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**BY ELECTRONIC SUBMISSION:** <http://www.fda.gov/dockets/ecomments>

Division of Dockets Management (HFA-305)  
Food and Drug Administration  
5630 Fishers Lane, Room 1061  
Rockville, MD 20852

**Re: Draft Guidance for Clinical Investigators, Sponsors, and Investigational Review Boards on Adverse Event Reporting – Improving Human Subject Protection [Docket No. 2007D-0106]**

Division of Dockets Management:

The Association of American Medical Colleges (AAMC) is a nonprofit association that seeks to improve the nation's health by enhancing the effectiveness of academic medicine. It represents all 125 U.S. and 17 Canadian accredited allopathic medical schools, nearly 400 major teaching hospitals and health systems, 96 academic societies, and the nation's 67,000 medical students and 104,000 residents. The AAMC is pleased that the FDA has acknowledged and has moved to address a significant problem in human subject protection: the inundation of IRBs with large volumes of individual adverse event reports that due to lack of context, detail, and analysis of clinical significance, do not assist and in fact hamper the ability of IRBs to protect the rights and welfare of human subjects. The AAMC is also gratified that the recommendations in the draft guidance are consistent with the suggestions provided by AAMC and others at the hearing held by FDA in March, 2005. Thus, FDA has recognized that the sponsor has the expertise, breadth of data, and responsibility for analyzing adverse events and determining if an unanticipated problem exists. Additionally, FDA is to be commended for providing specific guidelines on what constitutes a reportable unanticipated problem. However, the AAMC believes that the draft guidance can be improved and is pleased to offer suggestions for such improvement.

1. FDA is obviously aware that the HHS Office of Human Research Protections (OHRP) has also recently issued guidance on reviewing and reporting unanticipated problems. We believe it is essential that the guidances from these two agencies be harmonized wherever possible in order to assist implementation by sponsors, investigators, and IRBs. We therefore urge that FDA and OHRP work jointly to harmonize the guidance on this topic to the greatest extent possible. For example, the

OHRP guidance contains an algorithm for determining when an adverse event is an unanticipated problem. FDA could indicate in their guidance whether they concur with this algorithm and whether in FDA's view it is consistent with the FDA guidelines.

2. The guidance clearly notes that "to satisfy the investigator's obligation to notify the IRB of 'unanticipated problems', an investigator may rely on the sponsor's assessment and provide to the IRB a report of the unanticipated problem prepared by the sponsor." Moreover, the guidance indicates that if the sponsor reports an unanticipated problem directly to the IRB, the investigator need not provide a duplicate report. However, the guidance does not explicitly state that an investigator need not provide reports of adverse events that are not unanticipated problems. Because institutions and investigators tend to be overly cautious with regard to the regulatory agencies, we believe that providing such an explicit statement would have value as institutions implement the new guidance.

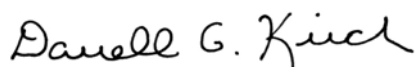
3. The guidance is silent on the timeframe for the reporting of an unanticipated problem by sponsors to investigators and IRBs, and this should be clarified. Similarly, it should be clarified that aggregated and analyzed adverse event reports that are found not to be an unanticipated problem may be provided to the investigator and IRB on the schedule adopted for safety reporting at study initiation.

4. The guidance for devices differs substantively because the regulations contain specific timeframes. These timeframes will in many cases prevent the meaningful aggregation and analysis of adverse events by the sponsor that the guidance provides for drugs and biologic products. Thus, the problem of adverse event reports that lack context, detail, and analysis of clinical significance cannot be meaningfully addressed for devices until the regulations are modified.

The AAMC appreciates the opportunity to provide comment and looks forward to working with the FDA and other stakeholders to further improve human subject protections.

Please contact Howard B. Dickler, M.D. ([hdickler@aamc.org](mailto:hdickler@aamc.org); 202-828-0567) of the AAMC staff for questions or clarification of these comments. We thank you again for the opportunity to express our concerns.

Sincerely,



Darrell G. Kirch, M.D.

President