

FDA PUBLIC HEARING CONCERNING THE REPORTING OF ADVERSE EVENTS TO INSTITUTIONAL REVIEW BOARDS

[Docket No. 2005N-0038]

The Cancer Therapy Evaluation Program (CTEP), Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI), National Institutes of Health (NIH) appreciates the opportunity to submit comments concerning the *Federal Register Notice* of February 8, 2005 (Document No. 2005N-0038). We wish to address three primary issues: 1) that Adverse Event (AE) reports submitted to IRBs should provide sufficient information and medical assessment so as to allow IRBs to discern the implications of the Adverse Events to clinical trials being conducted at their institution; 2) that Central IRBs for multi-institutional clinical trials can greatly reduce the administrative burden to local IRBs associated with adverse events while at the same time protecting research subjects through an appropriate assessment of Adverse Events occurring on these trials; and 3) that the provision to IRBs of consolidated reports of Adverse Events at specified intervals may have advantages over episodic reporting of Adverse Events, particularly for agents that are past their early phases of development. Each of these items is discussed in greater detail below.

- § CTEP sends copies of Adverse Events submitted to FDA to investigators, who are then to submit these to their local IRBs. Each of the Adverse Event reports submitted to FDA contains an assessment by CTEP medical staff of the event, an attribution of cause (e.g., agent, disease, other), an indication of how many similar events have occurred with the agent, and the total number of patients treated with the agent to date. This level of information is essential for allowing IRBs to discern the implications of the serious Adverse Events described in the reports to clinical trials being conducted at their institution.
- NCI has established two central IRBs (CIRBs) for review of large multi-institutional adult and pediatric trials. NCI's interest in establishing CIRBs for its multi-institutional trials was to improve access to clinical trials for patients and their physicians, to enhance the protection of research participants by providing consistent expert IRB review at the national level, and to reduce the administrative burdens on local IRBs. According to the CIRB model, a participating local IRB can designate the CIRB as the IRB of record for a particular protocol. If the local IRB makes that designation, the CIRB becomes the reviewing IRB for the life of the protocol, including review of Adverse Event reports. These procedures significantly reduce the regulatory burden for participating local institutions. Local investigators are required to report only local serious Adverse Events to their IRBs. Neither the local IRB nor the local investigator have direct Adverse Event reporting obligations to the CIRB. Instead, the CIRB receives Adverse Event reports through the NCI's nationwide reporting system. The CIRB tracks Adverse Events by protocol and, like any other IRB, requires amendment of consent forms when it considers it appropriate to do so. CIRB review of each serious Adverse Event report is posted on the private side of the CIRB website for access by local participating IRBs who may want

perspective on a serious Adverse Event that has occurred at their institution.

A broader application of CIRBs for multi-institutional clinical trials could significantly reduce the regulatory burden to local IRBs associated with review of Adverse Event reports while at the same time enhancing the protection of research subjects through expert IRB review at the national level.

§ CTEP acknowledges the importance of the concerns described in FDA=s announcement for the public hearing on AReporting of Adverse Events to Institutional Review Boards@. CTEP recognizes that it is difficult for IRBs and other review bodies to assess the implications of reported events for study subjects when such events are submitted individually and sporadically throughout the course of a study, especially when the submissions lack analysis and context. While episodic reporting of adverse events is necessary for investigational agents that are in early phases of clinical development, this approach may not be required once sufficient experience is gained with agents. CTEP, as the sponsor of many multi-institutional phase 3 trials, would be interested in exploring with FDA and with IRBs alternative approaches for providing information about adverse events for agents that are in their later stages of development. Consolidated reports at specified intervals (e.g., at the time of annual report submission) could provide IRBs with Adverse Event data with sufficient analysis and interpretation so as to allow IRBs to draw reasonable conclusions about the implications of the information for study subjects.