

**Statement for the Record
of the
Subcommittee on Oversight and Investigations
and the
Subcommittee on Health
of the
Committee on Veterans Affairs
Hearing on
The VA-Affiliated Nonprofit Research and
Education Corporations**

May 16, 2002

Submitted by Franklin J. Zieve, M.D., Ph.D.

§ **Background and Biography: Franklin J. Zieve, M.D.,Ph.D.**

For 25 years I have been ACOS for Research at McGuire VA Medical Center in Richmond. More importantly, I am Director of the Diabetes Health Center at McGuire, which recently was designated as one of two VA Centers of Excellence in Diabetes. I served as Acting Associate Chief Medical Director for Research in VA Central Office for 5 months in 1991 and have served on VA committees developing clinical guidelines for management of diabetes and lipid disorders. I have also twice been an inpatient at McGuire VA Medical Center, and I have been and am now a subject in clinical research studies. My VA connection goes back much further; when I was growing up I lived on the grounds of the Minneapolis VA Hospital. I now have over 30 years of federal service and am 58 years old, so economically it would make sense for me to retire today. I have no intention of doing so because I don't think I could find another position this rewarding. Today, however, I am on annual leave and testifying as a private citizen and as Chairman of the Board of McGuire Research Institute. I should stress that my testimony is not endorsed by either VHA or the National Association of Veterans' Research and Education Foundations.

My testimony focuses on the history of the IRB and Human Research Protection Program at Richmond VAMC. Our IRB was set up on an emergency basis because it had become clear that a research shutdown at our university affiliate was imminent. Because our program has been fully funded by our nonprofit, McGuire Research Institute ("MRI"), I start with a brief description of MRI.

§ **History of McGuire Research Institute**

McGuire Research Institute ("MRI") was established in November, 1989, to administer external research funds at McGuire VA Medical Center. 98% of the research administered by MRI is human research, and about 80% is FDA-regulated studies of new drugs and devices. For Calendar Year 2001, MRI had revenues of \$4.2 million and expenditures of \$4.0 million. In contrast, VA Appropriated research funds in Richmond were \$2.2 million. Of MRI's \$4.0 million in expenditures, 47% was for salaries, 20% for vendor services, 15% for supplies, 7% for travel and 3% for payment to research subjects. Thus, MRI is not a small add-on, but rather represents 2/3 of all research funding at McGuire VAMC. MRI has 82 employees, while the VA Research appropriation has 41 employees.

From the beginning the fiscal management of MRI has been very conservative; we have held administrative expenses to a bare-bones minimum, accumulating funds for a rainy day. Thus, we had resources available in 1999, when we suddenly had to make a large investment in our Human Research Protection Program.

Over 95% of the funds which flowed into MRI in its first years replaced funds kept at the affiliated medical school, Virginia Commonwealth University ("VCU"). When this movement of funds to MRI started, we found some research studies which had been

going on at McGuire without any VA knowledge. The money was at VCU; the drugs were dispensed from the VCU pharmacy, brought to the VA in paper bags and administered to our patients without any record in their VA charts. In addition to being contrary to regulation, this was dangerous; when a veteran comes to the Emergency Room, it is important for the doctor to know all the medications he is taking, including study drugs.

§ **Richmond's IRB and Human Research Protection Program**

Until August, 1999, McGuire VAMC used the IRB at the affiliated Virginia Commonwealth University ("VCU"). We were dissatisfied with the VCU IRB, but we underestimated the depth and importance of its deficiencies. After the research shutdowns at West Los Angeles and Duke, we immersed ourselves in the Human Subjects Protection regulations and policy guidance and concluded that the VCU IRB was so grossly deficient that we would have to split from them and establish our own independent IRB. When VCU received an FDA Warning Letter in August, 1999, it was apparent that a shutdown was imminent, and drastic action was indicated. The McGuire IRB held its first meeting on September 7, 1999, and has met weekly ever since. By the time VCU's human research studies were shut down by FDA and OPRR, we were sufficiently established and had enough of our protocols reviewed to avoid the shutdown.

Since the summer of 1999, we have continued to devote major MRI resources to our Human Research Protection Program ("HRPP"), which we feel is the most important current use for our funds. While our program is far from perfect, it has been successful enough to receive some recognition by others:

- § A full FDA audit Oct 30 – Nov 3, 2000, found us in compliance.
- § ORCA chose us to serve as the designated temporary IRB for a VAMC whose Assurance had been restricted.
- § We received a Special Contribution Award from the Undersecretary for Health for our IRB-related activities.
- § We have twice been invited to present at VA Day at PRIM&R.
- § We were Accredited with Conditions by NCQA after being surveyed Oct. 9-10, 2001; we hope to be the first VAMC to receive Full Accreditation.
- § The MIRB database, whose development we funded, has been installed at 19 VA Medical Centers.

Our IRB and HRPP are fully funded by MRI. In the first year of its existence, HRPP expenditures were \$474,000, as shown in the table on the next page.

Recurring expenses have remained significant; in Calendar Year 2001 total HRPP expenses were \$571,000 (\$391,000 for the IRB, \$147,000 for the Investigational Pharmacy, \$33,000 for training). Total IRB fees collected were \$170,000, so the ongoing MRI investment in the program is about \$400,000 per year.

McGUIRE HRPP: SOURCES AND USES OF FUNDS

9/1/99 through 8/31/00

SOURCES OF FUNDS

IRB Fees From Sponsors \$17,700.00

TOTAL INCOME

\$17,700.00

USES OF FUNDS

Bonuses (for passing ACRP exam) \$9,000.00

Business Meals \$872.42

Conferences (food for IRB meetings and training sessions) \$3,702.97

Equipment Purchased \$47,669.85

Office Supplies & Furniture \$25,457.62

Payroll: IRB Members \$106,380.33

Payroll: IRB Staff \$180,772.49

Postage and Shipping \$134.31

Printing and Publications (including copier page charges) \$12,118.97

Registration Fees (ACRP training course; IRB member training) \$22,507.00

Telephone \$1,287.56

Travel \$11,995.63

Vendor Services (database development; courier service) \$52,389.10

TOTAL EXPENDITURES

\$474,288.25

The ATTACHMENT shows the organizational chart of our HRPP and an excerpt from our HRPP Plan, summarizing the roles of the four key entities. Some noteworthy aspects of our HRPP are the training program, the Investigational Pharmacy, the monthly coordinator meeting, the payment of IRB members, the database, and Research Day. I would like briefly to discuss a few of these to demonstrate the scope of investment we have found necessary.

Training and Education – We have invested heavily in Human Research training and education. The focus on human subjects protection has hugely intensified in the past 3 years; the bar has – appropriately – been raised. Hence, an intensive training program was indicated. MRI has funded the following efforts:

- § We have sent all our IRB members to nationally recognized training sessions (PRIM&R's "IRB 101" or equivalent).
- § We have sent specific IRB members to meetings on Vulnerable Populations, Financial Conflict of Interest, and Genetic Studies.
- § We send multiple IRB members to each year's PRIM&R meeting.

- § We contracted with the Association of Clinical Research Professionals to put on a special one day course for our research coordinators. Subsequently we paid for all coordinators to take the ACRP certifying exam and offered a \$500 bonus to everyone who became certified as a Clinical Research Coordinator (“CCRC”). At present there are 20 CCRC’s at McGuire.
- § We sponsor a monthly coordinators’ meeting entirely devoted to human research issues.
- § We provide all our investigators with the book, Protecting Study Volunteers in Research; before they can submit a protocol to the IRB they must score at least 85% on the book’s test. All investigators also receive copies of the monthly Human Research Reports.

This may seem excessive, but we feel it is critically important that everybody at all levels be fully attuned to the nuances of human subjects protection. Certification for investigators does not yet exist, but it will shortly, and when it does MRI will require it of all our investigators. I will be surprised if within 3 years certification is not required for all human research investigators and study coordinators in this country.

Investigational Pharmacy – Another entity fully funded by MRI is our Investigational Pharmacy. Rather than reimbursing the VAMC pharmacy for filling research prescriptions, we have set up an independent VA Investigational Pharmacy which reports directly to the ACOS for Research. Since 80% of our studies involve investigational drugs, this provides critical and important controls. The investigational pharmacist will not fill a prescription unless (a) she has all the relevant drug and protocol information; (b) she has in hand a signed consent form; (c) the Electronic Patient Record contains a Clinical Warning describing the study and the study drug. This level of monitoring is difficult to achieve in a busy hospital pharmacy in which study drugs are less than 1% of all prescriptions; it is much easier with a dedicated investigational pharmacist whose sole duty is to maintain proper controls on investigational drugs. Having an independent VA Investigational Pharmacy is more expensive than reimbursing the VAMC pharmacy, but we feel the extra expense is well worth it.

Compensation of IRB Members -- IRB work is unique in its volume and intensity and in vesting critical responsibilities in a committee rather than an individual. Scientific and ethical review of about one thousand pages of material per week is significant work that cannot reliably be completed during an employee’s normal tour of duty. To assure that IRB review is serious and thoughtful rather than merely pro forma, IRB members are compensated by MRI, and IRB meetings are held outside their VA tours of duty. The IRB meets every Tuesday night, and meetings average three hours in length.

§ **Research Day**



Research Day – April 12, 2002

For the past 6 years, MRI has sponsored a Research Day Luncheon for veteran volunteers in research studies at McGuire VAMC. The picture was taken at this year's Research Day, which was attended by over 500 veterans. We believe this is the largest number of veteran research volunteers ever assembled in one place at one time. Research Day has been attended by visitors from Office of Research and Development, Office of Research Compliance and Assurance, and the General Accounting Office. The letter inviting veterans to Research Day solicits any complaints or concerns they may have about research or their participation. This represents real human subjects feedback – if you feel good about your research, you should be ready to spend some time listening to your volunteers.

In all the publicity about VA research, the veteran volunteer gets far too little credit. MRI regards its annual investment in this special Research Day as money well spent.

- **Conclusions from the Richmond Experience**

-- The fundamental concept underlying the Richmond HRPP has been that human subjects protection is more important than any other use of corporate funds. Having an uncompromising program requires major investments of time, effort and money. For this to work, the program must utilize a significant fraction of the effort of some of the best people in the hospital.

-- Without the resources of MRI, the Richmond HRPP would not exist in its present form. Only the availability of MRI funding saved us from being shut down along with VCU.

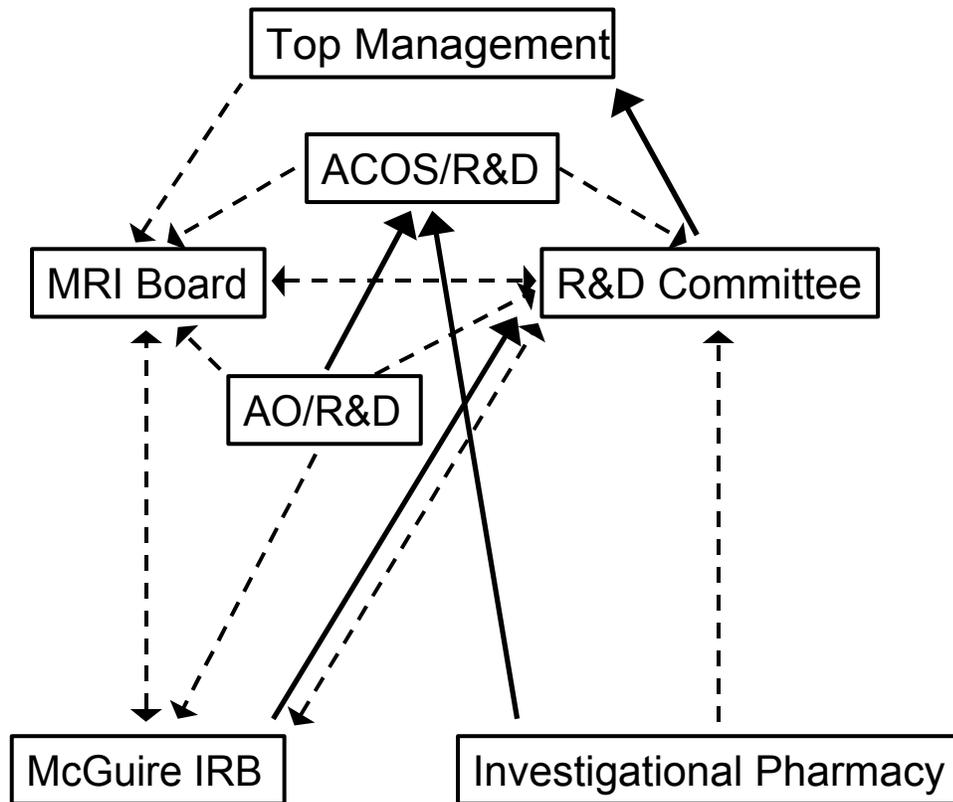
-- The complexity of human subjects-related regulations and paper flow makes an integrated IRB/HRPP database a prerequisite for success. Since no such program existed in early 2000, MRI contracted for and invested heavily in the development of the MIRB database, which has benefited 19 other VAMC's.

-- The NCQA accreditation standards are reasonable and achievable. The NCQA review process is new and presently imperfect, but by going through it, we have improved our HRPP and our IRB.

-- Having a minimal, pro forma program which fills out checklists, goes through motions and meets minimum requirements is neither difficult nor expensive. Having a substantive program which uncompromisingly protects veterans is very expensive.

-- The recent history of human research protection – everywhere, not just VA – has been one of failure to commit resources. Everybody wants a good program, but nobody is willing to pay for it – until they find themselves in the newspaper headlines (Duke, Johns Hopkins, Oklahoma, etc.). At that point these academic institutions have had to spend a fortune. This has not been enough to abolish completely the public perception that they are mistreating research subjects. It is very important that VA not go down this track.

ATTACHMENT
McGuire IRB/HRPP: Operating Relationships



V. Organizational Structure

The operating relationships of the HRPP are shown in the above chart. The key individuals are the Director, Chief of Staff, Associate Chief of Staff for Research (“ACOS/R&D”), Investigational Pharmacist, and the Chairpeople of the Research and Development Committee and the McGuire Institutional Review Board. The key entities are the Board of Directors of McGuire Research Institute, the Research and Development Committee, the McGuire Institutional Review Board, and the Investigational Pharmacy. The policymaking process occurs through deliberations of the McGuire Research Institute Board, the Research and Development Committee, and the McGuire Institutional Review Board. Interaction among these entities is facilitated by cross-membership among the three bodies.

- A. McGuire Research Institute (“MRI”) provides primary funding and administrative support for the HRPP. The governing body of MRI is the Board of Directors, of which the Director, Chief of Staff and ACOS/R&D are permanent members. The ACOS/R&D is the Chairman of the Board, and the Administrative Officer (“AO/R&D”) is the Executive Director and Chief Operating Officer of MRI.

- B. The Research and Development Committee (“R&D Committee”) oversees all research activities at McGuire VAMC. The Committee selects IRB members with appropriate scientific and non-scientific skills and delegates full authority and responsibility to the IRB for scientific and ethical review for all human research projects.

- C. The McGuire Institutional Review Board (“IRB”) serves as the human subjects subcommittee of the R&D Committee. The IRB reviews and approves, requires modifications in (to secure approval), or disapproves all human research activities in order to assure that the rights and welfare of individuals involved as research subjects in research conducted under McGuire VAMC auspices are being protected in accordance with federal regulations.

- D. The Investigational Pharmacy plays a central role in the HRPP. Research involving drugs comprises approximately 80% of the human research protocols reviewed by the IRB and 80% of the human subjects enrolled in research studies and represents our greatest vulnerability. The Investigational Pharmacy is uniquely situated in a gatekeeper position to manage human research risk vulnerability by monitoring the informed consent process, identifying need for improvement, developing corrective action plans, implementing these plans, and monitoring their effectiveness. The Investigational Pharmacist reports directly to the ACOS/R&D. The Investigational Pharmacist is a permanent *ex officio* member of the R&D Committee, and detailed submissions from the Investigational Pharmacist are a prominent part of every Continuing Review of a study involving drugs. Except for a few specialized cases where this is not feasible, the custody and dispensing of drugs involved in protocols approved by the IRB and R&D Committee are via the Investigational Pharmacy.