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September 10, 2009

Margaret A. Hamburg, MD
Commissioner
U.S. Food and Drug Administration
10903 New Hampshire Ave., Bldg. 1, Rm. 2217
Silver Spring, MD 20993

Dear Dr. Hamburg:

The Infectious Diseases Society of America (IDSAs), a professional medical society representing 8,600 infectious diseases physicians and scientists devoted to patient care, education, research, prevention and public health, is increasingly concerned about the effects of regulatory burden on the ability to perform badly-needed clinical research. In a recent policy statement, IDSAs identified five key areas in which pragmatic actions could be taken that would decrease duplicative and ineffective regulatory burden.¹ One of these five areas directly involves the U.S. Food and Drug Administration (FDA). Specifically, IDSAs proposes that one major aspect of the system for adverse event reporting from multicenter clinical trials is unnecessarily duplicative and expensive.

It is critical that adverse events occurring during the course of interventional biomedical research be identified and analyzed in a timely manner. Modern clinical trials include an efficient system for adverse event reporting and analysis. Adverse events from multicenter clinical trials are reported to the sponsor's Data Center, often over the Internet. These events can undergo initial analysis and categorization using software packages developed for that purpose. When needed, adverse events can be further analyzed at the Data Center by appropriate expert reviewers (nurses or physicians). In this way, adverse events from a multicenter trial can be analyzed in real-time. If concerns are identified, these can be reviewed by an independent Data Monitoring Committee, if one has been constituted for the study, and/or by the study's sponsor.

At present, adverse events also are reported to local Institutional Review Boards (IRBs), often to the IRB of every study site involved in the evaluation of a specific medication or device. Because contemporary clinical trials often enroll many participants and evaluate interventions for serious diseases, local investigators and IRBs receive a flood of off-site adverse event reports.² Importantly, neither the local investigator nor the local IRB has access to the information that would allow them to perform any meaningful analysis of individual adverse event reports (e.g., denominators that would allow calculation of rates of adverse events). As a result, the evaluation of off-site adverse event reports becomes a pointless exercise for local investigators and IRBs, and one that is estimated to consume 9% of the local IRBs time and resources.³

All parties involved – FDA, the National Institutes of Health, the Office of Human Research Protection [OHRP], representatives of local IRBs – agree that this parallel system of adverse event analysis is wasteful and does not contribute to the protection of the safety of research participants. Indeed, both FDA and OHRP raised concerns that this process might well detract from protecting research participants, because it diverts the time and attention of the local IRB.^{4,5} Of note, this wasteful system is not required by United States law or the Common Rule.

Recognizing this problem, FDA⁶ and OHRP⁵ each issued updated guidance for adverse event reporting and analysis. Both guidance documents highlighted that local IRBs are not required to review most off-site adverse event reports. Unfortunately, the two guidance documents differ on key points. FDA suggested that local IRBs should continue to receive and review off-site reports of certain kinds of unanticipated problems (a single episode of a serious event that is uncommon and strongly associated with drug exposure, a single occurrence that is not commonly associated with drug exposure but is uncommon in the study population, an adverse event that has been described but is occurring at an unexpected rate, etc.).⁶ In contrast, the OHRP guidance document suggests that local IRBs only be notified if there is a finding by the sponsor or the independent Data Monitoring Committee regarding patient safety.⁵

These differences between the guidance documents for adverse event reporting and analysis from two sister agencies of the Department of Health and Human Services are confusing to sponsors, investigators and IRBs. The need for disparate guidance documents is not evident. The responsibility for safeguarding the safety of research participants in multicenter clinical trials lies with the sponsor, its Data Center and the Data Monitoring Committee (if one has been constituted). As above, the local IRB cannot perform a meaningful analysis of adverse events, even if it had the resources to do so. For example, neither a local investigator nor a local IRB could identify “an AE [adverse event] that is described or addressed in the investigator’s brochure, protocol, or informed consent documents, but occurs at a specificity or severity that is inconsistent with prior observations⁶”; only the sponsor and its Data Center have access to the data elements that would allow such an analysis.

IDSA supports OHRP’s approach towards adverse events reporting and analysis for multicenter clinical trials and recommends that FDA issue guidance consistent with OHRP’s guidance. The involvement of research sponsors from industry and the federal government in this process may be helpful.

Thank you for your attention to this matter.

Sincerely,



Anne A. Gershon, MD, FIDSA
IDSA President

cc: Jerry A. Menikoff, MD, JD, Director, OHRP
Joshua Sharfstein, MD, Deputy Commissioner, FDA
Jesse Goodman, MD, Chief Medical Officer, FDA

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