QUERI

Maintaining Research Integrity: A Systematic Review of the Role of the Institutional Review Board in Managing Conflict of Interest

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PREFACE

Quality Enhancement Research Initiative's (QUERI) Evidence-based Synthesis Program (ESP) was established to provide timely and accurate syntheses of targeted healthcare topics of particular importance to Veterans Affairs (VA) managers and policymakers, as they work to improve the health and healthcare of Veterans. The ESP disseminates these reports throughout VA.

QUERI provides funding for four ESP Centers and each Center has an active VA affiliation. The ESP Centers generate evidence syntheses on important clinical practice topics, and these reports help:

- develop clinical policies informed by evidence,
- guide the implementation of effective services to improve patient outcomes and to support VA clinical practice guidelines and performance measures, and
- set the direction for future research to address gaps in clinical knowledge.

In 2009, the ESP Coordinating Center was created to expand the capacity of QUERI Central Office and the four ESP sites by developing and maintaining program processes. In addition, the Center established a Steering Committee comprised of QUERI field-based investigators, VA Patient Care Services, Office of Quality and Performance, and Veterans Integrated Service Networks (VISN) Clinical Management Officers. The Steering Committee provides program oversight, guides strategic planning, coordinates dissemination activities, and develops collaborations with VA leadership to identify new ESP topics of importance to Veterans and the VA healthcare system.

Comments on this evidence report are welcome and can be sent to Nicole Floyd, ESP Coordinating Center Program Manager, at nicole.floyd@va.gov.

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This report is based on research conducted by the Evidence-based Synthesis Program (ESP) Center located at the West Los Angeles VA Medical Center, Los Angeles, CA funded by the Department of Veterans Affairs, Veterans Health Administration, Office of Research and Development, Quality Enhancement Research Initiative. The findings and conclusions in this document are those of the author(s) who are responsible for its contents; the findings and conclusions do not necessarily represent the views of the Department of Veterans Affairs or the United States government. Therefore, no statement in this article should be construed as an official position of the Department of Veterans Affairs. No investigators have any affiliations or financial involvement (e.g., employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties) that conflict with material presented in the report.

EXECUTIVE SUMMARY

BACKGROUND

Ethical integrity in the conduct of health care research is essential for maintaining the public trust and support of such activities. Institutional Review Boards (IRBs) play a critical role in maintaining the ethical integrity of research by reviewing research protocols to ensure, among other things, that research participants receive safe and ethical treatment and provide informed consent, and that the potential for a conflict of interest is minimized. The purpose of this review was to catalog the literature on issues pertaining to IRBs, to identify the issue with the greatest number of published studies which might inform VA policy, and to assess the evidence regarding that issue, which were conflict of interest policies and the activities of the IRB.

METHODS

This project was nominated by Ranjana Banerjea, HSR&D & HSR&D Research Best Practices Workgroup (RGP). The goal was to describe the evidence regarding areas of interest in the ethical conduct of research, with a particular focus on the IRB and quality improvement initiatives. Further discussions resulted in the following key questions:

Key Question #1. What has been published regarding the IRB, and each of the following issues:

- Quality improvement initiatives as research
- Conflict of interest
- Studies requiring approval of multiple IRBs
- Genetic issues

Key Question #2. What is the actual evidence regarding the issue with the largest literature which may inform VA policy?

We searched the PubMed databases from 1/01/2000-2/11/2011 for articles related to our key questions. We limited the search to English language articles using search terms related to institutional review boards, informed consent, data use, conflict of interest, ethics, and quality improvement. We also completed related-article searches on four key articles. We also searched the websites of relevant organizations, including the Association of American Medical Colleges (AAMC), Public Responsibility in Medicine and Research (PRIM&R), and the Association for the Accreditation of Human Research Protection Programs, Inc (AAHRPP).

We screened titles and then abstracts, excluding any article not related to the topics listed in Key Question #1. Full articles that met the inclusion criteria were then sorted into the following categories: multi-center IRB; quality improvement as research; conflicts of interest; payments to patients, providers, or study participants (a potential for conflict of interest); genetics research (this category mostly pertained to data repositories and the ethics of using stored genetic material for subsequent studies); miscellaneous articles pertaining to Key Question #1; background articles; and rejected articles.

DATA SYNTHESIS

After performing the search and sorting the articles that met our inclusion criteria, we then selected for detailed review the area for which we identified the greatest number of relevant published studies and for which no VA policies were already in place. Because of the nature of these studies, no quantitative synthesis was possible; therefore our synthesis is descriptive.

PEER REVIEW

A draft version of this report was reviewed by seven technical experts, as well as VA Central Office leadership. Reviewer comments were addressed and our responses were incorporated in the final report.

RESULTS

We reviewed 4,302 titles and abstracts from the electronic search and an additional 490 from related searches for a total of 4,792 references. After applying inclusion/exclusion criteria at the abstract level, we excluded 4,327 references. We retrieved 163 full-text articles and on the basis of further review, we excluded another 47 references. A total of 116 references were included in the current review.

Key Question #1. What has been published regarding the IRB, and each of the following issues:

- **Quality improvement initiatives as research**
- **Conflict of interest**
- **Studies Requiring Approval of Multiple IRBs**
- **Genetic issues**

We describe here the results of the search we performed. Our goal for this key question was to provide a broad "lay of the land" picture of the available evidence but not a critical synthesis of the evidence.

Multisite Institutional Review Board Challenges

We identified 41 articles that dealt with the challenges of having to submit a research protocol to IRBs at multiple institutions. Most were descriptive studies of how the same application was reviewed by different IRBs. VA has recently implemented a process whereby multi-site VA studies can be reviewed by a single, centralized IRB. Consequently, a detailed review of this issue would not be helpful to VA. The VA Central IRB does not review all protocols that require multiple IRB review. An issue remains that when a protocol is conducted at both the academic affiliate and VA facility, it has to be reviewed by both institutions unless the VA facility has an arrangement to delegate review to the academic affiliate. Further, industry-sponsored studies require multiple IRB reviews and VA prohibits the use of independent (commercial) IRBs.

When Quality Improvement Initiatives Are Considered Research

Quality improvement is an increasingly important activity for health care organizations and also the subject of scholarly activity. Questions have been asked about what quality improvement activities constitute "research" in the context of requiring approval and oversight by an IRB. We

identified 31 publications on this issue. However, because VA has recently developed policy on this issue, a detailed review would not be helpful.

Conflict of Interest

We identified 11 publications that dealt with potential conflict of interest (COI) in research, both by investigators and by IRB members. This issue was the one for which we identified the most articles; therefore we selected it for more detailed review (see Key Question #2).

Payment to Patients

We identified nine publications that dealt with the ethical issues surrounding paying patients to participate in research studies or paying heath care professionals to recruit patients into these studies. Four of these articles were descriptive studies about the payments to patients. Across studies, the amount of payment appeared unrelated to the magnitude of the procedures to be performed or the time to participate in the study. Payments to patients ranged widely, from $5 to $2000, with a median of $155. Two studies by the same investigator assessed the potential reasons for payments to participants. The results indicate that investigators consider various factors in deciding whether and how much to pay study participants.

Genetics

We identified eight publications that dealt with potential ethical issues in genetic studies for which an IRB was asked to rule. These issues consisted of consensus recommendations for informed consent and studies describing variation across institutions in genetic policies.

Miscellaneous

Eighteen publications were potentially relevant to the IRB's role in maintaining research integrity but did not fall into one of the existing categories. These studies were a mix of surveys about ethical issues, particularly challenging scenarios that might require special rules (such as practice-based research networks, palliative care, and nursing research) and methods to evaluate the workings of the IRB.

Key Question #2. Detailed review of Conflict of Interest studies

COI, both financial and non-financial, is increasingly recognized as an important aspect of maintaining public trust in medical research. In reviewing the literature available on COI, we start with those studies that examined the goals of disclosure, in general, as well as what disclosure should include.

Purposes of Disclosure to the IRB

We identified four studies that dealt with the purposes of disclosure. Commonly reported goals included promoting informed decision making, respecting patients' perceived right to know, establishing or maintaining trust, minimizing risk of legal liability, deterring troubling financial relationships, and protecting research participants' welfare.

Who Has Policies around Disclosure?

Three studies were descriptive assessments of various institutions' COI policies. A conclusion common to all three studies was the wide variability in policies among institutions.

Two studies were descriptive assessments of COI policies within a single IRB. Again a common conclusion was variability in the policies.

Persons or Interests Requiring Disclosure

Four studies were descriptive assessments of policies specifying which persons or entities were required to disclose COI. All policies required research investigators to disclose, but beyond that commonality, policies varied substantially on the requirement for family members (i.e., parents, siblings, "de facto spouses," or other family members) of researchers to disclose COI.

Party to Which Disclosure Must Be Made

Five studies reported descriptive assessments of policies regarding the entities to whom disclosure needed to be made. All studies reported that all policies required disclosure to a university or institutional official or committee. Studies disagreed regarding disclosure to the IRB, varying from one percent of institutions requiring "initial" disclosure to the IRB, to 60 percent of the "top 10" National Institutes of Health (NIH)-funded research institutions requiring disclosure to the IRB, to the IRB having "a role" in review of investigators' financial relationships in about 75 percent of institutions. Differences in wording probably account for some of the differences in responses.

One study surveyed IRB chairs about the persons to whom IRB members' COI should be reported. Sixty-two percent answered that their IRB members reported their industry relationships to the IRB chair, 76 percent of respondents reported to the entire IRB, 53 percent of respondents reported to a group or individual within the organization but separate from the IRB, 7 percent reported to an entity external to the IRB and the institution that it serves, and 2 percent reported to an unnamed 'other.'

Managing Disclosure of Potential Conflicts of Interest

One study reported a descriptive assessment of how COI was managed. Within the policies of the 235 medical schools and other research institutions, disclosure was managed by divestment of interest (62 percent), withdrawal of the investigator from the project (61 percent), disclosure to the IRB or research subjects (0 percent), disclosure to the funding agency or sponsor (43 percent), disclosure to journals publishing findings (2 percent), disclosure to collaborating researchers (1 percent), a modification of research plan (59 percent), monitoring of the project (66 percent), requirement for additional peer review (7 percent), or public disclosure (59 percent).

Monitoring Compliance

No studies were identified that described how compliance was monitored.

Managing Noncompliance

Two studies described assessments of policies for managing noncompliance. As with other policies, policies for managing noncompliance varied widely.

Potential Harms of Disclosure

One study surveyed investigators, IRB chairs, and COI Committees about the potential negative effects of disclosure. These effects included the belief that disclosure might affect participant recruitment and enrollment, expressed by 63 percent (5/8) of investigators, 78 percent (18/23) of IRB chairs, and 79 percent (11/14) of COIC chairs; the belief that disclosure 'breaks down trust,' expressed by, respectively, 63 percent, 26 percent, and 21 percent; the belief that disclosure lengthens informed consent documents by, respectively, 38 percent, 26 percent, 29 percent; and the belief that disclosure lengthens the informed consent process, by, respectively, 38 percent, 9 percent, and 0 percent.

SUMMARY AND DISCUSSION

Key Question #1

The topic areas for which the largest number of studies has been published are the challenges of getting multiple IRB approvals for multi-site research studies and defining when quality improvement initiatives are considered research. Both are topic areas for which VA has recently implemented national policies designed to reduce complexity and uncertainty for researchers while maintaining appropriate safeguards for patients. These two topics account for 60 percent of the articles we identified.

Of the remaining studies, the next most common topic of study was COI, which we designated as the focus of key question #2 for an in-depth review. A modest body of research has been devoted to studies of payments to providers or patients for participating in research; these studies indicate wide variability and little relationship between the time expected for participant involvement and the payment.

We also identified a modest number of published studies about the ethics of genetic studies. This finding may be surprising, given the degree of interest in the topic in both professional and lay audiences.

Key Question #2

With regard to COI, we identified a modest number of published studies, almost all of them descriptive and some with substantial limitations (such as low survey response rates or restriction of the sample to a small number of sites). Many more studies have examined COI among research investigators than among IRB members reviewing proposed research. Nevertheless, the available evidence indicates potentially worrisome variation in practice across sites. We identified variation in four domains:

1. Who needs to disclose?
   Which members of the research project need to provide COI disclosures? This group could include principal investigator(s), co-investigators, research assistants, and other research staff.
2. What needs to be disclosed?
   This information includes not only direct financial interests, but also indirect financial support such as support for travel to attend meetings, and non-financial COI.
3. How distant a relationship may an individual have with an investigator and still be

required to disclose COI? This group almost always includes a spouse, but could also include children, parents, siblings, or other extended family members.
4. To whom does the information need to be disclosed? The target could be a specific official or committee of the IRB, or potentially the research participants.

RECOMMENDATIONS FOR FUTURE RESEARCH

Maintaining high ethical standards of conduct in research, both for the investigator and for IRBs, is a high prority for VA, and not one where VA can or should merely react to problems when they are identified. Rather, VA should aim that research conducted at all VA insitutions is held to the same high standard, much as it has done with clinical care over the past 15 years. To do so, VA should:

1. Conduct a descriptive study of current COI practices for investigators and IRB members at all VA facilities,
2. Use this information to determine which areas of current practices have unjustifiable levels of variation across sites,
3. Convene stakeholders to determine best practices for these processes,
4. Create VA-wide policy about these practices, and
5. Monitor implementation across facilities.

As an example, right now it is unknown whether VA facilities vary across the four dimensions of "who should disclose," "what to disclose," "how distant must an individual be related to an investigator to avoid disclosure," and "to whom should COI be disclosed." VA facilities may vary, possibly greatly, in these dimensions. VA has striven to provide, and patients have come to expect, one high standard of clinical care no matter which VA facility they visit. It is unreasonable for Veterans to expect differing ethical standards of research across VA facilities. Research-informed policy can ensure that COI disclosure be made as standard as clinical care, while allowing local flexibility when it is justified. Implicit in this statement is that defining standard COI policies, while a necessary condition, is not sufficient. Monitoring implementation is critical. AAHRPP has attempted to institute a common standard across VA facilities (at least those that are accredited) with response to a single disclosure threshold, disclosure from all individuals involved in the research, and management plans. One challenge is as a government agency VA must follow the government-wide ethics regulations that state federal employees may not have financial interests that relate to their work. All VA IRBs, that are accredited, have conflict of interest policies.

After this uniformity is accomplished, the next step will be to try and provide national VA guidelines on managing COI for individuals (investigators) and IRBs. While preservation of local autonomy is important for providing insitutions with the flexibility they need, some system-wide principles would be useful to help local sites inform COI management decisions. Non-financial COI will also need to be addressed at some point. Given the current imprecision with which non-financial conflicts are defined, the VA would best defer this topic until a greater degree of consensus is reached in the scientific community on how non-financial conflicts are defined.

Lastly, since many VA insitutions that conduct research have university affiliates, a potential complicating factor is the lack of harmony between VA COI and that of these university affliates.