the AE may be related to the drug(s). Elements in favour of a reasonable causal relationship include: <ul style="list-style-type: none"> • A favourable temporal relationship, • A positive dechallenge and/or rechallenge, • A plausible pharmacological/biological mechanism of action (whether proven or potential), • Previous knowledge of similar reaction with the drug(s), or • No other evident cause (e.g. previous disease, other drugs). 	≥1
Related - Insufficient information	There is insufficient information to evaluate the causal relationship between the AE and the exposure. Conservatively, the AE should be considered related to the drug(s) until a proper assessment is feasible (i.e. upon follow-up).	0 [I have ticked all 'not known']
Not related	There is no reasonable possibility that the AE is related to the drug(s). This implies that there is a plausible alternative cause for the AE that better explains the occurrence of the AE or that highly confounds the causal relationship between the drug(s) and the AE.	≤0 [I have ticked ≥1 yes/no]

References

⁽¹⁾Bradford Hill A. *The Environment and Disease: Association or Causation? Proceedings of the Royal Society of Medicine*, 58 (1965): 295-300.

⁽²⁾Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther*. 1981;30:239–45.