2.0 IMPROVING EXISTING STRUCTURES AND PROCESSES

2.1 Introduction

The Research Support Services Taskforce was charged, among other things, to develop a plan to provide better, more expeditious and user friendly support and service to faculty investigators and research sponsors. As part of this plan, the committee was charged to assure that administrative, management, and compliance services are provided in a responsive, timely and accountable manner. By having high quality expedited processing of all aspects of grant approvals, etc. and a frustration free expedited submission of proposals, corporate sponsors would come to value this and likely increase their investment in and expenditures with University of Minnesota faculty.

In order to accomplish this we looked at each and every step of developing a proposal and budgets, submitting and getting approvals, setting up accounts and monitoring inflow and outflow of funds, filing of reports and complying with all appropriate regulatory requirements. An overriding objective is to help faculty get corporate sponsored research and to protect them and the institution from untoward actions of regulatory agencies.

The current performance of committees and institutional service groups involved with industry-sponsored research in the AHC has been reviewed. The findings of the Research Support Service Taskforce are included, as are the new performance goals and recommendations for change.

2.2 Conflict Review Committee (Board of Regents' Conflict of Interest Policy) and Board of Regents' Academic Misconduct Policy

The AHC is committed to developing relationships with industry that will benefit the public, the AHC and its faculty, and industrial research sponsors. The University can do this while following its education, research and outreach/service missions. While the AHC is committed to developing these relationships, it is also committed to promoting and maintaining public trust in the judgment and conduct of its researchers and clinicians. The way the University can maintain and enhance this public trust is by assuring that these activities are conducted in accordance with the highest standards of integrity and ethics.

Assuring scientific integrity at the University of Minnesota is directed by the Board of Regents' Conflict of Interest Policy and the Board of Regents' Academic Misconduct Policy. The AHC will apply these policies in the firm belief that its researchers are honest, committed to protecting the public interest and their own integrity, and will adhere to the highest ethical standards in the conduct of their research.

The Academic Misconduct Policy provides the mechanism for dealing with cases of alleged scientific/academic misconduct. Procedures for reporting and managing allegations of research misconduct including: scientific misappropriation, interference, or misrepresentation; obstruction of investigations of research misconduct, and noncompliance with research regulations have been discussed at Responsible Conduct of Research workshops. These workshops have been run as of 1996 and will continue to be held.

Since 1994, the Medical School Conflict Review Committee (CRC) has reviewed all industry-sponsored research proposals with budgets exceeding $10,000. The CRC has served as the advisory group to the Dean of the Medical School on conflict of interest issues for medical school investigators proposing to conduct industry-sponsored research. To our knowledge, no other school in the AHC has such a committee. It appears that the CRC functions to eliminate all real or perceived conflict of interest.

2.2.1 Current Performance - Conflict Review Committee

The CRC has expanded its authority well beyond that detailed in Regents' policy to include review and approval of various things that have nothing to do with conflict of interest. The CRC currently requires that any potential conflict of interest must be eliminated before an investigator enters into an industry-sponsored research agreement. Federal regulation and Regents' Policy on Conflict of Interest allow some categories of potential conflict of interest to be managed through peer review or other mechanisms.

The average length from application to CRC approval is approximately one month. However, there are numerous applications that remain tabled or that go unresolved for many months - sometimes indefinitely.

It is a common occurrence, weekly or more often in meetings in the community, that business leaders or government officials disparage the University and the AHC because of difficulty in dealing with us. They commonly cite the Conflict Review Committee as needing substantial remediation and fault University leadership for not addressing this.

2.2.2 Current Performance - Application of Academic Misconduct Policy

Information regarding the application of Regents' Policy on Academic Misconduct is not available beyond the guidelines evident in the policy. The Office of the Vice President for Academic Affairs is responsible for the application of this policy and is the main point of contact.

2.2.3 Goals and Recommendations for Conflict Review Committee

We recommend that the current CRC be disbanded and a new Conflict of Interest Review and Management Committee (CRMC) be formed. (See the Executive Summary for the proposed new committee membership.) This new committee should acknowledge its more circumscribed role and restrict this to managing real or perceived conflicts. Many issues the old CRC has dealt with come under the purview of various other offices at the University such as ORTTA. For example, Sponsored Projects Administration has a major role to play in the overall grant process regarding budgets. If this and various other aspects of the grant process are respected, it will limit the scope of CRMC proposal review to nothing other than conflict of interest policy issues and with a directive or mandate to provide solutions that still permit the faculty to perform the corporate sponsored research except in the most unusual circumstances.

The CRMC should thoughtfully consider and, if necessary, actively assist faculty in preparing processes and plans to properly manage situations in which potential conflicts of interest may seem, to critical observers, to have the potential to bias research results. Some examples of ways for the organization to deal with this potential or with the perception for the biasing of research owing to financial gain include: putting any equity, stock options or warrants in

escrow until completion of multi-center trials and having the data file submitted or "locked" at the FDA; holding consulting money in escrow until a like occurrence; appointing an ad hoc peer review group to meet quarterly to review the research; and various other means.

Only in cases in which a potential conflict of interest is determined to exist, should applications be reviewed by the CRMC. The Committee should meet as often as necessary (no less often than bi-weekly) to review applications which might be referred to it.

The CRMC review process should be limited to addressing the issue of investigators' (or immediate family) external financial relationships and review and approval of the proposed plan to manage the perceived potential conflict. The Committee will review applications in less than 10 working days and may recommend approving or denying the plan for managing the potential conflict. It should be the preponderant outcome that a plan for management of the situation, not denial of the proposal, occurs.

The final decision authority should rest with the AHC, e.g., Vice Provost for Research or deans who may seek the recommendation of the Public Private Partnerships Committee at the University level for advice and recommendation if necessary.

The rationale for proposed management options is to protect the institution and its faculty and staff from real or perceived impropriety. The rationale is to restrict any realization of economic gains until the work has been corroborated or reviewed by others than the PI who will no longer be able to influence the results after the sponsor database is locked or after the final independently audited or peer reviewed report is issued to the sponsor. It should be noted that other management options could be developed, but they must unambiguously pass the "sniff test" for propriety in the public's opinion.

Income exceeding $10,000 per year received for consulting relationships or board appointments, and familial financial relationships which may introduce the potential for conflict of interest are all proposed to be managed in a manner similar to that described for the management of stock/equity or options.

Assistance should be provided to faculty in reviewing the policy and his/her external relationships, and in choosing the best management plan for assuring scientific integrity whenever a potential conflict of interest may appear that could potentially bias the outcome of the research. Department heads/directors and deans should be allowed to delegate authority for review of potential conflict of interest to the Research Support Service Office. If they elect to retain this authority and the responsibilities associated with it, the same performance relative to determining a management plan, and timeliness is expected.

Options for Managing Potential Conflicts of Interest

Potential conflicts of interest may be created by, but are not restricted to, the following relationships between the faculty member, their staff or immediate faculty and the proposed industry sponsor: owning equity, warrants, or rights to stock options, consulting agreements, and serving on advisory or other board appointments where some consideration is provided.

The conflict management plan for all potential conflicts of interest could include, among other things:

- A detailed description of the conflict management plan signed and submitted by the faculty member prior to the initiation of the project.
- Formation of an ad hoc scientific peer review committee that will:
- review the proposed study protocol, identify areas where there is concern about the potential to introduce bias, and review the management plan designed by the Research Support Service Manager and the faculty member to mitigate this, and,
- audit the study as it proceeds and upon completion (including the collection and analysis of data). If the industry sponsor is monitoring the regulatory compliance and clinical practice of the investigator, the AHC will not, in general, duplicate this review. If this review is not provided for by other objective means a system providing for spot checks will be instituted.
- A detailed post-contract completion report documenting the management process for the potential conflict of interest.

Ownership of stock/equity options or warrants exceeding $10,000 or more than 5% ownership interest of the entity (present market value) are proposed to be managed as follows:

- Human Clinical Trials: The stock/equity will be put in trust until such time the clinical trial database is "locked" by the sponsor. At this point in a study there has been data collected from single or multi-center trials and there is no longer an ability for the PI to influence this data.
- Animal Trials: The stock/equity options, etc., will be put in trust until the final quality assurance audit report is issued to the sponsor. This final audit is typically performed by an outside company/or service.
- "Bench"/Basic Research: The stock/equity options, etc., will be put in escrow or trust until peer review or independent audit of the final report to the sponsor is completed.

2.2.4 Goals and Recommendations Regarding Application of the Academic Misconduct Policy

The Vice President for Academic Affairs, as the responsible institutional authority for the Academic Misconduct Policy, should commission the faculty and staff to develop a Good Scientific Practices document to guide the conduct of research at the University of Minnesota.

2.2.5 Rationale

It is unlikely that the current CRC (established for the Medical School) would voluntarily relinquish much, if any, of the expanded authority it has assumed. The current committee does not represent all, or a majority of AHC schools as the newly constituted CRMC surely must. Requiring CRMC committee members to have had prior experience with industry/academic institution research relationships will protect the integrity of research (and thereby the public and the AHC) without compromising the ability of the AHC to cultivate research relationships with business and industry. It may be reasonable to provide some consideration for compensation or salary offsets for faculty serving on this committee, depending on how extensive the time commitment is.

The Research Support Service Office will provide support to faculty in reviewing the proposal and protocol, the PI's external relationships, the identification of any potential conflict of interest, and a plan to manage the potential conflict, should one exist. The Research Support Service Office will also provide biostatistical assistance to the PI to assure that the sample size and statistical design are adequate to answer the research question. Overall, the best way to

assure scientific integrity is to begin with a well conceived and well-designed study.

Department heads, institute directors and deans are currently responsible for determining whether an industry-sponsored research application should be sent to the CRC. Because deans are overburdened with a myriad of responsibilities the Research Support Service Office will perform this review, develop a management plan for any potential conflicts of interest, forward the disclosure and management plan to the CRMC, and provide information to the Department head and/or Dean for their information.

2.2.6 For More Information

Board of Regents' Policy: Conflict of Interest --- http://www.fdp.finop.umn.edu

Office of Research Integrity Advisory Document: Model Policy and Procedures for Responding to Allegations of Scientific Misconduct - April 1995 ---- http://www.os.dhhs.gov/phs/ori/policy/policy.html

University of Minnesota Board of Regents' Policy: Academic Misconduct ---- http://www.ortta.umn.edu/policy/respolcy.htm

Integrity and Misconduct in Research (Report of the Commission on Research Integrity) ---- http://law.house.gov/7.htm

2.3 Subjects Protection Programs (Human and Animal Subjects) Human Subjects

The Institutional Review Board: Human Subjects Committee (IRB) is an administrative body established to protect the rights and welfare of human research subjects recruited to participate in research activities conducted under the auspices of the University of Minnesota. The IRB has authority to approve, require modifications in, or disapprove all research activities that fall within its jurisdiction as specified by both the federal regulations and Regents' Policy.

The IRB carries out its responsibilities through review and approval of research, through continuing reviews of approved research, and through collecting and determining the significance of adverse events experienced during clinical research. PIs are required to report to the IRB any changes made to the research plan during the conduct of the study, and the incidence of serious or unexpected events.

The IRB is required to follow two sets of federal regulations: Department of Health and Human Services (DHHS) Regulations and Policies, and Food and Drug Administration (FDA) Regulations and Policies. The FDA regulates but does not usually support or conduct research. While the FDA is a DHHS agency, its regulatory mandate differs substantially from other DHHS agencies that conduct and support a significant amount of research.

The University of Minnesota IRB includes approximately 75 members that form six committee panels: 4 medical, 1 social sciences, and an executive panel. Each of the 4 medical panels and the social sciences panel meets once each month. Agendas for each medical and social sciences committee meeting may include as many as 30 different projects to review.

2.3.1 Current Performance - Human Subjects Protection Programs

Many faculty research investigators are not fully aware of all of the regulations, guidelines, and community standards by which their research applications will be judged. The application may be confusing and consent forms investigators submit for IRB review may reflect the research investigators' lack of familiarity with regulations, guidelines, and local standards.

In all but a very few cases, the minimum length of time it takes the IRB to review and approve a study application is 45 days. It is not uncommon for 60 days or more to elapse before final notification of approval of a clinical study is received by the PI .

In the review process of an application submitted to the IRB there are a number of processes in which time management could be improved. For example, the approval process is delayed when IRB staff must request additional information from the PI or changes prior to approval being granted. If improved information had been provided at the original submission, this recycling could be obviated. There may be considerable time delays when the proposal is back in the hands of the faculty member for his/her response to the IRB's questions and comments and there is additional time taken with the subsequent recycling through the process. These communications back and forth between the PI and IRB staff sometimes may be very simple but are often complex and can be time consuming to prepare. Responses are often further delayed by sending them through the mail.

The committee may approve the PI's response to stipulations or may add more stipulations, in which case the process is repeated. Overall, the "cycle" times can amount to a significant number of months when all is said and done.

PIs are frequently frustrated by the variable review between and within IRB committee panels. What may be approved by one committee panel may not be approved for a similar project reviewed by a different panel. While the regulations and guidelines do not change frequently, the application of these regulations and guidelines by individual IRB committees and, more commonly, the "local" standard, varies between committee panels, sometimes significantly.

After the proposed research is approved by the IRB and the PI is notified, the PI is thereafter responsible for complying with federal human subjects regulations and guidelines as the research is conducted. To assist faculty in meeting their responsibility, the IRB provides information to the research community in a subjects protection programs column that appears each month in the ORTTA publication - *Research Review*. The Subjects Protection Programs office collates these columns approximately annually, and provides the document to research investigators as a local guide to subjects protection. A member of the IRB administrative staff or a member of one of the committee panels participates in the annual Responsible Conduct of Research workshop to provide human subjects-related training to the University of Minnesota research community.

2.3.2 Goals and Recommendations - Human Subjects Protection Program

It is the expressed goal of the Research Support Service Taskforce to have the IRB review and approval/denial process for industry-sponsored research applications to be completed within 10 working days of application submission, without sacrificing the current high quality of the review.

The institution has an obligation and is committed to achieving the highest standard of compliance with all pertinent regulations. The institution, in consultation with and under the guidance of the IRB, could better protect the rights and welfare of human subjects in research by supporting and training its members and the research community.

The IRB should consider the possibility of assuring: (1) increased compliance with human subjects regulations as studies are in progress, (2) better quality of the pertinent information submitted to the IRB in research applications, and (3) greater efficiency of the overall IRB process through providing training, service, support, and information to faculty and staff; and (4) overall, more expeditious processing/or approval of proposals by decreasing or to the degree possible eliminating "cycle times." This could be accomplished by a variety of means, for example through a positive, visible IRB presence in frequent training sessions and consultation with PIs; and by continuing to provide information in the publication *Research Review*. Routine AHC e-mails and a web page dealing with a broad scope of human subjects protection issues are some of a number of things that would be helpful.

The IRB could develop a primer of local standards to aid faculty and staff in understanding the conduct of human subjects research. Developing local standards to guide investigators would address ongoing training, education and information needs and help to "raise the institutional consciousness" about the IRB's role and the important issues it deals with. Development of this primer of local standards would also increase the likelihood of consistent reviews of applications between and within committee panels.

The University should provide staff adequate in number to allow Subjects Protection Programs to actively and frequently train, consult, and provide information to the University research community not just at the time of protocol approvals. It appears that more executive level administrative staff are needed to support committee panels, manage the expected increased volume of research, and communicate to various members of the organization these very complex issues.

In order to appropriately value the important contribution to the institution and the time this requires, IRB committee members should be paid for their service in the form of salary offsets or other compensation. In addition, funds should be available to the IRB to enlist the advice of consultants when expert advice is required. If there were a small number of highly-trained committee members who worked a significant percentage of time and if they were compensated, we might need only one or two IRB committee panels. Providing compensation, training, and performance expectations for panel members would serve to create more efficient and responsive committees. Given the competing demands on faculty it's amazing we are able to get anybody to serve on current IRB panels. At the same time, consolidating the number of panels and committee members would increase the IRB's opportunity to provide a more even or consistent review of research applications. While it is recognized that this is an area of frustration for PIs, dealing with this phenomenon is a challenge even for NIH in their peer review system.

The IRB review process could be made more efficient by enabling the committee panels and investigators to interact via video-conference at the time of review of the proposal. In this way, the faculty member could address immediately on a "real time" basis many of the questions a committee panel might have. Additional time could be saved in the process by the faculty and IRB taking advantage of courier, e-mail, and fax services to get time-sensitive correspondence to and from faculty to make their life easier and provide for a more timely resolution to any issues.

2.3.3 Rationale

The University of Minnesota will be best protected from human subjects research regulation violations when the faculty and overall research community is well-informed, provided with high quality and timely staff support and by having studies randomly monitored. Understandably, the chief concern of the IRB is protecting human subjects; however, overall the institution directs little attention or staff time toward providing training, consultation, and support for faculty and research study colleagues. This is of deep concern, given the number of clinical trials ongoing at this institution (numbering in the thousands). The institutional authorities to whom the IRB staff report should be provided with resources that they could direct towards an increased commitment to serving the faculty on the part of the IRB office, in essence, extending their compliance function through education and providing information.

Providing appropriate assistance to faculty through the Research Support Service Office will improve the quality of research plans, human subjects research applications, and consent forms. The IRB has said that the most frequent reasons for delays in the review and approval process are deficiencies in information provided by PIs in applications and consent forms. This may occur for various reasons, including prior inexperience of the PI, who might be unfamiliar with the process and without sufficient time to take the care which must be taken to fill out the forms.

A major bottleneck in the IRB review and approval process of initial applications is at the level of the executive assistants. There are currently only two. These two staff members have a huge responsibility and must write all the response letters to PIs following IRB committee meetings. As many as 30 letters communicating the recommendations and actions may be required after any single meeting. Among a number of other things, many of these letters are complex and time consuming to write. In the current system, additional executive assistant staff would decrease the volume of letters to be developed by any one staff member and thereby increase the speed with which responses could be provided to faculty. It is imperative that additional executive staff be recruited.

Allowing PIs to appear before the IRB committee panel (via video conferencing) to answer questions and review their research should be seriously considered. The committee could ask questions and receive responses within minutes that, in the current process, could take a month or more to communicate and get reviewed. It has been suggested that approximately 75% of stipulations and deferrals could be managed immediately by allowing the committee and the investigator to communicate in real time. PIs will not be required to appear before the committee, but will be notified of the opportunity when a committee panel is meeting so that the PI could answer any questions and concerns about the proposed research. We envision a conference room where the faculty could go within a given time frame to link on line with an IRB review group.

Finally, faculty would be greatly assisted by receiving notice of the committee's decision as quickly as possible after it is made, ideally electronically with a paper copy to follow.

2.4 Subjects Protection Programs (Human and Animal Subjects) - Animal Subjects [OPRR Institutional Animal Care and Use Guidebook]

Every institution that falls under authority of the Animal Welfare Act and/or receives Public Health Service support for research and teaching involving laboratory animals must operate a program with clear lines of authority and responsibility for all matters surrounding animal use. Among other things this includes: establishing a properly functioning Institutional Animal Care Committee (IACUC), having procedures for self-monitoring, the provision of adequate veterinary care, having a program of occupational health to assure sound animal husbandry practices, and assuring quality maintenance of facilities for housing animals.

The IACUC must have at least five members. Membership must include: a veterinarian with program responsibilities, a scientist experienced in laboratory animal research, a non-scientist and an individual who has no other affiliation with the Institution besides membership in the IACUC. The IACUC has authority to approve studies/proposals, require modifications before approval, or withhold approval of proposals submitted to it for review. No research activity involving animals can begin unless it is first approved by the IACUC.

The IACUC is required to follow two sets of federal regulations: Public Health Service (PHS) Regulations and Policies, and United States Department of Agriculture (USDA) Regulations and Policies.

Federally mandated IACUC functions are to :

- Review, at least once every 6 months, the research facility's program for the care, use and housing of animals, using the USDA Regulations or Guide as a basis.
- Inspect, at least once every 6 months, all of the animal facilities, including animal study areas/satellite facilities, using USDA Regulations or Guide as a basis.
- Prepare reports of IACUC evaluations and submit the reports to the Institutional Official.
- Review and investigate legitimate concerns involving the care and use of animals at the research facility resulting from public complaints and from reports of non-compliance received from facility personnel or employees.
- Make recommendations to the Institutional Official overseeing animal care regarding any aspect of the research facility's animal program, facilities or personnel training.
- Review and approve, require modifications in order to secure approval, or withhold approval of those components of the proposed research activities related to the care and use of animals.
- Review and approve, require modifications in order to secure approval, or withhold approval of proposed significant changes regarding the care and use of animals in ongoing activities.
- Suspend an activity involving animals when necessary; take corrective action, and report this to the funding agency and USDA.

The University of Minnesota IACUC includes members that form one committee panel and an executive panel. The review panel meets once each month. Agendas for each committee meeting may include as many as 30 to 40 different projects to review. The executive committee of the IACUC meets less frequently.

2.4.1 Current Performance - Animal Subjects Protection Program

Over the past few years, considerable effort has been devoted to enhancing the awareness and improving the knowledge of faculty in the use of animals in their research. Internal and external regulations governing the use of animals in research, education and display have been presented to the faculty using a variety of methods. These efforts have resulted in distinctly improved submissions to the IACUC which has directly improved the quality and speed of the review process. Currently, the average length of time from application to the IACUC to approval is approximately 30 days. Since the IACUC consists of one committee panel, the review process is fairly consistent from project to project. Having a single committee also facilitates the efficiency of the review/approval cycle.

After the proposed research is approved by the IACUC and the PI is notified, the PI assumes responsibility for knowing and applying federal regulations and guidelines as the research is conducted. To assist PIs in meeting their responsibility, the IACUC provides information to the research community in a subjects protection programs column that appears each month in the ORTTA publication - *Research Review*. The Subjects Protection Programs office collates these columns approximately annually, and provides the document to researchers as a local guide to subjects protection. A member of the Subjects Protection administrative staff or a member of the committee participates in the annual Responsible Conduct of Research workshops to provide animal subjects related education and training to the University of Minnesota research community.

2.4.2 Goals and Recommendations - Animal Subjects Protection Program

Recently, administrative responsibility for the IACUC was assumed by a reorganized Office for the Protection of Research Subjects. This action directly addressed some of the problems or deficiencies. Among some of the issues that needed attention were the responsiveness of the staff to PI concerns, the quality of the written correspondence between the IACUC and faculty, and the organization of committee files. Notwithstanding these changes, as stated above, the review cycle remains at an average of 30 days.

It is the expressed goal of the Research Support Service Office to have the review and approval/denial process of industry-sponsored research applications to be completed within 10 working days of application, without sacrificing the current high quality of the review. Therefore some changes would be necessary.

Adequate staff numbers to allow the IACUC to continue to train, consult, and provide information to the University research community should be provided. There are many ways that the efficiency of the overall IACUC review process could be improved for example by having the IACUC: hand-deliver or courier the review materials to committee members; add executive personnel to help write stipulations, deferral, and approval letters; consider having executive personnel dictate letters or implement voice recognition transcription technology; consider having the person who develops the response letter also enter it in the database, and increase the number of student staff to assist with compiling application responses.

Recommendations in the human subjects protection section regarding providing the opportunity for investigators to meet with the committee panel via video conferencing, and communicating correspondence electronically in advance of the formal letter, apply to the animal subjects review process as well.

2.4.3 Rationale

The appropriate and considerate use of animals must be a guiding principal for science. The University of Minnesota will be best protected from animal subjects research regulation violations when the research community is well-informed and supported by the institution and randomly monitored for compliance. Understandably, the chief concern of the IACUC is protecting animal subjects; however, overall in the area of use of animals the institution probably does not direct sufficient attention or staff time toward providing training, consultation, and support for faculty and research study investigators. This is of deep concern given the amount of animal research ongoing at this institution, and the emotional and political sensitivity of the public regarding the appropriate care and use of animals in scientific experimentation. The institutional authorities to whom the IACUC staff report could direct resources to, and encourage an increased commitment to service on the part of, the IACUC office, in essence extending their compliance overview function.

Providing assistance to faculty and their staff through the Research Support Service Office should improve the quality of research plans as they pertain research applications involving animal subjects. The most frequent reasons given for delays in the review and approval process are lack of clarity or other deficiencies in information provided in the applications. This may be for various reasons, including prior inexperience of the PI, who might be unfamiliar with the process and the time or care that must be taken to fill out the forms, etc. In addition to increasing quality of the information provided to the oversight committees in the applications, the Research Support Service Office can assume much of the pre-review functions the IACUC must now perform thereby facilitating their function and allowing them to focus their time on decision making based on the most complete information.

Allowing faculty to appear before the IACUC committee panel (via video conferencing) to answer questions and review their research would allow the committee to ask questions and receive responses within minutes that could, in the current process, take a month or more to communicate and get reviewed. As with the IRB, it has been suggested that approximately 75% of stipulations and deferrals could be managed immediately by allowing the committee and the investigator, to communicate in "real time". PIs will not be required to appear before the committee but will be notified of the opportunity to respond immediately when the committee has questions and concerns about the proposed research. We envision a conference room where the investigators could go within a given time frame to link on line with an IACUC review group.

Finally, PIs would be greatly assisted by receiving notice of the committee's decision as quickly as possible after it is made via e-mail, fax, or a web page/data base.

2.4.4 For More Information Food and Drug Administration Information Sheets ---- http://www.fda.gov/oc/oha/toc.html

FDA Code of Federal Regulations (21 CFR Parts 50, 56) http://law.house.gov/cfr.htm

OPRR Protecting Human Research Subjects Guidebook http://www.nih.gov/grants/oprr/oprr.htm

University of Minnesota Subjects Protection Programs Homepage

University of Minnesota IRB: Human Subjects Committee: A Series of Articles Collected from the *Research Review*, September, 1995

IRB: Human Subjects Committee Application Form and Information Packet - Health and Biological Sciences

IRB: Human Subjects Committee Continuing Review of Approved Research Form

University of Minnesota IRB Membership List

OPRR Institutional Animal Care and Use Guidebook

1OPRR Protecting Human Research Subjects: Institutional Review Board Guidebook

2.5 Office of Research Technology Transfer Administration (ORTTA)

Responsibilities of the Office of Research Technology Transfer Administration are divided into two primary areas: Patents and Technology Marketing (PTM) and Sponsored Projects Administration (SPA). The mission of Patents and Technology Marketing1 is the identification, protection, and transfer of technologies from the University of Minnesota for commercial development in the public interest and with fair consideration for the transfer. Sponsored Projects Administration performs roles in managing grants and contracts including: grant application review, approval, and post-award grant administration functions. A "roles and responsibilities" document for sponsored research program management is now available. This document is expected to improve the management of sponsored research programs by defining responsibilities and clarifying roles for investigators, departments, units, and ORTTA.

From 1992-1996, the Academic Health Center (AHC) averaged 79 technology disclosures per year. This represents 48% of the University of Minnesota total for that time period. In fiscal year '95-'96, the AHC faculty generated nearly $6 million dollars in royalty income. This represents 92.8% of the total University of Minnesota royalty income for that year.

From 1992-1995, the AHC averaged per annum $139,700,000 in sponsored research expenditures. Of this total, $11,175,000 per annum was sponsored by business and industry. By comparison over this same time frame the Institute of Technology had an average of $57,920,000 in sponsored research expenditures, $4,750,000 of which were sponsored by business and industry; and the College of Biological Sciences had an average of $11,380,000 in sponsored research expenditures of which $625,000 was sponsored by business and industry.

ORTTA defines and assumes current specific responsibilities in terms of the following categories regarding grants and contracts: providing institutional oversight, notifying, expediting, approving, initiating, and providing local oversight.2

2.5.1. Current Performance - Patents and Technology Marketing (PTM)

Patents and technology marketing staff are notified via faculty members when an invention is to be disclosed. A form provided by ORTTA is filled out by faculty members (on paper) describing the nature of the technology being disclosed. PTM then makes a judgment as to whether to file a patent. If the decision to file is affirmative, the PTM representative typically might identify a law firm and lawyer they have a relationship with who has expertise in the given area. The disclosure is sent to them, and the PI is requested to send any supporting papers or documents or data that might be useful in developing the patent application. Generally, there will be discussion between the inventors and the drafting lawyer facilitated by PTM.

University policy stipulates that ORTTA will respond to a patent disclosure within 30 days. PTM for the AHC, says they try to respond within 10 working days. If PTM decides not to file a patent (which they do in about 75-80% of the cases), a final release is sent to the inventors. At that point, the inventors are free to file a patent at their own expense and have all rights to this invention to pursue as they wish. If this occurs, the University has neither financial obligation to nor benefits financially from anything that ensues.

PTM has an advisory group of investors, experts in technology, or technology-based companies that they, on occasion, use to help evaluate the potential market and general wisdom of going forward with the expense of the patent filing and prosecution.

A significant concern in this whole process is cost. Currently, PTM estimates that it might take on average $20,000 to fully prosecute a U.S. patent with the Patent and Trade Mark Office. Foreign filings incur considerably more expense given the need for country-based counsel and costs of translation into various

languages. The current University Patents and Technology Marketing office policy is, in general, that unless some corporate agreement or similar vehicle is in place or imminent at the time that actions are needed to be taken to continue to prosecute the foreign filings, these will be dropped.

In meeting with Dr. Severson he discussed the dilemma PTM faces: on one hand PTM solicits technology disclosures from faculty, and on the other hand PTM is in the position for a series of what are understandable circumstances to be able to pursue only ~20 - 25% to U.S. applications.

The next step after this process is final notification of the relevant department heads and deans regarding the filing of a patent by one of their faulty members. Subsequent to this, the next challenge going forward is licensing, in which a development agreement, option and/or outright sale or license is developed and negotiated.

In discussions with PTM it was described that they would ideally like to devote about 30% of their time to "marketing." Marketing is described as researching data bases, finding companies that have interests in a given technology, and ultimately contacting these companies and negotiating an agreement. It doesn't appear that responsibility for marketing faculty services is under the purview of ORTTA.

Contacts for outlicensing technology to companies are made via a host of methods including the Licensing Executive Society (LES). LES is comprised of licensing personnel from academic institutions, representatives of business and industry, and patent attorneys.3

It appears that PTM gets involved in all sorts of things that compromise the time they have available to aggressively market University faculty technologies. This includes getting drawn into conflict of interest matters and the issues raised by the Medical School's Conflict Review Committee. Many other internal issues (some directly and others perhaps not directly) in the purview of PTM distract the time PTM staff has to really actively and aggressively go out and market AHC/University of Minnesota technologies.

In addition, the Research Support Service Taskforce was left with the clear impression that some reorganization and redefinition of responsibilities of ORTTA and PTM needs to occur. This reorganization would need to cover a broad range of activities from the whole process of filing of patents and the protecting of intellectual property, to marketing the technology and executing licensing deals or new business start ups. Associated with this, it was the Research Support Service Taskforce's view that some enhanced level of staffing to meet these responsibilities needs to be achieved in order to maximize the return derived from innovation and discovery capabilities of faculty in the AHC.

The current performance of PTM is determined by the guiding premise that quality is more important than quantity. Decisions about filing patents are influenced, primarily, by the expected or imputed value of royalties to be received for the technology. This is a very difficult task to undertake as it is a very imperfect process that we all use to predict the future value of some technology. Venture capitalists who do this for a living might not be "right" more than two out of ten times.

2.5.2 Current Performance - Sponsored Projects Administration (SPA)

Proposal Process: The budget and related materials for proposed research are generally prepared by the PI and his or her staff in concert with the sponsoring organization. SPA is notified of any subcontracts, and generally via the BA 23 (though this requires full and accurate information) of any regulatory requirements which may govern the conduct of the research including human and animal subjects protection, environmental health and safety oversight, and conflict of interest review. SPA is also notified as to whether there may be any confidential or proprietary information in the proposed research. During the proposal development phase, SPA also provides institutional oversight for cost sharing. In processing the proposal, SPA staff make attempts to respond to the sponsor's and/or University's deadlines.

Grant or Contract Award Process: During the award process, SPA is responsible for the approval of the project budget, the terms and conditions defined in the grant or contract, and for the review and approval of the research agreement and its execution. Establishing the account to be used by the faculty member for grant expenditures is initiated by SPA staff. If pre-award arrangements between the sponsor and the University are required, these are reviewed and approved by SPA staff. Institutional oversight by SPA is required in order for the PI to accept and initiate work on all new awards.

Sponsored Project Management: SPA staff expedite and approve subcontract agreements and approve materials transfer agreements. Institutional oversight is provided to determine whether purchases of materials and services are allowable, reasonable, and in accordance with the project budget. Institutional oversight is provided by SPA when mandatory cost sharing or matching must be documented. SPA approval is required when any rebudgeting of a project is requested or costs are to be transferred. SPA expedites payment of subcontractor invoices and records program income (including unexpected income). Institutional oversight and responsibility for assuring compliance with the effort certification reporting policy also rests with SPA.

Project Closure: SPA is notified of the final technical report submission and retains institutional oversight for the same. SPA staff initiate and approve the writing and submission of all project close-out reporting except financial.

In evaluating the performance of current SPA responsibilities in terms of response time, it appears performance is compromised by a staff inadequate in number to manage the volume of projects, and by the variable quality of supporting materials in applications sent to SPA. The proposal and award processes for industry-sponsored research managed by SPA in the best case will generally take several weeks and in the worst cases several months.4

SPA staff spend much of their time reviewing industry-sponsored research agreements for intellectual property and publication rights. Once reviewed, changes to the research agreements must be negotiated with the faculty member and the sponsor. This may take numerous discussions back and forth and a considerable amount of time (phone tag, etc.). Staff time is also diverted to the review of confidentiality agreements, another responsibility SPA must bear. Indirect cost recovery (ICR) negotiation (while ICR is rarely, if ever, negotiable) is an added burden for SPA staff managing industry-sponsored research. That is, companies understandably may attempt to downwardly negotiate ICR. Overall it appears that there are many competing demands that must be dealt with by SPA that are time consuming, sometimes complicated, and difficult to prioritize under the current circumstances.

2.5.3 Goals and Recommendations - Patents and Technology Marketing

The AHC is uniquely positioned to dramatically alter the current paradigm for corporate sponsored research. The University of Minnesota is searching for innovative ways to serve our constituents, bring more research dollars to faculty, and create value. Untapped synergies exist within the University that could stimulate innovative approaches for health care products and services. Industry is looking for innovative partners willing to share their vision, risks, and goals and be responsive to the inexorable pressure to move technology to the market.

To accomplish this new way of doing business, we recommend the formation of a Business Development Office as a discrete functional unit within the

Research Support Service Office . The Business Development Office would coordinate, promote and serve the AHC corporate sponsored research program. This office will report to the Research Support Service Office director, and in turn to the AHC Vice Provost for Research or to whomever may have senior responsibility for research in the AHC.

An entire section devoted to discussion of the proposed function of the Business Development Office can be found elsewhere in this document.

The AHC is not deriving its fair benefit of the royalty streams currently managed centrally. The patents and technology marketing function for the AHC is undercapitalized.

Estimating the value of a patent at its filing is very difficult, if not impossible to do. Therefore, the more patents that are filed, the more likely it is a big winner will be realized. To put this in perspective, the drug Prozac had sales in 1996 of $2.8 billion comprising some 1/3 of all of Eli Lilly's revenue. Major pharmaceutical companies don't want to develop a drug with less than $500 million in annual projected sales.

That being the case, the AHC/University should file more patents on meritorious technology. The AHC filed about 20 patents last year. To add five more per year would only cost approximately $100,000.

2.5.4 Goals and Recommendations - Sponsored Projects Administration

SPA continues to observe and meet the proposal deadlines of research sponsors that impose submission deadlines, although research sponsored by business and industry is typically not deadline driven in the same manner as that sponsored by government agencies. SPA should assure that the proposal and submission processes for industry-sponsored research are completed within 10 working days of receiving the BA 23.

SPA should identify the areas of common problems in proposals and award processes and develop guidelines, information and an appropriate information plan and management plan to attempt to obviate these problems. This information should be provided to the AHC faculty and the Research Support Service Office. SPA should provide an on-site grant administrator to the AHC Research Support Service Office (with authority to approve and sign contracts, establish CUFS accounts, and authorize purchases).

By establishing a Research Support Service Office, the AHC will support faculty in developing budgets and assuring the degree possible compliance with all regulatory requirements that may apply to their research projects. The Research Support Service Office would also provide support for faculty as a liaison with SPA through preliminary contract review and negotiation of the areas in which most problems occur: intellectual property rights, publication rights or terms and conditions, indirect cost charges, etc.

Sponsored Projects Administration and the AHC should collaborate in revising/developing a standard research agreement for industry; and language for optional sections predetermined to be acceptable to the institution from which the Research Support Service Office can choose and use as contracts are negotiated.

2.5.5 Rationale

The AHC is committed to increasing research relationships with industry in order to aid faculty in their scholarly endeavors. Increasing the number of these relationships will further burden a system currently unable to respond in the 10 working day time frame, the Research Support Service Taskforce goal for the internal proposal review and award process. Providing assistance to faculty in all aspects of the "grant process", using a standard contract (or other "pre-approved" language), and/or otherwise reviewing and pre-negotiating the contract will significantly reduce SPA review and approval time. A close relationship between faculty and the Research Support Service Office (in both proximity and understanding of shared goals and objectives) will reduce errors and the overall time needed to negotiate contract changes. A Research Support Service Office-based SPA grant administrator with authority to approve contracts and establish CUFS accounts will assure that the proposal and award associated processes occur within the stated desired performance goal of no more than 10 working days.

2.5.6 For More Information

ORTTA Home Page ---- http://www.ortta.umn.edu

1See Business Development section for a thorough discussion of PTM.

2Roles and Responsibilities Document for Sponsored Research Program Management - 11/15/96.

3RSSO Meeting minutes 11/11/96.

4RSSO Meeting minutes 11/21/96.

2.6 Department of Environmental Health and Safety1

The Department of Environmental Health and Safety (DEHS) provides programs to protect the health and safety of all people on University campuses and works to assure compliance with applicable federal, state and local codes and regulations. DEHS is comprised of nearly 70 professional, technical, service, and student employees providing service to support University activities statewide. The Director of DEHS reports to the Assistant Vice President for Campus Health and Safety.

The overall application of regulatory authority regarding environmental health and safety has increased in general in society and also in academic settings. Some granting agencies require certification of compliance with environmental health and safety regulations at the time of application. Occasionally, depending on the nature of the research work, environmental permits for research may be required prior to award. Fines and criminal penalties assessed against research institutions found to have been out of compliance with environmental health and safety regulations have ranged as high as $1,000,000. There has been greater and greater enforcement and consequences for breaching environmental regulations and we can only anticipate this growing will be growing in the future.

Some of the federal, state, and local regulatory agencies involved with environmental health and safety are: the Occupational Safety and Health Administration (OSHA), Minnesota Occupational Safety and Health Administration (MnOSHA), Environmental Protection Agency (EPA), Minnesota

Pollution Control Agency (MPCA), Nuclear Regulatory Commission (NRC), Department of Transportation (DOT), Minnesota Department of Transportation (MnDOT), and metropolitan counties.

The general regulatory requirements of each agency include documented training of personnel, records retention, labeling, and incident reporting. Specific regulatory requirements exist for hazards often present in academic research settings including among other things: chemical, radioactive, biological, and physical.

2.6.1. Current Performance2

DEHS staff members assist academic units by establishing standards, interpreting regulations, reporting on compliance, providing technical services, recommending corrective actions and providing training resources. With respect to research, the goal of DEHS is to assure that research is carried out in a way that protects everyone within the University community; prevents accidents and minimizes exposure to hazardous agents and conditions; prevents degradation of the environment through responsible waste management and active waste reduction; conserves resources and minimizes losses; and achieves regulatory compliance.

Research involving recombinant DNA or other biological hazards; ionizing or nonionizing radiation; highly toxic, flammable or reactive chemicals; or known or suspected carcinogens must be reported on the Application for External Research, Training or Public Service Support (University of Minnesota BA 23 form).

Research applications that involve the use of recombinant DNA or other biological hazards (infectious agents and toxins) are reviewed by the Institutional Biosafety Committee (IBC). Investigators are required to file an application and description of the proposed research with the Biosafety Officer. Most applications can be reviewed and approved by the Biosafety Officer, but in cases in which he/she cannot, the IBC reviews all applications for which the Biosafety Officer requests recommendation from the full committee. The Vice President for Research is the institutional authority for implementing the Regents' Policy on the Use of Recombinant DNA and other Biological Hazards.

The Radiation Protection Division of DEHS is responsible for assuring certification of research laboratories in which radioactive materials are used. Approximately 400 University laboratories (>200 in the AHC) are certified. A Radiation Protection Division database assists in record keeping of certification, isotope inventory, and waste management. The Radiation Protection Division review committee is appointed by the University President.

The management of hazardous chemical use or of known carcinogens in research is not reviewed by any institutional oversight committee. Research investigators are often not aware of regulations related to the use and management of hazardous chemicals. Departments using hazardous chemicals are supposed to have developed and implemented a "chemical hygiene plan". Anecdotal experience would suggest that this may be performed at a variable level throughout the institution. Departments found to be out of compliance with the regulations regarding the management of hazardous chemicals are required to pay any fines assessed. Given the financial circumstances of various units, there may be little ability of a department to pay these fines. Thus, the charges or perhaps other penalties for mishandling of hazardous chemicals would revert to a college, or higher level. Therefore, there is considerable liability for the institution and individuals in administrative positions.

2.6.2 Goals and Recommendations

The Department of Environmental Health and Safety embodies the University's commitment to provide a safe and healthful environment for all students, faculty, staff, patients, and visitors. The DEHS commitment to service, and to the idea that assuring compliance with a vast array of complex regulations is best achieved through providing service, support and assistance, is evident and could serve as a model for other parts of the University.

The Research Support Service Office will assist DEHS faculty and research investigators in identifying hazards for which specific approval must be applied. To best perform their function, the Research Support Service Managers should enroll in all of the training courses provided by DEHS so as to be alert to these issues.

The AHC should develop a network of contacts between DEHS, the AHC, departments, lab safety officers, and lab techs to assure safety and compliance information is widely distributed. Information should travel both directions in this network that is back and forth between EHS and the research community.

The AHC should develop a PI, laboratory and laboratory staff certification program and database. BA 23s for research involving any of the regulated hazards should not be signed without evidence of laboratory and PI certification. Likewise, the AHC should require DEHS training for new faculty, staff, and students who plan to conduct or participate in laboratory research; and have some mechanism for updating and on some routine basis (i.e., yearly) do an inventory of all employees and students to pick up any who may have "fallen through the cracks."

The AHC should require and monitor the development, implementation, and compliance with a Chemical Hygiene Plan in all AHC schools.

2.6.3 Rationale

The Research Support Service Office can assist faculty research investigators and the DEHS by identifying research involving hazards regulated by DEHS. By identifying these hazards as early as possible in the project application process, the principal and associate investigators and DEHS will have time to prepare for management of the research hazard without delay. Since Research Support Service Managers will be dealing with these issues on a daily basis, it is likely that they will be better prepared to identify hazards and assist with DEHS applications after taking DEHS training courses.

The rationale for development of Chemical Hygiene Plans, research certification courses, and communication networks is that the protection of faculty, staff, and students, and overall institutional compliance can best be achieved through support and training.

2.6.4 For More Information

BA 23 - Application for External Research, Training or Public Service Support

University of Minnesota Regents' Policy on Research Involving Recombinant DNA and Hazardous Biological Materials

University of Minnesota Institutional Biosafety Committee Applications:

Artificial Gene Transfer and Recombinant DNA Form
Biological Toxin Usage Form
Infectious Agent Usage Form

University of Minnesota Radiation Protection Division

Application for the Possession and Use of Radioactive Materials Guide

1Environmental Health and Safety Brochure (6/96)

2RSSO Meeting Minutes 11/1/96

2.7 General Clinical Research Center

The General Clinical Research Center (GCRC) is supported by NIH funding in the amount of approximately $2.6 million yearly. The GCRC operates out of the Medical School Dean's Office with the Associate Dean for Research Dr. James White as the PI on this grant. Dr. Paul Robertson is the Director of the GCRC. This grant supports salaries of the GCRC staff, which includes a portion of the director's salary; the associate director's salary, nursing staff, administrative staff, dietitians, space, cooks, and professional support (see organizational chart). Among the personnel and facilities located in the GCRC are: dietary kitchen/staff, a statistician, an administrative core, nurses, and laboratories that are open 24 hours, 7 days each week. The GCRC is funded by the NIH grant for 7-8 beds daily but has 14 beds and 2 outpatient rooms assigned by the hospital.

2.7.1 Current Performance

The process for a faculty member submitting and gaining approval for a clinical trial submitted to use the GCRC is generally more or less as follows:

- The Director of GCRC typically gets contacted by the research investigator interested in using the GCRC.
- The Director of GCRC has the faculty member call Patrice Schaus, Director of the administrative core to get an application for submission, which is generally furnished via mail.
- After forms are completed by the faculty member/investigator they are copied (original + 25 copies) and delivered to the scientific advisory committee of the GCRC.
- The GCRC biostatistician reviews the proposals before the scientific advisory committee meets (the fourth Monday of every month) and gives suggestions and comments to the committee. (There may be times that not much time or any time is provided for this review by a biostatistician.)
- At the committee meeting the proposal is either approved or tabled.
- If the submission is tabled by the committee it is usually returned to the clinical investigator. The most common reasons for a proposal to be tabled are: because the GCRC form was not completed correctly, or the GCRC biostatistician was not consulted and there may need to be some design changes. Generally, a letter is sent to the clinical investigator requesting more information. The faculty member's response may satisfy the committee's stipulations, in which case the study can be approved by the director without full committee review. If there are more complex issues involved, at the director's discretion, the committee may need to meet to review responses.
- The average time it takes for approval of a protocol or study is 2 - 3 months; however, it may range beyond this.

The Director of the GCRC, Dr. Robertson, is concerned that the GCRC is not being used like it should. In meeting with the Research Support Service Office Taskforce, Dr. Robertson expressed the following concerns:

- The GCRC doesn't see more than 5% of the clinical research proposals or protocols of the institution since the committee reviews only 4-5 proposals/month.
- Many faculty are not well aware of what the GCRC can do for them and need to be better informed. Dr. Robertson does visit with Deans and some Department heads annually to "market" the GCRC and inform them of the GCRC capabilities but numerous heads and other senior clinical researchers are pretty much in the dark about the GCRC.
- It is increasingly difficult for University investigators to find funding for the types of clinical investigations the GCRC is intended to serve.
- That research investigators submitting studies should use the GCRC biostatistician before the proposal submission to optimize study design and thereby improve the likelihood of obtaining quick approval.
- The location of the GCRC and even physical condition are suboptimal.
- The cost to use GCRC for a trial might be high.

There are various economic base charges for patient care in the GCRC. The current cost categories for using beds in the GCRC are as follows: (per Dr. Robertson):

- Basic Research Day ("A" rate) - This GCRC patient stay is gratis to investigator and patient for routine studies.
- Medical Care Day ("B" rate) - This rate is for non-research related stays where any diagnostic procedure or treatment is done. The patient's insurance coverage must pay for this GCRC stay, i.e., "daily hospital rate".
- The "C" rate is charged for patients boarded in the GCRC because the hospital is overloaded.
- The "D" rate is designated for pharmaceutical, company sponsored Research - not investigator initiated research. These charges are paid by the

investigator and the sponsor of the study.

A disadvantage for faculty clinical investigators involved with industry-sponsored research is the daily rate for D days ($725). The rate is not competitive with other Drug Evaluation Units or Clinical Trial Units; therefore, most industry sponsors are not willing to pay this rate. Dr. Robertson stated that if the Medical School can retain the second floor of Masonic Hospital then perhaps the GCRC can fix rates much lower than the hospital fixed rate of $725. (However, in order to assure this, it would need to be cost accounted out.) On the surface, it seems as a free standing unit from Fairview University Medical Center that costs would be higher not lower.

In relation to compliance, the GCRC offers regulatory compliance service on each project. Suzanne Ganzhorn-Kotula, GCRC Nurse Manager, stated that the nurse involves the PI in the consent signing process with the patient. Additional attention to compliance matters is evident in that if a protocol deviation occurs, Dr. Robertson will contact the PI and make sure the proper changes are made both internally at the GCRC and that the IRB is informed. It is important to note that a major focus of the GCRC is patient protection.

Other than the obvious, there seem to be incentives for clinical investigators to use the GCRC:

- Nurse staff to assist and provide research support for the PI,
- Nurses to educate patients and form a partnership with the PI,
- Biostatistics support.

Dr. Robertson stated that he believed there were also disincentives to using the GCRC including, among others:

- Location (2nd floor Masonic Cancer Center),
- Older building and equipment
- Distance for the PI to travel from their normal or routine locale

2.7.2 Goals and Recommendations

Dr. Robertson and the Research Support Service Office committee discussed what has occurred at other institutions with respect to clinical trials coordinating centers and units and the potential for corporate sponsored research. A number of very superior and capable institutions have actively developed and marketed their clinical trials capabilities. Some examples include Duke, Massachusetts General, and Alabama, to name a few.

The Research Support Service Office work group raised the possibility of a clinical trials coordinating center, a "virtual" clinical trials unit and a "virtual" clinical research unit that wasn't necessarily fixed in one location, but was more a multifunctional group of health professionals who could deliver a desired outcome at various clinical settings. This appeared all the more important given the merger of University and Fairview hospitals and the multiple clinical sites within the Fairview System.

The potential benefits of integrating the GCRC with a Clinical Trials Unit (CTU) and Clinical Trials Coordinating Center were discussed. Some of these potential benefits are:

- The structure of the nursing staff for clinical trials and the GCRC under this concept could continue if the staff was unified and reported to one Director,
- Better facilities would be available and they would be part of the overall clinical services of the medical complex,
- Leveraging of personnel and capabilities across the organization could occur,
- A more aggressive and comprehensive marketing plan of our capabilities could be pursued,
- Nurse skills needed in a clinical trials unit are scientifically and detail oriented and could be applied in the optimal fashion,
- The clinical trials coordinating center could develop clinical trial coordinators who do non-patient care so that nurses have more time to work on clinical research and patient care.

These clinical trials coordinators would work with the PI and could provide non-patient care assistance to faculty involved in trials anywhere in the institution e.g., GCRC, the Cancer Center, or for other clinical trials and work on among other things:

- The paperwork/case report forms for trials,
- Compliance matters, and
- Data management.

The potential disadvantages of integrating the GCRC with a clinical trials unit discussed were:

- There might be financial pressures that would change the environment of or the current GCRC mentality to one of "money driven science"; however, the Research Support Service Taskforce felt that most research relies on money and that while the sanctimony of the GCRC's mission should be respected the fiscal realities and opportunities of doing corporate sponsored research should be recognized.

- There is some possibility of destroying the nature of the General Clinical Research Center, but it's difficult to see how this might occur.

- Dr. Robertson raised the point that NIH dollars would have to remain separate. Therefore, a separate administrative staff would be necessary for the two units. The Research Support Service Taskforce is not certain of this and believes there should be a way to do keep the funds flow and accounting separate without a major problem.

- There is no space currently assigned for a corporate sponsor's data auditors, and this would have to be found if a clinical trials unit/GCRC were formed.

A functional depiction of how a clinical trials coordinating center and clinical trials unit would work with other units doing clinical trials is shown in the figure below.

The potential utility of an overarching coordination of clinical trials in the AHC was suggested in considering the potential relationship of the GCRC and the Cancer Center with a clinical trials unit. As do trials in the GCRC, the Cancer Center must now also have a protocol review function in addition to the review

processes of all clinical trials that don't fall under the purview of either group.

This suggests the need for a Clinical Trials Coordinating Center to oversee and provide a coordinating function for all review processes.

The clinical trials coordinating center would:

- provide administrative support in consolidating review processes
- assist with compliance
- assist in marketing of clinical trials capability of faculty
- support biostatistics
- negotiate the most favorable arrangements for hospital beds and services

The GCRC would:

- provide a group of highly trained research nurses
- provide a host or other care/study functions such as dietary, etc.
- review study protocols for "fit" with the GCRC mission

The Cancer Center would:

- provide this advice and input to guide clinical trials on patients with cancer

2.7.3 Rationale

It would be very helpful to clinical investigators to have as much assistance as possible in proposing securing funds for performing clinical trials. This would also assist sponsors. This would enhance and facilitate the ability of faculty to perform their scholarly work, and train residents, fellows and students thereby benefiting their academic performance; and would facilitate, enhance, and promote faculty abilities to obtain external support for such studies.

The facilities would include research rooms and beds, perhaps anywhere in the institution, for comfortably taking care of subjects during clinical trials. Specialized research nursing and technical staff would be available to administer study protocols, perform minor procedures (blood pressure, blood drawing), subject specimen and data handling, and other research related tasks.

A clinical trials unit must be a service to faculty investigators, in all ways needed to assist in the successful conduct of each study. The cost of this service, in conjunction with the direct costs to cover the expenses of each study, must not exceed market pricing overall.

There are other advantages of the Research Support Services Office working with a clinical trials unit and clinical trials coordinating center:

- The Research Support Service Office would promote these capabilities outside of the institution and market this organization.
- The Research Support Service Office would help develop a survey of faculty to determine their needs and determine their satisfaction with these activities.
- In an overarching clinical trials Unit, clinical services and lab functions could be bundled, consolidated and negotiated internally to obtain the best price, or outsourced to obtain the best price and the best service to make us more competitive and/or more profitable.

2.8 Ongoing Compliance with Research Regulations

Institutional oversight committees are responsible for assuring compliance with federal, state, and local regulations, guidelines, and standards that govern the conduct of sponsored research. These committees include: the Institutional Review Board: Human Subjects Committee (IRB); the Institutional Animal Care and Use Committee (IACUC); the Department of Environmental Health and Safety (DEHS); and the Conflict Review Committee (CRC)1. Additional review and compliance committees are in place to review research protocols to be conducted in the National Institutes of Health sponsored research facilities in the AHC including: the General Clinical Research Center (GCRC) and the Cancer Center.

Each of these institutional committees has review and approval authority independent of the other institutional committees. As research proposals and applications are prepared, and after projects are approved, each clinical investigator is expected to be fully aware of and to comply with the myriad of regulations that guide the conduct of research. They are expected to do so when there are changes in their research, research protocols, or if there are other changes that affect these broad areas of compliance.

The federal and local agencies that govern the use of human and animal subjects, environmental health and safety issues, and the review of conflict of interest are provided in the appendices to this document.

Locally, the Vice President for Research and Dean of the Graduate School (VPRDGS) is the responsible authority for promoting research ethics and assuring regulatory compliance. A Director of Research Ethics and Regulatory Compliance position in the office of the VPRDGS has recently been created. The IRB and IACUC (which comprise the Subjects Protection Programs office) report to this office. The VPRDGS also bears institutional responsibility for assuring compliance with the conflict of interest policy, and biological safety policy on the use of recombinant DNA. The Department of Environmental Health and Safety otherwise reports to the Assistant Vice President for Campus Health and Safety.

Policies regarding scientific integrity and misconduct in research (academic misconduct) have been developed at the federal level by the Office of Research Integrity and have been adopted locally by the VPRDGS. It is not evident that the University of Minnesota has a committee review and approval process nor quality assurance monitoring program in place with respect to scientific integrity and misconduct in research; if it does it is not widely known. However, the University of Minnesota Board of Regents' Policy on Academic Misconduct does delineate the procedures for responding to allegations of scientific misconduct.

2.8.1. Current Performance of Compliance Functions

Monitoring compliance with most regulations governing research is currently limited to that provided in the review processes of University of Minnesota

regulatory committees prior to approval of a research study.

2.8.11 Subjects Protection Programs : Human Subjects (IRB) and Institutional Animal Care and Use Committee (IACUC)

Protection of subjects compliance monitoring activities are currently limited to collection of information regarding the proposed research in the application process, review of this information by local committees, and annual review of human subjects research by the IRB. Review committees must apply federal regulations, guidelines, and community standards before any research project involving human or animal subjects, regardless of funding source, is approved. Many investigators are relatively unaware of the regulations, guidelines, and community standards by which their proposed research will be judged. Except in a very few cases, the minimum length of time it takes to receive IRB approval is about 45 days; often times it can take considerably more time. IACUC approval can usually be obtained in approximately 30 days.

If the proposed research is approved by either of these committees, researchers must independently become aware of and then apply federal regulations and guidelines as the research is conducted. The only local mechanism for providing ongoing information on human subjects use or use of animals, is through a subjects protection programs column that appears each month in the ORTTA publication - *Research Review*. The Subjects Protection Programs office collates these columns approximately annually, and provides the document to investigators as a local guide to subjects protection programs.

2.8.12 Department of Environmental Health and Safety (DEHS)

The DEHS is committed to providing a service to researchers within their overall responsibility for protecting health and safety on an institution-wide basis This department provides assistance, training, and support to all researchers within the institution. Faculty and their research colleagues are often not fully aware of the additional compliance measures they may be required to take if their proposed research includes activity regulated by DEHS. This lack of awareness can result in delays in processing a grant and frustrations for the PI that could be avoided by early actions in the process to assist the investigator. Principal investigators are expected to know, and to comply with, DEHS regulations as the research project is conducted and to continue to do so if there are changes in research work.

2.8.13 Conflict Review Committee (CRC)

The CRC has expanded its authority in assuring compliance with National Institutes of Health and National Science Foundation regulation regarding Objectivity in Research and Investigatory Financial Disclosure Policy. The CRC has also evolved its own oftentimes unduly restrictive notion of the propriety of and conditions for corporate sponsored research. The expanded authority assumed by the CRC is beyond anything it was intended to do and was not instituted via any directive. Among other things, this expanded scope includes: review and approval of budgets, determination of whether sufficient resources are available, how a potential research services organization might function and a host of things that have nothing to do with true conflict of interest resolution. The institution has placed responsibility for review and approval of budgets and research agreements with SPA in ORTTA2, not with the CRC.

The CRC currently requires that any potential conflict of interest be eliminated before a faculty member enters into an industry-sponsored research agreement. This requirement has made the AHC extremely difficult to deal with and is a source for derision of the Medical School by the local business community. In numerous venues locally, the University is vilified for its occasionally obstructive actions in dealing with industry sponsors. Federal regulation and Regents' Policy on Conflict of Interest allow some categories of potential conflict of interest to be managed. It should also be noted that the FDA expressly allows for conflicts of interest to exist as long as they are disclosed. The FDA even recognizes that there will be situations in which an individual may have stock in or a consulting relationship with a company for which that the individual is doing a trial. It does not seem reasonable to require that all potential conflicts of interest be eliminated.

It is the unequivocal conclusion of the Research Support Service Office Taskforce that the CRC has unnecessarily delayed, duplicated, and confused the research application process through the excessively expanded authority it has assumed.

The average length of time it takes to receive CRC approval is approximately one month. That is because most grants are processed without any real conflict of interest concerns. However, in cases where there is some perceived conflict it may take many months and numerous meetings and conversations. In more than a few cases, proposals may be tabled indefinitely.

Compliance monitoring of conflict of interest issues post-CRC approval is conducted by the faculty member's department head.

2.8.14 Scientific and Scholarly Advisory Board

This board functions on an institution-wide basis. Allegations of scientific misconduct at the University of Minnesota, if they occur, are not made widely known. No information is available by which to judge the adequacy of local management of policies and procedures for responding to these allegations.

2.8.15 The General Clinical Research Center (GCRC)

The GCRC reviews, primarily for scientific merit, protocols for all research conducted in this inpatient and outpatient research facility regardless of funding source. The GCRC views industry-sponsored research in a less positive way than it does other sponsored research, in part, because the GCRC has obligations to fulfill in order to maintain its NIH funding. It is often difficult for clinical research investigators to obtain approval for industry-sponsored research protocols from the GCRC review committee.

The GCRC review committee often requires changes in protocols that have already been approved by the Food and Drug Administration (FDA) through application by the industry sponsor. This usually means that the research cannot be conducted at the GCRC. Corporate sponsors will seldom if ever agree to making protocol amendments at the request of individual centers, particularly in the case of a product that has proceeded to multi-center trials. Any protocol amendments that might be requested or needed result in long delays because of the need to apply for and receive FDA approval for such changes. The average length of time it takes to receive approval from the GCRC is 2 - 3 months. As stated in the GCRC section of this document, the Director of the GCRC monitors investigator compliance with the protocol and with regulations regarding the use of human subjects.3 However, it was uncertain as to precisely how this is done.

2.8.16 Cancer Center

The Cancer Center's Protocol Review Committee (CPRC) reviews all cancer related clinical research protocols proposed to be conducted in the AHC.

Approval by this committee is required before the application may be sent to the IRB. This has been recently formed and met to review protocols for the first time December 3, 1996. The expected length of time required to obtain approval from the CPRC is 30 - 45 days. No other information about the ongoing compliance function of this committee is available at this time. Coordination of the CPRC with the Research Support Service Office and Clinical Trials Coordinating Center, and the need to have 10 day turnaround, will present a challenge.

2.8.2 Goals and Recommendations

In general, but not always (e.g., IRB) many of the oversight functions of the various compliance committees are largely at the "front end," when a grant or contract is being submitted to seek approval. Often there is little to no ongoing monitoring. This is an unacceptable situation. In many cases there may be changes in circumstances that require compliance review. Because of this and the exposure of the institution, provision of monitors who could spot check ongoing compliance would benefit the institution.

The AHC should continue to provide support and information in the form of educational programs for investigators, in conjunction with electronic or other updates, to assure to the best degree possible that they are aware of the regulations. The AHC should also develop an explicit plan to monitor compliance with all regulations and policies.

The Vice President for Academic Affairs, has a policy on how public or confidential alleged scientific misconduct should be handled. A Good Scientific Practices document should be written and adopted to guide the conduct of research for faculty, staff, and students.

The desired performance with respect to management and scope of research review and approval processes is outlined in the sections of this document devoted to each committee.

2.8.21 Subjects Protection Programs

Research investigator compliance with regulations governing the use of human and animal subjects in research must be assured. The Subjects Protection Programs office must play a role in the development of an ongoing compliance review/quality assurance program to protect human subjects, investigators, and the institution. This compliance function is especially critical in research activities not regulated by the FDA. FDA regulated clinical trials are monitored frequently by sponsors to assure compliance with human subjects regulations. The institution should also monitor compliance with human subjects regulations, in order to protect itself, PIs and other employees, particularly for research not otherwise monitored by pharmaceutical companies or contract research organizations. This is the case with most NIH or department-sponsored clinical research.

2.8.22 Department of Environmental Health and Safety (DEHS)

DEHS should continue their service oriented approach to assuring compliance in the research project review and approval processes. DEHS should continue to provide and facilitate training for local (departmental, collegiate, or provostial unit) faculty, students and staff to assure the consistent application of and good compliance with research-related DEHS regulations institution-wide.

Departments, colleges/schools, and provostial units (or whatever might take their place) should assume greater local responsibility for protecting their interests and those of the institution in complying with DEHS regulations. An individual in each college/school should be identified as the designated responsible party for DEHS compliance. They probably should be paid for doing this.

2.8.23 Conflict Review Committee (CRC)

The Conflict Review Committee is not charged to perform ongoing compliance functions. Changes in PI's business relationships during the course of a study may necessitate further review by the CRC but this is not well understood by faculty.

2.8.24 Scientific and Scholarly Advisory Board

The institution has an obligation to protect the rights of the complainant and the respondent in cases of alleged scientific/academic misconduct. The institution also has a responsibility to educate, train, and encourage faculty, staff, and students to consider the rights and privileges with which they have been entrusted, the consequences for breaching that trust, and the processes for determining whether actual misconduct has occurred. Information sufficient to increase awareness of the institutional community should be provided to everybody on an ongoing basis. When cases of scientific/academic misconduct are alleged or found to have occurred, locally and nationally the circumstances involved in these might be used as "case studies" to increase the knowledge base of faculty and staff.

2.8.25 GCRC

The Director and staff of the GCRC should continue to monitor investigator compliance with research regulations for human subjects admitted to this facility. To do this effectively, however, they must coordinate this activity with Subjects Protection Programs.

2.8.26 Cancer Center

Ongoing compliance monitoring may not be a part of the Cancer Center Protocol Review Committee responsibilities, therefore this should be provided for by other means.

2.8.3. Rationale

Potential non-compliance with protection of subjects regulations places the institution and its employees at significant risk, but most importantly, the humans or animals involved. A plan for achieving and monitoring compliance needs to be developed and, once clearly defined, adopted. Random review or audits by compliance review staff would increase the attention to these regulations institution-wide.

Assistance to faculty and other research investigators during the protocol review and approval processes will bring specific compliance issues to their attention before the project begins. By virtue of the Research Service Office's actions, the quality of applications, research plans, and compliance will be improved and will benefit science, patients, PIs and the institution.

Requiring each college/school to assure compliance with DEHS regulations should improve awareness of the need for compliance and assist DEHS.

Assistance to faculty and other research investigators in identifying areas of their research to which DEHS regulations apply early in the proposal review and approval process will avoid delays which may have occurred in the past if such a review had been postponed. As with subjects protection programs regulations, if a plan for compliance with DEHS regulations is developed and clearly explained, it is much more likely to be followed and therefore the level of compliance in the overall institution will be raised and improved. This is increasingly important as local and federal agencies have become more aggressive in prosecuting DEHS breaches imposing significant fines and sometimes even criminal sentences.

When an investigator is alleged to have erred, or found to have engaged in scientific/academic misconduct, the institution suffers. Raising the level of awareness of these matters to the University would underscore the importance. The institution should develop a readable, engaging Good Scientific Practices document to guide faculty, staff, and students in the responsible conduct of research. Cases of breaches of scientific integrity, whether here or elsewhere, could be used as case studies for faculty, staff and students.

The GCRC and IRB should cooperate in developing a compliance review program for the GCRC. The GCRC Director and staff should have all details of the IRB approved research plan to perform the most meaningful compliance reviews. This same type of thing would likely have to occur with patients entered under the Cancer Center protocol reviews.

2.8.4 For More Information

Food and Drug Administration Information Sheets ---- http://www.fda.gov/oc/oha/toc.html

FDA Code of Federal Regulations ---- http://law.house.gov/cfr.htm
(21 CFR Parts 50, 56, 312,361, 511,514, 571, 812, 813)

Federal Register ---- http://lay.house.gov/7.htm

Docket No. 93N-0445
Objectivity in Research (Volume 60, Number 132)
Investigator Financial Disclosure Policy (Volume 60, Number 132)
Financial Disclosure by Clinical Investigators (Volume 61, No. 44)
Frequently Asked Questions.....(Volume 61, Number 129)
Protection of Subjects (Volume 61, Number 192)

Board of Regents' Policy: Conflict of Interest ---- http://www.fdp.finop.umn.edu

Office of Research Integrity

http://www.os.dhhs.gov/phs/ori/policy/policy.html

Advisory Document: Model Policy and Procedures for Responding to Allegations of Scientific Misconduct - April 1995

University of Minnesota ---- http://www.nih.gov/grants/oprr/oprr.htm

OPRR Animal Care Guidebook http://www/nih.gov:80/grants/oprr/library_animal.htm

NIH Policy for GCRCs

NCI Policy for Cancer Centers

Integrity and Misconduct in Research ---- http://law.house.gov/7.htm (Report of the Commission on Research Integrity)

University of Minnesota Subjects Protection Programs Homepage

1See sections Subjects Protection Programs, Assuring Scientific Integrity, Biohazards and Other Health and Safety, and Clinical Research Center.

2Roles and Responsibilities Document for Sponsored Research Program Management - Draft 11/15/96.

3RSSO Meeting Minutes - 11/11/96.

FEEDBACK

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