

the form of a documented AE, and data that are classified as an ADR. An additional scale, that is, a scale that is an alternative to the Naranjo scale, is the RUCAM scale (243).

Bright (244) reveals issues that can impair discovery of a cause, that is, of a connection between the drug and the AE, as follows. Recognition of a relationship between a drug and an AE can be impaired where the AE is a common condition in the population of study subjects, where there is a time delay between drug use and the AE, and where the AE occurred in a different organ in the body than the organ that was being treated by the drug.

The fact that gray areas need to be navigated when assessing causality is revealed by the following excerpt from Clinical Study Protocol on a study of leukemia (245). The fact that gray areas are involved is evident from the terms, “reasonable possibility,” “[a]nother cause . . . is more plausible,” and “current knowledge . . . indicates.” The excerpt from the Protocol reads:

**Causality.** The Investigator is to assess the causal relation (i.e., whether there is a reasonable possibility that the study drug caused the event) using the following definitions:

**Not Related:** Another cause of the AE is more plausible; a temporal sequence cannot be established

with the onset of the AE and administration of the investigational product; or, a causal relationship is considered biologically implausible.

**Unlikely:** The current knowledge or information about the AE indicates that a relationship to the investigational product is unlikely.

**Possibly Related:** There is a clinically plausible time sequence between onset of the AE and administration of the investigational product, but the AE could also be attributed to concurrent or underlying disease, or the use of other drugs or procedures. Possibly related should be used when the investigational product is one of several biologically plausible AE causes.

**Related:** The AE is clearly related to use of the investigational product.

Another example of a Clinical Study Protocol that reiterates part of the Naranjo criteria is cited (246,247). This Protocol concerned a study of prostate cancer.

#### b. Where Adverse Events Caused by the Disease Are of the Same Type as Adverse Events Caused by the Study Drug

One of the issues that arises with adverse event reporting, is how to capture and report a drug-related adverse event that is also associated with the disease alone (without drug). An answer is to monitor the frequency of the

<sup>243</sup>Miljkovic MM, Dobric S, Dragojevic-Simic V. Consistency between causality assessments obtained with two scales and their agreement with clinical judgments in hepatotoxicity. *Pharmacoepidemiol. Drug Saf.* 2011;20:272–85.

<sup>244</sup>Bright RA. Strategy for surveillance of adverse drug events. *Food Drug Law J.* 2007;62:605–15.

<sup>245</sup>A randomized, multicenter, open-label, phase 3 study of the bruton’s tyrosine kinase (BTK) inhibitor ibrutinib versus ofatumumab in patients with relapsed or refractory chronic lymphocytic leukemia/small lymphocytic lymphoma. NCT01578707; Phase 3. ORIGINAL PROTOCOL PCYC-1112-CA.

<sup>246</sup>Clinical Research Protocol. Study title: PREVAIL: a multinational phase 3, randomized, double-blind, placebo-controlled efficacy and safety study of oral MDV3100 in chemotherapy-naïve patients with progressive metastatic prostate cancer who have failed androgen deprivation therapy protocol no: MDV3100-03.

<sup>247</sup>Clinical Study Protocol available as supplement to, Beer TM, Armstrong AJ, Rathkopf DE, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. *New Engl. J. Med.* 2014;371:424–33.