Departmental and Institutional Strategies for Reducing Fraud in Clinical Research

Daniel I. Sessler, MD, and Andrea Kurz, MD

In recent years the anesthesia community has learned of major fraud in clinical research committed by Scott Reuben[1] and Joachim Boldt.[2] In November 2011, Donald Poldermans, an even more prominent perioperative investigator, was fired by Erasmus University for fraud. And most recently, 8 of Yoshitaka Fujii's publications were retracted after more than a decade of controversy.[3,4]

The extent of malfeasance and fraud in clinical research is unknown, but it is likely that data selection, incomplete blinding, undeserved authorship, and post hoc designation of primary outcomes are relatively common. In contrast, the most egregious types of fraud, such as outright fabrication or deliberate manipulation of results, are presumably rare. But even occasional episodes do enormous damage to confidence in clinical research results and patient trust, to say nothing of degrading the reputation of involved institutions. And most importantly, incorrect results may be incorporated into clinical practice with consequent harm to countless patients. Any degree and amount of fraud in clinical research is thus unacceptable. The purpose of this commentary is to discuss departmental and institutional strategies to reduce the risk of fraud in clinical research.

Consider the way clinical research was typically done in the past, and still often is. A single investigator develops a protocol, applies to the IRB, identifies qualifying patients, obtains consent, randomizes and provides treatment, evaluates outcomes, manages study data, does the statistical analysis, and writes a manuscript. This approach is acceptable if allocation is fully concealed until randomization, blinding is complete (i.e., identical-looking treatment and control drugs are provided by the pharmacy), and blinding is maintained throughout data analysis.

Principal investigators have legal and moral responsibility for their studies, and nothing we propose in any way diminishes this ultimate responsibility. We nonetheless believe that it is risky for a single investigator to control every aspect of a study. Instead, we advocate a central structure that distributes specific research functions among individuals or teams. A distributed approach not only provides substantial protection against malfeasance and fraud, but can also be the most efficient way to structure research with the highest degree of compliance and regulatory oversight. Some support for this approach is provided by Nath et al. who reviewed all retracted MEDLINE papers between 1982 and 2002 and found that papers retracted for fraud were nearly twice as likely to have a single author, and had significantly fewer authors.[5] The perspective for our recommendation are the systems that we have implemented in the Department of Outcomes Research at the Cleveland Clinic and how they integrate with institutional controls.

All anesthesia-related clinical research at the Cleveland Clinic is coordinated by the Department of Outcomes Research, 1 of 6 departments in the Anesthesia Institute. Major steps in prospective research include (1) approval by the Anesthesia Institute Research Committee; (2) approval by the Clinic's IRB; (3) patient screening and consenting; (4) randomization; (5) enrollment and protocol procedures; (6) measurements and outcomes evaluations; (7) data management; (8) statistical analysis; and (9) manuscript preparation. We generally delegate responsibility for these functions to separate teams. Retrospective studies undergo a similar process except that steps 3 to 6 do not apply, and step 7, which includes retrieval of appropriate data, is handled by one of our registry teams.

A single person is responsible for all communication with the IRB, including original applications, renewals, amendments, and reports of protocol deviations and adverse events. This coordinator also confirms that every study being done in the department is currently approved. Patient consent is usually obtained by a separate team, with each member specifically trained for each study. Every consent is evaluated by an independent monitoring team that confirms that (1) the approved and current version was used and signed appropriately; (2) a note was inserted into the medical record (to alert clinicians and other investigators); and (3) the patient was entered into the clinic's clinical trials management database (to alert clinic-level research regulators).

We recently switched to a Web-based randomization system, which provides considerable advantages and protections in comparison with sealed envelopes and similar techniques. For example, the Web-based system permits

From the Department of Outcomes Research, Anesthesiology Institute, Cleveland Clinic, Cleveland, Ohio.

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Address correspondence to Daniel I. Sessler, MD, Michael Cudahy Professor and Chair, Department of Outcomes Research, Cleveland Clinic, 9500 Euclid Ave., P77, Cleveland, OH 44195. Address e-mail to DS@OR.org. On the world wide web: www.OR.org.

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complicated stratification and requires investigators to confirm that patients meet enrollment criteria. But perhaps most important, it restricts access to authorized (i.e., unblinded) investigators and records who accessed the system, the date and time of randomization, the specific patient, and the treatment allocation. This allows us to confirm that, per good research practice, randomization was done at the last possible point in time, which reduces postrandomization withdrawal from studies and, importantly, reduces the risk of selection bias. And of course we subsequently confirm that patients actually received the allocated treatment.

Enrollment and protocol procedures must be separated from measurements and outcomes evaluations unless the study is fully double-blind, for example, by a central pharmacy. Otherwise, we assign completely separate teams to each set of functions. Transfer of data from case report forms to custom-designed study databases is a shared responsibility of investigators and data-entry personnel, with full blinding maintained. Thus no investigator can evaluate blinded outcomes as a study progresses. Values in the database are then 100% checked against case report forms and source documents (i.e., the electronic medical record) by an independent monitoring group that is otherwise uninvolved in the study. Upon study completion, paper case report forms are archived at a remote secure site; electronic data are secured on central clinic servers under strict access control.

Once verified by the monitoring group, data are submitted to our statistical team. Their analysis is based on the a priori statistical plan approved by the Research Committee, using predefined primary and secondary outcomes. This approach prevents "fishing" and inappropriate post hoc selection of outcomes, with consequent overestimation of significance levels. Results of the study are presented to the Executive Committee or Data and Safety Monitoring Board only at predefined interim analysis points.

And finally, unblinded results are presented, for the first time, to the principal investigator upon completion of the study. Statisticians coauthor the resulting manuscript in recognition of their effort, but also to ensure that the results are presented completely and accurately. As a final protection, papers published by members of the department are cross-checked by the Research Committee, which would presumably detect complete fabrications.

In addition to controls imposed by the Department of Outcomes Research, 5 administrative groups within the clinic conduct random (or rarely, for-cause) audits of clinical research projects. The IRB, Legal, Finance, Research Compliance, and Office of Sponsored Research all conduct audits that are typically in-depth, multiday processes. Among these groups, a fair fraction of studies are selected for audit. Individual fraudulent articles might well escape scrutiny, but it is highly unlikely that an investigator could sustain a long-term pattern of fraudulent activity without detection by a random audit.

The systems we present are appropriate for active research departments that can support centralized research functions. The Department of Outcomes Research, for example, has >35 full-time equivalents exclusively devoted to clinical research. This is a larger research infrastructure than most anesthesia departments can afford. Our point is not to discourage clinical research in smaller research units. Thus, not every level of separation will be practical or even desirable in particular departments. And in smaller departments, centralization might instead occur at the institutional level. But to the extent that various functions can be distributed among research personnel, the ability of any individual to propagate fraud will be reduced. Furthermore, information technology solutions—such as Web-based randomization, central databases, and central storage for regulatory paperwork and case report forms—will improve oversight. Departmental research committees can also contribute to central oversight. It is apparent, though, that some departmental or institutional commitment and investment is needed to create at least some clinical research infrastructure.

Because clinical research has become so highly regulated, it is now expensive and difficult. If clinical research was ever something physicians could do in their spare time at little expense and with few resources, it certainly no longer is. The overwhelming majority of clinical research thus now requires substantial support by skilled personnel. Centralizing this support and distributing specific functions does not necessarily increase cost. In fact, we believe that specialization improves efficiency and reduces cost because individuals responsible for specific aspects of research become experts in their areas, and thus work both faster and at higher quality than would otherwise be possible.

The risk of fraud is probably greater for investigator-initiated studies than for trials conducted by corporate sponsors. The reason is that sponsors have legal obligations to assure that the validity of data presented to national regulatory bodies such as the United States Food and Drug Administration. Sponsors thus usually closely monitor trial conduct and source-document integrity. (Sponsored trials are not necessarily free from bias or error, but the problems are more likely intrinsic to the design or result from failure to publish adverse results.) Departments and institutions might thus best focus their monitoring and controls on investigator-initiated studies.

Just as individual studies have limitations, the structure we advocate cannot prevent all research misconduct. Our local systems keep risk relatively low for single-center studies coordinated by our department. However, cutting-edge science nowadays is often multidisciplinary and requires collaboration with investigators in other departments and countries. Risk increases to the extent that research teams rely on investigators outside their own department, and thus remote from our oversight mechanisms.

Furthermore, multicenter research frequently involves exchange of ideas and skills independent from data acquisition (i.e., protocol design, analysis strategy, and manuscript preparation). For example, a study may start with an idea from an investigator at an international site that is refined by departmental faculty. Patients may then be enrolled at sites in 2 or 3 other countries, blood samples sent for special analysis to yet another country, and finally the statistical analysis done at the Clinic.

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Investigator-initiated multicenter research perhaps presents the greatest fraud risk. For example, language constraints, privacy rules, varying regulations in different countries, and especially financial limitations mean that it is rarely possible to audit collaborators outside the primary institution. But to varying degrees, risk can nonetheless be mitigated. Strategies appropriate for multicenter research include Web randomization, central review of case report forms, regular communication with all the investigators, and sophisticated statistical comparisons among sites.

In summary, it is impossible to prevent all research fraud, just as it is impossible to prevent all financial fraud. However, robust systems and distributed responsibility reduce risk. We encourage departments and institutions to develop and implement systems that foster clinical research integrity.

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