

**JOINT LEGISLATIVE AUDIT AND REVIEW COMMISSION
OF THE VIRGINIA GENERAL ASSEMBLY**

**Indigent Participation
in Medical Research at
Virginia's Medical Schools**

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Preface

In recent years, there have been heightened concerns at the national level about the adequacy of protections that are provided to human subjects in research studies. In November 2000, the Joint Legislative Audit and Review Commission (JLARC) directed a study of indigent participation in medical research in Virginia's teaching hospitals. One of the reasons for this study is to assess whether an adequate level of protection is provided to all Virginians who participate in human subject research, including the most vulnerable and/or indigent citizens.

Virginia has three medical schools, University of Virginia (UVA), Virginia Commonwealth University (VCU), and Eastern Virginia Medical School (EVMS), which account for most of the indigent health care provided and most of the medical research conducted. Therefore, the study examined whether these three schools had strong internal oversight procedures in place to afford adequate protections to all research subjects.

In Virginia, there is no evidence at this time that a lack of protections has led to physical harm, but compliance problems with federal regulations led to a recent suspension of more than 1,500 studies at VCU. This suspension provided examples of the consequences for a school when its internal oversight function is flawed. The suspension also had a substantial impact on the university community.

The major finding of this review is that while it appears there are no longer systemic problems with human subjects research at VCU, there are still some areas in which all three schools could improve. Improvements in the protection of vulnerable groups, such as pregnant women, children, minorities, and low-income persons, can be accomplished through periodic onsite audits of selected medical research studies and the collection of basic, aggregated data on study participants.

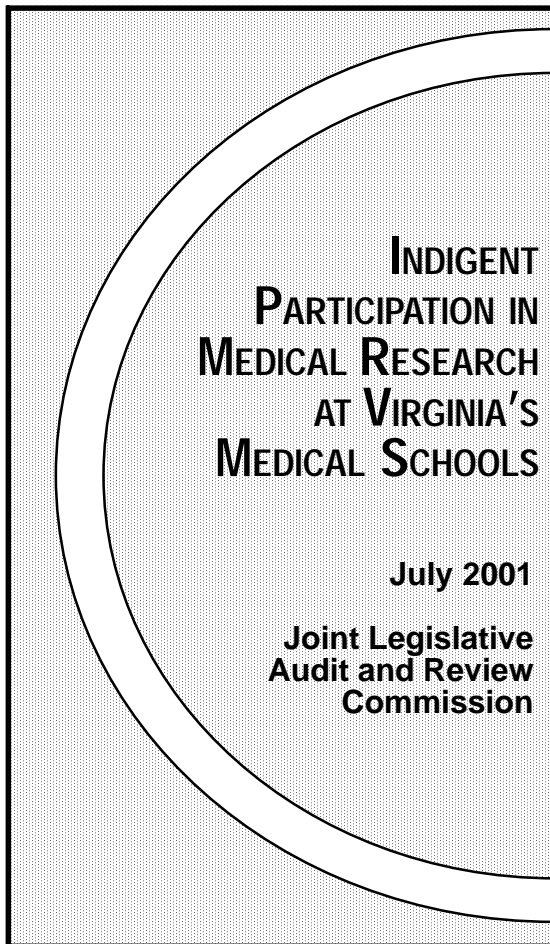
While these areas of needed improvements were identified in the report, each of the schools engages in certain practices that appear to promote the appropriate protection of study participants. The schools currently appear to have limited knowledge of each other's best practices, and therefore may benefit from greater knowledge and emulation of some of these practices employed by their peers. These "best practices" are noted in several exhibits throughout the report.

On behalf of the JLARC staff, I wish to express our appreciation for the assistance and cooperation provided during this review by the university administrators, study investigators and staff, and the institutional review board staff at UVA, VCU, and EVMS.

Philip A. Leone
Director

July 3, 2001

JLARC Report Summary



Medical research, often called clinical trials, involves studies to determine the effectiveness and safety of drugs, therapies, or medical devices for use by people. Medical research can advance the understanding of the biological basis of disease and unlock new strategies for disease prevention, diagnosis, treatment, and cures. However, the conduct of medical research in this country is under increased scrutiny. Several incidents at top universities have been recently reported in which the safety of clinical trial participants was compromised.

The national dialogue on the conduct of medical research is not specifically focused on the abuse of indigent patients or

other potentially vulnerable groups. Rather, more scrutiny is being given to the procedures of the institutional review boards (IRBs) and research investigators at the universities who are charged with protecting the safety of all people who enroll in medical research studies. One concern is that the growth of medical research is outpacing the ability of universities to ensure the rights and welfare of human research subjects.

In Virginia, there are three major schools that conduct medical research: Virginia Commonwealth University (VCU), the University of Virginia (UVA), and Eastern Virginia Medical School (EVMS). These schools are projected to receive over \$311 million in total research funding and \$143 million in medical research funding in 2001. UVA's funding levels exceed the other schools, accounting for \$195 million in total research funding and \$80 million in medical research funding. These three schools also provide the majority of inpatient and outpatient hospital health care to low income or uninsured patients. In 1999, VCU alone provided 31 percent of all the charity care provided by all the hospitals in Virginia, and VCU and UVA together provided the majority of the Medicaid-funded hospital care.

This study of indigent participation in medical research in Virginia's teaching hospitals was directed by the Joint Legislative Audit and Review Commission (JLARC) in November 2000. One of the reasons for this study is to assess whether an adequate level of protection is provided to all Virginians who participate in medical research, including the most vulnerable and/or indigent citizens. Because Virginia's medical schools are also the main providers of indigent care, there has been some legislative concern that the willingness of indigent citi-

zens to participate in studies may be unduly influenced by the benefits of doing so, such as receiving health care services. Therefore, the study examines whether the universities have strong internal oversight procedures in place to afford adequate protections to research subjects.

This report presents the results of the JLARC staff assessment of human research subject protections at each of the three Virginia schools that conduct medical research. To complete the assessment, the study examined recent external reviews of university research oversight activities, compared the IRBs' funding and oversight activities, and conducted an onsite audit of 15 medical studies in order to determine whether there is adequate protection of all Virginians who participate in medical research.

The JLARC staff assessment has resulted in two major findings. First, the recent federal suspension of all human subject research activities at VCU provides an example of what can happen to a school when the internal oversight function is flawed. For a time, VCU's ability to conduct critical medical research and to compete for research dollars was diminished. VCU compounded its own problems with the oversight function, by not promptly acknowledging these problems and responding with corrective action plans – contributing to the ultimate suspension of the research.

Second, as the result of their own initiatives and the suspension of research at VCU in late 1999, all three schools have been making important changes to oversight procedures for medical research; however, further improvements in identifying and protecting potentially vulnerable groups are still needed. While it appears there are no longer systemic problems with human subjects research at VCU, there are still some areas in which all three schools could improve. Improvements in the protection of vulnerable groups, such as pregnant women, children, minorities, and low-income

persons, can be accomplished through: (1) periodic onsite audits of selected medical research studies to ensure compliance with regulations, including verification of the voluntary nature of participation by study subjects, and (2) the collection of basic, aggregated demographic data on study participants and the identification of potentially vulnerable populations, in order to document whether certain groups have equitable access to share in both the risks and benefits of medical research. This report provides a number of recommendations to achieve these improvements, and highlights some of the best practices of each of the schools.

Federal Agencies Suspended All Human Subject Research at VCU, Which Had a Significant Impact on the VCU Community

Two of the major federal agencies that are responsible for the oversight of compliance with human subject protections for behavioral and medical research are the Food and Drug Administration (FDA) and the Office of Human Research Protection (OHRP). In carrying out these oversight responsibilities, OHRP and FDA evaluate all written allegations or indications of non-compliance with federal regulations from any source. According to federal officials, OHRP and FDA suspend research only after institutions have been given time to correct deficiencies.

The federal audits of VCU (by both FDA and OHRP) began in 1998 in response to complaints made directly to OHRP from one research subject on each of two separate studies, and a routine audit conducted by FDA. A complaint was lodged against one longitudinal study by a father of twins who objected to sensitive questions included in a mailed questionnaire to his twenty-year-old children. A complaint about another study came from a participant who said that the study procedures for drawing blood from participants were changed without his con-

sent. The complaints of study participants, and the lack of a prompt, constructive response by VCU to the allegations and federal concerns, caused a series of events, culminating in the severest penalty that can be lodged against a school — the suspension of all human subject research studies, regardless of the source of funding (VCU had 1,563 such studies at the time of its suspension). The time period from the initial suspension of all research at VCU until the final corrective actions proposed by VCU were accepted by the federal agencies lasted 15 months, ending in March 2001.

Beginning in January 2000, VCU implemented substantial changes, invested significant resources, and redesigned its human subject protections program. To address its problems, VCU realigned its IRB functions, increased its human subject research training, revised its standard operating procedures, upgraded its computer tracking system for research activities, developed a comprehensive IRB website, increased facility and staff resources to support IRB activities, replaced its former IRB committee with three new panels, created two new compliance and education positions, and hired an outside contractor to re-review more than 1,500 behavioral and medical research studies. These changes came with a high price in terms of dollars, staff hours, the negative impact of the suspension in stalling the progress on studies, and the negative impact of the suspension upon the prestige of the university.

Recent federal audits conducted at UVA and EVMS did not have the same negative impact as the VCU review because both schools were responsive to federal concerns. However, VCU's audit experiences did have a positive and constructive impact on both UVA and EVMS. For example, after VCU's suspension of research, both schools hired outside contractors to audit their IRB procedures and activities to en-

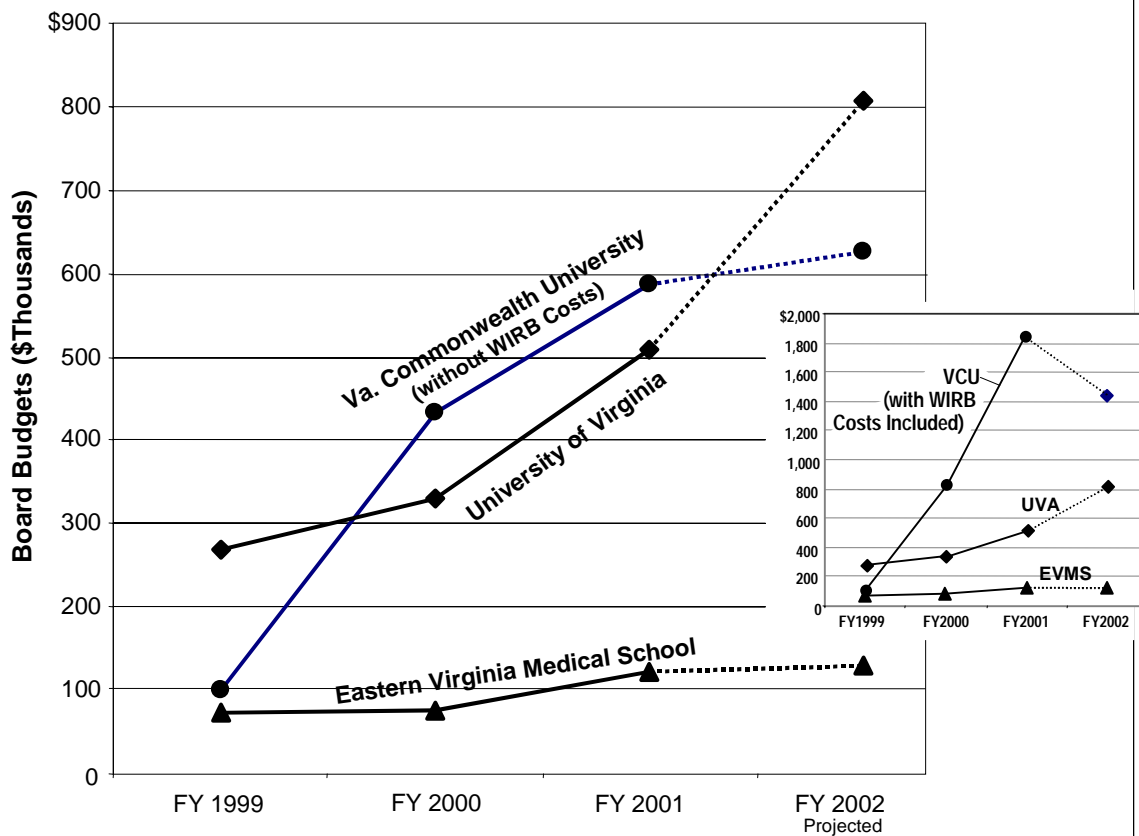
sure compliance with federal regulations concerning human subject protections. In order to ensure that each school stays in compliance with federal human subject regulations, a recommendation is contained in the report for the three schools to periodically hire outside contractors to evaluate IRB oversight activities, and for each school to compare its performance with recently completed federal audits at peer institutions.

All Schools Have Improved Their Research Oversight Activities During the Past Year, But Additional Safeguards are Needed to Ensure the Voluntary Participation of Vulnerable Groups, Including the Indigent

The recent suspension of all human subject research at VCU caused all three schools to re-evaluate their commitment to IRB activities and to review their operating procedures. Each school has made many important changes to its oversight procedures. As of March 2001, UVA was responsible for the oversight of 1,292 active behavioral and medical research studies, VCU was overseeing 1,263 studies, and EVMS was overseeing 712 studies.

As shown in the figure on the following page, the level of funding for IRB activities has increased dramatically since 1999 (prior to the suspension of research at VCU) for both VCU and UVA. VCU is projected to spend more than six times its 1999 sum on the oversight function in 2002, UVA is expected to spend three times more, and EVMS is expected to spend almost two times more. Due to the suspension of all research, VCU was required to hire an outside contractor to perform reviews of all human subject research studies. While the work of the contractor is ongoing, it is being reduced as VCU resumes more of its IRB activities. These costs for the outside contractor, which have exceeded \$1.6 million to date, are shown in the inset chart in the figure.

Comparison of Institutional Review Board Budgets, Fiscal Years 1999 – 2002



Note: Due to the suspension of all research at Virginia Commonwealth University by the federal government in January 2000, VCU hired the Western Institutional Review Board (WIRB) to be the institutional review board of record. The resulting increase in the budget is reflected in the inset chart.

While each school has made many improvements to its IRB activities over the past year, some problems were noted during site visits, and some additional safeguards or improvements are needed at one or more of the schools. Some of the areas needing improvement are summarized in the bulleted points that follow.

- All schools have recently updated their standard operating procedures, which describe how federal regulations will be implemented by the IRB.

However, as recommended by the federal oversight agency, only VCU has initiated the development of a manual designed to describe the study investigator's research responsibilities. A recommendation in the report states that all schools should develop investigator manuals.

- One past audit finding at VCU was the failure by those conducting the study to include several federally-required items in the study participant's con-

sent form. JLARC staff conducted a content analysis of each school's consent form guidelines and found that each school is currently providing sufficient and appropriate guidelines. A recommendation in the report, however, states that there are some best practices that could be incorporated by each school to improve the overall readability and content of the form.

- The education of all staff involved with the research process is key to gaining compliance with human research principles and requirements. While each school has improved its human research training requirements, only UVA has gone beyond federal requirements and required that all key study personnel, regardless of the source of funding, receive training. A recommendation in the report states that all schools should require that all key study personnel, regardless of funding, should receive training commensurate with each person's level of involvement in the oversight and/or study process.
- The purpose of having an IRB is to help ensure that appropriate steps are taken to protect the rights and welfare of human subjects at all stages of the study. To more fully achieve this objective, however, it appears that IRB staff need to routinely visit selected medical research studies and verify study plans are not changed, that participant consents have been obtained appropriately, and that regulatory documents are completed. At the present time, only UVA conducts such onsite audits on a limited basis. A recommendation for improving IRB procedures by ad-

ressing the need for continuing onsite review of research studies is included in the report.

- JLARC staff conducted an audit of 15 medical research studies, and found potential compliance problems at each university. At VCU, one study investigator failed to re-consent study participants at their next clinic visit (following the approval for the study to continue) as was explicitly required by the outside contractor. Another study investigator was unable to find one consent form, and a third study investigator used an unapproved consent form. At UVA, one study investigator failed to obtain IRB approval prior to enrolling more patients than had previously been approved, and another study investigator improperly obtained an oral consent from a study participant. At EVMS, one study investigator failed to have consent forms witnessed despite the study plan explicitly stating this would be done. A recommendation that the JLARC audit findings should be communicated to all study investigators, in order to avoid potential regulatory and consent problems, is included in the report.
- In order to adequately safeguard all potential study participants, including vulnerable groups, JLARC staff found that each school must improve its ability to identify and monitor the participation in studies of vulnerable groups. While the studies reviewed were not sufficient to draw broad conclusions on this point, it appeared that projects that served more potentially vulnerable populations (such as minorities or poor/uninsured) also had higher rates of consent errors. JLARC staff found that the universal lack of

data on the basic demographics of study participants undermines the ability of the schools to ensure the protection of vulnerable populations. Therefore, another improvement recommended in this report is that, throughout the study process, the study investigators should collect and submit to the IRB basic, aggregated demographic data, and data on the characteristics of the populations which are related to the need for additional protections (for example, poor/uninsured subjects, or pregnant women).

While these areas of needed improvements were identified, each of the schools engages in certain practices that appear to promote the appropriate protection of study participants. These “best practices” are noted in several exhibits in Chapter II of the report. The schools currently appear to have limited knowledge of each other’s best practices, and therefore may benefit from greater knowledge and emulation of some of these practices employed by their peers.

Note: Copies of the full report on this study are available from the JLARC offices (804) 786-1258, and will also be posted on JLARC’s website (<http://jlarc.state.va.us>)

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I. Introduction

Medical research, often called clinical trials, involves studies to determine the effectiveness and safety of drugs, therapies, or medical devices for use by people. Medical research can advance the understanding of the biological basis of disease and unlock new strategies for disease prevention, diagnosis, treatment, and cures. In the United States, medical research is a large and growing industry. Each year, a variety of government agencies (such as the National Institutes of Health and the Food and Drug Administration), pharmaceutical companies, health maintenance organizations, and companies that develop medical devices and equipment provide millions of dollars for medical research studies. These studies are conducted by universities, private hospitals, physicians, and a variety of other private organizations.

In 1999, the federal government contributed about \$5 billion for medical research to more than 550 universities surveyed by the National Science Foundation. Total medical research funding to these schools in 1999 was 25 percent greater than 1996 funding. Additionally, it is estimated that the pharmaceutical industry currently spends about \$9 billion annually on medical research. The National Institutes of Health (NIH) has seen its funding triple since 1985, with another \$2.8 billion increase, or a 14 percent rise, proposed for 2002. This increase will allow NIH to support 34,000 more research grants.

Medical research in this country is under increased scrutiny. Several incidents at top universities have been recently reported in which the safety of clinical trial participants was compromised. Closer to home, in December 1999, two federal agencies, the Office of Human Research Protection (OHRP) and the Food and Drug Administration (FDA), temporarily suspended all research involving human subjects at Virginia Commonwealth University (VCU). Both OHRP and FDA cited VCU for administrative deficiencies in its institutional review board (IRB) and noncompliance with federal regulations.

The national dialogue on the conduct of medical research is not specifically focused on the abuse of indigent patients or other potentially vulnerable groups, such as children, minorities, or pregnant women. Rather, more scrutiny is being given to the procedures of the IRBs and research investigators at the universities who are charged with protecting the safety of all people who enroll in medical research studies. One concern is that the growth of medical research is outpacing the ability of universities to ensure the rights and welfare of human research subjects.

In Virginia, there are three major schools that conduct medical research: Virginia Commonwealth University (VCU), the University of Virginia (UVA), and Eastern Virginia Medical School (EVMS). One of the challenges for Virginia's research universities is to ensure that each school has the research infrastructure (facilities, equipment, research faculty and staff, and graduate students) in place so that it can successfully compete for research dollars. A major concern with moving forward with

cutting edge research, however, is the protection of human research subjects. The competition for increasing research dollars must be coupled with strong internal oversight procedures at the universities. All clinical trial participants are supposed to be protected through rigorous oversight procedures and informed consent based on full disclosure of potential risks and benefits.

It is important to note that these three schools also provide the majority of inpatient and outpatient hospital health care to low-income or uninsured patients. Thus, one of the reasons the Commission directed this study is to assess whether an adequate level of protection is provided for all Virginians who participate in medical research, including the most vulnerable and/or indigent citizens. Because Virginia's medical schools are also the main providers of indigent care, there has been some legislative concern that the willingness of indigent citizens to participate in studies may be unduly influenced by the benefits of doing so, such as receiving health care services. Therefore, the JLARC review examines whether the universities have strong internal oversight procedures in place to afford adequate protections to all research subjects.

The following sections of this chapter provide a general discussion of the protection of human subjects participating in medical research and federal efforts to improve research involving human subjects. The chapter also provides an overview of the indigent care provided and medical research funding at Virginia's three medical schools. Finally, a discussion of the research methodology used for addressing the study issues is provided at the end of this chapter.

PROTECTION OF HUMAN SUBJECTS PARTICIPATING IN MEDICAL RESEARCH

The core of modern ethics regarding all research with human subjects is based on the Nuremberg Code, which was created as a set of standards by which to judge the atrocities committed by the Nazis during World War II. In 1979, a federal commission crafted *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research*. These documents are commonly accepted as defining the ethics of practicing medical research.

The Belmont Report identifies three principles for human subject protection:

- **Respect for persons.** Individuals should be treated as independent decision makers, and should be provided with enough information to make an informed decision about study participation. Individuals with diminished capacity or potential vulnerability (such as children, the elderly, the mentally ill, the economically disadvantaged, or minorities) may have difficulty making an informed decision, so extra care must be taken to protect them.

- **Beneficence.** Researchers must ensure the well-being of all study participants by maximizing the possible benefits and minimizing the possible harms of the research process.
- **Justice.** Individuals should receive an equitable distribution of both the research burdens and benefits of the research (for example, the inclusion and exclusion criteria in the selection of research subjects should be fair and without bias).

The Belmont Report warns that the selection of research subjects needs to be scrutinized in order to determine whether some classes (such as welfare patients, particular racial and ethnic minorities, or persons confined to institutions) are being selected simply because of their easy availability, their compromised position, or their manipulability, rather than for reasons directly related to the problem being studied.

Most detailed human subject protection regulations are at the federal level. The *Code of Virginia* also has regulations that apply to any Virginia agency or institution that conducts or proposes to conduct human subject research that is not already covered under federal regulations. The *Code* requires the informed consent of study participants and requires institutional review of the studies. The *Code* regulations apply to individuals licensed, registered or certified as health practitioners by the State (§ 32.1-162.16 – 162.20, and § 54.1-2407).

The federal government, through the Office of Human Research Protection (Code of Federal Regulations, Title 45, Part 46) and the Food and Drug Administration (Code of Federal Regulations, Title 21, Parts 50 and 56), promotes adherence to the ethics of *The Belmont Report* through three basic protection mechanisms: (1) a requirement for university-wide assurance of compliance with federal regulations through submission of a Multiple Project Assurance (MPA) plan; (2) requirements for the review of research by university level institutional review boards (or IRBs); and (3) requirements for the informed consent of subjects. Each of these protection mechanisms is discussed below.

First, the federal regulations require research institutions to contractually agree to abide by all federal regulations through the submission of a MPA. This written plan specifies in detail how the regulations will be operationalized by the research institution, including how it will maintain an adequate oversight program and procedures for the protection of human research subjects. The MPA is only required for federally-sponsored research. However, most institutions voluntarily extend the procedures and protections to all research conducted at the institution to ensure that the protection of human research subjects will be carried out equally, regardless of a study's funding source. The university's MPA is the principal compliance mechanism for the federal agencies. According to OHRP staff, this assurance system is being replaced with a new system called the Federal Wide Assurances, but it is not fundamentally different in terms of the assurances required.

Second, the federal regulations outline the composition, requirements, responsibilities, and authority of IRBs. The IRB is the body within the university that ensures compliance with federal regulations. The IRB is charged with protecting the autonomy of subjects, minimizing study risks and maximizing study benefits to the subjects and the society at large, assuring fairness in the distribution of study risks and benefits, and protecting vulnerable populations. IRBs must have at least five members, including one non-scientist and one community member. In addition, if an IRB regularly reviews research that involves a vulnerable category of subjects, such as children, pregnant women, mentally disabled persons, or low income individuals, federal regulations indicate that consideration should be given to the inclusion of one or more members who are knowledgeable about and experienced in working with these groups. Together, IRB members must have sufficient experience and expertise to provide a responsible review of the study plans submitted. According to an on-line OHRP training module, IRBs have the:

authority to approve, require modification in, or disapprove all research activities.... [and] to suspend or terminate previously approved research that is not being conducted in accordance with the IRB's requirements, or that has been associated with unexpected serious harm to subjects.

Therefore, all activities at the university involving research, both behavioral and medical, with human research subjects must be submitted to the IRB for initial and continuing review and approval.

Third, the regulations specify in great detail the requirements of study researchers and the IRBs in securing voluntary informed consent from research subjects. Informed consent is the process of communicating key facts about a research study to potential participants so that each has the information needed to decide whether or not to participate. Informed consent is documented by means of a consent form that is written, signed, and dated once the potential participant has received all the necessary information. The IRB activities at each of the schools, and the process for obtaining informed consent, will be discussed in more detail in Chapter II.

FEDERAL EFFORTS UNDERWAY TO IMPROVE RESEARCH INVOLVING HUMAN SUBJECTS

The federal government contributes more than half of all the academic medical research funding received by institutions across the country. In order to receive federal dollars, each institution must provide assurances to the government that it will comply with all federal regulations concerning human subject research. The federal government, mainly through the agencies under the Department of Health and Human Services (the Food and Drug Administration, the National Institutes of Health, and the Office of Human Research Protections), have worked to improve research involving human subjects in a number of ways over the past decade. First, the agencies

have tried to correct the exclusionary problems of past research by requiring that, when appropriate, more minorities, children, and women are included in federally-funded research projects. Second, the agencies continue to monitor the universities' compliance with federal regulations concerning human subject protections. Finally, the agencies have evaluated the oversight capabilities at the universities for protecting human research subjects and are implementing necessary reforms and emphasizing how the existing federal regulations should be applied.

In the 1990s, the Federal Government Required Medical Research Projects to Seek Greater Participation by Minorities, Women, and Children

Three regulatory changes were made during the 1990s that demonstrated the shift in the federal government's policy towards allowing minorities, children, and women to be included in medical research studies. First, in 1993, the Food and Drug Administration (FDA) released new guidelines for including women and minorities in clinical research. Second, the following year, the National Institutes of Health (NIH) published guidelines implementing a statutory requirement that women and minorities be adequately represented in federally-funded research. Third, the Food and Drug Modernization Act of 1997 required that all medications prescribed for children must be tested in children before the drug can be licensed. This Act provided drug companies with a significant financial incentive (a six month extension of their patent) for testing their drugs on children, which has led to a sharp increase in research on children. The implementation of drug research with children has caused some concern that there has not been sufficient time to implement ample protections.

The IRBs at the universities, in conjunction with the study investigators, must ensure compliance with these new federal regulations. The current administration has proposed a 14 percent increase to NIH, which would bring its total budget to \$23 billion, and some of this increase will be used to lend support to research initiatives that involve minorities, women, and children. The increase includes funds targeted to the Office of Research on Women's Health (increasing its budget from \$28 million to about \$50 million), and boosts spending at the new National Center for Minority Health and Health Disparities by 20 percent to \$158 million.

In concert with its new requirements, NIH has developed a strategic plan to reduce and ultimately eliminate the health disparities experienced by minorities. In the past, most medical research was conducted on white males. However, there is compelling evidence that minorities suffer from differences in the incidence, prevalence, mortality, and burden of diseases and other adverse conditions. Some of these health disparities include a shorter overall life expectancy as well as higher rates of cardiovascular disease, cancer, infant mortality, diabetes, asthma, and strokes, among others. The NIH is supporting this effort to address the health disparities through funding research, career development funding, public information and community outreach, and requirements that projects seek greater participation by minorities.

Past research conducted on white men also does not translate well to the medical needs of women. The thalidomide tragedy of the late 1950s resulted in a protectionist and exclusionary policy of the FDA towards women in clinical trials. Between 1977 and 1993, the FDA specifically prohibited the inclusion of women of childbearing age in studies that tested new drugs because of concerns about the impact of experimental drugs on fetuses. Now, however, there is a realization that not all women of childbearing age are likely to get pregnant, and it is possible to reduce the risk of fetal exposure through the study design. In addition, there may be gender differences in the effectiveness of various drugs, therapies, or treatments.

There are several valid reasons for the recent move to include children in research studies. Historically, drugs prescribed to children have not been specifically studied for use within pediatric populations. Instead, physicians calculated pediatric doses of drugs based on information from adult clinical trials. Studies have shown that the course of diseases, and how drugs affect disease and the body, differ markedly for children compared to adults and animals. Therefore, lacking adequate information, doctors may be unwilling to prescribe certain drugs for their pediatric patients. Furthermore, testing in adults and animals cannot substitute as alternatives to testing in children. According to the FDA, appropriate and careful research involving children will reduce the risk of harm to all children from exposure to practices and treatments that have not been tested on children in any way. Finally, new therapies are needed for diseases that specifically affect children.

The need to increase minority, women, and children's representation in medical research trials was an important concept to consider as JLARC staff examined the prevalence of minorities and/or low-income participants in medical research at Virginia's medical schools. Another point for consideration is that these medical schools also tend to be the main providers of charity care, so the proportion of minorities and/or low-income participants in medical research may reflect their overall proportion in the patient population for the medical school. Chapter II assesses the prevalence of low-income participants in selected medical research projects, and whether the consent procedures appear adequate given the nature of the study and the potential risk to the subject.

Federal Agencies Find Compliance Problems in Top Research Universities

In a recent article in the *New England Journal of Medicine*, the former U.S. Secretary of Health and Human Services stated that the need to strengthen protection of human subjects is rooted in four disturbing national trends in clinical research:

- First, researchers may not be doing enough to ensure that research subjects fully understand all the potential risks and benefits of a clinical trial, which are the core elements of informed consent. Some of these failures highlight the vulnerability of participants, such as an incident in which a nursing home resident was allegedly forced to participate in a study under the threat

of expulsion from the home. Other failures found were characterized as an erosion of informed consent, such as aggressive recruitment tactics or misrepresentations of the true nature of the study research procedures.

- Second, too many researchers are not adhering to standards of good clinical practice. The FDA has identified cases at the nation's most prestigious research centers in which researchers failed to disqualify unsuitable subjects, to report side effects as required, to ensure the research procedures were followed, and to ensure that the study staff had adequate training.
- Third, institutional review boards (IRBs), the key element of the system to protect research subjects, are under increasing scrutiny (IRBs are the entity within the university that is charged with protecting subjects of research through enforcing federal regulations). Investigations by OHRP revealed that IRBs have excessive workloads and inadequate resources.
- Fourth, the nature of clinical trials is changing. Potential conflicts of interest and ethical dilemmas are increasing. Researchers and companies working together can blur the boundaries between a researcher's self interest and scientific judgment.

Two of the major federal agencies that are responsible for oversight of compliance with federal regulations for behavioral and medical research are the FDA and OHRP. As mentioned previously, all institutions engaged in federally-funded human subject research must provide assurances to Department of Health and Human Services (DHHS) that the institutions will comply with federal regulations. In carrying out their oversight responsibilities, OHRP and FDA evaluate all written allegations or indications of non-compliance with federal regulations (also known as "for cause" audits) from any source. The FDA also conducts routine audits on specific regulations governing the way drugs and medical devices may be used in a research setting. Due to the small size of its office, however, OHRP does not conduct routine audits.

The possible outcome of a federal compliance oversight audit can range from no compliance problems found to the most serious sanction, which is the suspension of all human subject research at the audited institution. According to federal officials, however, suspension of all human subject research occurs only after institutions have been given sufficient time to correct deficiencies.

Since 1990, OHRP has conducted audits of more than 40 research institutions, including VCU and UVA. The federal audits of VCU (by both the FDA and OHRP) began in 1998 and resulted in the suspension of more than 1,500 behavioral and medical research studies in December 1999, due to administrative deficiencies, non-compliance with federal regulations, and possible psychological harm to a family whose children were involved in a longitudinal study of twins. The time period from the initial suspension of all human subject research at VCU until the final corrective actions were accepted by the federal agencies lasted 15 months.

In 1995, OHRP audited UVA and found administrative problems with the way the IRB reviewed its behavioral research studies. This resulted in a temporary suspension of about a dozen research studies until the studies could be re-reviewed by a new IRB committee. These federal audits at VCU and UVA, and other external audits for compliance with federal regulations for human subject protections, will be discussed in more detail in Chapter II.

Federal Agencies Require Improvements to the Oversight Responsibilities for Human Subject Protections

Currently, DHHS is in the process of implementing several initiatives aimed at addressing some of the recent problems found in the conduct of medical research. These initiatives are intended to promote or improve the safety of participants, government oversight, and study investigator responsibility. DHHS plans to: (1) improve education and training in conducting human subject research for all key study personnel, and make such training a condition of receiving federal funds; (2) issue specific guidelines on informed consent, which reaffirm the expectation that research institutions and sponsors should audit records for compliance; (3) issue new monitoring guidelines for study investigators, and for boards that monitor data to ensure studies are safe; (4) issue additional documents to clarify conflict of interest issues for biomedical research; and (5) pursue legislation to authorize the FDA to levy civil monetary penalties (up to \$250,000 per investigator, or up to one million dollars per research institution) for violations of informed consent and other regulations.

The next section provides information on the Virginia's medical schools and the provision of health care services to indigent persons. In addition, a comparison of each school's total and medical research funding is provided.

INDIGENT CARE AND MEDICAL RESEARCH AT VIRGINIA'S MEDICAL SCHOOLS

Providing health care to indigent persons and conducting medical research are two important, but largely separate functions of each of Virginia's medical schools. Based on the prevalence of low-income persons in the population served by these institutions, one would expect that low-income persons might also be included in some medical research studies. One reason for the study mandate is to determine whether low-income people may be over-represented in medical research studies in order to obtain needed health care services.

However, in interviews with university officials, JLARC staff found that how and when these two functions overlap is not known at the university level. In many cases, this information is also not captured at the research study level. Several reasons have been given for this lack of information on the number of indigent persons used in medical research studies. First, the federal government and other study spon-

sors do not routinely require study investigators to capture basic demographic and health insurance information on participants. Second, there is a reluctance to collect this information because of the requirement that all persons should have an equal opportunity to be included and benefit from the research. There is a fear that collecting such data might bias the selection criteria. Third, some studies are designed to target certain populations (such as women, children, or minorities) because of the need to determine the efficacy of the drug or medical intervention for that population. Therefore, simply looking at data, without examining the purpose of specific studies, may lead to misleading conclusions about participation rates by indigent or other vulnerable populations.

The following sections provide information for each medical school on the amount of indigent care provided, as well as the amount of funding received for medical research and for all research. In order to address the question of the prevalence of indigent persons in medical research studies, JLARC staff examined 15 medical research studies and collected basic demographic and health insurance information. The focus of the JLARC staff inquiry, however, was on whether all study participants were participating in the study based on informed and voluntary consent, including the indigent and potential vulnerable populations. The results of that review are discussed in Chapter II.

Virginia Commonwealth University and University of Virginia Hospitals Are the Main Providers of Health Care to Indigent Persons

In Virginia, there are three major medical schools that provide most of the health care to indigent patients: VCU, UVA, and EVMS. According to the Virginia Indigent Health Care Trust Fund, the definition of “indigent” is any person whose annual family income is equal to or less than 100 percent of the federal poverty level (in 1999, this was \$16,700 annually for a family of four). This definition is used to determine how much a hospital may be reimbursed for part of the cost of providing charity care (hospital care for which no payment is received). Hospitals are reimbursed through the Virginia Indigent Health Care Trust Fund, which is a public/private partnership involving the state government and the acute care hospitals. The Fund was established to help equalize the burden of charity care among the hospitals. However, in order to be more inclusive for purposes of this study, JLARC staff used a broader definition of indigent, which includes any person who is on Medicaid, is uninsured, or has no means of payment for health care.

Table 1 shows how much inpatient and outpatient hospital health care is provided to indigent persons by each of the three medical schools. In 1999, VCU received over \$152 million in payments for health care provided to Medicaid or uninsured, low-income patients. VCU alone provided 31 percent of all the charity care provided by all the hospitals in Virginia. In 1999, UVA received over \$98 million in payments for health care provided to Medicaid or uninsured, low-income patients, and provided 15 percent of the charity care in Virginia. VCU and UVA together provide the majority of the Medicaid-funded inpatient and outpatient hospital care. Sentara Hospital in Nor-

Table 1 Amount of Inpatient and Outpatient Hospital Health Care Provided to Indigent Persons by Virginia's Medical Schools in 1999				
Medical Schools	Total Revenue for All Patients	Total Medicaid Payment	Total Charity Care Provided**	Total Indigent Care Trust Fund Payments or Disproportionate Share
Virginia Commonwealth University (Medical College of Virginia)	\$432,508,600	\$87,732,607	\$120,371,479	\$65,079,451
University of Virginia	\$459,032,698	\$63,414,086	\$59,630,774	\$35,120,339
Eastern Virginia Medical School (Medical College of Hampton Roads)*	\$408,343,863	\$36,416,770	\$14,149,662	\$1,252,377
Sentara Norfolk General	\$298,330,000	\$13,020,785	\$14,043,964	\$1,703,848
Children's Hospital of The King's Daughters	\$110,013,863	\$23,395,985	\$105,698	(\$451,471)
Notes: * Eastern Virginia Medical School has an affiliation with most Tidewater area hospitals; however, its closest affiliations are with Sentara Norfolk General and the Children's Hospital of the King's Daughter. ** Charity care is somewhat inflated because the hospitals report the full price as the cost for providing this care. Source: Virginia Health Information. <i>The 2000 Industry Report</i> (www.vhi.org). Data is for the 1999 reporting year.				

folk, which is part of the EVMS network of hospitals, is also one of the top five hospitals in dollars of charity care provided in the State, even though its overall percentage of total charity care provided is less than five percent.

The University of Virginia's Medical Research Funding Exceeds Other Schools

VCU, UVA, and EVMS all have national reputations in conducting medical research. In addition, according to 1999 data reported to the National Science Foundation, UVA is ranked 57th, VCU is ranked 107th, and EVMS is ranked 175th out of 589 schools nationwide for total research funding. In terms of medical research funding, the schools are also ranked high (UVA is 50th, VCU is 62nd, and EVMS is 92nd).

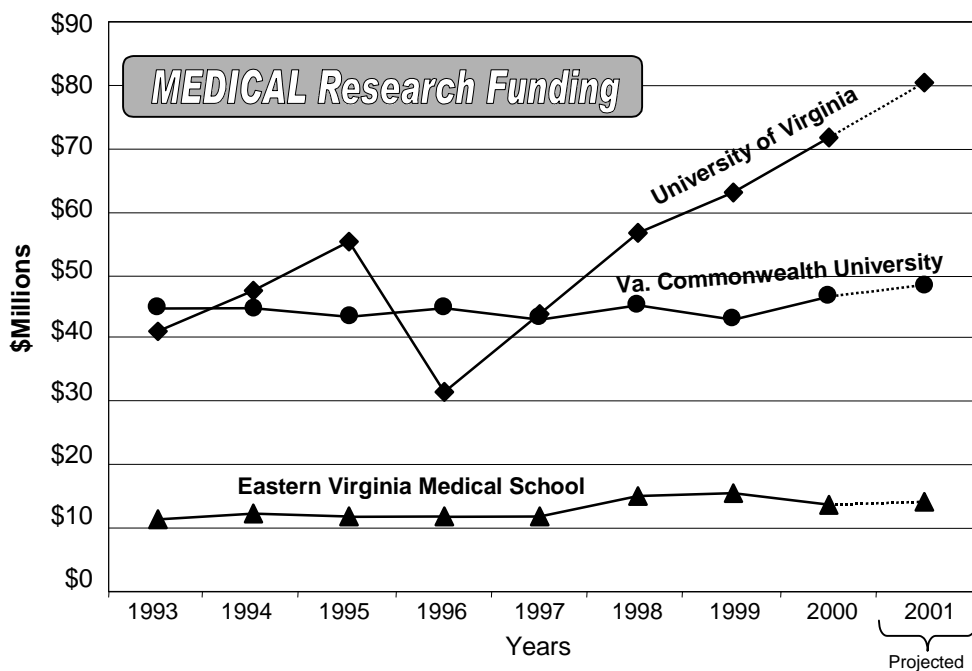
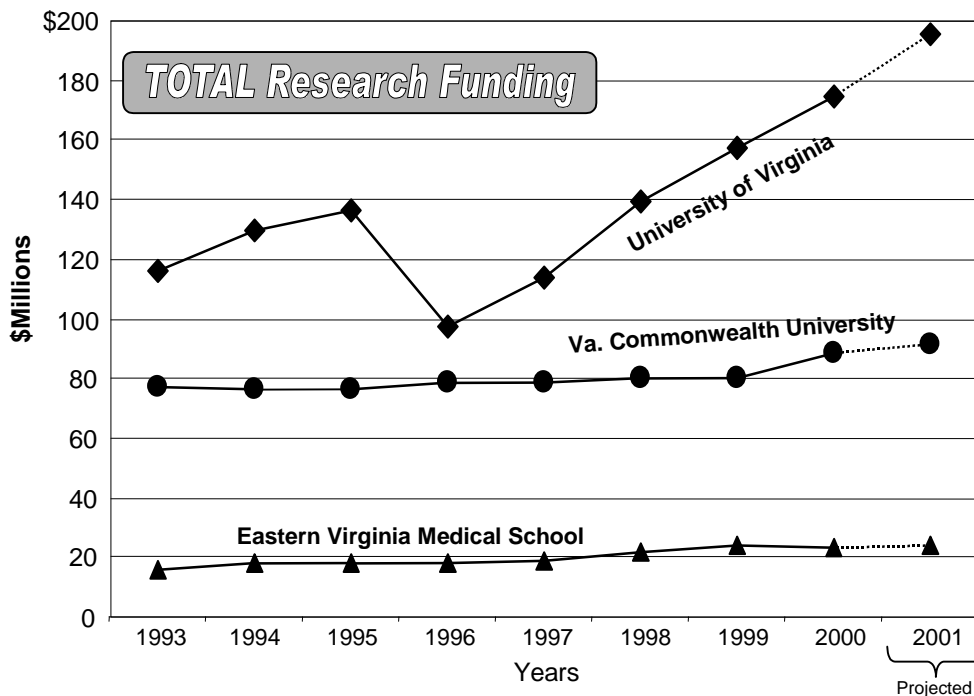
However, as shown in Table 2, UVA received more research funding overall, more medical research funding, and more federally-funded medical research than both VCU and EVMS. Federal funding has some advantages, because these funds tend to be more stable and span more years than private funding. (For total research funding, medical research funding, and national rankings for all three schools, from 1993 through 2001, see Appendix A.)

Figure 1 shows that from 1993 to 2001, UVA also benefited from a continual increase in total research and medical research funding (except for a decrease in reported funding in 1996 due to changes in how UVA reported data), while funding at VCU and EVMS remained relatively flat. In the early 1990's, UVA and VCU received comparable amounts of private and federal funding for medical research. In 2000, UVA received about \$72 million for total medical research funding, VCU received almost \$47 million, and EVMS received about \$14 million. UVA received 54 percent

Table 2 Profile of Funding at Virginia's Major Medical Research Universities in 1999			
Characteristic	UVA	VCU	EVMS
All Research			
Total Funding (in millions)	\$157.5	\$79.8	\$24.1
National Ranking (N=589)	57 th	107 th	175 th
Medical Research			
Funding (in millions)	\$63.1	\$42.9	\$15.7
Medical Funding as Percent Of Total Funding	40%	54%	65%
National Medical Research Ranking	50 th	62 nd	92 nd
Federally-funded Medical Research			
Federal Medical Funding (in millions)	\$39.6	\$23.5	\$8.4
Federal Medical Funding as Percent of Medical Research Funding	63%	55%	53%
Source: Data were obtained from the National Science Foundation report on <i>Academic Research and Development Expenditures, Fiscal Year 1999 [Early Release Tables]</i> .			

Figure 1

University Research Funding Trends, 1993 – 2001



Note: There is a decrease in the reported funding for UVA in FY 1996, according to UVA officials, due to a change in how data were reported to the National Science Foundation (NSF).

Source: JLARC staff analysis of data from the NSF annual reports from 1996 through 1999 on *Academic Research and Development Expenditures*. Data from 2000 were provided by the universities, as they reported it to the NSF. Projections for 2001 were provided by the universities.

more total medical research funding and 77 percent more federal medical research funding than VCU.

Based on what is occurring at the federal and the State levels regarding medical research, Virginia's medical schools have reviewed and improved their human subject protections. The next chapter provides the JLARC staff assessment of the oversight of human subject protections at each of the schools.

JLARC REVIEW

The study of indigent participation in medical research in Virginia's teaching hospitals was directed by JLARC at its November 2000 meeting. The genesis of the study was a series of planning meetings held by the Commission in September, October, and November of 2000. As a result of these meetings, the Subcommittee proposed, and the full Commission approved in November 2000, several new areas for staff review (under its general statutes laid out in §30-58.1 of the *Code of Virginia*).

In order to address the study topic, this review of medical research was designed to address two issues:

- Do the three Virginia medical schools ensure adequate protection for all Virginians who participate in medical research, including the most vulnerable and/or indigent citizens?
- What is the impact to the study participants, researchers, and the universities when the schools do not meet federal standards for providing human subject protections?

Research Activities

To assess human subject protections at Virginia's medical schools, JLARC staff conducted four primary research activities: (1) structured interviews, (2) site visits, (3) data requests and analysis, and (4) document reviews. The research was completed between January and May 2001.

Structured Interviews. At each of the three schools, interviews were conducted with university officials, IRB members and administrative staff, and selected principal investigators and study staff conducting medical research studies. The purpose of the interviews was to inquire about medical research oversight activities and the procedures that are in place to protect the participants in the studies. In addition, a federal official, responsible for the oversight of human subjects research, was interviewed to gain a national perspective on medical research and federal oversight activities.

Site Visits. JLARC staff conducted site visits at each of the three medical schools. In addition to interviewing the IRB members and staff, and selected study investigators, three types of activities were conducted at each university. JLARC staff: (1) observed a meeting of the IRB committee, to learn how the committee conducts initial and continuing reviews of medical research projects, including how it protects human research subjects; (2) attended training sessions on human subjects research, including issues concerning when a third party consent is required and the appropriate use of the consent process when children are involved; and (3) conducted an audit of a sample of individual medical research studies.

The third activity, the audit of individual research studies, was completed in order to determine whether adequate protections exist for all participants in medical research, including vulnerable or indigent persons. Because none of the universities capture data at the university level on the demographics or health insurance status of study participants, JLARC staff requested each university to develop a list of medical research projects that were more likely (based on the research setting, the title of the research study, and/or the target population) to include participants with Medicaid or no health insurance. From this list, JLARC staff selected five research studies at each school that had at least ten participants in each study.

As a result, JLARC staff audited 15 medical research studies, with an enrollment of 727 study participants. For each of the studies, JLARC staff conducted a review of regulatory documents (such as appropriate approval of initial and continuing study applications by the institutional review board, and serious adverse event reports), interviewed study staff on the informed consent process (to ensure that participation is voluntary and based on the understanding of the purpose, risks, and benefits of the study), and reviewed randomly selected consent forms. The consent forms for 342 study participants were individually reviewed for compliance with federal regulations and university requirements.

A detailed description of the outcomes of these site visits and the demographics and health insurance status of study participants are discussed in Chapter II. Copies of the data collection instruments are provided in Appendix B.

Data Requests and Analysis. In order to supplement the interviews and site visits, the JLARC staff requested additional information from each school. This request included: (1) information documenting the institutional review board's activities, workload, staffing, and funding; (2) copies of all external reviews of the institutional review board, and any internal reviews conducted on individual medical research studies by IRB staff; and (3) total and medical research funding for recent years.

In order to determine the amount of inpatient and outpatient hospital care provided to indigent persons by each of the three medical schools, JLARC staff utilized the Virginia Health Information report, *The 2000 Industry Report: Virginia Hospitals and Nursing Facilities*. This report provided information on total hospital reimbursements from all sources, total Medicaid reimbursements, the amount of charity care

provided, and indigent payments made to each of the schools for the most recent year that data were available, which is 1999.

Document Reviews. JLARC staff reviewed a variety of university documents, including the institutional review board's standard operating procedures manual, the institutional assurances of compliance for conducting research (known as the Multiple Project Assurance or MPA), results of internal and external audits, documentation of institutional review board activities, individual research study plans, and human research subject training resources. In addition, JLARC staff reviewed various federal regulatory documents, Internet web sites, and articles on human subject research in order to gain a national perspective on medical research issues.

REPORT ORGANIZATION

This report is organized into two chapters, including this introduction. The introduction provided information on the protection of human subject participants in medical research, the federal efforts to improve the oversight of medical research at the university level, and the funding of medical care and medical research at Virginia's three medical schools. Chapter II focuses on how human subject protections are carried out at each of the Virginia medical schools, including a discussion of how the university's institutional review board conducts its oversight activities, recent federal audits of oversight activities, and a JLARC staff audit of selected medical research studies. The purpose of the audit was to assess human subject protections at the study level. Based on this audit, JLARC staff provide recommendations for improving the protections of all persons enrolled in medical research studies, including vulnerable or indigent persons.

II. Assessment of Human Subject Protections at Virginia's Medical Schools

As described in Chapter I, there is a national concern that the growth of medical research is outpacing the ability of universities to ensure the rights and welfare of human research subjects. Therefore, each institution must find ways to balance the desire for research dollars with the protection of human research subjects. The recent federal suspension of all research activities at Virginia Commonwealth University provides an example of what can happen to a school when the internal oversight function is flawed. For a time, VCU's ability to conduct critical medical research and to compete for research dollars was diminished.

This chapter presents the results of the JLARC staff assessment of human research subject protections at each of the three Virginia schools: Virginia Commonwealth University (VCU), University of Virginia (UVA), and Eastern Virginia Medical School (EVMS). To complete the assessment, the study examined recent external reviews of university research oversight activities, compared the institutional review boards' funding and oversight activities, and conducted an onsite audit of selected research sites. The purpose of these research activities was to determine whether there is adequate protection of all Virginians who participate in medical research, including the most vulnerable and/or indigent citizens.

This assessment led to the finding that, in part due to the suspension of all research studies at VCU in December 1999, all three schools have closely reviewed their oversight procedures and have made important changes. While it appears there are no longer systemic problems with human subjects research at VCU, there are still some areas in which all schools could improve. This chapter provides recommendations to achieve these improvements and highlights some of the best practices of each of the schools.

Both the institutional review boards and the study investigators share the responsibility to ensure the safety and welfare of participants, including the most vulnerable. Each school must improve its ability to identify and safeguard potentially vulnerable groups, such as pregnant women, children, minorities, and low-income persons. One way this can be accomplished is through periodic onsite audits of selected medical research studies to ensure compliance with regulations, including the voluntary participation by the study subjects.

In addition, a universal lack of data at all of the schools on the basic demographics of study participants undermines the ability of the schools to ensure the protection of vulnerable populations. The lack of data is also contrary to the National Institutes on Health (NIH) initiatives to increase the participation of minorities, children, and women in medical research studies. Therefore, throughout the study process, study investigators should collect and submit to the institutional review board basic, aggregated demographic data on study participants, and data on the character-

istics of potentially vulnerable groups, in order to document whether certain groups have equitable access to share in both the risks and the benefits of medical research.

EXTERNAL REVIEWS OF THE MEDICAL SCHOOLS FOR HUMAN SUBJECT PROTECTIONS

Each university that is engaged in federally-funded human subject research must provide written assurances, called Multiple Project Assurance (MPA), to the United States Department of Health and Human Services (DHHS). Through these written assurances, the university indicates that it will comply with federal regulations concerning human subject protections. Due to limited staff resources at the two federal agencies charged with regulatory oversight — the Food and Drug Administration (FDA) and the Office of Human Research Protections (OHRP) — the safety of human subjects in research studies rests primarily at the university and study investigator level. As a consequence of limited resources that are available, the federal agencies typically limit their in-depth investigations of institutions to those with written allegations or indications of non-compliance with federal regulations. Since 1995, the FDA and/or OHRP have investigated both VCU and UVA for potential compliance problems, and EVMS was reviewed as part of a routine audit. The reasons for these audits and the outcomes of each of these audits are described below.

Federal Agencies Suspended All Behavioral and Medical Research at VCU in December 1999, and Did Not Fully Remove Restrictions Until March 2001

As with most federal audits, the review of VCU's compliance with human subject regulations began with complaints made directly to OHRP regarding two separate studies. A complaint was lodged against one longitudinal study by a father of twins who objected to sensitive questions that were included in a mailed questionnaire to his twenty-year-old children. The other complaint was from a participant who said that the study procedures for drawing blood were changed without his consent. In addition, the FDA, during the same time period, conducted a routine audit. The complaints of study participants and VCU's responses to the allegations caused a series of events, culminating in the severest penalty that can be lodged against a school — the suspension of all human subject research, regardless of the source of funding.

A review of the sequence of events leading up to the suspension in December 1999 of all research involving human subjects at VCU revealed an ongoing dispute between the university and the federal oversight agencies. Both the OHRP and FDA identified problems with the oversight of human subject research and VCU's standard operating procedures as early as August 1998. However, VCU did not immediately remedy the problems cited and did not respond to the federal agencies' requests for new standard operating procedures and corrective action plans in a timely manner. VCU officials also disagreed with the allegations made in the complaints against the two studies.

As shown in Exhibit 1, communications went back and forth between VCU officials and federal officials for 16 months before the federal agencies took punitive measures. Both federal agencies suspended VCU's human subject research activities in late December 1999. Both FDA and OHRP's correspondence cited numerous administrative deficiencies and noncompliance with federal regulations concerning human subject protections. According to federal officials, there also was at least some psychological harm done to the study participants who lodged the initial complaints. OHRP removed its suspension in late January 2000 (subject to the implementation of a proposed corrective action plan and the re-review of all suspended research by an outside contractor, which has taken more than a year and is still in progress). In March 2001, FDA removed its final suspension, which allows VCU to resume the review and oversight of research regulated by FDA.

According to federal officials, VCU received the most severe audit sanction, which is the suspension of all human subject research at the institution, because of the lack of satisfactory responses received from university officials over a long period of time. Once the suspension was ordered, VCU officials acknowledged some serious administrative and compliance problems, and immediately began work to correct them.

Beginning in January 2000, VCU implemented substantial changes, invested significant resources, and redesigned its human subject protections program. Changes made by VCU included:

- reorganizing all IRB functions to be accountable to the university president;
- training more than 400 research investigators and research staff, all IRB administrative staff, IRB committee members, and senior university administrative officials on human subject protections;
- rewriting the IRB's standard operating procedures to comply with federal regulations;
- upgrading the automated data system for tracking all research activities;
- developing a comprehensive website with IRB materials and other human subject protection resources;
- increasing the resources to support IRB activities, including office space, staffing, supplies, and equipment;
- replacing the former IRB committee with three new panels (and plans are underway for a fourth panel devoted to the review of cancer studies);
- creating two new positions, Director of Compliance and Director of Education; and

Exhibit 1 Timeline for Federal Audits of Virginia Commonwealth University Leading to the Suspension of Research Activities		
Dates	Office of Human Research Protection (OHRP)*	Food and Drug Administration (FDA)
August and December 1998	OHRP requests that VCU respond to allegations of non-compliance on two research studies with federal regulations for the protection of human subjects.	In August, FDA conducts a routine audit and finds that the institutional review board's (IRB) standard operating procedures do not reflect FDA regulations. FDA requests new procedures, but VCU does not comply with the request in a timely manner.
November 1998 and February 1999	VCU responds to OHRP that its institutional review board did not find any instances of non-compliance with the two research studies.	
May 1999		FDA conducts a repeat site visit and again requests VCU to develop new standard operating procedures. VCU does not comply with the request in a timely manner.
July and August 1999	OHRP restates its position that VCU is not in compliance with federal regulations and directs VCU to take corrective actions.	In August, FDA issues a warning letter to VCU for its failure to develop new standard operating procedures and suspends VCU's use of expedited review of FDA research studies. VCU responds to FDA that it does not agree with its findings.
September 1999	VCU continues to disagree with federal findings on the two research studies and identifies limited corrective actions it intends to take.	
December 1999	OHRP finds VCU's corrective action plan to be unsatisfactory, issues additional findings and concerns regarding VCU's system for protecting human subjects, directs additional corrective actions, and suspends all federally-funded human subject research.	FDA expresses concern to VCU about its failure to produce acceptable IRB operating procedures. VCU delivers updated procedures. FDA indicates that the revised procedures are not satisfactory and suspends VCU's ability to enroll new subjects in current FDA studies and states that no new studies can be reviewed by VCU's IRB. Instead, VCU is required to hire an external reviewer.
January 2000	VCU responds to OHRP (January 6 th). OHRP finds the response to be unsatisfactory and suspends all human subjects research, regardless of funding source (January 11 th). VCU delivers detailed corrective action plan to OHRP (January 28 th). OHRP lifts suspension of research, subject to the implementation of the corrective action plan and the re-review of 1,563 active studies by an external review board.	VCU contracts with Western Institutional review board to serve as VCU's IRB of record and notifies the FDA. This contractor will also meet the requirements set by OHRP for re-review of all research studies.
June 2000	OHRP approves VCU's reconstituted institutional review board.	FDA accepts VCU's new standard operating procedures, but still requires external review of FDA studies.
December 2000	OHRP removes all restrictions on VCU's Multiple Project Assurance Plan.	
January and March 2001		In January, FDA conducts an audit of VCU. In March, FDA removes final restrictions from VCU. Once VCU trains its institutional review board on FDA federal regulations, it can begin reviewing FDA sponsored studies.
* The Office of Human Research Protection was formerly called the Office of Protection from Research Risks.		
Source: JLARC staff analysis of correspondence from the Office of Human Research Protection, the Food and Drug Administration, and Virginia Commonwealth University.		

- hiring an outside contractor to re-review more than 1,500 behavioral and medical research studies and assume all IRB administrative functions.

These changes came with a high price in terms of dollars and staff hours required to redesign its human subject protections oversight function. The payment to date for the outside contractor alone is \$1.6 million (additional budget increases are discussed later in this chapter).

In addition to its review of the external audits of VCU, JLARC staff also interviewed university officials, study investigators, and a study sponsor concerning any impact on study participants, students, investigators, study sponsors, and the university resulting from the suspension of research. These findings are discussed below.

- **Impact on study participants.** Most study participants were not adversely impacted by the suspension of research because OHRP permitted VCU to convene an internal group, which reviewed studies and allowed previously enrolled subjects to continue in a study when it was in the best interest of the subject, such as a cancer trial participant. This provision also allowed two new subjects to be enrolled in a study with prior approval by OHRP. The group reviewed 268 requests out of the 1,563 suspended research studies and approved 208. These studies then received a high priority for review by the outside contractor.
- **Impact on students.** Some students were unable to complete their degrees as originally planned or experienced layoffs from jobs funded by research projects. VCU established a special committee to compensate graduate students whose educational programs were disrupted by the suspension of research. Ten students submitted requests for tuition assistance; eight were approved for a total cost of \$14,229. One graduate student, a co-investigator on a study, had to push back his graduation from May 2001 until August 2001 and did not receive any additional compensation because he was already funded as a graduate teaching assistant.
- **Impact on study investigators.** Some investigators were unable to meet their commitments to sponsors. VCU has documented that 92 research trials with a value of \$8 million in FY 2000 and 77 studies with a value of \$5.8 million in FY 2001 were initially affected by the suspension (many of these studies continued after they were reviewed by the outside contractor). One study investigator indicated that he “borrowed” funds from his study to keep his staff employed. Another study investigator indicated that she experienced financial and career setbacks from losing a \$50,000 grant from the United States Army because she could not complete her current project on time. Two unknown impacts are how many sponsors canceled studies or the potential value of studies that study investigators did not submit for funding.

- **Impact on study sponsors.** Because many VCU study investigators are subcontractors to multi-site studies, they were not able to submit the required data to their multi-site coordinators. This, in turn, prevented the coordinators from meeting their obligations to the sponsors.
- **Impact on the university.** Besides the impact on the overall university budget devoted to IRB activities, VCU is also dependent on having quality researchers in order to compete for research grants. During JLARC staff interviews with study investigators, several mentioned that faculty left the university due to the suspension. Although it is unknown how many faculty separated from the Health Sciences Schools as a result of the suspension, the overall number of separations increased from 53 in FY 1999 (before the suspension) to 70 in FY 2000, and 48 more have resigned in FY 2001 (July 1, 2000 through February 28, 2001). Several investigators mentioned that the university has lost prestige with study sponsors due to the suspension, and it will take time to regain their confidence.

Federal Agencies Also Conducted Compliance Audits at the University of Virginia and Eastern Virginia Medical School

Both OHRP and the FDA conducted compliance audits at UVA and EVMS from 1994 to 1999. These audits did not have the same outcome as the VCU review, because both schools were responsive to federal concerns by correcting cited deficiencies in a timely manner.

While UVA and EVMS initiated most changes to their IRB procedures before the VCU audit experience, both schools have closely followed VCU's audit experiences and adjusted their research oversight programs accordingly. For example, after VCU's suspension of research, each school hired outside contractors to audit its IRB procedures and activities to ensure compliance with federal regulations concerning human subject protections.

University of Virginia. JLARC staff reviewed correspondence documenting three federal compliance audits and one external audit conducted at UVA between 1994 and 2000. Each is described below.

- In 1994, OHRP found two major problems with the IRB committee that reviews behavioral research studies. The first problem was the lack of appropriate continuing review procedures, and the second, was the absence of a non-scientist on the IRB. Based upon this audit, the federal agencies suspended all federally sponsored behavioral studies until the studies could be re-reviewed and re-approved by a new IRB. The impact of this suspension was minimal, because the number of studies was less than 12, and these studies were re-reviewed and approved within a month. UVA had to submit to OHRP a corrective action plan and quarterly reports for a year.

- In 1995, FDA conducted a routine audit of the IRB to determine whether the procedures for the protection of human subjects complied with federal regulations. FDA cited UVA's IRB for a failure to have written procedures for the initial review of studies, the periodic review of studies, investigator agreements, and other administrative operations. UVA corrected cited deficiencies promptly.
- In 1999, FDA conducted another routine compliance audit. FDA requested that UVA amend its procedures to address the issue of not using expedited review (in lieu of the required full review by the IRB) approval for emergency use of a drug. UVA responded and amended its procedures promptly.
- In 2000, UVA hired outside consultants to review its compliance with federal regulations for human subject protections, including the IRB organization and structure, education and training programs, written policies and procedures, and resources. The report noted that UVA had many strengths, including staff and operating procedures. It also highlighted specific areas that could be improved. UVA developed an action plan to address the suggestions provided in the report.

Eastern Virginia Medical School. JLARC staff reviewed one federal compliance audit and one external audit conducted at EVMS in 1999 and 2000. Each is described below.

- In 1999, FDA conducted a routine review of the IRB to determine whether the procedures for protection of human subjects complied with federal regulations. It concluded that there were not any significant deviations from FDA regulations.
- In 2000, EVMS invited the Western Institutional Review Board (the same outside contractor that was hired by VCU) to assess the current IRB operations at the medical school. Specifically, the contractor was asked to assess office operations, paper flow, appropriateness of staffing, committee meeting process, information systems, compliance with federal regulations, and billing procedures. Recommendations from the Western Institutional Review Board included a realignment of the IRB reporting structure, procedural changes for IRB board members to reduce potential conflicts of interest, more IRB administrative staff, a more visible location for the IRB office, more equipment to support the IRB office, and more overall funding for IRB activities. The report also highlighted some regulatory compliance problems that needed to be reported to the federal oversight agency. EVMS has addressed some of the issues, but it appears it has not fully addressed the funding issues (see budget discussion on pages 25-28).

During interviews with UVA and EVMS, it was evident that during the past two years, each school has closely monitored the outcome of the federal compliance

audits at VCU and across the country. Therefore, both schools were conducting self-assessments and identifying vulnerable areas that could be improved. UVA staff mentioned that they routinely request federal compliance audit letters from OHRP and FDA, under the Freedom of Information Act, or access this information from the federal agencies' websites. On an ongoing basis, each school should continue this self-assessment activity in order to protect human subjects and avoid federal sanctions. OHRP is currently developing a self-evaluation tool for use by IRB boards and administrators, which will aid in their self-evaluation activities.

***Recommendation (1).* Each of the schools should continue to periodically hire outside contractors or peer institutions to review its institutional review board operations to ensure compliance with federal regulations concerning human subject protections. In addition, each school should routinely conduct self-evaluation audits by utilizing the federal evaluation tool, and by comparing its performance with federal audits recently completed at other schools. This process should help each school identify and take any necessary actions to ensure that it could pass similar compliance audits.**

INSTITUTIONAL REVIEW BOARD FUNDING AND ACTIVITIES

The institutional review board (IRB) is the internal university committee charged by the federal government with the oversight of research conducted with human subjects at a university. IRB committees have the authority to approve, disapprove, and require modifications in all human subject research studies. IRBs also have the authority to address allegations of investigator non-compliance. IRBs were created in the 1970s to be locally-based oversight boards. This task has become more difficult in recent times because many research projects are national studies spanning multiple sites, and the university-level IRB may be limited in its authority to require changes to the study plan and the consent form.

Another problem experienced by IRBs is that the resources for IRB activities historically have been a low priority within universities' budgets. A consequence of this is that IRB members and staff may not be adequately trained on federal regulations, and may be assigned more tasks than members can effectively handle. In recent years, however, many universities have realized that they would not pass federal compliance audits, and have tried to address the problems of the past by increasing IRB resources.

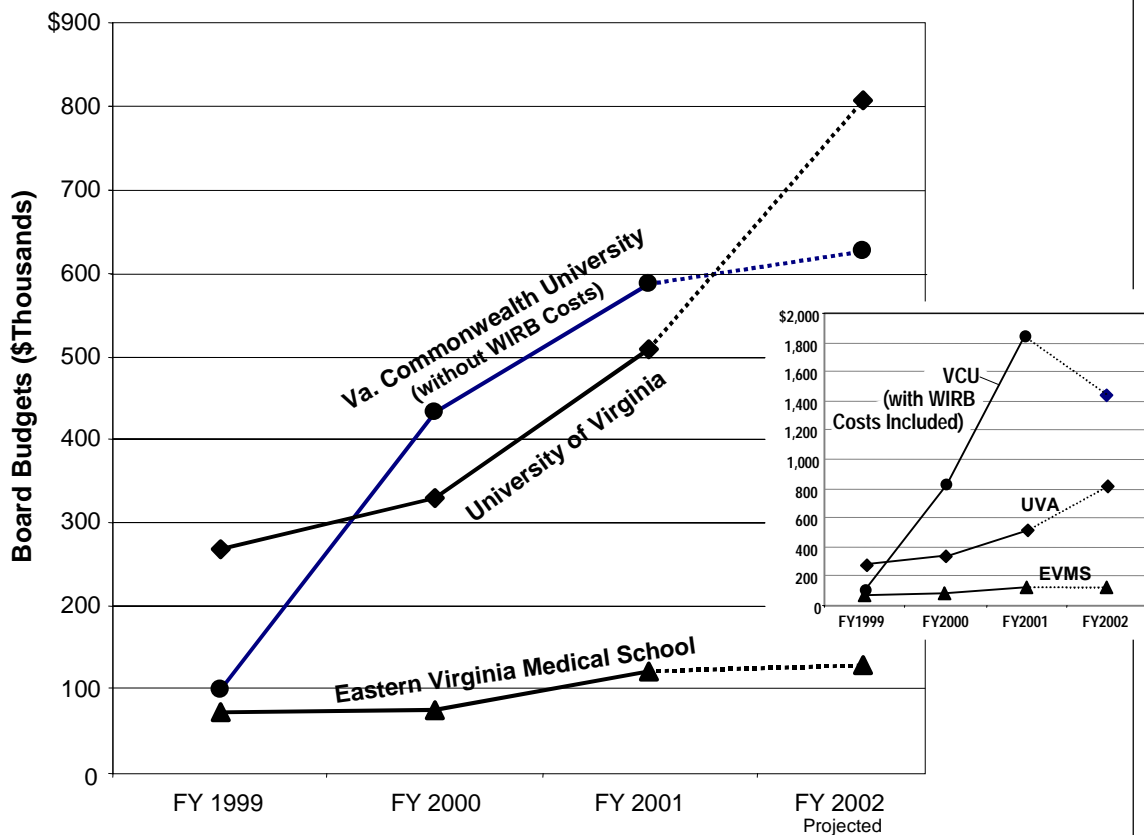
This section includes a review of the resources devoted to IRB activities, and a comparison of key IRB oversight responsibilities at each of the three schools. It also includes a series of best practices that each school has implemented that may benefit the other schools.

Institutional Review Boards' Budgets Have Increased at VCU, UVA, and EVMS

As shown in Figure 2, the level of funding for IRB activities has increased dramatically since 1999 for both VCU and UVA. A pivotal event for both schools appears to be the suspension of research at VCU during FY 2000, which highlighted the problems associated with not having enough staff and resources devoted to IRB oversight activities. VCU is projected to spend more than six times its 1999 sum on the oversight function in 2002; UVA is expected to spend three times more, and EVMS is expected to spend almost two times more. EVMS, which receives a third of the total research funding of VCU and one sixth of the funding of UVA, has a lower level of IRB funding overall and less growth in funding over the past few years.

Figure 2

Comparison of Institutional Review Board Budgets, Fiscal Years 1999 – 2002



Note: Due to the suspension of all research at Virginia Commonwealth University by the federal government in January 2000, VCU hired the Western Institutional Review Board (WIRB) to be the institutional review board of record. The resulting increase in the budget is reflected in the inset chart.

Source: Data provided by Virginia Commonwealth University, University of Virginia, and Eastern Virginia Medical School.

Due to the temporary suspension of all human subject research at VCU by the federal government in December 1999, VCU was required to hire an outside contractor, the Western Institutional Review Board (WIRB), to perform the initial and ongoing review of both behavioral and medical research studies, except studies approved for exemption. This step allowed VCU the time to rebuild the university's entire oversight program for human subject protections while the contractor reviewed and monitored the ongoing research projects. VCU's costs, with contract costs included, are shown in the inset chart in Figure 2. The contract with WIRB has already cost VCU more than \$1.6 million and may cost an additional \$800,000 in FY 2002 (the actual cost will depend on the rate at which VCU begins to assume IRB activities related to reviewing ongoing research studies).

In addition to the different levels of financial support for IRB activities, the three schools spend allocated funds differently. As shown in Table 3, EVMS spends most (80 percent) of its total budget on IRB administrative staff, but has very little university support in its overall level of funding, funding for training, facilities support, and computer systems support. Also, EVMS' salary expenditures for university officials providing IRB oversight are considerably less compared to VCU and UVA, and it is the only school that does not compensate IRB committee chairs for their time commitment. While EVMS receives fewer total research dollars than the other schools, it still needs to maintain an appropriate level of IRB resources to ensure that the oversight functions for medical research are maintained in a quality and timely manner. This is particularly important because EVMS plans to implement a second IRB this summer.

The two IRB committee members at EVMS interviewed by JLARC staff stated that current EVMS administrative staff perform very well, but EVMS needs more staff and funding, especially if it is to add a second IRB committee. In addition, an external review of the current IRB operations (conducted in September 2000) also concluded that more fiscal support is needed to support the current level of research grants at the medical school.

If the amount of funds that VCU expended on an outside contractor is excluded, VCU and UVA have comparable overall budgets in FY 2001 for IRB activities (UVA is \$500,000 and VCU is \$580,000). VCU's projected overall budget for FY 2002 is lower than UVA's, which reflects the elimination of some one-time costs that VCU incurred as the result of its research suspension. VCU spent 41 percent of its funds on IRB administrative staff, compared with UVA's 60 percent. At the present time, VCU spends more money than UVA on university oversight, facility costs (one-time costs), and training and staff development, which reflects corrective action remedies VCU had to implement to meet federal requirements and raise the standards of operation.

Between FY 1999 (prior to the suspension of research at VCU) and FY 2001, all of the schools increased the number of full time administrative staff devoted to supporting the work of the IRB committees. These changes are summarized below.

Table 3 Institutional Review Board (IRB) Budgets for Oversight of Behavioral and Medical Research Studies, Fiscal Year 2001			
Budget Categories	Virginia Commonwealth University	University of Virginia	Eastern Virginia Medical School
Total IRB Administrative Staff Compensation (salaries plus benefits)	\$240,150	\$306,000	\$98,934
Number of Full Time Staff	8	6.45	3.5
Salary Costs for University Officials Providing IRB Oversight	\$93,654	\$54,700	\$15,000
FOR VCU ONLY: Costs for Western Institutional Review Board activities (contract)*	\$1,250,000	Not applicable	Not applicable
Facilities (rent, utilities, furniture, supplies, etc.)	\$ 139,306**	\$27,300	\$4,830
Training/Staff Development/Travel Costs (including IRB committee member training and travel)	\$22,297	\$15,500	\$2,500
Compensation of IRB Members/Buy-out of time	\$39,475	\$67,291	\$0
Systems Support/Database costs	\$19,448	\$33,138	\$0
IRB Committee Activities (related to preparing and conducting meetings)	\$3,329	\$3,240	\$2,000
Other Costs	\$29,457	\$0	\$0
Total Costs	\$1,837,116	\$507,759	\$123,264
Notes: * Due to the suspension of all research at Virginia Commonwealth University by the federal government, the Western Institutional Review Board was hired to be the institutional board of record. ** Includes one-time costs associated with renovation of space, furnishings, and computers Source: Data provided by Virginia Commonwealth University, University of Virginia, and Eastern Virginia Medical School.			

- Virginia Commonwealth University:** VCU increased its IRB administrative staff from 2 to 8. The current positions include a director, two administrative support positions (to be filled), four IRB coordinators to support four IRB committees, and an administrative assistant. In addition to IRB administrative staff persons, VCU has allocated two staff positions for a Director of Education (to be filled) and a Director of Compliance Oversight (currently a part-time position). Both positions will be located in the Office of the Vice President for Research.

- **University of Virginia:** UVA increased its IRB administrative staff from 3.65 staff positions to 6.45 positions. The current positions include a director, three administrative support positions, a computer support person, and a cancer center IRB coordinator.
- **Eastern Virginia Medical School:** EVMS increased its IRB administrative staff from 1.5 staff positions to 3.5 positions. The current positions include an IRB administrator, two administrative support positions, and a half-time compliance coordinator.

All Schools Have Improved Their Research Oversight Activities During the Past Year, But Onsite Audits of Individual Studies Are Needed

The suspension of all human subject research at VCU has made all three schools re-evaluate their commitment to IRB activities and review their operating procedures. As a result of this review, each school has made several important changes to oversight procedures. As of March 2001, UVA was responsible for the oversight of 1,292 active behavioral and medical research studies, VCU was overseeing 1,263 studies, and EVMS was overseeing 712 studies.

In order to assess how the schools are performing their oversight responsibilities since the VCU suspension, JLARC staff compared each school on several key aspects: (1) standard operating procedures, (2) standardized materials for the use by IRB members and study investigators, (3) education and training, and (4) the initial and continuing review of research studies by the IRBs. In the past, the Virginia schools have been cited for non-compliance in one or more of these areas. Overall, JLARC staff found that no systemic problems currently exist at the schools, and all schools appear to be in compliance with federal regulations in most areas.

This section describes the IRB activities reviewed and some deficiencies that were identified. In addition, some best practices of the universities are highlighted. "Best practices" are based on a comparative analysis of each school's IRB activities and procedures, and highlight several common sense items that appear to improve the administration or monitoring of human subject research.

Standard Operating Procedures (SOPs). IRBs must develop a manual of standard operating procedures (SOPs) to communicate how the various federal and university human research subject regulations will be implemented. Failure to have and follow these required written procedures for IRB functions and operations is one of the major non-compliance items that federal agencies cited during recent audits of VCU and other major schools across the country. The federal regulations for SOPs are contained in Chapter 21, *Code of Federal Regulations (CFR)* 56.108, 56.115 (a) (6), and 812.66. These federal regulations place a strong emphasis on the need for IRBs to create a manual that clearly states their authority, policy, and procedures for the uniform performance of the oversight function.

Within the last year, each of the Virginia medical schools has updated and improved its SOPs. Based on the JLARC staff review of the content of the schools' SOPs, it appears that these documents contain the elements that are required by the federal regulations. Exhibit 2 presents several operating procedures that were considered best practices at each of the schools.

VCU is the only school that currently does not post its SOPs on its website. The university does, however, have an initial draft of an Investigator's Manual on the website, which mirrors the content of the SOPs. This appears to be a good way to improve the education of study investigators on their roles and responsibilities in protecting human subjects. However, important sections of this manual are incomplete, including those describing campus resources for study investigators, requirements for specialized research (gene therapy and genetic testing), and most importantly, investigator responsibilities (responding to IRB actions, filing for continuing review and study plan changes, and reporting serious side effects). The investigator's manual is not a federal requirement at this time, but OHRP strongly recommends that institutions develop and distribute IRB guidelines to study investigators to improve compliance with federal regulations. At the present time, neither UVA nor EVMS have an investigator's manual, but they do distribute IRB guidelines to study staff and/or have included this information on their websites.

Exhibit 2

“Best Practices” Implemented by the Schools for Standard Operating Procedures (SOP)

- UVA's SOP manual is in a format that is particularly conducive to timely dissemination of updates to sections of the manual without requiring reprinting the entire document. Each distinct policy references the appropriate regulations and indicates the date of the last revision.
- VCU's SOP manual is organized based on the FDA IRB checklist, which makes it easy to verify full compliance.
- VCU has an Investigator's Manual under development, which provides study investigators the federal requirements for conducting human subjects research.
- UVA and EVMS have its SOP manuals posted on their Internet sites.
- UVA has an excellent IRB management and reporting software program to track studies through initial submission, continuing and modification approvals, and adverse side effects reports. It also uses automated email notifications for investigators and IRB members, which streamlines the submission and notification processes.
- UVA has specific requirements for approval of advertisements for potential study participants. Each advertisement must be pre-approved by the IRB, and have an IRB logo, an IRB study identification number, and expiration date on all forms of advertisement.

Source: JLARC staff analysis of various documents, including online resources and university websites, manuals, and federal regulations.

Recommendation (2). Virginia Commonwealth University should add its Standard Operating Procedures to its website and complete the investigator's manual to ensure that IRB members and study investigators have easy access to information concerning their oversight and research responsibilities. As recommended by the federal oversight agency, both the University of Virginia and the Eastern Virginia Medical School should develop investigator manuals.

Standardized Materials Regarding the Review and Submission of Documents for Use by IRB Members and Study Investigators. The federal regulations for SOPs require each university to develop uniform procedures for IRB members to review documents, and for study investigators to submit various regulatory documents, but it does not delineate how these checklists or tools should be developed. Each school has recently developed a variety of standardized tools to facilitate communication and regulatory compliance. Most of these tools are easily accessible to IRB members and study investigators on the schools' IRB websites. These materials include templates for many required submission forms, and for creating a participant consent form that contains appropriate language and regulatory components. Based upon the JLARC staff review of these materials, all three schools appear to have developed a variety of tools that ensure that critical regulatory elements are included.

One past compliance problem found at VCU and other schools during recent federal audits was the failure to include several items in the consent form document that are required in Chapter 21 CFR 50.25. Therefore, JLARC staff conducted a content analysis of each school's informed consent templates to check for the presence of specific elements required by federal regulations, and to check for additional elements required by federal regulations when appropriate. During the site visits, JLARC staff noted several additional consent elements that appeared to be particularly useful in fully informing the participant about the nature of the study (see Appendix B for the JLARC staff checklist for all consent form elements). The JLARC staff review of the consent form templates found that each school is providing sufficient and appropriate consent guidelines, including all of the federally required elements.

Exhibit 3 presents examples of best practices found in consent form templates. Each school should incorporate the best practices of the other schools. Some of templates have language that better address important matters, such as the disclosure of conflicts of interest, the confidentiality of information, policies for payment for injuries incurred as the result of participation in the research study, policies regarding when a subject's participation in a study may be terminated, drug warnings, and information regarding who to call to ask questions about the study, participant rights, and injuries. EVMS had the most complete and readable consent form template. It included all the critical elements, additional elements, and the elements that appeared to improve the overall content of the form.

Exhibit 3

“Best Practices” Implemented by the Schools for Providing Consent Form Templates and Standardized Materials

Participant Consent Form Template

- EVMS' format and headers are in plain language and easy to understand (consent form language is required to be understandable by federal regulation 21 CFR 50.20).
- VCU invites the potential study participant to “take home an unsigned copy of this consent form to think about or discuss with family or friends before making your decision.”
- EVMS lists all investigators involved in the study, not just the principal investigator.
- UVA has good directions on when and how to disclose investigator conflicts of interest in a consent form.
- EVMS instructs the researcher to use a concise table or calendar to list expected timeframes for visits, what will be done at each visit, and expected compensation when study visits and procedures are complex.
- UVA provides clear language on their approach to safeguarding the confidentiality of participants' personal information: “absolute confidentiality cannot be guaranteed; however, we will take every precaution to protect your privacy.”
- UVA includes language that states, “Medical treatment for physical injury directly resulting from the research procedure that is not covered by your insurance will be provided free of charge at the University of Virginia.”
- Both VCU and EVMS provide good language on why the study investigator may stop a subject's participation at any time.
- VCU has warning language for studies involving drugs stating that if a study drug is to be taken home, “Only the study subject can take the study drug. It must be kept out of reach of children and persons who may not be able to read or understand the label.”
- EVMS has a good section on “Whom Do You Call If You Have Questions or Problems,” which lists separately a contact person for questions about involvement in the study, participants' rights, and how to deal with injury related to the study. OHRP also recommends that contacts for participants' rights and study-related injuries should not be involved in the study, thereby minimizing possible conflicts of interest.
- UVA requires that all persons required to sign the consent form must also print their names (which is not found on other schools' forms) in addition to their signature, and write the date of their signatures.
- UVA provides directions for when it is appropriate to include a statement, signature line, printed name line, and date line for a person providing surrogate consent for a participant unable to sign his consent.
- EVMS clarifies the roles of study personnel by requiring investigators or their authorized personnel to sign a detailed statement that they have been actively involved in the consent process. UVA requires every principal investigator to sign a similar but less detailed statement.
- UVA's requires an IRB stamp of approval, which identifies both the approval and expiration dates of the consent form. Identifying both dates helps to ensure that the current consent form is being used.

(Exhibit continues on the next page.)

Exhibit 3 (Continued)**“Best Practices” Implemented by the Schools for Providing Consent Form Templates and Standardized Materials****General Practices**

- VCU and UVA have all of the necessary IRB forms easily available for download on its Internet site.
- VCU's application form for IRB review includes questions regarding potential study populations that address three levels of information: (1) population demographics (such as age and gender), (2) populations where additional protections may apply (such as poor/uninsured and nursing home residents), and (3) populations federally recognized as vulnerable (such as children and pregnant women). Studies involving one of the federally recognized vulnerable populations are directed to justify their inclusion and specify precautions or consent processes to safeguard these groups.

Source: JLARC staff analysis of various documents, including online resources and university websites, manuals, and federal regulations.

***Recommendation (3).* Each of the schools should review the informed consent templates of the other schools in order to incorporate best practices into its own consent form templates and improve the overall comprehension and content of individual forms.**

Education and Training on Protecting Human Subjects in Research.

As was indicated in Chapter I, one of the federal improvements being sought by Department of Health and Human Services (DHHS) is aimed at addressing inadequacies in research protections. Therefore, DHHS is undertaking an aggressive effort to improve education and training. The federal objective is “to ensure that all clinical researchers, research administrators, IRB members, and IRB staff receive appropriate training in bioethics and other issues related to research involving human subjects.” The NIH has initiated the first step by requiring that all key study personnel (all individuals responsible for the design and conduct of the study) involved in NIH-supported research be trained on human subject protections by October 2000. Lack of appropriate training for IRB members, staff, and study investigators was one of the problems cited at VCU.

Each school has made considerable progress in the past year in providing meaningful training to researchers, IRB members, and IRB staff on the ethics, research practices, and regulatory requirements of conducting research with human subjects. All three schools are fully compliant with the NIH directive for training key study personnel. However, only UVA has gone beyond federal requirements and required that all study personnel, regardless of the source of funding, receive training. The UVA training is documented with a certification letter. UVA developed this training policy because of the NIH directive on training and the requirement of the UVA Multiple Project Assurance contract with OHRP to hold all research studies to the same standards.

In addition, JLARC staff reviewed and took each school's tests for those engaged in human subject research. These tests are part of the training requirements for certain IRB staff, study staff and/or study investigators. JLARC staff found that VCU's test is the most comprehensive and challenging. However, EVMS' test on human subject research appears to be too basic. The test does not adequately emphasize procedures for conducting research on human subjects, ensuring informed consent, and safeguarding participants.

Exhibit 4 presents the best practices for education and training activities. If education is the key to compliance, then these schools should exceed minimum federal requirements for training and ensure that all IRB members, IRB staff, and all key research staff directly involved in obtaining consent or conducting research with human subjects are appropriately trained in safeguarding participants and meeting federal regulations.

Recommendation (4). Each of the schools should review the training and education requirements, resources, and tests of the other schools in order to incorporate best practices into its training program. Best practices, if not currently in place, should include: (1) the development of training resources and tests concerning human subject protections that are comprehensive, and include detailed information concerning the informed consent process, especially with regards to vulnerable populations; (2) the implementation of a requirement that all IRB members and IRB staff should be trained

Exhibit 4

"Best Practices" Implemented by the Schools for Training and Education on Human Subjects in Research

- UVA has the most comprehensive requirements for education, requiring IRB members and staff, and all key personnel listed on study plans (all investigators, not just the principal, and study coordinators) to annually pass a test. Certificates of all key personnel that took training are part of its regulatory files.
- VCU and UVA require different levels of knowledge for IRB members and staff compared to study investigators and staff.
- VCU provides a comprehensive resource for human subject research test preparation (*Protecting Study Volunteers in Research, A Manual for Investigative Sites*, by Cynthia McGuire Dunn et al.)
- VCU's human subject research test is the most comprehensive and challenging.
- UVA provides correct answers for missed questions on its tests, ensuring comprehension and compliance.
- VCU's website provides links to additional educational resources, including an excellent basic tutorial by the University of Minnesota.
- UVA documents its IRB management database with test results.

Source: JLARC staff analysis of various documents, including online resources and university websites, manuals, and federal regulations.

and pass an annual test; and (3) the implementation of a requirement that all key study personnel, including the principal investigator, co-investigators, and study coordinators, regardless of a study's funding source, should be trained and pass an annual test. All required training should be commensurate with the person's level of involvement in the oversight and/or study process.

IRB Initial and Continuing Review of Studies. The purpose of an IRB is to ensure that the appropriate steps are taken to protect the rights and welfare of human subjects in research at all stages of the study. This is accomplished through meaningful initial and continuing reviews of all research study plans, serious adverse event reports, consent forms, and related documents that address the research that involves the participation of human subjects. However, recent federal audits of VCU and other research institutions have found various inadequacies involving the initial and continuing review of research studies. According to federal requirements, these reviews must be "substantive and meaningful." This means that during initial reviews, studies must be individually presented and discussed at a full IRB meeting, and the IRB must systematically consider issues such as the equitable selection of subjects, subject recruitment, privacy and confidentiality, and special protections required for vulnerable subjects. During continuing review, which is at least an annual review of study progress reports, studies must also be individually presented and discussed at a full IRB meeting. Past federal audits have found that many IRBs neglect to fully discuss the continuing reviews in the same manner as the initial reviews.

In order to assist in reviews of research studies, both UVA and EVMS IRB committee members are likely to contact the study investigator directly if there are any questions or concerns about the study plan or consent process. EVMS may also bring the study investigator to a meeting of the full IRB committee to answer questions if the initial study submission was rejected. According to one IRB committee member, VCU's IRB members have been reluctant to communicate directly with study investigators during the review process because the members do not see this as necessary part of conducting the review of the study plan.

In most cases, each of the schools limit its continuing review of research to: reviewing and approving requested amendments and modifications to the study plans, reviewing serious adverse event reports, and reviewing an annual review of the progress reports of studies (VCU's outside contractor is performing most of these functions while VCU is focusing on rebuilding their oversight capabilities). Federal regulations, however, state that these continuing reviews should be conducted "at intervals appropriate to the degree of risk, but not less than once per year." Both UVA and EVMS implement this part of the regulation by requiring follow-up reports on the more serious adverse event reports. In addition, these schools require progress reports on higher risk studies that are tied to the number of subjects enrolled, not a time interval. For example, at EVMS, on a study of pregnant women experiencing toxemia, a progress report was required after each subject was enrolled to ensure the safety of study participants.

However, if the purpose of this continuing review is to analyze a study and determine if the anticipated risks and benefits are reflected in the actual experience of the subject, the best method for doing this is through an independent evaluation conducted by IRB staff during routine onsite visits to the study site. Chapter 21 of the *Code of Federal Regulations* (56.109(f)) gives the IRBs “the authority to observe or have a third party observe the consent process and the research.” Each of the schools have a process for investigating complaints of studies, but only UVA’s IRB staff, on a limited basis, go to study sites and conduct routine audits of regulatory requirements and the consent documents. EVMS currently has a draft plan on how it intends to conduct routine audit plans of study sites.

VCU does not currently have routine audit plans, but reports that they are working to develop them. During the exposure meeting with JLARC staff, VCU indicated its outside contractor has conducted 170 onsite study audits since February 2000. However, VCU officials could not provide a summary of the outcomes of these audits. Further, these audits are part of VCU’s effort to address compliance issues. This is different than having a plan to ensure that the audits can be accomplished over the long term. The fact that VCU does not have these plans was indicated in its April 2001 response to a JLARC data request, in which it reported that it “intends to develop a formal plan for internal audits of protocols through its Compliance Oversight Office.” Also, during the exposure process, VCU indicated that the development of these routine plans was in process, and not complete.

Exhibit 5 presents some of the best practices for each of the schools for performing initial and continuing review of medical research studies. The examples used in this exhibit were limited to activities that are already in place as routine procedures. The exhibit does not describe, for example, procedures that were provided by VCU’s outside contractor as a short-term solution to correct problems or procedures that are currently under development by VCU.

<p style="text-align: center;">Exhibit 5</p> <p style="text-align: center;">“Best Practices” Implemented by the Medical Schools for the Initial and Continuing Review of Studies</p>
<ul style="list-style-type: none"> • UVA and EVMS IRB members routinely contact study investigators with any questions or concerns about their study. EVMS invites the study investigator to the IRB committee meeting if the IRB’s initial review rejected the study plan. • UVA and EVMS require follow-up reports on selected serious adverse event reports. • UVA and EVMS require progress reports to be submitted at intervals based on the assigned degree of risk for the study. • UVA conducts limited routine onsite audits of research studies.
<p>Source: JLARC staff analysis of various documents, including online resources and university websites, manuals, and federal regulations.</p>

Based on JLARC staff's onsite audits of 15 research studies to evaluate compliance with regulatory requirements (discussed later in this Chapter), routine onsite reviews of selected studies should be conducted in order to fully ensure that a study plan has not been changed, that consents have been obtained appropriately, and that regulatory documents are complete. For some studies, onsite reviews are conducted by the study sponsor or by staff of one of the research centers, such as the UVA Cancer Center. The recommended onsite audits could be conducted by IRB staff or by an outside contractor. The priority of these onsite audits should be tied to the degree of risk assigned to the study and the frequency with which reviews by study sponsors, or other internal reviews, are conducted.

Recommendation (5). Each of the schools should improve the IRB procedures for continuing review of research studies by incorporating the best practices of the other schools. At each school, the following activities should take place: (1) IRB members should routinely contact the study investigators directly with any questions or concerns about the study under their review; (2) IRB members should implement procedures to indicate when serious adverse event reports require follow-up reports; (3) IRB members should require more frequent progress reports for studies with a greater expected degree of risk to the study participants; and (4) IRB staff or an outside contractor should conduct routine onsite visits to selected studies, the priority for which should be tied to the assigned degree of risk and the frequency of study-sponsored reviews or other internal reviews.

AUDIT OF SELECTED MEDICAL RESEARCH STUDIES AT EACH OF THE MEDICAL SCHOOLS

While it is the responsibility of the IRBs to ensure that study investigators comply with regulations to safeguard study participants, the safety and welfare of research studies ultimately rests with the study investigator. In order to address the study mandate to assess whether there is adequate protection of all Virginians who participate in medical research, including the most vulnerable or indigent citizens, JLARC staff conducted site visits to review individual medical research studies at VCU, UVA, and EVMS. There were three main purposes for these site visits: (1) to review regulatory documents, including consent forms, to ensure compliance with federal and university requirements; (2) to interview study investigators and study staff on their informed consent process to determine if adequate safeguards are in place; and (3) to document some demographic information on study participants, in order to determine whether adequate protections exists for potentially vulnerable groups.

Because none of the schools capture data at the university level on the demographics of study participants, JLARC staff requested each university to develop a list of medical research studies that were more likely (based on research setting, title of the research study, and/or target population) to include participants who are on Medicaid, who have no health insurance, or who are members of minority groups. From

this list, JLARC staff selected five research studies at each university. As a result, JLARC staff audited 15 medical research studies, with an enrollment of 727 study participants. In addition, the consent forms for 342 study participants were closely reviewed for compliance with regulations. Appendix C contains information on the specific studies, study participant information, and JLARC staff audit findings.

The general study topics selected for review at each school and the sponsorship of the studies are listed below.

- **Virginia Commonwealth University.** Studies included the following topics: diabetes, strokes in African-Americans, high blood pressure, cholesterol levels in heart disease patients, and sickle cell anemia in African-Americans. Three of the studies were sponsored by NIH and two were sponsored by private companies.
- **University of Virginia.** Studies included the following topics: DNA banking for cancer patients, strokes in African-Americans, asthma in emergency room patients, chemotherapy in head/neck cancer patients, and cancer tests for lung cancer patients. Three studies were sponsored by NIH, one study was sponsored by a private company, and one study had no outside sponsor.
- **Eastern Virginia Medical School.** Studies included the following topics: HIV drug therapy, blood clot prevention during pregnancy, sleeping disorder drug treatment, emergency contraception, and evaluation of sickle cell anemia patients in the emergency room. One study was sponsored by NIH, three studies were sponsored by private companies, and one study had no outside sponsor.

The remainder of this section presents the results of the JLARC staff audit of individual medical research studies at VCU, UVA, and EVMS. Overall, the research study investigators and study staff appear to take their responsibility for safeguarding study participants seriously. However, each of the schools had individual studies that had various degrees of non-compliance problems regarding certain regulatory documents and consent forms. Problems found with regulatory documents and consent forms ranged from minor, isolated mistakes, to a few more serious study plan deviations. In addition, while the number of individual studies reviewed was not sufficient to draw a broad conclusion at this point, it did appear that the studies that tended to serve more vulnerable populations were also the ones that tended to have more problems with the matter of obtaining properly executed consent forms.

Individual Medical Research Studies Are in General Compliance Regarding Regulatory Documents, But Some Problems Were Found with the Consent Forms

According to the FDA, “when good procedures are developed, written, and followed, the rights and welfare of the subjects of research are more likely to be adequately protected.” Therefore, JLARC staff’s audit included a review of selected fed-

eral regulatory documents (the original IRB approval of the study, reports of serious adverse events that may be related to participation in the study, and IRB approvals for the study to renew annually or to be modified). In addition, in order to assess the consent process for all people, including the vulnerable, JLARC staff interviewed study investigators and study staff on their informed consent process and reviewed actual consent forms for study participants to determine if adequate safeguards are in place.

The JLARC staff audit also assessed how well the study files were maintained and whether study staff could produce the requested regulatory and consent documents easily. At VCU, all study staff were able to easily retrieve requested regulatory documents; four out of the five studies had easily retrievable consent forms. At UVA, three out of five study staff were able to easily retrieve requested regulatory documents; all studies had easily retrievable consent forms. At EVMS, four out of five study staff were able to easily retrieve regulatory documents and consent forms.

Exhibit 6 summarizes the audit results of regulatory documents and the consent forms. Overall, each school had several strengths in its regulatory compliance, but each school also had one or more potential compliance problems. These findings reinforce the need for the IRB staff to conduct routine study site visits in order to audit regulatory compliance and to ensure the overall safety of study participants. JLARC staff also conducted a content analysis of the current consent forms and found that most of the consent forms in use by the 15 medical research studies were in general compliance with federal regulations.

Two of the three potential compliance problems shown in the exhibit for VCU were particularly troublesome because they occurred since the suspension of research, during which time the university emphasized improving regulatory compliance and oversight of research studies. In one study, on stroke prevention for African Americans, the study investigator failed to obtain a new consent form from several study participants after he was approved to resume the study. This requirement was part of the approval letter sent by VCU's outside contractor, who was the IRB of record. As a result of the JLARC staff visit, the study investigator notified the IRB of its omission and indicated that he will obtain new consents from the study participants at their next clinic visit.

The potential compliance problems found at UVA highlighted the need for all study investigators to be reminded of proper consent procedures, and the need for clarifying the procedures for obtaining oral consent from study participants. In addition, study investigators need to be reminded that changes cannot be made to the study plan without prior IRB approval.

EVMS had only one potential compliance problem found during the JLARC staff audit. The potential problem occurred on a study of blood clot prevention in pregnancy, in which the study staff did not obtain the signatures of witnesses for the consent form, despite the fact that the submitted study plan indicated that this would be done. The EVMS problem highlights the confusion JLARC staff found at all schools

Exhibit 6**Summary Findings of JLARC Staff Audit of Medical Research Studies for Regulatory Compliance and Consent Process****Potential Compliance Problems Found at Virginia Commonwealth University**

- One study investigator failed to re-consent study participants on their next clinic visit as explicitly required in the approval letter by IRB [potential violation of federal regulation 21 CFR 50.27 (a)].
- One study investigator was unable to provide the signed informed consent form for one study participant [potential violation of federal regulation 21 CFR 50.27 (a)].
- One study investigator used a version of the consent form that had not received IRB approval when obtaining the consent of two patients [potential violation of federal regulation 21 CFR 50.27 (a)].

Potential Compliance Problems Found at the University of Virginia

- One study investigator failed to obtain IRB approval before enrolling three patients more than had been previously approved by the IRB [potential violation of federal regulation 45 CFR 46.103 (b) (4) (iii)].
- One study investigator improperly obtained an oral consent by not having a witness sign the consent form as required by regulations [potential violation of federal regulation 21 CFR 50.27 (b) (i)].
- Two study investigators were unable to provide copies of their Investigator's Agreement as required by the UVA IRB.

Potential Compliance Problems Found at Eastern Virginia Medical School

- One study investigator did not bring requested regulatory documents (such as the IRB approved study plan, adverse event reports, and any modifications to the study plan) to the audit meeting. Therefore, JLARC staff were unable to ascertain the status of the regulatory documents.
- One study failed to have consent forms witnessed, despite the fact that the study plan explicitly stated that this would be done. [potential violation of federal regulation 45 CFR 46.103 (b) (4) (iii)].

Source: JLARC staff's onsite audit of 15 medical research studies at VCU, UVA and VCU, Spring 2001.

concerning witnessed consents. At each school, there appears to be a lack of consistency across studies on when and if a witnessed consent is needed. In addition, there appears to be some confusion regarding who is considered an appropriate witness, such as study staff or family members.

Recommendation (6). Each of the schools should review the JLARC staff audit findings for all schools and communicate these to all study investigators, in order to reduce potential regulatory and consent problems. Topics that should be addressed include, but should not be limited to: use of only IRB-approved consent forms, appropriate procedures for storing completed consent forms, required signatures on consent forms, the need for IRB approval prior to changing the study plan, procedures for obtaining oral and witnessed consents, and the process for obtaining consent from potentially vulnerable study participants.

Additional Safeguards are Needed to Ensure the Voluntary Participation of Vulnerable Groups, Including the Indigent, in Medical Research Studies

JLARC staff also assessed whether there is adequate protection for all persons enrolled in medical research studies, including potentially vulnerable or indigent persons. There was some legislative concern that since these medical schools are also the main providers of inpatient and outpatient hospital care, the willingness of study participants to participate in studies may be unduly influenced by the perceived benefits of doing so, such as receiving health care services.

In order to address this issue, JLARC staff collected basic demographic information and health insurance information, when available, to identify potentially vulnerable persons who participated in each of the 15 medical research studies. In addition, JLARC staff compared this information to an overall consent error rate. The consent form error rate is calculated by dividing the number of consent forms found to have at least one error (although several consent forms had multiple errors) by the number of consent forms audited for a selected study. Errors ranged from minor, isolated mistakes (such as lack of dates or missing pages), to a few more serious regulatory problems previously discussed.

In general, each school had at least one study for which no errors in consent forms were identified, but each school also had at least one study with a high rate of errors (more than 45 percent). For the studies audited by JLARC staff, there does appear to be a relationship between projects that serve more potentially vulnerable populations and higher rates of consent form errors. Listed below are some of the findings of the information that is summarized in Table 4 for each school.

Virginia Commonwealth University. The key findings for VCU include:

- One study of heart disease had no consent errors, but served populations with almost no minorities and almost no low-income/uninsured participants.

Table 4 Selected Demographics and Informed Consent Audit Results for University Research Studies					
Study Description (N = Number of study participant consents audited)	Selected Demographics				Consent Form Error Rate*
	Average Age	Percent Female	Percent Minority	Percent Low Income or Not Insured	
Virginia Commonwealth University Effect of Fasting on Diabetics and Non-Diabetics (N=13)	36	85%	69%	0%	23%
Stroke Prevention for African-Americans (N=23)	58	43%	100%	68%	48%
Long-Term Treatment for High Blood Pressure (N=7)	69	0%	14%	14%	14%
Lowering Cholesterol in Patients with Heart Disease (N=23)	63	9%	9%	4%	0%
Long Term Effects of Drug in African-American Sickle Cell Anemia Patients (N=15)	38	40%	100%	53%	27%
University of Virginia DNA Banking for Patients with High Cancer Risk (N=25)	51	80%	6%	N/A	20%
Stroke Prevention for African-Americans (N=27)	58	59%	100%	44%	0%
Distinguishing Asthma Wheezing in the Emergency Room (N=52)	31	81%	46%	22%	58%
Chemotherapy in Head/neck Cancer Patients (N=24)	50	25%	8%	58%	0%
Cancer Tests for Lung Cancer Patients (N=23)	63	61%	17%	26%	13%
Eastern Virginia Medical School HIV Drug Therapy (N=20)	43	15%	15%	10%	0%
Blood Clot Prevention During Pregnancy (N=17)	31	100%	41%	18%	76%
Sleeping Disorder Drug Treatment (N=10)	52	60%	10%	30%	0%
Emergency Contraceptive (N=30)	22	100%	20%	N/A	0%
Evaluation of African-American Sickle Cell Anemia Patients in the Emergency Room (N=32)	28	53%	100%	100%	56%
* The Consent Form Error Rate is the number of consent forms with at least one error divided by the number of consent forms audited. Consent form errors included lack of appropriate signatures and dates, use of wrong form, missing pages, and a failure to re-consent.					
Source: JLARC staff audit of medical research studies at the three universities, Spring 2001.					

- Two studies (of diabetics and stroke prevention) that serve the highest proportion of minorities and low-income/uninsured participants also had high rates of consent form errors.
- One study on stroke prevention for African-Americans, which serves a population with a high potential for diminished capacity due to previous strokes, had a higher percent of low-income/uninsured participants (68 percent) than other VCU studies audited. Almost half (48 percent) of the 23 consent forms reviewed contained errors. In addition, this is the study in which five study participants were not reconsented when the study was reviewed and approved by VCU's outside contractor.
- The study on the long-term effects of a drug on sickle cell anemia patients serves all African-Americans, and had the second highest pool of low-income/uninsured participants among VCU studies reviewed. One out of every four study participant files reviewed contained consent form errors. Also, the study investigator was unable to provide the signed informed consent form for one patient.
- The study on fasting in diabetics and non-diabetics serves mostly minority participants (69 percent), but no low-income/uninsured. It had a 23 percent consent form error rate. The study also used an unapproved version of the consent form in obtaining the consent of two patients.

University of Virginia. The key findings for UVA include:

- The study on chemotherapy in head/neck cancer patients is a good example of a study involving moderate risk, serving a relatively high proportion of low-income/uninsured (58 percent), and at the same time having no consent form errors.
- The stroke prevention study among African-Americans at UVA (this study is part of the same multi-site study as the stroke prevention study audited at VCU). The UVA site also serves a population with a high potential for diminished capacity due to previous strokes, but serves somewhat fewer low-income/uninsured (46 percent) than the VCU site. The UVA site, compared to the VCU site, had no consent form errors. However, the study investigator did not obtain IRB approval before enrolling three participants more than had previously been approved by the IRB.
- The study on asthma wheezing in the emergency room serves mostly women (81 percent). Almost half of the participants are minorities (46 percent), but only about one-fifth (22 percent) are low-income/uninsured. This study shows a high rate of consent form errors (58 percent). The study staff also improperly obtained an oral consent by not having a witness sign the consent form as required by regulations.

Eastern Virginia Medical School. The key findings for EVMS include:

- Three studies had no consent form errors, but served populations with few minorities, and few low-income/uninsured participants.
- The study on blood clot prevention during pregnancy had no witnesses for three-quarters of the consents reviewed, despite the study plan stating that witnessed consent would be obtained.
- The study evaluating African-American sickle cell anemia patients in the emergency room serves 100 percent low-income/uninsured, but 56 percent of the consent forms reviewed had errors.

As the result of the JLARC staff audit, it is clear that it is difficult for the three schools to ensure adequate protections for potentially vulnerable groups if these groups have not been systematically identified throughout the IRB review and approval process. At the present time, the only federal regulations requiring basic demographic information are limited to NIH-sponsored studies. Currently, NIH requires study investigators to provide, during the initial application process, the gender, race, and ethnicity data on the population of potential research subjects. The purpose for this requirement is to have some way of verifying at subsequent study reviews that certain groups of study participants enrolled are not unfairly over or under-represented in the research study. NIH does not require study investigators to identify health insurance information, which can be used to identify those persons with low income or no insurance.

While each school requires study investigators to at least submit some basic demographic information or identify potentially vulnerable groups on their initial study plan application for IRB review and approval, improvements are needed to monitor the representation of these groups throughout the study process. For example, VCU's initial study plan application does include questions regarding potential study populations that address three levels of information: (1) population demographics (such as age and gender), (2) populations where additional protections may apply (such as poor/uninsured and nursing home residents), and (3) populations identified in federal regulations as vulnerable (such as children and pregnant women). In addition, VCU requires studies involving the latter group to justify their inclusion and specify precautions or consent processes to safeguard these groups. However, while this information projects which groups will likely be included in the study plan and whether special protections may apply, it also needs to be updated when the study investigator submits required progress reports and close-out reports. This information, in aggregate form at the study level, should be provided to allow the IRBs to monitor the prevalence of vulnerable groups in the studies.

Recommendation (7). Each of the schools should implement data collection procedures to ensure the fair and equitable treatment of potentially

vulnerable populations in research studies. The data should be submitted during the initial study application process (for those projected to serve), and updated in progress and close-out reports (to reflect the actual number served). Data collected, in aggregate form at the study level, should include basic demographic data (such as age, sex, and race), and data on the characteristics of the population which are related to the need for additional protections (for example, poor/uninsured subjects, or pregnant women).

Appendixes

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Appendix A

Total Research, Medical Research, and Federal Medical Research Funding and Rankings from 1993 to 2001

Characteristic	VCU (\$Millions)	UVA (\$Millions)	EVMS (\$Millions)
2001 – projected			
Total Funding	\$91.7	\$195.5	\$24.3
Medical Research Total Funding	\$48.6	\$80.4	\$14.1
Medical Research National Ranking	N/A	N/A	N/A
Federal Medical Research Funding	\$26.7	\$50.8	\$6.0
Federal Medical Research Funding as % of Total Medical	55%	63%	43%
Biomedical and Bioengineering Research	\$0.8	\$2.9	\$0.0
2000			
Total Funding	\$88.2	\$174.5	\$23.3
Medical Research Total Funding	\$46.7	\$71.8	\$13.8
Medical Research National Ranking	N/A	N/A	N/A
Federal Medical Research Funding	\$25.7	\$45.4	\$8.4
Federal Medical Research Funding as % of Total Medical	55%	63%	61%
Biomedical and Bioengineering Research	\$0.8	\$2.6	\$0.0
1999			
Total Funding	\$79.8	\$157.5	\$24.1
Medical Research Total Funding	\$42.9	\$63.1	\$15.7
Medical Research National Ranking	62	50	92
Federal Medical Research Funding	\$23.5	\$39.6	\$8.4
Federal Medical Research Funding as % of Total Medical	55%	63%	54%
Biomedical and Bioengineering Research	\$0.0	\$2.2	\$0.0
1998			
Total Funding	\$80.5	\$139.1	\$21.7
Medical Research Total Funding	\$45.0	\$56.7	\$15.2
Medical Research National Ranking	59	55	N/A
Federal Medical Research Funding	\$25.1	\$36.4	\$6.9
Federal Medical Research Funding as % of Total Medical	56%	64%	45%
Biomedical and Bioengineering Research	\$0.0	\$2.0	\$0.0
1997			
Total Funding	\$79.0	\$114.1	\$19.1
Medical Research Total Funding	\$43.1	\$43.8	\$11.9
Medical Research National Ranking	56	55	98
Federal Medical Research Funding	\$22.7	\$29.0	\$8.0
Federal Medical Research Funding as % of Total Medical	53%	66%	67%
Biomedical and Bioengineering Research	N/A	N/A	N/A
<i>Table continues on next page.</i>			

Table A-1, continued

**Total Research, Medical Research, and Federal Medical Research
Funding and Rankings from 1993 to 2001**

1996			
Total Funding	\$79.0	\$97.3	\$17.7
Medical Research Total Funding	\$44.8	\$31.5	\$12.0
Medical Research National Ranking	52	42	94
Federal Medical Research Funding	\$24.6	\$23.2	\$8.4
Federal Medical Research Funding as % of Total Medical	55%	74%	70%
Biomedical and Bioengineering Research	N/A	N/A	N/A
1995			
Total Funding	\$76.5	\$136.7	\$17.8
Medical Research Total Funding	\$43.2	\$55.1	\$12.1
Medical Research National Ranking	N/A	N/A	N/A
Federal Medical Research Funding	\$24.9	\$26.6	\$7.8
Federal Medical Research Funding as % of Total Medical	58%	48%	64%
Biomedical and Bioengineering Research	N/A	N/A	N/A
1994			
Total Funding	\$76.6	\$129.5	\$17.9
Medical Research Total Funding	\$44.7	\$47.7	\$12.3
Medical Research National Ranking	N/A	N/A	N/A
Federal Medical Research Funding	\$26.4	\$24.7	\$7.7
Federal Medical Research Funding as % of Total Medical	59%	52%	63%
Biomedical and Bioengineering Research	N/A	N/A	N/A
1993			
Total Funding	\$77.1	\$115.8	\$15.8
Medical Research Total Funding	\$44.9	\$41.2	\$11.2
Medical Research National Ranking	N/A	N/A	N/A
Federal Medical Research Funding	\$27.3	\$22.3	\$7.2
Federal Medical Research Funding as % of Total Medical	61%	54%	64%
Biomedical and Bioengineering Research	N/A	N/A	N/A
<p>Note: There is a decrease in the reported funding for UVA in 1996, according to UVA officials, due to a change in how data were reported to the National Science Foundation's (NSF).</p> <p>Source: JLARC staff analysis of data from the annual reports from NSF 1996 through 1999 on <i>Academic Research and Development Expenditures</i>. Data from 2000 were provided by the universities to NSF, but have not yet been published in an annual report. Projections for 2001 were provided by the universities to JLARC staff.</p> <p>NSF web links:</p> <p>1999 tables - http://www.nsf.gov/sbe/srs/srs01407/start.htm</p> <p>1998 report - http://www.nsf.gov/sbe/srs/nsf00330/start.htm</p> <p>1997 report - http://www.nsf.gov/sbe/srs/nsf99336/start.htm</p> <p>1996 report - http://www.nsf.gov/sbe/srs/nsf98304/start.htm</p>			

Appendix B

JLARC Study of Indigent Participation in Medical Research at Virginia's Teaching Hospitals Protocol Information

University:		Date of Audit	
Research center or affiliation			
Principal Investigator			
Name		Phone	
Title		Email	
Study Coordinator			
Name		Phone	
Title		Email	

Protocol #	Original IRB Approval Date		
Protocol Title			
Type of Sponsor	Federal		
No sponsor	Private		
	Other		
Type of Original IRB Review	Exempt	Expedited	Full Board
Subjects	Date 1 st Enrolled	# Approved	# Enrolled
Regulatory Documents	Present?	Comments	
IRB Approved Protocol	Yes No N/A		
Investigators Agreement	Yes No N/A		
Adverse Event Reports	Yes No N/A		
Advertising Approvals	Yes No N/A		
Modifications & Continuations	Yes No N/A		

Received requested documents?	
<input type="checkbox"/> Study description	<input type="checkbox"/> Advertisement(s)
<input type="checkbox"/> Current consent form	<input type="checkbox"/> Inclusion/exclusion criteria
<input type="checkbox"/> Research Plan information on gender and race/ethnicity (NIH funded only)	
Comments	

Subject Information

Protocol # _____		Subject Identifier _____	
Demographics	Age _____	Sex _____	Race _____
Insurance Status	Private _____	Medicaid _____	Self-Pay _____
	Unknown _____	Other: _____	No means _____
Latest Consent Form		Date of last form signed: _____	
Signatures	Present?		Comments
Subject's signature	Yes	No	N/A
Subject's initial on every page	Yes	No	N/A
Study coordinator's signature	Yes	No	N/A
PI's or physician's signature	Yes	No	N/A
Witness' Signature	Yes	No	N/A
Comments _____			

Protocol # _____		Subject Identifier _____	
Demographics	Age _____	Sex _____	Race _____
Insurance Status	Private _____	Medicaid _____	Self-Pay _____
	Unknown _____	Other: _____	No means _____
Latest Consent Form		Date of last form signed: _____	
Signatures	Present?		Comments
Subject's signature	Yes	No	N/A
Subject's initial on every page	Yes	No	N/A
Study coordinator's signature	Yes	No	N/A
PI's or physician's signature	Yes	No	N/A
Witness' Signature	Yes	No	N/A
Comments _____			

JLARC Staff Checklist for Content Review of Consent Forms Currently in Use	
	Federally Required Elements
	A statement that the study involves research
	An explanation of the purposes of the research
	The expected duration of the subject's participation
	A description of the procedures to be followed
	Identification of any procedures which are experimental
	A description of any reasonably foreseeable risks or discomforts to the subject
	A description of any benefits to the subject or to others which may reasonably be expected from the research
	A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject
	A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained
	For research involving more than minimal risk, an explanation as to whether any compensation, and an explanation as to whether any medical treatments are available, if injury occurs and, if so, what they consist of, or where further information may be obtained
	<i>An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject, for the following:</i>
	Research questions
	Rights questions
	Injury questions
	A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits, to which the subject is otherwise entitled
	Additional Elements Federally Required When Appropriate
	A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant), which are currently unforeseeable
	Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent
	Any additional costs to the subject that may result from participation in the research
	The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject
	A statement that significant new findings developed during the course of the research, which may relate to the subject's willingness to continue participation, will be provided to the subject
	The approximate number of subjects involved in the study
	Additional Elements of Good Practice
	What factors exclude persons from participating in study (not required by VCU)
	Explanation of randomization (if appropriate)
	Payment for participation is clear
	Consent form is readable
	Study plan title & IRB number (note: IRB number not required by EVMS)
	Length of the consent form in number of pages
	Indication of page number compared to total number of pages (for example, "Page 1 of 5")
	IRB stamped approval
Source: Federal regulations 21 CFR 50.20, 50.25 (a) (1-8), 50.25 (b) (1-6), and JLARC staff analysis.	

Appendix C: Medical Research Study Data from the JLARC Staff Audit

School	Study Title	Type of Original IRB Review	Risk Assessment	Does Study Have Annual Internal/ External Audit	Type of Sponsor	Original IRB Approval Date	Date First Subject Enrolled	Number of Subjects Approved to Enroll
EVMS	A Multi-Center, Double-Blind, Phase III, Adjuvant-Controlled Study of the Effect of 10 Units of HIV-1 Immunogen (Remune) Compared to IFA Alone Every 12 Weeks on AIDS and HIV Progression-Free Survival in Subjects with HIV Infection and CD4 T Lymphocytes between 300 and 549 Cells/uL Regardless of Concomitant HIV Therapies	Full Board		Yes	Private	6/13/1996	6/27/1996	2,500 all sites
EVMS	A Randomized Controlled Trial to Compare Standard Heparin Therapy Versus a Low Molecular Weight Heparin (Fragmin) for Prophylactic Anticoagulation in Pregnancy	Full Board	Moderate	Yes	Private	2/02/1998	3/20/1998	208
EVMS	Long-term, Open-Label, Multi-center Extension Trial of Xyrem (Sodium Oxybate) Oral Solution for the Treatment of Narcolepsy	Full Board		Yes	Private	5/04/1999	7/26/1999	8 to 10
EVMS	A Prospective, Randomized, Double-Blind Multi-center Study to Compare the Efficacy, Safety and Tolerance of CDB2914 with Levonorgestrel as an Emergency Contraceptive Agent	Full Board		Yes	NIH	6/16/1999	11/08/1999	250
EVMS	The Reticulocyte Count: Is it Needed in the Evaluation of Patients Presenting with Typical Sickle Cell Pain Crises?	Expedited		No	EVMS	3/14/2000	Jun-00	200

Appendix C: Medical Research Study Data from the JLARC Staff Audit

School	Actual Number of Subjects Enrolled	Number of Consents Audited by JLARC	Percent of All Consents Audited by JLARC	Average Age of Subjects Audited*	Percent Female Subjects Among Audited*	Percent Racial/ Ethnic- Minority Subjects Among Audited*	Percent Poor/No Insurance Subjects Among Audited*	University & Federally Required Documents Provided & OK	Comments on Regulatory Documents	Files Easily Re- trievable?
EVMS	43	20	47%	43	15%	15%	10%	Yes		Yes
EVMS	91	17	19%	31	100%	41%	18%	Yes		No
EVMS	10	10	100%	52	60%	10%	30%	Yes		Yes
EVMS	120	30	25%	22	100%	20%	N/A	Yes		Yes
EVMS	68	32	47%	28	53%	100%	100%	No	Did not bring study plan or modifications &	Unknown

* Calculations based on number of participants for whom there is data, assuming those missing would be proportionally like those present.

Appendix C: Medical Research Study Data from the JLARC Staff Audit

School	Percent of Consents Audited by JLARC With at Least One Problem	Comments on Consent Form Issues	Emphasis on Consent Process	General Comments
EVMS	0%		Strong	Max enrolled is 43, active enrollment at time of audit is 20
EVMS	76%	13 consents not witnessed; 1 consent not initialed every page.	Strong	Example of confusion over witness policy - study plan page 4 said staff would obtain witnessed consent, many current patients' consents not witnessed. Total enrolled is 91, active enrollment at time of audit is 30.
EVMS	0%		Strong	Example of issue of witness policy needing clarification - study coordinator and witness line the same on consent forms.
EVMS	0%		Strong	Even though insurance status is unknown, the study does involve the uninsured and poor.
EVMS	56%	Recent issue - 9 witness not sign; 1 study coordinator not sign; 11 every page not initialed; 1 witness not date; 9 Principal Investigator (PI) not date.	Adequate	

Appendix C: Medical Research Study Data from the JLARC Staff Audit

School	Study Title	Type of Original IRB Review	Risk Assessment	Does Study Have Annual Internal/ External Audit	Type of Sponsor	Original IRB Approval Date	Date First Subject Enrolled	Number of Subjects Approved to Enroll
UVA	DNA Banking for Individuals with a Predisposition to the Development of Cancer	Expedited	Minimal	No	None	7/25/1995	N/A	N/A
UVA	African-American Antiplatelet Stroke Prevention Study (Secondary Stroke Prevention Study in the African-American Community: Ticlopidine vs. Aspirin)	Full Board	Standard of Care	Yes	NIH	6/10/1997	9/03/1997	24
UVA	Techniques for Distinguishing Asthma from Other Causes of Wheezing in the Emergency Room	Full Board	Minimal	No	NIH	6/24/1997	8/19/1997	240
UVA	A Randomized Phase III Multi-center Trial of Neoadjuvant Docetaxel (Taxotere) Plus Cisplatin and 5-Fluorouracil Followed by Concomitant Chemoradiotherapy in Patients with Locally Advanced Squamous Cell Carcinoma of the Head and Neck	Full Board	Moderate	Yes	Private	4/13/1999	8/10/1999	30
UVA	A Prospective Study of the Prognostic Significance of Occult Metastases in the Patient With Resectable Non-Small Cell Lung Carcinoma	Full Board	Minimal	Yes	NIH	2/08/2000	3/21/2000	100

Appendix C: Medical Research Study Data from the JLARC Staff Audit

School	Actual Number of Subjects Enrolled	Number of Consents Audited by JLARC	Percent of All Consents Audited by JLARC	Average Age of Subjects Audited*	Percent Female Subjects Among Audited*	Percent Racial/ Ethnic- Minority Subjects Among Audited*	Percent Poor/No Insurance Subjects Among Audited*	University & Federally Required Documents Provided & OK	Comments on Regulatory Documents	Files Easily Re- trievable?
UVA	51	25	49%	51	80%	6%	0%	Yes		Yes
UVA	27	27	100%	58	59%	100%	44%	No	Did not have approval to enroll additional patients	Yes
UVA	151	52	34%	31	81%	46%	22%	No	Missing Investigators Agreement, UVA IRB requires	Yes
UVA	24	24	100%	50	25%	8%	58%	No	Missing Investigators Agreement, UVA IRB requires	Yes
UVA	23	23	100%	63	61%	17%	26%	Yes		Yes

* Calculations based on number of participants for whom there is data, assuming those missing would be proportionally like those present.

Appendix C: Medical Research Study Data from the JLARC Staff Audit

Percent of Consents Audited by JLARC With at Least One Problem		Comments on Consent Form Issues	Emphasis on Consent Process	General Comments
School	Problem			
UVA	20%	Recent issue - Study coordinator did not date one consent. Old issue - One consent missing 2nd page of clinical consent; one consent with no witness signature; one consent signed after expiration date; one consent not signed by person who explained; one research consent missing one page and not dated; husband signed his name for wife to participate in presence of witness.	Adequate	
UVA	0%	Recent issue - over enrolled 3 without prior IRB approval [CFR 46.103 (b) (4) (iii)]. Old issue - Participant made an "X" and his wife signed.	Strong	
UVA	58%	Old issue - one patient was orally consented, form noted and signed by sub-PI but no witness - [21 CFR 50.27 (b) (i)]; 17 consents not witnessed; 15 not initialed on every page.	Weak	
UVA	0%		Strong	File contains case examples of (1) IRB ensuring all PI's trained, (2) new PI box on consent form, and (3) study with overall moderate risk, many Medicaid patients, strong emphasis on consent, AND no consent issues.
UVA	13%	Recent issue - one patient did not initial every page; one patient signed but not date consent.	Strong	Sometimes sign up for study same day as receive cancer diagnosis or only a couple of days before surgery. But strong consent process compensates for minimal time for patient to deliberate.

Appendix C: Medical Research Study Data from the JLARC Staff Audit

School	Study Title	Type of Original IRB Review	Risk Assessment	Does Study Have Annual Internal/ External Audit	Type of Sponsor	Original IRB Approval Date	Date First Subject Enrolled	Number of Subjects Approved to Enroll
VCU	Effect of Fasting on Gluconeogenesis and Glucogenolysis in Patients w/ Type 2 Diabetes Mellitus	Full Board		No	NIH	8/11/1995	7/28/1998	20
VCU	African-American Antiplatelet Stroke Prevention Study (Secondary Stroke Prevention Study in the African-American Community: Ticlopidine vs. Aspirin)	Full Board	Minimal	Yes	NIH	2/12/1998	N/A	1800 all sites
VCU	A Prospective, Multinational, Multi-center, Double-Blind, Randomized Active-Controlled Trial in Patients w/ Essential Hypertension to Compare the Effect of Valsartan 80 & 160 mg., with or without the Addition of Hydro-chlorothiazide, Once Daily to that of Amlodipine 5 and 10 mg Once Daily, with or without the Addition of Hydro-chlorothiazide, on Cardiovascular Morbidity and Mortality	Full Board	Minimal	Yes	Private	5/01/1998	8/31/1998	N/A
VCU	The Effect of LDL Cholesterol Lowering Beyond Currently Recommended Minimum Targets on Coronary Heart Disease (CHD) Recurrence in Patients with Pre-existing CHD	Full Board	Minimal	Yes	Private	4/30/1998	7/07/1998	35
VCU	Multi-center Study of Hydroxyurea in Sickle Cell Anemia (MSH) Patient's Follow-up	Full Board	Moderate	No	NIH	2/22/1996	10/02/1996	19

Appendix C: Medical Research Study Data from the JLARC Staff Audit

School	Actual Number of Subjects Enrolled	Number of Consents Audited by JLARC	Percent of All Consents Audited by JLARC	Average Age of Subjects Audited*	Percent Female Subjects Among Audited*	Percent Racial/ Ethnic- Minority Subjects Among Audited*	Percent Poor/No Insurance Subjects Among Audited*	University & Federally Required Documents Provided & OK	Comments on Regulatory Documents	Files Easily Re- trievable?
VCU	13	13	100%	36	85%	69%	0%	No	Used unapproved consent form for two patients	Yes
VCU	53	23	43%	58	43%	100%	68%	Yes		Yes
VCU	7	7	100%	69	0%	14%	14%	Yes		Yes
VCU	31	23	74%	63	9%	9%	4%	Yes		Yes
VCU	15	15	100%	38	40%	100%	53%	Yes		No

Appendix C: Medical Research Study Data from the JLARC Staff Audit

School	Percent of Consents Audited by JLARC With at Least One Problem	Comments on Consent Form Issues	Emphasis on Consent Process	General Comments
VCU	23%	Old issue - 2 patients consented with unapproved version of consent form [21 CFR 50.27 (a)]; 1 consent form neither the PI nor witness (RN) dated after signing.	Strong	
VCU	48%	Recent issue - 5 patients not re-consented with WIRB form but in clinic 2-4 times [21 CFR 50.27 (a)]; 1 witness not sign; 2 every page not initialed; 3 consents study coordinator signed as such then again as witness, 2 signed by coordinator but dated a month later; 1 PI did not sign. Old issue - 1 daughter signed for participant; 1 patient could not write so marked an "X" - no family as witness.	Adequate	Case files have example of quarterly review by WIRB.
VCU	14%	Old issue - date change on consent without explanation.	Strong	One of the 7 patients disenrolled because study test disqualified them. Recent issue - Good example of getting VA IRB approval to provide marketed drug to patient while suspension issues dealt with.
VCU	0%		Adequate	Case example of potential for doctor - patient relationship being coercive in consenting - if patient does not have a doctor, PI can become primary physician. There were 21 enrolled at time of audit, 10 disenrolled screen failure (audited two of these).
VCU	27%	PI could not find informed consent form for one patient [21 CFR 50.27 (a)]. Recent issue - One subject not initial choice of follow-up, only checked box. Old issue - study coordinator signed as witness but PI never signed; one consent was an Old issue consent form with a blank for the person who provided consent information to fill in their name, no name was entered.	Weak	They took about a half an hour to find four other consent forms. 3 patients have died.

Appendix D

Agency Responses

As part of an extensive data validation process, State agencies involved in a JLARC assessment effort are given the opportunity to comment on an exposure draft of the report. Appropriate technical corrections resulting from written comments have been made in this version of the report. Page references in the agency responses relate to an earlier exposure draft and may not correspond to page numbers in this version.

This appendix contains the following responses::

- University of Virginia
- Eastern Virginia Medical School
- Virginia Commonwealth University

JUN 6 2001



UNIVERSITY OF
VIRGINIA

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EXECUTIVE VICE PRESIDENT
AND CHIEF OPERATING OFFICER

June 5, 2001

Philip A. Leone, Director
Joint Legislative Audit and Review Commission
Suite 1100, General Assemble Building Capitol Square
Richmond, VA 23210

Dear Phil:

President Casteen asked me to respond to your letter of May 23, 2001. Many thanks for providing the draft copy of your report, *Indigent Participation in Medical Research at Virginia's Medical Schools*. You and your staff have done a very good job with a difficult topic, and have developed a good background in the complicated field of bioethics and human subjects protection.

We find no serious factual errors which need to be addressed. With one exception, your recommendations are also very reasonable. In several of these, your recommendations parallels actions we have already begun to improve our efforts in the protections of human participants.

As we have mentioned to your staff, we are somewhat concerned with your final recommendation (7) in which you suggest that we record health insurance information for our participants. While we wholeheartedly agree that we must be aware of the special problems of vulnerable populations, and that economically-disadvantaged individuals are one of these vulnerable groups, we are not sure that the collection of health insurance information is the best way to achieve that goal. We are grateful for the opportunity to review the draft report.

Sincerely,

A handwritten signature in dark ink, appearing to read "Leonard W. Sandridge".

Leonard W. Sandridge
Executive Vice President
and Chief Operating Officer

LWS:kaf

cc: John T. Casteen, III
Gene D. Block
David J. Hudson



EASTERN VIRGINIA MEDICAL SCHOOL
OFFICE OF RESEARCH
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JUN 5 2001

TELEPHONE (757) 446-8480
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June 4, 2001

Philip A. Leone
Director of Research
Joint Legislative Audit and Review Commission
General Assembly Building, Suite 1100
Richmond, Virginia 23219

Dear Mr. Leone:

Thank you for the draft report, Indigent Participation in Medical Research at Virginia's Medical Schools and for the opportunity to provide verification and editorial review. The report is excellent and we plan to use the final version as a resource in the administration of our Institutional Review Board. We would, however, like to provide clarification and comment on three general areas of the draft. These areas are: 1) Procedural Policies of the EVMS IRB; 2) Possible Noncompliance in Audited Protocols; and 3) EVMS Responses to the JLARC Recommendations.

1. Procedural Policies of the EVMS IRB

A. Required Training

EVMS will expand its requirement for education in the protection of human subjects involved with research. In addition to existing policies for NIH-funded studies, our training requirement will apply to all types of sponsored studies and will be required of all investigators, staff, and other individuals who are responsible for the design and conduct of a study involving human subjects. EVMS is a community-based school and we are currently formulating plans to include our community physicians and their staffs into our training population.

In addition, we will modify our SOP's to clarify the definition of "key personnel" involved in the conduct of human subject research.

B. Best Practices

Exhibit 2 – Standard Operating Procedures

Best Practices	EVMS Comments
VCU's SOP's are organized based on the FDA Checklist	EVMS has a completed FDA Checklist available for auditors with page numbers referencing each item in the SOP's.

VCU has an Investigator's Manual under development, in addition to their SOP's.	EVMS used to have a separate guidebook from the SOP's but FDA auditors suggested that all information be combined into one document, the SOP's. EVMS will require each investigator to sign an agreement to abide by IRB regulations, similar to what is currently done for community faculty (Attachment 1).
UVA has an excellent IRB management and reporting software program to track studies.	EVMS currently utilizes IRB databases but is in the process of evaluating software programs for expanded IRB operations.
UVA has a requirement that all advertisements must be approved by the IRB, have an IRB logo, an IRB identification number and expiration date.	EVMS also requires that all advertisements be pre-approved by the IRB. The IRB will now require an identification number, logo, and expiration date for advertisements.

Exhibit 3 – Consent Form Templates

Best Practices	EVMS Comments
VCU and UVA have a sentence that instructs the participant to ask the study staff to explain any words or information not clearly understood.	Page A2 of the EVMS Consent Form contains the statement "Please take your time to make your decision and feel free to ask any questions you might have."
UVA, regarding the confidentiality of personal participant information, provides clear language expressing "we will take every precaution to protect your privacy."	The EVMS Consent Form states "all health information will be maintained in strict confidence, but we cannot guarantee absolute confidentiality." This is similar to the language recommended by the National Cancer Institute, in its publication "Recommendations for the Development of Informed Consent Documents for Cancer Clinical Trials", August 1998.
VCU has warning language for drug studies that states "Only the study subject can take the study drug. It must be kept out of reach of children and persons who may not be able to read or understand the label."	EVMS will now require similar warning language in its consent forms.

UVA requires that all persons required to sign consent forms must also print their names in addition to their signatures.	EVMS will require similar requirements on it's consent forms.
UVA requires an IRB stamp of approval, which identifies both the approval and expiration data of the consent form.	EVMS also requires the IRB stamp of approval for consent forms. EVMS used to include a stamp for the expiration date but discontinued this practice at the suggestion of the auditors of the Western IRB. They felt that an expiration date on a consent form would require the re-consenting of each subject in each study when the consent form expired annually (or sooner for higher risk studies). We will re-evaluate this policy.

Exhibit 4 – Training and Education

Best Practices	EVMS Comments
UVA provides correct answers for missed questions on its tests, ensuring comprehension and compliance.	EVMS does as well.

2. Possible Noncompliance in Audited Protocols

"One study investigator did not bring requested regulatory documents (such as the IRB approved plan, adverse event reports, and any modifications to the study plan) to the meeting. Therefore, JLARC staff were unable to ascertain the status of the regulatory documents."

The investigator, an emergency room physician at a local hospital and Chair of the Emergency Medicine Program, met with the JLARC auditors in a conference room down the hall from the IRB office. The investigator brought all copies of the subject consent forms and assumed the protocol and any other study documents needed could have been located in the IRB office. (They could have, if the request had been made). There were no adverse events associated with the protocol, so there are no adverse event reports to supply. There have also been no modifications to the study plan.

Regarding Exhibit 6. "One study failed to have consent forms witnessed, despite the fact that the study plan explicitly stated that this would be done. [potential violation of federal regulation 45 CFR 46.103 (b) (4) (iii)]."

This study was last approved under our former version of SOP's, which required that all consent forms have a witness sign the form. The purpose of the witness' signature was to signify there really was a person signing the consent. In the process of revising the SOP's, it was determined this was an unnecessary step and a revision was made to the policy. The witness signature required for this study was not related to protecting vulnerable subjects.

The revised policy requires the witness' signature when the consent process is conducted through oral translation, such as in cases where the subjects can not read or can not read English. In this case, the witness' signature means that the witness was present and witnessed the entire consenting process. This is stated on the revised consent forms.

The lack of witness signatures for the consent forms did violate earlier EVMS IRB policies and was a deviation from the protocol, although the signatures would not be required under the current SOP's. We have clarified the signature requirement with the appropriate study personnel.

3. Response to JLARC Recommendations.

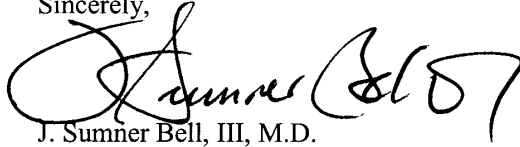
Recommendations	EVMS Comments
Periodically hire outside auditors. Compare federal audits with own schools performance.	EVMS will adopt routine auditing programs for studies conducted by EVMS full-time salaried faculty.
Develop Investigator Manuals	FDA recommended that we combine all information under one document, the SOP's. We will supplement information currently in our SOP's about investigator responsibilities with an Investigator Agreement Packet that delineates required policies and procedures and sources for information on human subjects' protections.

Each medical school should review informed consent template of the other school's in order to incorporate best practices.	In developing the EVMS consent form, the templates of many schools across the nation, as well as NCI, were reviewed for the best practices.
Each of the medical schools should review the training and education requirements, resources, and tests of the other school's to incorporate the best practices.	EVMS is continuing to re-evaluate the training resources and is planning to move to the NCI training model, with CME credit, supplemented by an EVMS module.
Each of the medical schools should improve the continuing review process by incorporating the best practices of the other schools.	EVMS is developing plans for an audit program of study files.
Each of the medical schools should review the JLARC findings for all of the schools and communicate these to all study investigators.	Good topics for training!
Each medical school should implement data collection procedures to maintain basic demographic and health insurance information in aggregate form, on the participation of potentially vulnerable studies.	No one has ever requested this information before. It would be possible to report this subject information in continuing reviews and closeout reports. For some studies, it would be difficult to project the socioeconomic status and race of potential subjects (such as in a cardiac study of valve replacement). However, EVMS is sensitive to the need to avoid unnecessary exclusion of subjects and to protect potentially vulnerable subjects. We will, therefore, consider the collection of such data when it is appropriate.

Finally, the suggestion that the EVMS human subjects' protections quiz is too basic, is a criticism well taken. In fact, we discussed with the JLARC auditors our plans to move to the NCI, "Human Participant Protections Education for Research Teams", for which CME credit is available, and supplement it with training specific to the EVMS IRB. While we feel that the current training modules and quiz satisfy the NIH requirements, we are working on improvements. (A quiz is not required by NIH.)

Thank you again for sharing this report with us and for taking our comments into consideration.

Sincerely,

A handwritten signature in black ink, appearing to read "J. Sumner Bell, III, M.D.", with a large, stylized initial "J" and a long, sweeping underline.

J. Sumner Bell, III, M.D.
President
Eastern Virginia Medical School

A handwritten signature in black ink, appearing to read "Evan R. Farmer, M.D.", with a stylized "E" and "F" and a long, sweeping underline.

Evan R. Farmer, M.D.
Dean and Provost
Eastern Virginia Medical School

A handwritten signature in black ink, appearing to read "William Wasilenko", with a stylized "W" and "W" and a long, sweeping underline.

William Wasilenko, Ph.D.
Director, Office of Research
Eastern Virginia Medical School



JUN 5 2001

Office of the President

V i r g i n i a C o m m o n w e a l t h U n i v e r s i t y

June 5, 2001

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Mr. Philip A. Leone
Director
Joint Legislative Audit and Review Commission
General Assembly Building
Suite 1100
Richmond, Virginia 23219

Dear Mr. Leone:

Thank you for the opportunity to review and comment on the May 23, 2001, draft report entitled "Indigent Participation in Medical Research at Virginia's Medical Schools" by the Joint Legislative Audit and Review Commission.

Overall, I found the report to be both comprehensive and informative. Your recommendations will be of considerable assistance to Virginia Commonwealth University as well as to other institutions in Virginia conducting medical research. VCU will begin immediately to address the recommendations contained in the report.

I was particularly pleased to see the JLARC auditors recognize the tremendous progress VCU has made in rebuilding its system for protecting the rights and safety of human subjects participating in medical research. Following the suspension of our human research program by OPRR/OHRP on January 11, 2000, we greatly expanded the size of our IRB office; developed new educational materials to train IRB members and staff, investigators, and other key research personnel in ethics and federal regulations; developed new IRB material and application forms; finalized standard operating procedures that are cross-linked to federal regulations; and developed an investigator's manual to assist investigators in correctly following federal regulations and IRB requirements. Furthermore, VCU has now completed the required re-review of previously active protocols as well as established the process for review of all new protocols submitted since the suspension. At this point, VCU is fully operational with four approved IRB panels and plans to add an additional panel in the near future. A new Office of Compliance Oversight and Education is now in place as well.

As you have undoubtedly discovered, in many cases our IRB rebuilding effort has gone beyond the OHRP/FDA requirements by including additional elements and processes that will further protect the rights and safety of human research subjects. Please be aware, however, that we are still implementing our plan, and some improvements in our IRB system were not obvious to your

Mr. Philip A. Leone
June 5, 2001
Page two

auditors. Finally, one of the major elements in the draft JLARC report was the auditors' determination of what constitutes "best practices." As you may know, the OHRP has recently initiated a major effort to identify "best practices" to ensure uniformity of procedures to be followed by all IRBs in the human research field. As a result, there may be some conflict between the JLARC and OHRP recommendations.

Attached are comments by our IRB office on its review of the JLARC draft report and our written plan for implementing compliance oversight. I trust this information will be helpful to you and am available should you have any additional questions or comments.

Best regards.

Sincerely,

A handwritten signature in black ink, appearing to read "E. Trani", written in a cursive style.

Eugene P. Trani
President

emj

attachments

copies: Dr. Marsha R. Torr, Vice President for Research
 Dr. Roy W. Pickens, Associate Vice President for Research

VCU Compliance Plan

VCU has developed a written plan for expanding its human subjects research oversight responsibilities. The plan includes:

- (1) A comprehensive education program designed to assure that each research investigator has demonstrated an understanding of both federal regulations and university policies concerning the protection of human subjects. This part of the oversight plan has been fully implemented.
- (2) Development of a human subjects web-site that provides clear instructions to Principal Investigators regarding the preparation, submission, review, and approval of research protocols involving human subjects. The web-site outlines reporting requirements relative to human subjects protections, and it provides answers to frequently-asked questions. This part of the oversight plan is fully implemented.
- (3) Visitation by Oversight staff members to departments that conduct research involving human subjects. These visits include a summary of regulations, outline of oversight responsibilities of department heads for research conducted in their departments, and instructions on where they can turn for further information. This part of the plan is partially implemented. The visits to departments will be a continuous process.
- (4) Hiring of two people whose primary responsibility is to exercise oversight over two areas of research, the Massey Cancer Center and the General Clinical Research Center (GCRC). A person has been recruited for the GCRC responsibility and is in the process of training.
- (5) Creation of an Office of Compliance Oversight and Education (OCOE). Dr. Charles R. McCarthy, former Director of OPRR (now OHRP) serves as the Director. He has one assistant and a second is being recruited. The OCOE has developed procedures for evaluating allegations of non-compliance, and when non-compliance is confirmed, it has authority to impose sanctions on those who are found to be non-compliant. Six such procedures have taken place. Three persons have been disciplined. Most of the allegations have come from whistle blowers. We view the emergence of whistle blowers as an indication of the growth of a healthy climate of respect for subjects and compliance with regulations and policies.
- (6) Conducting site visits and audits of ongoing research, particularly research projects that involve significant levels of risk to subjects. WIRB (under contract from VCU) has initiated these site visits and has made approximately 170 such visits over the past year and a half. The VCU OCOE site visits will include the following: (a) a check to see that approved protocols are actually being followed; (b) a check to see that inclusion and exclusion criteria are carefully observed; (c) a check to see that informed consent documents are current and that they conform to regulations and to stipulations imposed by IRBs; (d) that informed consent procedures are followed from the time of recruitment until the research project is complete; (e) that data are carefully collected and stored; (f) that confidentiality is maintained by investigators and staff; (g) that conflicts of interest, if any, are fully disclosed to the IRB for decision; (h) that, where appropri-

ate, a data and safety monitoring board is created to exercise oversight of the study; (i) that serious adverse event (SAE) reporting together with assessment of the cause of the SAE is prompt and thorough; (j) that continuing IRB review is carefully conducted in a timely fashion; (k) that changes in protocols are promptly reported to IRBs and that they are not implemented without IRB approval. This process of site visits is in an early stage. It will expand and evolve over time.

The responsibility of WIRB for performing IRB activities for VCU is gradually decreasing as the VCU IRBs and office become more efficient and are increasingly able to take over these responsibilities. At present, plans are to shift all WIRB IRB responsibilities back to VCU for each protocol at the time of the protocol's annual review. For the near future, however, VCU will allow WIRB to conduct industry-sponsored, multisite, clinical trials involving FDA-regulated products only.

June 5, 2001

Virginia Commonwealth University Comments on JLARC Draft Report (5/23/01)

- Page iii, line 4-5. Technically, VCU did not lose its ability to conduct medical research or the ability to compete for research dollars. Instead, VCU temporarily lost its federal assurance to conduct human subjects research. Also this did not affect our ability to submit new grant applications for funding. In fact, VCU continued to compete for research dollars during the suspension and re-development period.
- Page iv, line 15. Correction: "... included in a mailed questionnaire to his adult children." Whether the children were minors or adults is an important difference.
- Bottom of page iv through top of page v. Correction: The VCU corrective action plan was submitted to OHRP and approved three weeks after the MPA suspension. All human research activity was suspended during this period unless participating in the research was beneficial to the subject. This policy continued until the protocol had been re-reviewed. To our knowledge, no human subject was injured as a result of the MPA suspension.
- Page vi, line 17. The outside contractor (WIRB in Olympia, WA) was hired to perform re-reviews of all protocols active at the time of the MPA suspension and to perform initial reviews of new protocols submitted during this time. The VCU Richmond IRB has been re-assuming these responsibilities as our system grows and becomes more experienced.
- Page vi, line 18. Clarification: "... of all human subject research studies, and the work of the contractor is quickly being reduced as more and more VCU IRB panels are activated."
- Page viii, first complete bullet. Contrary to information in the report, VCU is in compliance with the federal directive to provide training to all key study personnel on DHHS-funded research. Since this is primarily a sponsor issue and not an IRB regulatory issue, this information was collected by our Office of Sponsored Programs Administration (OSPA). OSPA provides a letter with all federal grant applications that certifies "each investigator or individual identified as 'key personnel' (have) been trained in the protection of human subjects in research" and is signed by both the PI for the project and the Director of the Office of Sponsored Programs Administration (see <http://views.vcu.edu/ospa/nih-irb.htm> for a copy of the sponsor letter). The forthcoming revision of the IRB web page will also require the PI to certify that all research personnel (students, faculty, or staff) have been adequately trained to carry out their responsibilities.
- Page viii, second complete bullet. Correction: VCU conducts site visits to ensure investigators are following IRB-approved procedures in conducting their protocols. Until the present time, this function has been conducted exclusively by WIRB (first VCU IRB panel), while VCU Richmond IRB concentrated on IRB re-development issue. Since February, 2000, WIRB has site visited 170 investigators at VCU to ensure their research is in compliance with WIRB approved protocols. VCU has also established an Office of Compliance Over-

sight and Education (OCOE) located in the Office of the Vice President for Research. The OCOE is administratively separate from the IRB to ensure no conflict of interest between the OCOE and the IRB. The OCOE also has the responsibility to ensure all VCU investigators and staff receive the necessary training in federal regulations. Up to this point, the OCOE has focused exclusively on ensuring federal regulations are being accurately followed in the review and approval of IRB protocols. However, shortly the OCOE will begin investigator/lab site visits along with WIRB. On the prospective side of compliance, Dr. Charlie McCarthy, former Director of OPRR (now OHRP) and Director of the OCOE has visited with a number of investigators, departments, and schools to ensure protocols are being initially developed in compliance with federal regulations and within the capability of the research group.

- Page ix, first complete bullet. The statement (“...it appeared that projects that served more potentially vulnerable populations also had a high rate of consent errors.”) is certain to raise concerns. While no details are presented in the Executive Summary, later (on page 22 of the draft report) JLARC provides more details about the audit exercise. We intend to follow-up your findings with our own audit review.
- Page ix, first complete bullet. Correction: The statements “JLARC staff found that the universal lack of data on the basic demographics of study participants undermines the ability of the schools to ensure the protection of vulnerable populations.” is not entirely accurate. We routinely collect information on gender, age, and if the subject is “poor/uninsured” at the top of page 4 in our IRB Application Form (see http://www.vcu.edu/irb/vcu_submiss.pdf), including whether the subject is a member of a vulnerable population or has other special characteristics that may require additional protections. Also the information contained in the IRB Application Form is reviewed and verified by the IRB panel in its review of the protocol.
- Page ix, first complete bullet. Information: The report states “...the study investigators should collect and submit to the IRB basic, aggregated demographic and health insurance information regarding study participants.” Details about a person’s health insurance is not a regulatory requirement as it is not generally considered an IRB issue. However, we do go beyond the regulations and ask whether the person is “poor/uninsured.” We are planning to require investigators to provide aggregate demographic information at their annual reviews and this will be considered as part of the review of the protocol. We do not enter this information into our office database at the present time, however, as it is not required by federal regulatory agencies.
- Page 5, last paragraph. Information: Be aware that the MPA is currently being phased out by the federal government and at this time institutions can no longer apply for an MPA. The MPA is being replaced by a Federal-Wide Assurance (FWA), which is a completely revised and fundamentally different type of assurance plan. VCU is currently in the process of shifting to a FWA, as I am sure are the other Virginia research universities.
- Page 7, first sentence under heading. Correction: This should read “.....more than half of all academic medical research funding”. Industry provides more than the federal government in supporting medical research.

- Page 12, last sentence of first paragraph. Information: Be aware that OHRP has developed a new self-evaluation form that allows institutions to conduct routine self-audits. Also, be aware that OPRR (now OHRP) never conducted a site visit at VCU before suspending the VCU MPA.
- Page 12, last line. Correction: Should read "...and failure of the IRB to consider possible psychological harm to parents by information obtained from their adult children who were involved ...".
- Page 13, first three sentences. Correction: This statement is somewhat misleading as it implies VCU was shut down for a period of 15 months. The shut-down period was actually only 3 weeks (from January 11 to January 28, 2000). In fact, during the shut-down period OPRR/OHRP permitted VCU to continue to conduct protocols that were in the best interest of the patients. Protocols became active as soon as they were re-reviewed. Over time the total number of re-activated protocols increased steadily as more and more VCU IRB panels became active. For the last several months we have been requiring that all protocols be submitted to the VCU IRB for review except those involving FDA-regulated projects to be sent to WIRB for review. Our future plans call for restricting WIRB to the review of only industry-sponsored, multisite protocols involving FDA-regulated products.
- Page 25, lines 9 and 10. Repeat: Again, OHRP did not suspend our ability to conduct research, only our authority to conduct research. In addition, our ability and authority to compete for research dollars were not affected.
- Page 26, lines 7-9. Information: VCU requires this information to be provided by investigators on the IRB Application Form. If members of a vulnerable population are indicated as the focus of a protocol, this information is considered by the IRB in its review of the protocol, and the results of the discussion are incorporated into the minutes of the meeting. Obviously, in large-scale population-based epidemiological studies, individual members of vulnerable population groups may be inadvertently and unknowingly captured in the population sample. In other cases (e.g., prisoners) we operate under very strict regulatory control, must have a prisoner representative on the IRB panel, and may be required to submit such protocols to the Secretary of the U.S. Department of Health and Human Services for prior review and approval. The VCU IRB (including WIRB) rigorously follows these regulations.
- Page 26, first sentence of last paragraph. Correction: There is not a universal lack of data (on basic demographics of study participants) at all of the schools. VCU collects information on subject characteristics in our IRB Application Form, the IRB panel correlates the accuracy of this information with information provided in the protocol during its review, and the IRB panels strictly follow federal guidelines in review of protocol involving vulnerable populations.
- Page 27, first sentence. Information: As mentioned previously, the MPA has been replaced by the FWA, which must be adopted by all institutions receiving federal awards within the next 1-1/2 years. Also, the FWA must be submitted to OHRP at DHHS for approval.

- Page 27, last line. Correction: Again, it was adult children.
- Page 28, lines 4-6. Information: This is actually an MPA issue rather than a regulatory requirement. In January 2000, we were required by OPRR/OHRP to suspend only federally-funded research. However, since we had previously elected to include a statement in our MPA (at the encouragement of OHRP) that indicated we would treat all protocols the same regardless of sponsorship, we were obligated to close down all research and not just federally-funded research.
- Page 28, first complete paragraph. Correction: Again, VCU was allowed to continue protocols in which participation was in the best interest of the subject. This included a number of therapeutic clinical trials. Also, I don't think it is entirely correct to say VCU "ignored" the federal agencies' requests for new SOPs and a corrective action plan. It would be more correct to say VCU was not able to complete these tasks by the required deadlines.
- Page 28, first complete paragraph, last sentence. Information: VCU officials did not "disagree" with the allegations made by the two individuals. The IRB was asked by OPRR/OHRP to investigate the allegations and to report back to them. The VCU IRB did so but the results of the re-reviews did not satisfy OPRR/OHRP.
- Page 28, last 3 lines. Clarification. The "psychological harm" in both cases was (1) subject anger over research nurse using a different method of blood draw than had been approved by the IRB, and (2) father anger over adult children subjects being asked to provide sensitive information on health histories of mother and father.
- Page 29, Exhibit 1, Column 1, June 2000. The restriction prohibiting the review of non-behavioral research was removed 2 days later when additional behavioral scientists were added to IRB Panel A. Also, this did not occur in September as indicated. In September, we activated our second IRB panel as a general panel but specializing in biobehavioral protocols.
- Page 29, Exhibit 1, Column 2, August and December 1998. Correction: Need to add "in a timely manner" to the end of the last sentence. This also needs to be added to the end of the last sentence in May 1999.
- Page 29, Exhibit 1, Column 2. Addition: Add new category "January 2001" and indicate "FDA conducts audit of VCU system for protecting human subjects in research."
- Page 30, second bullet. Addition: ("...training more than 400 research investigators, research staff, IRB administrative staff,"). Also add ("special training was also provided to senior university administrative officials (e.g., President Trani, Vice President for Research Torr, and Associate Vice President for Research Pickens) about their administrative responsibilities in ensuring the protection of the rights and safety of human subjects."
- Page 31, top bullets. Addition: "development of investigator's manual" to list of significant changes made by VCU.

- Page 31, second bullet at bottom of page. Correction: “VCU established a special committee to compensate graduate students whose educational programs were disrupted by the suspension of research.”
- Page 35, Recommendation (1). Information: This will obviously be expensive and perhaps even unnecessary: (1) OHRP is currently developing a self-evaluation tool for use by IRB boards and administrators, and (2) PRIM&R has recently announced a national IRB accreditation program which will be similar to the AAALAC accreditation program being used in animal research oversight.
- Page 35, last two lines. Information: Low budgets do not necessarily equate with poor training. Also, because this problem has now been corrected at VCU “....is that IRB members and staff were not adequately trained....”.
- Page 36, last two lines. Change: “...and ongoing review of all research studies except studies approved for exemption.”
- Page 40, second line. Addition: “....meet federal requirements and raise the standards of operation.”
- Page 40, Bold Statement. Correction: VCU is conducting onsite audits and has been doing so since February 2000 (N=170 to date). The Office of the Vice President for Research has created a new Office of Compliance Oversight and Education that is administratively separate from the IRB office. This office is operational and is now beginning to assist the IRB with onsite inspections. More details on this issue have been provided earlier in these comments. A written description of these onsite activities is submitted with this letter.
- Page 42, second complete paragraph, first sentence. Information: We could post our SOPs on the web at the present time. However, OHRP has advised us to put only the Investigator’s Manual on our website because it contains essentially the same information as the SOPs and is easier to read.
- Page 42, second complete paragraph, lines 5-10. Information: The missing sections in the VCU Investigator’s Manual are awaiting the selection of the new Director of the Office of Compliance Oversight and Education (OCOE). The position description of the director has been developed, posted, and applications have been received. The first meeting of the selection committee is presently being scheduled. Selection of a new director of this office is expected to occur in the next several weeks.
- Page 42, second complete paragraph, lines 10-15. VCU also provides IRB guidelines to investigators on its website (see http://www.vcu.edu/irb/irb_regulations.html).
- Page 42, Recommendation (2). Information: As addressed previously, we could add our SOPs to the VCU IRB website, but OHRP suggested VCU include only the Investigator’s

Manual on its IRB website as it contains the same information as in the SOPs and is more readable.

- Page 44, first complete paragraph, lines 7-10. Clarification needed: The JLARC staff checklist is identical to the OHRP checklist except for the addition of 2 items. Are you recommending that we use the JLARC checklist instead of the OHRP checklist?
- Page 44, first sentence of last paragraph and elsewhere. Clarification needed: Several times you use the term “best practices”. There are, of course, many different ways of accomplishing the same objective. Who determines “best practices”? Are you suggesting VCU, UVA, and EVMS use the “best practices” selected by JLARC in Exhibit 3?
- “Best Practices”. Information: OHRP recently contracted with the Institute of Medicine (IOM) to identify standards for accreditation of human subject research programs. Two organizations have been charged with responsibility to develop accreditation standards including “best practices”. VCU is working closely with one of these organizations – Public Responsibility in Medicine and Research (PRIM&R) -- to identify “best practices”. VCU is disturbed to find that the auditors have self-determined certain procedures to be “best practices” and intend to use them to review IRBs at different institutions.
- Page 45, Exhibit 3, General, first bullet: Addition: “VCU and UVA have all the necessary forms”. Both UVA and VCU have all of the necessary forms available on their websites for download by investigators (see http://www.vcu.edu/irb/vcu_consent.html).
- Page 45, Exhibit 3, Participant Consent Form Template, bullet 10. VCU provides the name, address, and telephone number of both the Principal Investigator and the IRB Director as the contact points on its consent form (see http://www.vcu.edu/irb/vcu_template.pdf). (Note: typo in the last bullet, change “data” to “date”.)
- Page 46, lines 3-4. Information: Recognize that IRBs require investigators to write consent forms in a manner that is both readable and understandable by potential subjects. Thus, some of the differences across VCU, UVA, and EVMS may reflect difference in the populations studied.
- Page 47, first complete paragraph. Correction: The VCU MPA holds us to 45 CFR 46 regardless of the source of funding. Since there are no training requirements in 45 CFR 46, we are in compliance with our MPA. Similarly, OHRP, the regulatory agency, does not require “all key personnel to be trained”. Only one sponsor (NIH at DHHS) requires this. At VCU, our IRB requires that only the Principal Investigator is trained. VCU investigator training requires investigators to read a special book on ethics and human subjects regulations, pass a written examination based on the content of the book, and to submit their certificate of completion to the IRB along with grant/protocol applications and the IRB Application Form. Since training of all “key personnel” is a sponsor requirement, this is handled through our Office of Sponsored Programs Administration (OSPA). OSPA requires all key personnel be trained for NIH grant submissions. Both the PI and the Director, OSPA, sign a letter accom-

panying the grant submission indicating the names of key personnel who have been trained. VCU is not out of compliance with NIH requirements for NIH-funded studies.

- Page 48, Exhibit 4. Addition: We believe the following statement represents another best practice. “VCU provides different levels of training to investigators, IRB members and chairs, and faculty members in general. Special training is also provided to senior VCU administrators, including the President of VCU (the MPA signatory official), on their responsibilities regarding oversight of the VCU IRB system.
- Page 48, Exhibit 4, last bullet: Addition: VCU also documents investigator training in its IRB database. When investigators complete their training in ethics and federal regulations, they receive a printed certificate of completion from the testing center (CME). This certificate must be presented to the IRB office at the time of protocol submissions or give permission to have the exam results sent electronically to the IRB office.
- Page 50, first 4 lines. Clarification needed: We suspect there may be some misunderstanding here. The primary and/or secondary reviewers of protocols on all of our IRB panels routinely contact study investigators with questions that arise about the protocols before and/or during the review. This would not happen, of course, if a protocol raised no unresolved issues and was approved by the IRB panel.
- Page 50, first complete paragraph, lines 4-6. Correction: WIRB is not “reviewing studies quarterly until the corrective action plan is totally implemented”. Quarterly review is the standard practice at WIRB for all protocols. They review all protocols on this basis regardless of the institution.
- Page 51, lines 6-8. As indicated earlier, VCU has been conducting routine study audits and have conducted 170 since February, 2000. We have also developed and staffed the Office of Compliance Oversight and Education that will independently assist the VCU IRB with this effort. At present the office is directed by Dr. Charles McCarthy, former Director, OPRR. We are also ensuring compliance by providing education information (e.g., decision trees) on our IRB website and also meeting with investigators and departments in advance of IRB application to ensure federal regulations are being followed in the development of the protocol. A written copy of this plan is attached to these comments.
- Page 52, Exhibit 5. Additions: VCU should be added to all of these bullets. We routinely contact study investigators about concerns. Our policy is to require follow-up on adverse event reports as necessary, require progress reports at selected intervals depending on the risk of the study (no longer than annually), and conducts routine onsite audits of protocols (the latter has been described in greater detail in an earlier part of these comments).
- Page 52, Recommendation (5). Information: Although the names of the universities are not mentioned, as indicated above, VCU is already fully in compliance with this recommendation.

- Page 54, line 5 from bottom. Correction: Instead of saying “violation”, it would perhaps be more accurate to say “... deviations, and distinguish those that are inappropriate from those that are due to medical necessity”.
- Page 55, Title Heading. Information: The term “general compliance” implies shades of compliance, when actually a protocol is either in compliance or is not in compliance.
- Page 56, Exhibit 6, VCU Strengths, bullet 2. Information: Using a “surrogate consent” is illegal under Virginia law. Under Virginia law, not any relative can serve as a surrogate. Apart from the subject, consent can be given only by a court-approved legally authorized representative (LAR).
- Page 58, Recommendation (6). Information: VCU is currently following this recommendation and we expect the other universities are doing so as well. We would be reluctant to put the JLARC report on our website if the report contained factual errors without also following it with our comments.
- Page 59, second paragraph. Information: As was pointed out earlier, this examination may not stand the test of scientific scrutiny, and therefore these conclusions may not be warranted.
- Page 59, bullets under VCU. Information: Recognize that the representation of women and minority groups in protocols is largely determined by the nature of the study, the targeted population, and the catchment area from which the subjects are drawn. Therefore, you would expect to see no women enrolled in studies of prostate cancer. Similarly, if you are conducting a study in a catchment area with a high prevalence of a certain minority group, you are likely to get an over-representation of that group in your subject population.
- Page 61, 1-3 bullets at top of page. Information: Again, as stated above, this over-representation may be due to the nature of the study (stroke prevention for African-Americans), the inclusion/exclusion criteria, and the catchment area served, rather than a deliberate attempt to recruit low income people as subjects. In other words, the representation of subjects recruited may be due to multiple factors, which can only be examined in relation to the nature of the study and other factors.
- Page 61. Question: We would like to know if these “consent errors” were examined in light of the nature of the study, IRB approved modifications to the study, expertise of the person conducting the review, etc.
- Comment: Page 63, first several lines of the first complete paragraph. Information: VCU already requires this information, and we would assume the other universities do as well. By simply stating in principle what needs to be done, your report makes it sound as if some of the universities are not already doing this. This is criticism by omission, which makes current practices sound worse than they are.
- Page 63, Recommendation (7). Correction: VCU (and we imagine other Virginia IRBs as well) routinely collect basic demographic information on their IRB Application Form. This

information is evaluated by the IRB panel as part of the protocol review. It is evaluated at multiple levels including the nature of the study. If the characteristics of the predicted subjects are not representative of the catchment area from which the study is drawn, this is considered by the IRB panel and the Principal Investigator is asked to justify the subject selection/recruitment. This information is not aggregated by the IRB office because it is somewhat meaningless, given the factors that contribute to subject selection. For example, a university may appear to have an over-representation of minority subjects where in fact this is due to the nature of the catchment area, the types of diseases over-represented in that population, the interest/strengths of the investigators in certain areas, etc. The VCU office collects information on whether the subjects are poor/uninsured (as this is a factor that relates to consent validity), but we do not collect information on health insurance as this is not required by federal regulations and doing so would seem inappropriate to the mission of the IRB.

- **Health Insurance. Information:** The JLARC draft report urges VCU to collect health insurance information. This implies that all uninsured persons are a “vulnerable group” needing special protections. The NIH, while advocating protection for vulnerable groups, has never considered lack of health insurance to be a criterion for judging vulnerability. VCU includes, as required by regulations, information about costs to subjects in every consent document. The fact is that participation in research rarely adds any cost burden to subjects. VCU IRBs, in the interest of equitable distribution of burdens and benefits of research in accord with the Belmont Report, carefully avoid using health insurance as a criterion for inclusion or exclusion of potential subjects in research.
- **Page 63, Recommendation (7). Comment:** Nevertheless, we think your question about representativeness of subjects in protocols is a valid question and needs to be addressed. However, the best way to answer this question might be to conduct an independent study to collect detailed information from investigators on issues related to subject selection and recruitment. This would be a much better way to answer this question than by utilizing IRB data that is following federal regulations and is not required to collect such information.
- The progress that VCU has made over the past 18 months is not sufficiently recognized. In addition to completely re-building its entire system for human subjects protection, VCU has assumed a leadership role in this area (e.g., answering queries from IRBs at other institutions about how to do things, sending other IRBs copies of our SOPs and other materials for their use). In this leadership role, the VCU IRB has recently sponsored a national forum to address unresolved issues related to the need to obtain informed consent from individuals who are not the primary subjects in a protocol but about whom information is being provided by the primary subject. VCU convened a meeting to address this issue that included presentations by bioethicists, researchers, and regulatory officials. This meeting generated considerable interest at the national level and has been subsequently considered by several national regulatory and scientific advisory groups.
- Also, it is not sufficiently recognized that the VCU IRB panels in Richmond have been operational for only a few months and still need considerable experience (seasoning) that will be evident in the operation of other IRBs that have been operational much longer. Given that the VCU IRB is still in the development mode, the report focused primarily on what exists at

the present time and did not consider elements that were still in development and would be implemented later.

- Our new program for ensuring the safety of human subjects in research has recently received unconditional approval by both OHRP and FDA following rigorous audits. Both organizations seemingly recognized that the continued development of the IRB program will be necessary and seasoning will be needed.

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