The Center for Drug Evaluation and Research (CDER) of the Food and Drug Administration (FDA) is responsible for ensuring the safety and effectiveness of human drug products. CDER recognizes the value of therapeutic agents and encourages innovation in their development. CDER tries to ensure that approved drugs are accompanied by labeling that describes the benefits and risks of the drugs and provides good directions for use.

The Bleeding Academic Research Consortium (BARC) is an example of such efforts. An independent group, BARC includes members of academic research organizations, cardiovascular professional societies, pharmaceutical and cardiovascular device manufacturers, the National Institutes of Health, and the FDA (CDER and Center for Devices and Radiological Health). The FDA participated in a 1-day meeting in February 2010 to discuss bleeding and how it should be defined and captured in clinical trials. Many drugs used to decrease cardiovascular events do so by inhibiting platelet function or coagulation; they almost invariably cause increased bleeding. Properly describing the nature and consequences of that bleeding is critical in these drug assessments.

The FDA supports the use of standardized end point definitions that have been validated and properly reflect clinical outcome. Although not yet validated or associated with clinical outcome, BARC is a step in the right direction. A comprehensive analysis of extensive databases of prospectively acquired bleeding data linking various bleeding definitions and components of these definitions to clinical outcomes would be optimal. It would also be helpful to map the definitions to source data elements.

BARC proposes 5 bleeding types. Type 0 is no bleeding. Type 1 is bleeding that “is not actionable” and does not cause the patient to seek medical attention. Type 2 bleeding includes any clinically overt sign of hemorrhage that “is actionable” and requires diagnostic studies, hospitalization, or treatment by a healthcare professional. Type 3 bleeding is divided into 3 categories, a through c, and includes clinical, laboratory, and/or imaging evidence of bleeding with specific healthcare provider responses. Type 3a bleeding includes any transfusion with overt bleeding and overt bleeding plus a hemoglobin drop of ≥3 to <5 g/dL. Type 3b bleeding includes overt bleeding plus a hemoglobin drop of ≥5 g/dL. Type 3c bleeding includes intracranial hemorrhage and intraocular bleeding compromising vision. Type 4 bleeding is coronary artery bypass grafting (CABG)-related (within 48 hours), and type 5 bleeding is fatal. Fatal bleeding is categorized as intracranial, gastrointestinal, retroperitoneal, pulmonary, pericardial, genitourinary, or other.

Questions that BARC needs to address include why a 48-hour window was selected for CABG-related bleeding, but a 72-hour window was selected for a peri-CABG event using the universal definition of myocardial infarction; why a type 1 bleed is called “not actionable” when the patient may “take action” and discontinue medication because of bleeding without seeking medical attention; and why an intraocular bleed compromising vision is thought to be equivalent to an intracranial hemorrhage for BARC type 3c bleeding when we do not know whether this intraocular event, albeit serious and debilitating, is associated with clinical outcome. With respect to a type 1 bleed, a patient discontinuing medication without discussing the bleeding event with a healthcare professional could have an unfavorable outcome, especially if the patient had recently undergone stent placement. Additionally, from a regulatory standpoint, it would be important to determine whether a type 1 bleed should have been interpreted as a type 2 bleed. For example, what if a patient misinterpreted a gastrointestinal bleed as a hemorrhoidal bleed, leading to a delay in the diagnosis? Tracking this time delay could be critical, especially in the diagnosis of cancer in a clinical trial.

We encourage all sponsors to interact early with the FDA to discuss drug development, clinical trial design, and end points. Although standardized end points and definitions are helpful, they may need to be tailored according to the type of trial and to the particular drug and population being studied. In any development program, a thorough evaluation of...
dose-response is required. We recommend studying multiple doses in phase 3 trials to explore and confirm dose response. It is often useful to capture data elements for several bleeding definitions in a clinical trial and subsequently to conduct multivariate analyses to determine what baseline factors and components of particular bleeding definitions are associated with outcome. BARC places CABG-related bleeding into a separate class, without documenting that the CABG association per se leads to a different clinical implication of a given bleeding event. Nevertheless, there may be a rationale for capturing clinical context because it may alter the benefit-risk relationship in those settings, and clinical contexts other than CABG merit consideration, such as, other surgical procedures or percutaneous coronary intervention.

The FDA acknowledges the importance of BARC’s global approach to a consensus set of bleeding definitions and encourages similar efforts. Although definitions are important, what is even more critical is how the data are collected. Through collaboration, we can address these issues and improve the quality and efficiency of clinical trials.

Disclosures
This article reflects the views of the authors and should not be construed to represent FDA’s views or policies. The authors report no conflicts.

Reference

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