These comments illustrate a recurring theme that occurs for all FDA-regulated clinical trials. This theme is that, where causation cannot be established by the clinical trial, information on causality is expected to materialize once the drug is marketed in the general population.

VIII. ASSESSING CAUSALITY

a. Using Raw Data on Adverse Events to Acquire Cause-and-Effect Data on ADRs

The Naranjo questionnaire consists of 10 questions that capture information regarding any given adverse event (237,238,239,240). These questions are shown below:

1. Are there previous conclusive reports on this reaction?
2. Did the adverse event appear after the suspected drug was administered?
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?
4. Did the adverse reaction reappear when the drug was readministered?
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?
6. Did the reaction reappear when a placebo was given?
7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?
10. Was the adverse event confirmed by any objective evidence?

The questionnaire includes factors such as prior adverse reports, the timing of the adverse reaction, whether the adverse reaction stopped when the drug was discontinued and whether it reappeared when the drug was resumed, dosage levels, and alternative causes of the AE (241). The questionnaire uses a point system, with assigned points being added or subtracted to the overall score depending on the questionnaire responses to the questionnaire. These calculations yield a total score, that informs the drug safety scientist whether the cause was "highly probable," "probable," "possible," or "doubtful." In detail, Naranjo scores of 9 or 10 indicate that an event was "definitely" an ADR; scores of 5–8 rate the likelihood as "probable"; scores of 1–4 are "possible"; and scores of less than 1 are "doubtful" (242). To summarize, the Naranjo algorithm, or a similar decision-making process, bridges the gap between raw data taking

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