

Healthcare Information & Decision Equation: **Information** → **Decision** → **Action** → **Outcome**  
 Is it true → Is it useful → Is it usable?

### Key Points About Safety Evidence

- **Safety** issues concern risks and harms which are events that cause problems with meaningful outcomes (morbidity, mortality, quality of life, functioning) or cause other unwanted effects.
- **Terms** “safety, risk, harm, adverse event, adverse effect, ADE” are often used interchangeably.
- Harms are infrequent, hard to find and are usually not the topic of study (not determined *a priori* and therefore there is a greater likelihood that findings are due to chance).
- There are potential limitations of RCTs and systematic reviews of RCTs that are not specifically focused on safety questions when the RCTs —
  - May not have reported or fully reported adverse events (e.g., loss of subjects during run-in period).
  - May be of insufficient duration
  - May have relied upon small populations (eg, sampling error or power issues)—**BEWARE OF NON-SIGNIFICANT FINDINGS!** Non-significant findings could be chance effects, could be due to insufficient numbers of patients to find differences between groups—or could truly be due to no difference between groups.
- Harms are often reported from weaker science such as case report data, database research, observational studies or low quality RCTs.
  - Reminder: With rare exceptions, cause and effect can only be reliably concluded from valid RCTs.
- If outcome measures are not identified *a priori*, it increases the possibility that the findings are due to chance.
- **High discontinuation rates** in studies may result in agents appearing safer than they actually are.
- When effective interventions are no longer available (eg, have been discontinued by the manufacturer) due to poor safety data – which could be inaccurate – patients may be harmed.

**Safety data are, therefore, usually not strong and often likely due to chance.**

### Where to Look

- Review FDA site: Medical Review; review drug label.
- Systematic reviews of RCTs dealing with harms should be sought, but harms may not be detected if some of the included trials do not report harms or if harms are described in various ways in different studies.
  - In some cases, systematic reviews may falsely indicate lack of harms that are subsequently detected in large, well-designed and conducted RCTs.

Search for observational studies, keeping in mind that observational studies are prone to bias.

### Considerations & Critical Appraisal Issues

- In RCTs, the safety population should be only those who receive the intervention.
- Unless a study is powered for harms, lack of statistically significant differences may mean there is no difference or it may mean it is still unknown if there is a difference. Confidence intervals are useful in evaluating harms. Review confidence intervals (CI) for non-significant findings to discern if there is a clinically meaningful difference between the groups within the confidence interval.
- Review multiple studies. Look for patterns.
- Note if support exists for the harm (eg, biologic plausibility, relatedness in outcomes, dose-response relationship).
- Review the exclusions: Exclusion of patients otherwise likely to experience side-effects may affect generalizability of results of adverse events reporting (eg, may happen if patients are restricted to those who are not naïve or may occur through a run-in and exclusion period).
- Review drop-outs due to adverse effects.
- If composite endpoints are used for efficacy, are they used for safety?
- Caution is especially warranted for new agents.
- Beware of the potential for overreacting to possible harms and the risk of creating unintended consequences.

### Bradford Hill Criteria for Supporting Considerations of Causality [Delfini Comments or Paraphrasing]

Caution is urged in applying the criteria below as these are neither requirements, nor guarantees, of causality and may not be reliable—but they may be worthwhile to consider:

1. Strength of Association [aka estimates of effect];
2. Consistency—has it been repeatedly observed by different persons, in different places, circumstances and times?;
3. Specificity [eg, a specific kind of cancer is seen in more people who smoke than in those who do not];
4. Temporal relationship;
5. Biological gradient [eg, dose-response relationship];
6. Plausibility [supportive, but not required as is dependent upon what is currently known];
7. Coherence—not seriously in conflict with generally known facts of the natural history and biology of the disease;
8. Experiment [experimental support];
9. Analogy [potential for following a pattern such as a virus known to cause birth defects; therefore, maybe that another does too].

HILL AB. THE ENVIRONMENT AND DISEASE: ASSOCIATION OR CAUSATION? Proc R Soc Med. 1965 May;58:295-300. PubMed PMID: 14283879; PubMed Central PMCID: PMC1898525.

**Additions AHRQ:** Lack of alternative causes, drug levels in body, resolves or improves after discontinuation, & recurrence with restarting.

<http://www.effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=327>