



AAMC, COGR Comment on HHS Draft Guidelines on Clinical Research Misconduct

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Dear Mr. Pascal:

Thank you for your invitation to comment on the Office of Research Integrity's draft guidelines for assessing possible research misconduct in clinical research and clinical trials. As you know, the Association of American Medical Colleges (AAMC) represents the nation's 125 accredited medical schools, over 400 teaching hospitals, and 91 academic and scientific societies. We are joined in these comments by the Council on Governmental Relations (COGR), a nonprofit organization representing 143 of the most research-intensive universities in the United States. The guidelines touch on two themes that are fundamentally important to our memberships: the promotion of clinical research, in all its forms, to improve public health and the paramount responsibility to conduct this research ethically.

The guidelines were developed ostensibly to assist institutional officials and members of institutional inquiry and investigation committees as they handle allegations of research misconduct related to human patient studies and clinical trials. For the guidelines to be beneficial, they should provide clear guidance on the types of evidence, appropriate procedures, and various authorities necessary for the institution to respond effectively to alleged misconduct.

Our comments focus on specific sections of the guidelines below. In general, however, we are very concerned that mandatory language (e.g., "shall" or "must") is used throughout, with insufficient indication that the guidelines themselves are not binding upon awardee institutions, except as they describe express statutory or regulatory requirements. By contrast, the draft guidelines fail to instruct that in conducting a misconduct inquiry or investigation an institution must comply faithfully and fully with its own written policies and procedures, as required by 42 C.F.R. § 50.101.

We are concerned as well that the guidelines incorrectly characterize an institution's reporting obligations to ORI by using the terms "inquiry" and "investigation" interchangeably. Moreover, the draft guidelines blur critical distinctions among several elements of an inquiry and investigation that have been long established in federal policy. The draft fails to distinguish properly between "research records" and "medical records" and gives insufficient attention to the application of federal policies, such the requirement to protect the privacy of personally identifiable medical information (detailed in the discussion of Section X below), or to the complex and variable network of state laws that restrict access to medical records without express patient authorization. Finally, the guidelines make *prima facie* assumptions about the reliability of an allegation--treating stated accusations on a par with empirical evidence, neglecting to discuss the rights of the accused, etc.--that appear to favor the accuser over the accused in an institution's response to the allegation, and, therefore, are entirely inappropriate.

Section III: Definitions

As defined, *clinical research* relies on the involvement of "people having or suspected of having a clinical disease, and appropriate control subjects." Under the Common Rule, "research" with human beings includes studies of existing data (e.g., identifiable archived tissue or medical records) conducted pursuant to an IRB's waiver of the consent requirement. It is not clear whether these guidelines will apply to archival research, particularly genetic studies, conducted under a waiver of consent. If so, the guidelines must be modified accordingly, as the subjects/patients will not have authorized access to their medical records for the purpose of auditing the research record. Different types of clinical research rely on vastly different sources of data and thus affect the kinds of data that may be considered as evidence in consideration of an allegation of research misconduct. For consistency and clarity, ORI should rely on the definitions of research and human subject employed in the Common Rule.

The guidelines broadly define *research record*, including any record that "reasonably may be expected to provide evidence of information regarding the proposed, conducted, or reported research that constitutes the subject of an allegation of research misconduct." The guidelines also define source data and source documents by a broad list of examples, but do not distinguish, for example, how the research record differs from other types of record. Only fabrication and falsification within the research record would constitute scientific misconduct. Such distinction is not made within the guidelines.

The definition of *discrepant data* is unacceptable:

Discrepant data are data that have been identified as questionable by a

complainant (a.k.a. "whistleblower") or investigating body or that appear to be suspect on the basis of various tests (see Section VII). The discrepancy need not be limited to quantitative research "data" such as measurements of blood pressure.

As stated in our discussion of section VII below, the allegation made by a complainant of a data discrepancy should not be presumed to have the same level of credibility as a determination by an institutional investigating body. The AAMC and COGR agree with ORI that qualitative information may also be at issue in an allegation of research misconduct, but certainly the process for determining fabrication or falsification of qualitative information presents uniquely problematic aspects for an inquiry or investigation. The guidelines do not advise on such problems.

Section V: Persons Who May be Responsible for Committing Research Misconduct

This section establishes that any member of a research team may be responsible for research misconduct and should be considered possible respondents under an inquiry or investigation. The guidelines must emphasize that, while any member of the research team possibly may be a respondent, our legal system is based on the presumption of innocence of the accused and therefore a charge remains an allegation until proven. As noted above, the guidelines should be revised to emphasize that an institution is required to afford the respondent a fair process in accordance with the institution's own written policies and procedures for the investigation of misconduct.

As the guidelines acknowledge, most allegations of fabrication or falsification in research are resolved without a finding of misconduct. Such resolution is usually aided by the cooperation of the involved parties. An institution's demonstrated respect for the rights of the accused is beneficial not only for fairness, but to avoid the appearance of a presumptive or adversarial process that might discourage openness and cooperation from members of the research team.

Section VI: Sources of Information

The guidance states, "the patient medical chart or file represents the primary source of data for all clinical research, and the research file should state those data accurately." The statement is incorrect. Not all clinical research relies on the medical chart as the primary source of data. Even when the research record is derived in whole or in part from information in the medical record, the research record and the clinical record remain legally distinct. The health care provider, not the researcher, controls access to the medical record, and is responsible for compliance with all state laws and regulations and all institutional policies that govern the use or disclosure of confidential medical information.

The section should explicitly note that the research record is frequently separate from the patient record, and that the research record may be accurate when the patient record is not. The medical chart and ancillary records provide *potential* sources for independent verification of data or other information entered in research data forms, but they can also be misleading due to inadvertent errors in processing, etc.

In the case of clinical trials, research records are specifically identified by the protocol and not everything in the patient's medical record corresponds to research data.

Section VII: Identification of Discrepant Data

The guidance distinguishes among three sources for identifying discrepant data:

"a whistleblower who is a member of the clinical study team recognizing a pattern of discrepant data, observing another team member recording falsified or fabricated data, or being instructed by a superior to falsify or fabricate data.

"a review and comparison of data by clinical site personnel or coordinating center personnel.

"a routine quality assurance audit of patient medical files and research records."

This section groups together widely differing sources of allegations and would serve only to confound a pre-inquiry. In the first item, recognizing (and reporting) a pattern of discrepant data is markedly different from reporting that one witnessed another team member recording falsified or fabricated data. More different still is the case where an individual reports being instructed to falsify or fabricate data (in this case, it not only remains to be determined that data were fabricated or falsified, but also that the accused and not the accuser or other individual was responsible). The third item, again, equates the patient medical record with the research record. The possible sources of data discrepancy should rather be grouped according to the level and type of information needed to ascertain whether a concern exists, and whether such discrepancies in fact may pertain to *research* misconduct.

The section on statistical methodologies is wholly inappropriate in this section. Statistical methodologies, expertly performed, may be employed in an inquiry as a test of a hypothesis of misconduct drawn from other observations. The methodology must be employed and interpreted with the assistance of a qualified statistician. It is sufficient for the guidance to cite standard works on statistical analysis in detection of

misconduct; the level of detail provided in these paragraphs is superficial and unnecessary.

The AAMC and COGR also believe, as we have suggested elsewhere, that the use of the term "whistleblower" in administrative and legal proceedings should be discouraged. It has an unnecessarily colorful and at times pejorative connotation that can undermine the status of those who report misconduct responsibly. In addition, the term "whistleblower" is generally applied only to the originator of an allegation and not to those who may corroborate facts or otherwise assist with an inquiry or investigation, and is thus too narrow in scope. As noted in other AAMC statements, more suitable descriptors of those who report or provide information on suspected misconduct are "complainants" or "witnesses." These terms are more neutral and better define the role of such individuals in the investigative process.

Sections VIII and IX: Reporting of Discrepancies and Notifications

The section on Notification contains the statement "If the pre-inquiry assessment indicates that misconduct in clinical research may have occurred, a formal inquiry or investigation is warranted . . . and ORI should be notified immediately. . ." The AAMC and COGR believe that terminology used in the guidelines should conform to the regulatory scheme for misconduct investigations; thus, the terms "inquiry" and "investigation" should not be used interchangeably. As specified in 45 C.F.R. § 50.103, "inquiries" are internal institutional matters. As further specified in 45 C.F.R. § 50.104, ORI is notified only upon completion of the inquiry, or in the event that the institution discovers a possible criminal violation, an immediate health hazard, an immediate threat to federal property, federal funds, or the interests of the complainant, or if it appears likely that the incident will be reported publicly. Unlike an internal inquiry, an institution must notify ORI prior to commencing a formal "investigation."

If the section were interpreted literally, the guidance could appear to require an institution to report to ORI after the pre-inquiry ("ORI should be notified immediately") clearly constituting an impermissible and unwarranted alteration from current regulation.

The section on additional considerations for allegations of research misconduct involving Multi-Center Clinical Trials is too scant for so complex an issue. Laudable efforts are being made to consolidate and centralize institutional review board responsibilities in multi-center trials; similar efforts may be required on other aspects of these trials, including misconduct investigations. This is a very complex issue and demands further consideration with input from the research community, the NIH, and other agencies.

Sections X: Conducting the Formal Inquiry

The AAMC's and COGR's most fundamental concerns with the draft guidelines focus upon consideration of medical records as evidence in conducting a formal inquiry and investigation. As indicated above, the guidelines do not provide sufficient clarification for how institutional committees should rely on the patient medical record or other sources to identify fabrication or falsification in the research record. Disagreement between these records is not of itself proof of misconduct; it is possible that the medical record or other information is itself erroneous or incomplete or may indicate egregious behavior (such as negligence on the part of other individuals) apart from research misconduct.

The draft briefly acknowledges that state laws and statutes may restrict the use of patient medical records and further states that use of patient medical records is "generally" granted when the patient consents to participate in PHS-funded research. We find that protections for the use of patient medical records are far more significant than indicated in the draft, and it is uncertain whether PHS guidance on patient consent is sufficient to allow an institution's use of patient medical records for investigations of research misconduct. The guidelines make only passing reference to state laws and fail to counsel institutions that under some state laws, access to medical records may be limited by the scope of disclosures authorized in the consent form. The guidelines do not mention federal law or the new Standards for Privacy of Individually Identifiable Health Information (45 CFR Parts 160 and 164), which apply to our institutions.

For example, the guidelines recommend that:

[institutional] investigating staff prepare a redacted set of records to be used for investigational purposes and analyses. In the redacted records, identify subjects only by a number (preferably the assigned study number), with all subject names and other associated identifiers removed."

Such procedure would, we believe, not be considered sufficient for de-identification of private health data under the new Standard for the Privacy of Individually Identifiable Health Information. The absence of consideration of the new federal regulations is particularly frustrating because the ORI would seem particularly well-positioned to speak with authority on the application of such regulations. At this stage of an evolving and complex national debate on patient privacy and informed consent, the guidelines must consider the extent to which authority for the use of medical records to address misconduct allegations are provided in the patient consent form. The draft guidelines do not do this.

Conclusion

AAMC and COGR do not believe that the draft guidelines can be finalized without

substantial rethinking and revision and more thorough consideration of the treatment of medical records in assessing allegations of research misconduct. Moreover, from the draft guidelines' brief paragraph under section II ("Purpose"), we are unclear on what need the guidelines are intended to serve and why the ORI feels it necessary to develop them. What does the document contribute to implementing or complying with carefully established federal policy on research misconduct investigations?

The only novel issue raised by the draft guidelines, we believe, is that relating to "medical records" versus "research records" in the context of responding to allegations of scientific misconduct. However, the use of medical records for such purposes raises complex issues that the document fails to illuminate in a satisfactory way. Further, development of these guidelines would benefit from stronger input from the research community, perhaps through a workshop or conference that should include clinical researchers, administrators, counsel to research organizations, and other individuals with pertinent expertise. If the guidelines are not able to advise institutions in a clear, convincing, and useful way, they should be withdrawn.

Sincerely,

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