- *Classification of adverse events as induced by disease versus induced by the study drug.* Proper alignment of any given AE with the safety definitions might require an awareness of whether the AE was induced by the disease, induced by the study drug, produced by the simultaneous presence of both disease and study drug, or produced by the study drug in combination with lingering biochemical or physiological effects from a previously administered drug.
- *Classification of adverse events by considerations used by statisticians.* This further develops the topics of intent-to-treat (ITT) analysis and per protocol (PP) analysis.
- *Classification of adverse events as anticipated versus unanticipated.* An awareness of this classification can influence how AEs are reported to regulatory agencies.
- *Using adverse event data to acquire cause-and-effect information on ADRs.* An awareness of this issue can also influence how AEs are reported to regulatory agencies. This introduces the Naranjo algorithm.
- *Paradoxical ADRs.* The paradoxical nature of some AEs may impair an investigator's ability to anticipate these AEs before embarking on a clinical trial, and may impact the way the paradoxical AEs are reported to regulatory agencies.
- *Monitoring and evaluating adverse events.* This material constitutes a shift in the chapter from issues that are medical and scientific, to issues relating to the processes of managing drug safety reporting. This introduces the job of the data manager, and a form called the Case Report Form (CRF).
- *Adverse events—capturing, transmitting, and evaluating data on adverse events.* This introduces the topic of transmitting and routing of reports of AEs, from any given clinical trial.
- *Forms for reporting of adverse events.* This reveals special forms for capturing AEs from individual patients, for use in clinical trials, or for use by the general public outside of any clinical trial.
- *Risk minimization tools.* This focuses mainly on *Dear Healthcare Professional* letters. Candid, unbiased accounts of risk minimization tools, such as *Dear Healthcare Professional* letters, consent forms, and package inserts, are available from published courtroom cases. Information about the content of these letters can also be found on the FDA's website at the location, "Approved Risk Evaluation and Mitigation Strategies (REMS)." The most comprehensive and reliable source of information on REMS is that which is published on the FDA's website, for any given drug, at the same time that the FDA publishes its *Approval Letter*.
- *Patient-reported outcomes.* PROs encompass both safety and efficacy reporting.
- *Data and Safety Monitoring Committee.* This Committee plays a major role in regulated clinical trials. The Committee meets at regular intervals, reviews data on safety and efficacy, has the authority to unblind data, and recommends (but does not mandate) changes in the clinical trial. A typical recommendation is that of halting the clinical trial.

b. Examples of Adverse Events

The example of interferon-alpha-2b (IFN-alpha-2b) provides a concrete example of various adverse events. This drug is mainly used for treating melanoma (9), leukemias and

[9]Hauschild A, Gogas H, Tarhini A, et al. Practical guidelines for the management of interferon-alpha-2b side effects in patients receiving adjuvant treatment for melanoma: expert opinion. Cancer 2008;112:982–94.