Plan for Insuring Adequate Protection of Participants in Clinical Trials

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Plan for Insuring Adequate Protection of Participants in Clinical Trials

Executive Summary

We live in an era where advances in science, particularly biology and biotechnology, are introducing revolutionary new ways to promote health and treat disease. The federal government, foundations and corporations are promoting these advances through unprecedented levels of research funding, and commensurably, the University of Michigan faculty have been attracting research support at extraordinary levels, mostly funding from the NIH and the pharmaceutical industry.

Simultaneously, the last five years have ushered in a new era of strict expectations of compliance with regulations, particularly those covering research involving human volunteers. In this new regulatory environment, many peer institutions have been sanctioned or fined and their images tarnished. The University of Michigan has been fortunate to have escaped such situations, in part because of our own diligence.

The UM must continue to be diligent, and has therefore developed a plan for a Human Research Participant Protection Program (HRPPP) that (1) addresses compliance at all levels, (2) addresses the needs and concerns of our faculty and staff, while enhancing support of their research, and (3) will serve the institution's needs for the next 10-20 years (i.e., not a Band-Aid solution).

This proposed initiative consists of seven major components:

- Improvement in coordination and information-sharing across campus through the formation of the Human Research Coordinating Council (HRCC);
- Enhancement of the operation of the University's compliance review committees (IRBs, etc.);

- A compliance oversight, review and remediation (Office of Research Compliance and Review/ORCR) function;
- Accreditation of our human subjects protection program;
- A training program, dubbed Program for the Education and Evaluation of Responsible Research and Scholarship (PEERRS);
- Enhancement of data management education and resources, through formation of Center for the Advancement of Clinical Research (CACR); and
- A computer network-based system to support research management, regulatory education and training certification, and compliance audit functions (MPRIME).

Meeting these institutional needs is a joint responsibility. The plan is led by the Office of the Vice President for Research (OVPR), but its success requires the active participation and collaboration of many stakeholders. On the administrative side, this includes the Provost, Chief Financial Officer, General Counsel, and Medical School leadership. On the day-to-day operational level, the plan's success requires buy-in from the faculty, staff and students involved in human-subject research.

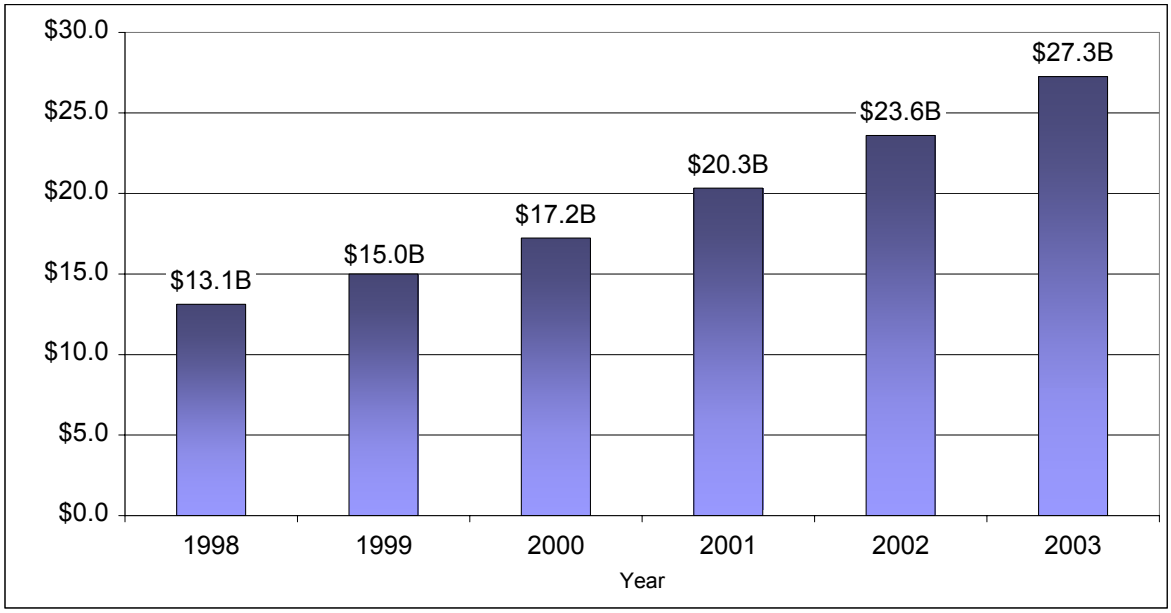
1. Human-Subject Research Enters a New Era of Strict Regulation and Heightened Expectations

A) Recent Growth in Life Sciences Research

Activity in life sciences research has grown tremendously over the last decade, both nationally and at the University of Michigan. The budget for the National Institutes of Health (NIH), the nation's predominant sponsor of the life sciences and human biology research, has almost doubled over the last five years, from $13 billion in 1998 to $27 billion in 2003 [Figure 1].

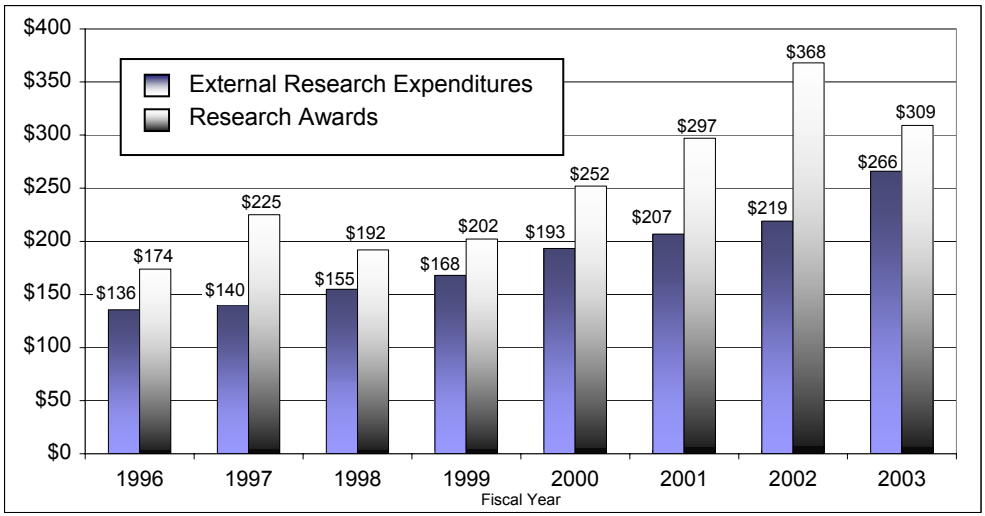
- **NIH Budgets rising to $27.3B in 2003**
- **Medical School research growing at 10%+ per year**
- **Oversight caseload for human subjects research increasing by 300% over last several years**

Figure 1
National Institutes of Health: Budget Growth/Projections, 1998-2003



Spending trends for life sciences research at the University of Michigan parallel those of the NIH. Total UM life sciences research expenditures (which encompass research in the Medical School as well as biologically- and health-related work in other UM units) grew from $242 million in 1998 to $366 million in 2002. Medical School research expenditures from external sources have more than doubled over the last seven years, from $136 million in 1996 to $266 million in 2003, averaging 10.2 percent per year [Figure 2]. New research awards (which fund research for several years into the future) have been rising at a similar rate since 1996, growing 9.6 percent annually.

Figure 2
UM Medical School Research Expenditures and Awards, FY1996-FY2003



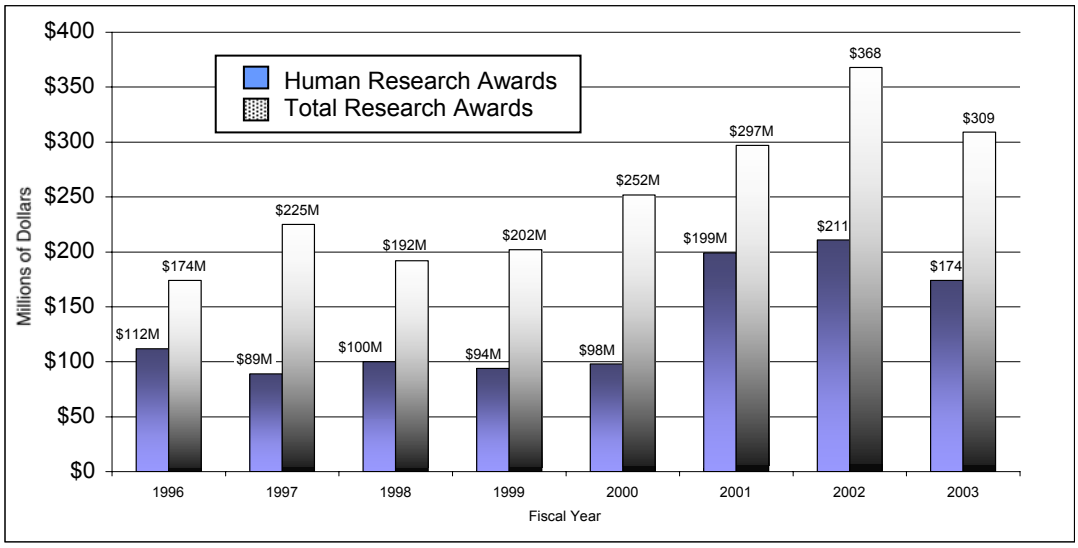
Annual Percent Change

Research Expenditures from External Sources
FY96-FY03 10.2%

Sponsored Research Awards
FY99-FY01 9.6%

A sizeable fraction of new research awards in the Medical School support projects that involve human subjects. Figure 3 shows the Medical School's recent experience, comparing total research awards to those that involve human subjects. The large jump from FY2001 to FY2002 is caused primarily by two large, multi-year awards. One supports the General Clinical Research Center ($33.6 M over 5 years) and the other is the Pritzker Neuropsychiatric Disorders Research Consortium ($39.2M over 5 years).

Figure 3
Medical School Sponsored Research Awards - Total & Human Research Projects, FY1996-FY2002



Growth in research activity involving human subjects and the associated regulatory oversight is reflected in the increasing caseload of the Medical School Institutional Review Board (IRB-MED), the body that must review the Schools' human research projects before work can begin. In the six years from 1997 through 2003, the number of review actions -- deliberations and decisions recorded by the IRB-MED -- grew 400 percent, from 1200 in 1997 to 6000 in 2001 [Figure 4]. Review actions include reviews of applications for approval of new human subjects protocols, periodic reviews of continuing protocols, examinations of adverse events that show up in subjects, and reviews of protocol changes. (See Section 3B for more on IRBs.)

Figure 4
Institutional Review Board (IRB) Actions, 1997-2003

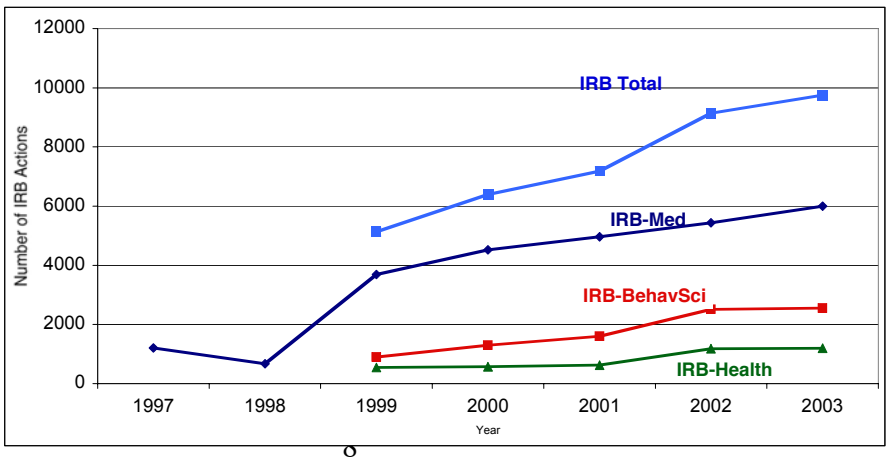


Figure 4 shows that activity by the other two Ann Arbor campus IRBs is also growing, but at a slower rate. Actions by the IRB, which reviews all human research in the behavioral sciences, grew by 180% over the last three years. The IRB that reviews non-Medical School, health-related human research showed increased activity of 115% since 1999.

B) The Compliance Universe for Human Subject Research

Regulations

Research involving human participants must adhere to extensive laws, regulations, and guiding principles. In addition, federal law and regulations specify the manner in which the University must carry out its oversight functions through Institutional Review Boards (IRBs) and other committees. Prominent compliance standards related to the conduct of research with human volunteers cover:

- basic Department of Health and Human Services (DHHS) requirements for conducting human research,
- Food and Drug Administration requirements for use of experimental drugs and devices,
- federal agency requirements for human use of radioisotopes and for biosafety (including human gene therapy),
- federal financial conflict of interest regulations, especially as they relate to financial interests related to research with human volunteers,
- federal regulations regarding scientific misconduct, and,
- sponsored project requirements to assure proper review and approval by local committees (Institutional Review Board, biosafety committee, conflict of interest committee, etc.) prior to acceptance of federal funds.

The University is authorized to conduct research involving humans through its Federal Wide Assurance (FWA), the formal agreement between the University and the

federal government, specifying the principles and compliance practices the institution must follow in protecting human research subjects. The guiding federal regulations that the University follows under its FWA are found in Title 45 Part 46 Subpart A of the Code of Federal Regulations. The institution has assured the federal government that it will comply with these rules for all federally-sponsored research, as well as all other human subject research regardless of sponsorship -- even unsponsored work. Suspension of an institution's FWA -- which may occur when human research infractions have been discovered by federal agencies -- can potentially lead to temporary cessation of much or all federally funded research until the violations have been corrected.

Campus Oversight Bodies

The primary vehicle for compliance oversight on campus is the Institutional Review Board (IRB). The Ann Arbor campus has six IRBs operating at present - four devoted exclusively to Health System human research, one to all non-Health System health-related human research, and one for all behavioral science human research. Each IRB is composed of UM faculty from relevant disciplines as well as at least one non-scientist member as well as members with no affiliation with the University. In addition, staff provides administrative support to the Boards and assist faculty applying for project review. The Medical School IRBs meet weekly; the two other IRBs meet monthly.

Compliance oversight carried out by:

- **6 Institutional Review Boards**
- **2 Conflict of Interest Committees**
- **Institutional Biosafety Committee**
- **Subcommittee on Human Use of Radioisotopes**
- **Biosafety (OSEH)**
- **Administrative "tracking" by DRDA**

Conflict of Interest Committees review situations where a faculty or staff member may have financial or other conflicts between his or her job responsibilities (including the conduct of research or supervision of students) and an outside interest, such as through ownership of a company or a consulting position with an outside entity. Two Conflict of Interest Committees composed of faculty and staff members operate at the

UM -- one within the Medical School and one for the rest of campus. These bodies review significant outside financial and management interests and work with faculty and staff to establish safeguards against actions being inappropriately influenced by a conflict. Safeguards may include involvement of non-interested parties in advisory roles or rearranging oversight responsibilities within a research project. In human research, conflicts of interest can arise, for example, when a faculty member wishes to conduct research on a new drug while at the same time serving as a consultant to the company testing the drug or holding a large financial interest in the sponsor. Conflict of interest situations may require Regental approval under the conditions of the State of Michigan conflict of interest statute before the relevant grant or contract can be executed.

Human Gene Therapy research must be reviewed by the Institutional Biosafety Committee (IBC) before work begins. This committee also reviews for safety any research involving recombinant DNA, whether from human sources or other organisms. The IBC reports its conclusions to the appropriate IRB if human research is involved, and continues to monitor a project's safety record over time.

Responsibility and Accountability

Administratively, all sponsored research involving humans, conflict of interest, or recombinant DNA is noted on the Proposal Approval Form, which is routed from the faculty investigator to departmental and school/college officials for signature and then to the Division of Research Development and Administration (DRDA), the sponsored projects office. The Vice President for Research has institutional sign-off for many of these compliance responsibilities. In addition, OVPR appoints members to the non-Medical School IRBs and other oversight committees, provides administrative support, and is involved in responding to federal inquiries and the investigations they may spawn. In all of these activities, OVPR works closely with the Office of the General Counsel and the relevant schools and colleges.

Because the responsibility for specific oversight or review is distributed across several vice presidential areas or schools and colleges, in the summer of 2000, Vice

President Ulaby established the Human Research Coordinating Council (HRCC). This body meets to share information about members' compliance roles. HRCC members have also contributed to the development of the plan described later in this document. (See Section 3A for more on the HRCC.)

Even with the advent of the HRCC, a number of coordination issues still need attention. For example, the determinations of some compliance committees should be taken into consideration during the work of other committees, yet a smooth and efficient mechanism for sharing information may not finally be in place until the proposed MPRIME system (See Section 3E) becomes operational. Also, the University does not have a uniform method for addressing noncompliance, in part because evidence can turn up in any one of several committee reviews, and because our committees are *review* bodies, not investigatory or enforcement bodies. Furthermore, the institution does not currently have an efficient means to craft in a coordinated fashion its response to new regulations or to inquiries from regulatory agencies. Whereas the proposed plan will not completely eliminate all of these shortcomings and associated vulnerabilities, it goes a long way towards facilitating better coordination and communication.

C) The Federal Oversight and Compliance Environment

Simultaneous with, and in response to, the growth in biomedical research nationally and locally, the environment for federal research compliance has changed dramatically. Federal agencies are interpreting human research, financial, and other regulations that apply to universities more strictly than even just a few years ago. Consequently, universities are becoming increasingly vulnerable to sweeping compliance investigations, heavy fines, federal suspensions of research, and requirements to conduct expensive re-reviews of current research to demonstrate compliance. In some cases, faculty researchers have even faced criminal penalties. Table 1 lists a few

universities found out of compliance, and indicates the penalties levied against the universities and, in some cases, faculty members.

One of the most serious cases of noncompliance listed in Table 1 occurred at the University of Minnesota. Over time, a number of problems were uncovered: the production and sale by a Minnesota research program of an investigational anti-rejection drug which had not been approved as safe, effective and ready for commercial licensing; diversion of research program revenues to the program director's personal bank account; and longstanding and serious disregard for federal drug testing regulations. The situation cost the University tens of millions of dollars in fines, legal fees, and spending to establish new monitoring and accountability systems for the campus.

The list in Table 1, which represents a small sample of a much longer list, includes institutions with large medical programs sanctioned for discovered noncompliance and where financial penalties (fines) were incurred. The vulnerability of universities has become more pronounced in recent years because a university is more frequently being held accountable for noncompliance by even a single investigator who is unaware of, flouts, or simply ignores federal regulations or policies. This is a new and frequently disturbing reality for both faculty members and administrators. Even though several University of Michigan research projects have been subjects of investigations, and noncompliance has indeed been uncovered in some cases, the institution has been fortunate to avoid the major sanctions and penalties that have been levied against others. This is in part because of our own diligence in overseeing research compliance and for the diligent and forthright manner in which we conduct and report about our own internal inquiries. Yet we also know that our current system of education and monitoring is not as robust as it should be. The expanding external oversight and vastly greater volume of specific inquiries has pushed us into a more reactive mode than we would like. The University's oversight system is simply not capable of the kind of education, prospective review and remediation that can help us identify and correct noncompliance as thoroughly as we want.

Table 1
Examples of Recent Federal Research Compliance Sanctions/Penalties

- **University of Minnesota**
  $32M fine
  $10M-$12M outside legal fees
  $10M-$12M internal system improvements
  Investigation of human research infractions led to discovery of extensive violations by individual faculty and the institution.
- **New York University**, $15.5 M fine for inflated research grant costs
- **Medical College of Georgia**
  $6.1M fine and prison terms for Principal Investigators for financial fraud
- **University of California at San Diego,** $4.7M fine for misuse of investigational medical device
- **University of Washington**
  $3.6M fine for misuse of investigational medical device
- **Thomas Jefferson University**
  $2.6M fine for fraudulent data in grant application (Federal fine negotiated down from $7.9M.)
- **University of Chicago**
  institution fined $250K
  PI fined $400K for misapplication of funds/financial fraud
- **University of Wisconsin**
  Principal Investigator falsified collaborators on grant proposal; led to substantial personal fines and 3-month prison term

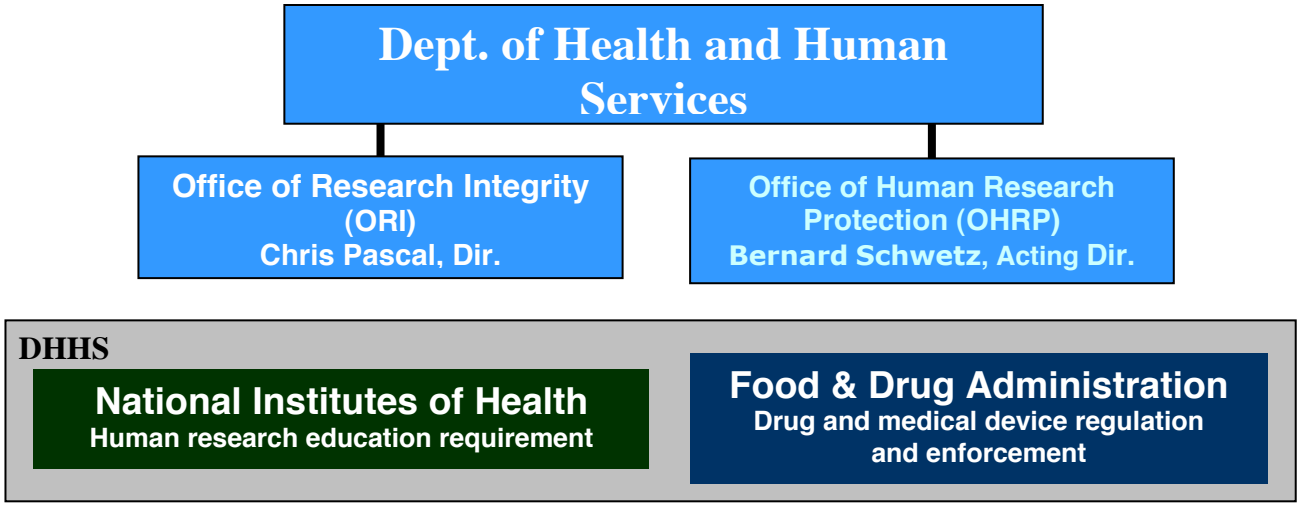
D) Federal Oversight of Human Research

Human subject protection concerns have prompted Congress to commission the General Accounting Office (GAO) to develop reports about human research and the protections being provided by institutions conducting this research. Among its conclusions, the GAO found that compliance was becoming a great burden on the oversight systems of research institutions as currently constituted. The Inspector General (IG) with responsibility for the Dept. of Health and Human Services (DHHS) has also issued numerous, highly critical reports on the state of the human volunteer protection system. The IG reports state that the compliance system nationally is at the breaking point. Several bills have been submitted to the House and Senate covering

both large issues (for example, the expansion of the federal human subject system to non-federally funded entities) and small (for example, the composition of IRB).

Compliance with human research regulations is an area of special vulnerability for universities. Two agencies within DHHS are the primary oversight bodies for human research -- the Office for Human Research Protections (OHRP) and the Food and Drug Administration (FDA). These two bodies have slightly different responsibilities and quite different operating practices when it comes to human research. In addition, the Office of Research Integrity (ORI) may become involved in any research misconduct inquiry, whether related to human research or other kinds of research. (Other federal agencies have compliance responsibilities, even with regard to human research, but those mentioned above are the most important at the UM.) See Figure 5.

Figure 5
Major Federal Agencies with Research Compliance Responsibilities



A number of human research-related mishaps or investigations have resulted in significant national publicity with repercussions for the institution and university research generally. The death of a young man in a 1999 University of Pennsylvania gene therapy experiment raised public and Congressional awareness of additional areas of concern, including individual investigator compliance with FDA requirements governing investigational drugs and devices, general biosafety, quality assurance in gene vectors, and coordination between IRBs and Institutional Biosafety Committees (which review the safety of biological agents in human gene therapy protocols). The

University of Pennsylvania situation also re-ignited concerns that research is being inappropriately steered by outside financial interests of the investigators, since the principal investigator of the Penn research had a financial interest in the success of the therapeutic approach under study.

The following Table 2 is a list of the significant academic institutions where the research program was suspended or restricted for various periods of time. Some of these programs have been or are involved in legal suits brought for violations of human subjects protections and institutional deficits in oversight.

Table 2
Selected Institutions Investigated by OHRP or FDA for Human Subjects-Related Infractions

- **Rush Memorial Hospital** (1999) Conflict of interest, generally deficient oversight system. Multiple Project Assurance (MPA) suspended.
- **University of Illinois at Chicago** (1999) Conflicts of interest, inadequate informed consent, performance of non-approved work, general inadequacy of system. MPA suspended.
- **Virginia Commonwealth Univ.** (1999) Inadequate informed consent; protocol changes without IRB approval; general inadequacy of overall system. MPA suspension. $4M spent to keep research projects functioning during OHRP suspension, increase in IRB operating budget of $1 million/year
- **University of Pennsylvania** (1999) Death of a human gene therapy patient led to FDA findings of poor informed consent and investigator compliance. Suspicions of financial conflicts of interest. All work at the Center for Human Gene Therapy suspended.
- **Duke University Medical Center** (1999) Systemic noncompliance, poor report from random site visit. MPA suspended.
- **Johns Hopkins University** (2001) Death of a normal volunteer associated with use of a substance not approved for human use by the FDA. Temporary suspension of MPA. Major systemic issues uncovered regarding operation of the IRB system.

E) The Pharmaceutical Industry/University Partnership

The pharmaceutical industry sponsors many of the clinical trials conducted through our Health System. These projects are usually initiated in one of two ways. A UM faculty member approaches a pharmaceutical company with a proposal to test an innovative use of a particular drug or class of drugs produced by that firm, or alternatively a company will seek medical centers to carry out trials to test the safety and/or efficacy of a new drug or medical device, or new use of an existing drug or device. These projects permit our faculty to be involved in the development of the latest drug therapies, which benefits our patient population as well as make our faculty aware of these new treatments. Research expenditures of tens of millions of dollars are made annually at the UM to conduct these kinds of projects.

In most instances, a pharmaceutical company will provide some data safety monitoring of its own for the projects it sponsors. But the UM must also have in place the infrastructure to support the research and the compliance oversight necessary to carry out industry-sponsored clinical studies in accordance with the strict rules mandated by the FDA. The University must have sufficient numbers of staff and faculty with the proper training and experience to conduct the data monitoring on a day-to-day basis and who can be assigned to specific projects as needed. Hence, we must have the capability to provide appropriate training and certification to these data-monitoring staff.

2. Recent UM Compliance-Related Activities

UM research compliance systems have faced continuing challenges resulting from the growing volume of required reviews, new regulations, new interpretations of existing regulations, and lack of direct coordination among various review committees. Note that research review responsibilities, although predominantly in OVPR, require close coordination, depending on the compliance matter, with functions under the Executive Vice President for Medical Affairs, Chief Financial Officer, Provost, and consultation with the Office of the General Council.

Compliance-related activity falls into three categories: 1) routine audits or reviews of the University conducted by external entities such as OHRP or the FDA; 2) internal investigations of specific projects or complaints, as requested by OHRP; and 3) internal investigations conducted to explore allegations of wrongdoing or complaints submitted by UM staff or faculty or research subjects, or other questions raised within the institution.

A) Routine Agency Audits and Reviews

The Food and Drug Administration initiates audits through its direct contact with UM researchers or compliance committees. Individual research projects under FDA jurisdiction and individual investigators who are sponsors of investigational new drugs (that is, compounds registered with the FDA for clinical testing) are audited directly by the FDA without notification of the institution. We estimate that on the order of 10 inquires occur each year, although the University has no way to know ahead of time when FDA plans to undertake a particular audit or investigation; only sporadically does OVPR or other UM administrative or oversight bodies learn of these inquiries after the fact.

The FDA does routinely audit the IRB-MED every five years. This involves selecting a sample of campus research projects under FDA jurisdiction, and then reviewing study

and patient records, all regulatory aspects of the research itself, and the IRB review process for each of these projects.

Other compliance audits that involve UM research include the regular accreditation reviews of our animal care facilities and practices. The American Association for Accreditation of Laboratory Animal Care (AAALAC) comes to the University every three years for a multi-day visit. Preparations for these visits involves months of work by numerous staff, including inspections and evaluations of all animal care sites, personnel and practices.

Other regular research-related inspection visits to campus -- all of which require significant preparation and, often, responses -- include inspections from the U.S. Department of Agriculture related to animal research regulation; National Cancer Institute reviews of NCI-sponsored projects; Nuclear Regulatory Commission inspections regarding the Ford Nuclear Reactor and general radioisotope use on campus; and the U.S. Environmental Protection Agency reviews of research waste management, state certification of radiation-producing devices, and annual compliance reports as part of the institutional audits (covered by OMB Circular A-133).

The UM also is subject to many unscheduled audits and reviews. Some are "not-for-cause" visits, which will occur when agencies such as DHHS, FDA, or an Inspector General have some questions about how institutions handle particular compliance situations. The agency will then send a small team to campus for one or more days of meetings and records review.

Other unscheduled visits will be labeled "for-cause," and be prompted either because of a national issue that calls for investigation or because an agency (again DHHS, FDA, possibly OMB for financial matters) has learned of possible problems with a specific research project and wishes to check it out.

B) Internal Investigations Requested by External Entities

During the last four years, the OHRP has opened seven compliance files on University of Michigan situations in response to concerns lodged directly with the

federal agency by research subjects or the public. Upon receipt of any concern within its jurisdiction, OHRP immediately contacts the institution in question and directs it to conduct an investigation and submit a comprehensive report that includes all institutional documents associated with the research in question.

Once the University responds, the agency then reviews our response and either requests answers to additional questions or makes a determination on the basis of the submitted material. Eventually, OHRP publishes its determination on its web site as a "compliance determination letter," as described in Section 1D above.

Although each inquiry is somewhat unique, all involve some or all of the following steps, usually conducted and/or coordinated by OVPR:

- Initial interviews (which are often lengthy or multiple) with all faculty and staff involved in the research under review.
- Assembly and review of administrative and financial documents related to the project in question. This can include obtaining materials from centrally kept records from University archives as well as those of the applicable school/college, department, and individual researcher. Project records may go back in time for years, in some cases, decades.
- Involvement of the IRB or other review committees, either through the committee chair(s) or through meeting(s) with the entire membership.
- Assembly of a committee to review records and, in some cases, takes statements from parties involved in the research.
- Extensive consultation with the Office of General Counsel as the internal inquiry is conducted and a response prepared.
- Meetings involving the Vice President for Research, other executive officers, the appropriate dean(s), and chair(s) to discuss data or reports prepared by staff or a review committee.
- Preparation of a formal response to OHRP, which will include complete documentation of all background documents or data collected to help the institution reach the conclusions documented in its response.

A "simple" response where the questions asked are not highly detailed and the research project has been underway only a short period of time will frequently require

60 days of work. Some complex inquiries have required work by a dozen or more people whose time investment totaled several thousand hours.

In addition, when the University conducts these investigations, we sometimes learn of other noncompliance. When that occurs, the UM reports this to the requesting agency along with our plans for addressing the noncompliance. This, too, adds to the time and effort invested, but also demonstrates our serious investment in maintaining a campus climate of compliance.

C) Investigations/Audits Initiated Internally

In the last four years, the University has reviewed at least 325 inquiries from staff or subjects filed directly with the institution, based on estimates of the calls made to the campus IRB offices. These inquiries arise as part of the normal functioning of a system that encourages participants to bring forward their concerns, questions and complaints as a way of managing oversight of particular projects and of the system in general. In many cases, the concern is as minor as checking that a project has been properly approved. In other times, participants may express concerns about how a particular investigator has interacted with him or her. All consent forms provide human volunteers with institutional contact instructions for how to report concerns and to whom.

There has been a significant increase in questions, concerns, or complaints received and resolved internally – in part because we, the applicable University offices, are being more receptive and responsive to complaints lodged with the IRB or with OVPR, and in part because subjects are more aware of their rights due to greater publicity about problems that have occurred during human research. In most cases, the IRB staff is able to address and resolve the complaints, but in a few instances when the complaint turns up the possibility of significant noncompliance, an investigation is undertaken following some or all of the steps described in the previous section with similar time investments.

The University also initiates some investigations after making an internal determination that particular compliance issues are in need of review. These almost always call for an extensive inquiry.

Occasionally an internal inquiry can "blossom" into a major investigation. For example, the UM initiated in late 1999 an audit to evaluate the compliance record of 11 active human-gene-therapy projects conducted by nine faculty investigators. This audit ensued after the nation learned of the University of Pennsylvania's human gene therapy project in which a young man died in September 1999. The compliance deficiencies

uncovered by the Penn investigation prompted OVPR to take a look at the University's human gene therapy projects.

OVPR hired external clinical auditors to conduct routine compliance reviews of the 11 UM human gene therapy projects. The audit uncovered indications for concern for three studies conducted by Dr. Alfred Chang, UM professor of surgery, sufficient to warrant referral to the IRB for further investigation. The IRB, acting through a subcommittee, reviewed the three studies plus a fourth and concluded that Dr. Chang had breached IRB Rules in carrying out those protocols.

The violations found by the IRB included: (a) lack of documentation of informed consent, (b) unreviewed/unapproved deviations from protocols, and (c) failure to report adverse events.

Based on those findings, the IRB suspended all of the clinical studies on which Dr. Chang was principal investigator, pending completion of a full investigation by OVPR.

An Ad-Hoc Committee appointed by the Vice President for Research did an extensive and thorough review that required the expenditure in excess of 3000 person-hours by the Committee members, in addition to dedicated office space and the assignment of UM staff support to the Committee. The committee concluded that Dr. Chang, although a caring physician and skilled surgeon, breached IRB Rules in 179 instances across five protocols. The breaches, in the committee's view, were serious, frequent, and pervasive, involving 94 subjects and touching on virtually every aspect of clinical research, from data management and record keeping to subjects' rights and protocol adherence. The FDA is continuing its investigation of Dr. Chang and may further sanction his research activities.

The University accepted the report of the Ad-Hoc Committee and restricted Dr. Chang's privileges to conduct research with human volunteers for three years.

The University of Michigan, in its final report to the federal government on the investigation and during subsequent face-to-face meetings with federal regulators, described several of the multi-faceted and coordinated initiatives underway to enhance and strengthen the University's Human Research Participation Protection Program. The

initiatives described in Section 3 of this document represent the further elaboration of the directions described to OHRP and FDA.

D) Faculty Perceptions of the Current Compliance Environment

Many faculty involved in clinical research are feeling "under siege" on many fronts. Compliance requirements governing human research are becoming more detailed and extensive. At the same time, there is growing pressure for the institution and the profession to both provide clinical care and conduct clinical investigations. All combined, the professional life of clinical faculty members is becoming so complicated that the quality of their work (not to mention their morale) is being jeopardized. To be successful, the proposed plan under development must recognize and address these concerns in a serious way.

Faculty Frustrations

- **Compliance becoming more complex**
- **Publicity of noncompliance causing anxiety and reducing morale**
- **Difficulty balancing demands of clinical care and clinical research**
- **Administrative and clinical research support not sufficient to meet needs**

Publicity about clinical research noncompliance investigations also contributes to faculty fears and pressures. Faculty worry that news reports decrease public confidence in all clinical research, especially when investigators found to be out of compliance are characterized in the media as "wrongdoers." In this climate, some faculty become uncomfortable with conducting clinical studies because of the associated cloud of mistrust hanging over them.

At the same time, investigators understand the need for good data management and quality assurance in clinical research. Unfortunately, faculty cannot always find properly trained individuals to take on this work, or other tools on campus that would assure that data records and compliance documents are complete, accurate and up-to-

date. This situation puts them (and the institution) at risk when research projects are undertaken with inadequate support.

Other pressures on faculty stem from backlogs that occur in contract negotiations, in IRB project review, and in other compliance reviews. The combined review process may take as long as 3-18 months. When these actions cannot be completed in a timely fashion, it puts our faculty at a disadvantage with peers at other institutions who are also competing for clinical trial project sponsorship. Delays leading to competitive disadvantage is particularly troubling for clinical investigators, since they have fewer opportunities to obtain multi-year funding from sponsors such as the NIH as is the norm for their colleagues who conduct laboratory-based research. Instead, clinical investigators must assemble many short-term industry contracts to support their human research trials, and then fit this work into a schedule already full of clinical care responsibilities.

All of these factors contribute to a climate that discourages many fine faculty from pursuing clinical research. This situation alone calls for the University to do everything it can to reduce the complexity and pressures associated with proper conduct of human research and the compliance requirements that must be fulfilled.

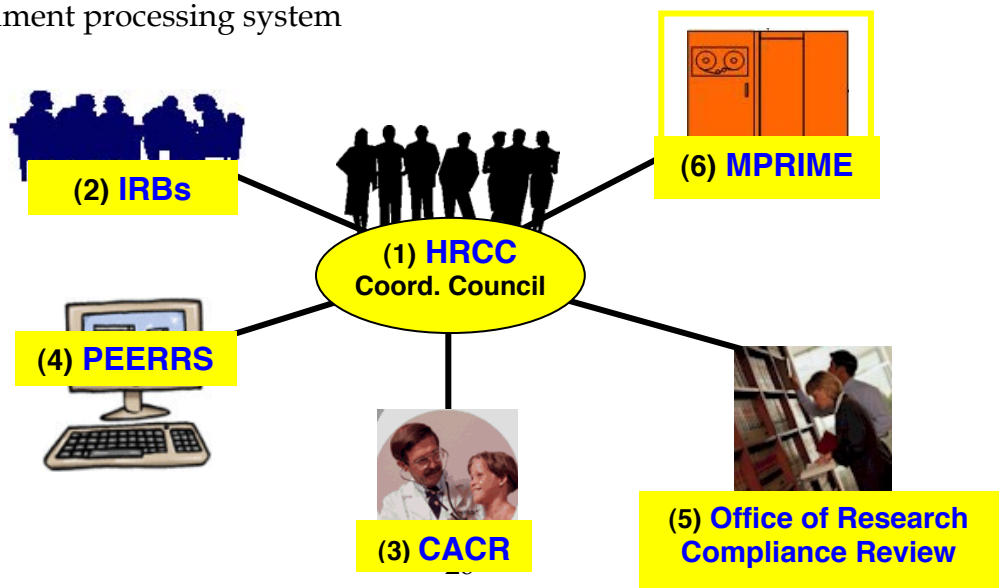
3. The UM Human Research Participants Protection Plan (HRPPP)

The plan for insuring adequate protection of volunteers who participate in clinical trials encompasses the development of a coordinated administrative structure with associated information technology, training, and auditing/data monitoring enhancements to address the needs and institutional issues described above.

The plan is ambitious in both its scope and the magnitude of the change that will be effected for clinical faculty and the investigations they undertake. It is intended to bring about a cultural change that should improve the working conditions of faculty and staff conducting this research, lead to better research compliance practices, and create a more satisfying research environment for all involved.

The plan includes six elements:

1. Establishment of a University-wide Human Research Coordinating Council (HRCC);
2. Enhancing IRB capacity and capabilities;
3. Providing clinical research support;
4. Requiring education and certification for all individuals involved in human research;
5. Conducting random compliance reviews of clinical research protocols and guiding national accreditation efforts; and
6. Developing a web-based, comprehensive and coordinated administration and document processing system



A) Human Research Coordinating Council (HRCC)

In order to improve coordination among and between the various University entities charged with responsibilities for specific oversight or review, it was decided in the summer of 2000 to establish the Human Research Coordinating Council (HRCC) under the chairmanship of the Vice President for Research. This body shares information about members' roles and responsibilities and has contributed directly to the development of the plan described in this report. Initially, the HRCC met frequently to develop an overall plan. Now it meets on an as-needed basis, with support provided by the Office of Research Compliance Review. The HRCC membership is listed in Table 3.

Table 3
Human Research Coordinating Council Membership

Fawwaz Ulaby, Vice President for Research (HRCC chair)
Judith Nowack, Associate Vice President for Research (HRCC -Vice Chair & Conflict of Interest chair)
Steven Goldstein, Associate Dean, Medical School (HRCC -Vice Chair)
John Mather, Director, Office of Research Compliance Review (HRCC Executive Secretary)
Associate Provost (Faculty Affairs)
Edward Goldman, Asst. General Counsel, Health System
Rachel Nosowsky, Asst. General Counsel, OGC- Health System
Steven Kunkel, Associate Dean, Rackham
Eleanor Singer, Sr. Research Scientist, ISR
Robert Todd, Associate Vice President, OVPR
Robert Cody, Professor of Internal Medicine (IRB-MED co-chair)
Vernon Sondak, Professor of Surgery (IRB-MED co-chair)
Daphna Oyserman, Assoc. Professor of Social Work (IRB-BehavSci co-chair)
John O'Shea, Curator, LS&A Anthropology (IRB-BehavSci co-chair)
Charles Kowalski, Professor of Dentistry (IRB-Health co-chair)
Alfred Franzblau, Professor of Public Health (IRB-Health co-chair)
Open (UM Health System Compliance chair)
Marvin Parnes, Associate Vice President for Research & Exec. Director of Research Administration
Michael Imperiale, Professor of Microbiology and Immunology (IBC chair)
Jon-Kar Zubieta, Asst. Professor of Psychiatry (Human Use of Radioisotopes committee chair)

Michael Hanna, Biological Safety Officer, Occupational Safety & Environment
Open, Assoc. VP for Finance
Robert Moenart, Executive Director, University Audits
Staffing provided by the Office of Research Compliance Review (ORCR)

B) Enhancement of the IRB System

A fundamental requirement for a robust Human Research Participants Protection Program is a well-organized, well-staffed, and well-run IRB. Major steps have been taken to enhance the capacity of the IRB system across campus but particularly in the University of Michigan Health System. During 2001, the IRB-Med grew from one to four functioning boards in order to provide sufficient attention to the growing volume of protocol submission reviews, protocol renewals, and adverse event reports. Enough new members have been recruited and trained to decrease the number of protocols for which any individual IRB-MED member serves as the primary reviewer, thereby enhancing the depth and detail of each review, both by the primary reviewer and at the convened board meetings. The training for new IRB members has been regularized and enhanced and now incorporates a period of apprenticeship to established reviewers. IRB members, which now number 45 UM faculty and 5 community members for the four Medical School IRBs, devote 6 hours per week in meetings reviewing protocols and discussing reviews and other compliance issues, plus another 6-12 hours weekly reading submissions to prepare for meetings.

Simultaneously, the administrative capacity of the IRB-MED office has been greatly increased. A new Director of Clinical Research Services, who serves as administrative director for the IRB-MED functions, has been hired and has filled several new support positions. The office has moved to larger and more visible office space, and the information technology supporting the IRB-MED office has been re-designed to better serve information flow and process management. The system ultimately will interface with a university-wide sponsored projects and compliance infrastructure, MPRIME, described below in Section F.

The annual budget for the IRB-MED increased from about $450,000 in 1998 to $1,500,000 in 2002. Financial support for the IRB-MED will continue to be the responsibility of the Medical School, while policy guidance, support, and consultation will be provided by the Office of the Vice President for Research. The Vice President for Research is the Institutional Official for Human Research Protections on record with the federal Office for Human Research Protections. No further major financial investments in the IRB-MED are anticipated in the near future.

Likewise, the two IRBs administered by OVPR -- IRB-Health and IRB-BehavSci -- have undergone significant upgrades in staffing and support to better match faculty needs. The current staff for the two IRBs is 8, up from 3 in 1998, and the budgets for these two IRBs has grown to $412,000 from $183,000. Also, these IRBs have completely revamped their data management systems and have instituted a new and more comprehensive application form that better serves the information needs of IRB review. The new form permits investigators to review step-by-step the information being provided to the IRB. This reduces the chances that the IRB will not have all of the information it needs to act on any given proposal, thereby streamlining the overall review process for the faculty investigators.

C) Office of Research Compliance and Review (ORCR)

The Office of Research Compliance and Review (ORCR) was activated this October 2003 with the recruitment of Dr. John H. Mather to be its first Director. This office will apply the principles of Continuing Quality Improvement (CQI) and when fully staffed will assess the implementation of federal and state existing and new regulatory requirements and university policies regarding the University's Human Research Participants Protection Program (HRPPP). ORCR reports to the OVPR and is expected to coordinate its activities with the Offices of the Executive Vice President for Medical Affairs, CFO and General Counsel. The jurisdiction of ORCR will be all of the University's research activities involving human subject research. It will provide the secretariat to the HRCC [see item A above].

Audits/inspections of human subjects research, including clinical trials, better assure the effective management of public and private funds, and demonstrate good stewardship of the institution's resources. It is acknowledged that audit/inspection functions should be located administratively outside of and beyond the level of the schools and colleges. By verifying that specific policies and procedures are being followed, audits can assist in detecting, correcting, and preventing noncompliance, and in ensuring the protection of human participants. The OVPR has chosen to vest authority and responsibility for auditing in a distinct and separate office: the Office of Research Compliance Review (ORCR). When coupled with an accreditation and education and training activities, ORCR will provide a well-formulated response strategy, with audits/inspections serving to reduce the likelihood of future noncompliance. These additional responsibilities are delegated to ORCR.

In summary, the primary scope and areas of responsibility for ORCR are:

- Conduct not-for-cause audits of research projects involving human subjects for compliance with OHRP, FDA, federal agency and University policies;
- Conduct reviews for compliance with OHRP, FDA and other federal agency policies, as requested of the University by these agencies;
- Initiate and conduct periodic reviews of the operations of the University of Michigan Human Research Participant Protection Program (HRPPP) subsystems involving human subject research projects for compliance with OHRP, FDA, federal agency and University policies;
- Direct and coordinate the initiative leading to Association for the Accreditation of Human Research Protection Programs (AAHRPP) accreditation of the University's Human Research Participant Protection Program (HRPPP) [see item D]; and
- Direct and coordinate a University-wide educational initiative to train faculty, students and staff on the ethical conduct of research with human participants, including the administration of the PEERRS activity [see item E below].

The office staff will be expected to provide expert advice on a number of program issues as they affect the responsible conduct of research. These will include subject matter expertise on new regulations affecting research such as the HIPAA privacy regulations, provide advice and oversight for investigator-sponsors of investigational drugs and devices, provide outside quality oversight as required by Good Clinical and Good Manufacturing Procedures.

In general, ORCR is expected to promote the overall goal of protecting human subjects in research while minimizing vulnerabilities for the University as a whole and assisting individual investigators in their ethical obligations to research subjects or participants.

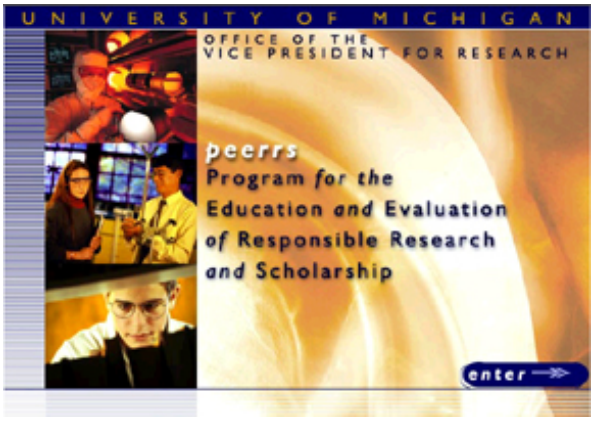
D) Accreditation of Human Research Participant Protection Programs

The Association of the Accreditation of Human Research Protection Programs (AAHRPP) was established in 2001 and initiated its accreditation of Human Research Protection Programs in 2003. To date, it has fully accredited three institutional programs and one Qualified accredited one program and more will receive their notifications by the end of this year. The University is fully committed to voluntarily seek accreditation of its HRPPP by AAHRPP. The initial Self-Assessment has begun which should be completed by early spring 2004 and submitted to AAHRPP for its review.

E) Program for Education and Evaluation of Responsible Research and Scholarship (PEERRS)

An important element of the enhanced UM Human Research Participants Protection Program is the development of foundational training and certification testing for all individuals engaged in or associated with research involving human subjects at the University. The Program for the Education and Evaluation of Responsible Research and Scholarship (PEERRS) is a web-based program that is designed for training and certifying faculty, staff and students who work with human subjects, although some of its modules are equally relevant to all members of the university research community in that they cover the basic rules and professional norms for the responsible conduct of research by any researcher, irrespective of the field of study.

For those seeking certification, certificates will be awarded for passing web-based tests on relevant topics. A score of 80% is required to pass each test (100% for human subjects modules), which may be taken as many times as necessary without penalty.



Faculty, staff and students involved in research will initially complete a short survey to determine his or her certification requirements based on the individual's roles and responsibilities. An individualized, easy-to-update profile of required, recommended and optional courses/certifications will then be generated. Users will be able to go directly to certification tests after completing the initial survey, or view course modules prior to taking a test.

Initially, courses and certification will be offered in the following subject areas:

- **Foundations of responsible research conduct**: ethical responsibilities related to plagiarism/data falsification/publication/intellectual property/others, basic misconduct definitions and reporting responsibilities, summary of other PEERRS modules.
- **Research administration**: UM procedures/forms, PI responsibilities, budgets and project accounts, pre-/post-award activities, understanding indirect costs, federal regulations.
- **Conflict of interest guidelines**: definitions and recognizing potential conflict situations, responsibilities toward students/colleagues, consulting and conflict of commitment, tech transfer issues.
- **Human research, regulatory and ethical obligations**: basic modules in three tracks -- biomedical sciences, health sciences, and social sciences -- covering history of human research protections, fundamental principles and regulations, federal definition for "Human Subject," principles of the Belmont Report, purpose and function of Institutional Review Boards.
- **Animal research, regulatory and ethical obligations**: principles and regulations, basics of animal care, reporting requirements, procedures for obtaining approval to use animals in research.

Each module includes a series of 20-30 web pages containing basic information, examples and case studies, and additional background material. Users can send questions and comments about the courses through an online form. Modules will be added later covering mentor/trainee relationships and publication practices, as well as advanced topics in human subjects research and training for faculty who are members of oversight committees (IRB, UCUCA, COI).

Development of PEERRS is the responsibility of the Office of the Vice President for Research. Direct administrative responsibility for PEERRS will be transferred to ORCR during FY04.

PEERRS Timeline

- Module development ..... July, 2001 - May, 2002
- Faculty committee review and recommendations ..... June-July, 2002
- Module usability testing ..... July-August, 2002
- Module modifications based on faculty review and usability test results ..... June - October, 2002
- Review by faculty review committee..... November, 2002- February, 2003
- Final changes/production coding ..... March-May, 2003
- PEERRS becomes available to campus ..... June, 2003
- Human subjects modules added to curriculum ..... November, 2003

F) Center for the Advancement of Clinical Research (CACR)

CACR has been part of the Medical School since 2001 and was created from the reorganization of a prior initiative called the Center for Clinical Investigation and Therapeutics (CCIT) that had been launched by the EVPMA in 1998. The purpose of CACR is to facilitate innovative clinical investigation by providing, in coordination with the University of Michigan's NIH-funded General Clinical Research Center (GCRC), the infrastructure to advance investigator-initiated clinical research at the University of Michigan through a set core services. CACR consists of five Cores and an Outcomes Tracking Unit. The five cores are: Administration, Research Development, Education and Certification, Research Support, and Biometrics and Outcomes. The Research Support Core is composed of three units: Project Management and Monitoring, Study Coordination and Conduct, and Human Subjects.

The Administrative Unit of CACR oversees the management and direction of all of the cores of CACR as well as serving as the central focus of new directions in clinical research for the Medical School. The Outcomes Tracking Unit focuses on the study of systems and processes used in clinical research and in CACR. The Unit's mission is to do "research on clinical research" to learn and improve methods used in the conduct of clinical research both within the Medical School and more globally.

The Research Development Core provides: "Think Tank Committees" to facilitate the development and implementation of investigator-initiated clinical research protocols by providing assistance in protocol preparation, study design, accounting and budgeting services, and a funding finder service. The Research Development Core is also overseeing a project to develop an informatics system to electronically manage the conduct, human subject management, data management, and regulatory management and reporting of all aspects of a clinical research protocol.

The Education and Certification Core provides the Medical School with educational programs and certification in the conduct of clinical research to investigators and their support staff, and ongoing educational seminars and programs on related clinical research topics.

The Research Support Core provides assistance to investigators in carrying out their clinical research protocols through the services of its three units. 1) The Project Management and Monitoring Unit (PMM) provides: project managers and monitors for multi-centered on and off-site clinical trials, and internal monitors for on-site studies at the request of the PI. This unit has developed a Clinical Research Regulatory Checklist for use by investigators in the development and conduct of clinical research studies to assist in achieving regulatory compliance. The checklist is available on-line and PMM supports a help desk to answer investigators questions in this area. 2) The Study Coordination and Conduct Unit provides: study coordinators and nurse coordinators who can provide a variety of services including study coordination, subject screening and scheduling, regulatory document preparation (IRB documents), adverse event reporting, case report form completion, data collection and study close-out. 3) The Human Subjects Unit currently is developing a web portal to list all studies in the health system that are currently recruiting human subjects and developing a subject registry for patients and community volunteers interested in participating in clinical research studies in the Health System.

The Biostatistics and Outcomes Research provides expertise in clinical trial design, outcomes research, quality of life research, database development, database

management and data analysis for multi-center clinical trials and multi-disciplinary research.

When fully staffed in early 2004, CACR will have about 50 FTEs of employees. CACR is housed in 10,000 square feet of space in Lobby M of Domino's Farms. This space includes offices for all personnel, as well as exam rooms dedicated to clinical research..

G) MPRIME: The Michigan Program for Research Information Management and Education

The Michigan Program for Research Information Management and Education (MPRIME) will support the protection of human subjects in research by improving the administration and approval processes for protocols involving human subjects. Sponsored by the Office of the Vice President for Research, with support from MAIS and the Medical School, the MPRIME project will help the University handle the growing number of protocol submissions and help investigators manage the increasing complexity and scrutiny of regulations governing human subject research.

The MPRIME project has selected the Webridge web-based software product as the primary tool for automating human research management processes. During the next several months, the University will work with Webridge to configure the product to automate and improve these processes across the University.

In its initial phases, MPRIME will encompass the IRB Med, IRB Behavioral Science, IRB Health, IRB Flint, IRB Dearborn, the General Clinical Research Center (GCRC) and the Protocol Review Committee/Cancer Center (PRC/CC). Other compliance committees will also be involved in protocol review and approval processes. Future phases will automate additional compliance committee processes, and will create a data warehouse for integrated reporting. The initial phases of MPRIME will be focused on human subject research. Planning for automating end-to-end research administration will be initiated in 2004. The primary features of MPRIME are outlined in Table 4.

Table 4
MPRIME Features

- A unified research application used across human research compliance committees
- Online development of research applications using "Smart Form" questions and answers for easy navigation
- Role-based workflows for compliance committee review and approval processes with electronic signatures
- Version control for research applications and supporting documents
- IRB meeting management (including agendas and minutes)

- Verification of investigators training certification using the PEERRS database
- Data warehouse for integrated reporting to support accreditation and audit requirements
- Interface from the M-Pathways database to populate profiles of key personnel

Automated processes supporting the research management will greatly enhance the service to our researchers, improve compliance with regulations, and reduce the cycle time for application approval. Multiple versions of documents can be eliminated as an electronic format (including revision histories) available online ensures that each user in the application process has access to all of the changes from previous reviewers. Centralization of storage and archiving of protocol applications will allow data warehousing and analysis of trends, in addition to rapid access to the data for auditing of protocols by compliance personnel.

MPRIME Timeline

Define MPRIME functional requirements	March 2003
Issue RFP to identify MPRIME vendor product	April 2003
Deadline for bids	May 2003
Conduct in-depth evaluation and select vendor	May - July 2003
Executive Officers approval for vendor selection	August 2003
Contract negotiations with Webridge	August - October 2003
MPRIME Implementation Kickoff	November 2003
MPRIME implementation	December 2003 – December 2004
IRB Med, GCRC, Cancer Center	July 2004
IRB BehavSci/Health, Flint, Dearborn	Nov 2004
Data Warehouse, reporting	Dec 2004
Research Administration/Proposal Management Planning	Mid 2004

4. Budget

Total cost for implementing the programs described in this report includes approximately $2.2M in one-time costs (of which $425K was provided by the National Institutes of Health) and $1.65M in added base-budget allocations.

5. Compliance Plan Schedules