Statement Regarding Adverse Event Reporting

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Good morning/afternoon. My name is Howard Dickler, M.D. and I am the Senior Consultant at the Division of Biomedical and Health Sciences Research at the Association of American Medical Colleges (AAMC). Prior to joining AAMC in January 2005 I was the Senior Associate Dean for Research and Graduate Studies at the University of Maryland School of Medicine. In that position I was responsible for oversight of the Human Research Protections Program. Prior to that I was the Chief of the Clinical Immunology Branch at the National Institute of Allergy and Infectious Diseases where I helped found two national multi-center trial networks and design the initial trials carried out by those networks. I have also served as a chairman of a data safety monitoring committee and have served on the IRB of the National Cancer Institute. I represent the AAMC, which in turn represents the nation's 126 medical schools, more than 400 teaching hospitals, and 94 professional societies representing about 105,000 academic medical faculty. Biomedical and health sciences research involving human subjects takes place at all of these institutions, and all of them have human subjects protection programs in place. In developing our comments and recommendations for this hearing, we have consulted with numerous individuals at these institutions, including directors of human subjects protection programs, research and clinical research deans, and university counsels.

Our recommendations have several goals. **First** and most important is to ensure that medically and scientifically relevant data on adverse events are communicated to IRBs in a timely manner that will facilitate their central role in protecting human participants in clinical trials. **Second** is to ensure that IRBs remain focused on the task for which they were created: to make an ethical determination that risks to human subjects have been minimized to the greatest extent possible, that the risks are reasonable in relation to anticipated benefits if any, and that the risks, benefits, and alternative options are clearly communicated to the potential participants in the informed consent process. IRBs were never intended to act as scientific review or data monitoring committees. **Third** is to propose a process that will promote responsible and effective adverse event reporting during the conduct of multicenter clinical trials in order to stem the flood of non-aggregated, unanalyzed adverse event reports that currently inundates human research protection programs. This massive burden drains resources that could be better used in protecting human subjects, is inefficient and wasteful because duplicative efforts are undertaken at each site, and can be ineffective because essential information and analysis are often absent from the reports. **Fourth,** to use, as much as possible, language in existing regulations to construct this process, thereby easing and speeding the implementation of changes.

If one were to create an ideal approach and process to accomplish these goals, what would the characteristics be? We would suggest the following characteristics:

1. For adverse events that occur at other sites in a multicenter trial (external adverse events), IRBs should be given summary reports of serious, unexpected events that are possibly, probably or definitely related to the study. These summary reports would contain all available relevant and aggregate information and statistics, an evaluation of that information, a determination of whether or not risk was involved, and if risk were involved, a recommendation as to a study change (temporary suspension, termination, protocol modification, change in the consent).
2. Local event reporting (internal adverse events) would remain largely unchanged; IRBs would continue to receive and review all individual reports of serious, unexpected and related events for local subjects, along with the investigator's assessment about whether the event involves risks and necessitates a change in the protocol or consent.
3. The full IRB would continue to focus on the ethical decisions that are its mandate.
4. The process could be accomplished with no or minimal additional expense, and without the creation of new and additional committees or entities
5. The rules would be largely identical for drugs, biologics and devices.
6. All of the responsible parties - the investigators, the sponsor, and the IRBs, would review the summary and the determination of whether risk was involved and whether study changes and full IRB review were needed.
7. The process would be implemented as soon as possible via the issuance of guidance that builds as much as possible on current regulatory language.

Recommendation: We recommend that the sponsor be made responsible for the preparation of the summary adverse event report described above for a number of reasons. First, of the responsible parties, only the sponsor has study-wide data. Second, the sponsor may be in possession of additional data from other studies using the same drug, biologic or device. Third, the sponsor employs individuals with the medical and scientific expertise needed to examine the data and make determinations about risk. Third, the language in the existing regulations for medical devices lends itself to this approach. This language requires reporting to the IRB and to the sponsor all unanticipated adverse device effects as soon as possible but not later than 10 days after the investigator learns of the effect. Then, "sponsors are required to report the results of an evaluation of a reported effect to reviewing IRBs and investigators within 10 working days after the sponsor receives notice of the effect." We believe that an effective and manageable adverse event reporting process for multicenter trials can be established by issuing guidance (and eventually regulations) making the following additions and changes to this language: (1) This requirement should apply to studies of drugs, biologics and devices. (2) The word evaluation should be defined to mean the preparation of a summary report for all unexpected, serious and related adverse events, which contains all available relevant and aggregate information and statistics, an evaluation of that information, a determination of whether or not risk was involved, and if risk were

involved, a recommendation as to a study change (temporary suspension, termination, protocol modification, change in the consent). (3) The investigator and the IRB (for the latter usually one or a subgroup of clinician investigator members of the IRB) will review the report and recommendation, and, in cases where the sponsor determined that risk was not involved, have the option of making a different determination. All adverse events determined to involve risk by any of the parties will be rapidly communicated to the full IRB. Those that do not will be forwarded in summary fashion at the time of continuing review. All adverse events that do not meet the criteria of serious, unexpected, and related will be aggregated, analyzed, and forwarded to investigators and IRBs for continuing review.

We believe that if these recommendations are adopted, the goals stated at the beginning of our presentation will be reached. A process will be in place where the full IRB is allowed to focus on its ethical mandate, all the responsible parties are appropriately involved, and multiple line of protection exist for human subjects. Additionally, this approach will greatly reduce the flow of paperwork to IRBs, and will increase the efficiency and effectiveness of review of unanticipated serious adverse events.

While we feel we have proposed a process that can work well, we must also note that this process is based on trust, and is dependent on the sponsor carrying out its role in a complete, honest, and responsible manner. Certain recent events have cast a shadow on that trust. Should future events further erode the confidence and trust placed in the sponsor, this process will have to be revised. In that situation it is likely that a new and more costly mechanism will have to be created, under either the FDA itself or its designee, to perform these tasks.

We thank you for holding this hearing and seeking solutions for a problem that is an obstacle to strong human subject protections.