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EVALUATION OF THE SYSTEMATIC CLINICAL TRIALS PROTOCOL APPROVAL PROCESS AT A MATRIX CANCER CENTER

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EVALUATION OF THE SYSTEMATIC CLINICAL TRIALS PROTOCOL APPROVAL PROCESS AT A MATRIX CANCER CENTER

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By

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CHAPTER I

INTRODUCTION

The National Cancer Institute (NCI) estimates that approximately 555,550 people die of cancer each year in the United States. This is an average of a little more than 1,500 people per day and ranks cancer as the second leading cause of death behind heart disease.[1] In 2007, an astonishing 1,444,920 new cancer cases are anticipated to be diagnosed.[2] It is through scientific research and the necessary employment of clinical trials that advances are made to fight this dreadful disease.

A breakthrough or advancement made in the treatment of cancer begins with basic research of cells and tissues in the laboratory. Once a particular treatment or technique is developed, and proven to be successful in animal models, it can then be evaluated in people through clinical trials. Clinical trials follow a rigorous scientific process to answer specific questions relating to the newly developed therapy or technique. A clinical trial is the only mechanism to determine the true effectiveness of a promising new therapeutic being investigated.[1] Thus, any unnecessary delays in approving a clinical trial protocol increases the time before that trial can begin enrolling patients and therefore gain approval for new treatment options.

The International Conference of Harmonization Good Clinical Practice (ICH GCP) guidance document defines a protocol as "a document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial." The ICH

GCP further goes on to describe that the protocol gives the rationale and background for a trial. The World Health Organization's (WHO) Handbook for Good Clinical Research Practice states that "the study protocol is the core document communicating trial requirements to all parties who have responsibility for approval, conduct, oversight, and analysis of the research." Thus, before any trial can begin accruing patients, its protocol, along with a study's informed consent, must be thoroughly reviewed and approved by a network of entities to ensure that a study's protocol outlines a trial that is safe and effective.

A recent study conducted at the Vanderbilt-Ingram Cancer Center (VICC) and at VICC Affiliate Network (VICCAN) sites indicated that two particular processes took longer than all others involved in their clinical trial protocol approval process. These two particular processes were the Scientific Review Committee review process and the Contracts and Grants approval process.[3] This was contrary to what the authors expected, in that, they believed the IRB review and approval process would take the longest. Many of the challenges reported by the authors of the study at the VICC parallel those encountered in the protocol approval process at UT Southwestern. A closer examination of these parameters is needed.

The Harold C. Simmons Comprehensive Cancer Center (SCCC) at UT Southwestern Medical Center is a matrix cancer center and relies upon the interactions between other institutions and departments to conduct all phases of its cancer research. Thus, the processes involved in approving a clinical trial protocol also rely upon the interactions between other institutions and departments. This is where many challenges and various

institutional administrative barriers arise. Therefore, it is the goal of this practicum report to formally evaluate and document the protocol approval process at the SCCC at UT Southwestern. The report will also identify unwarranted time delays in the process and provide feasible resolutions to expediting the overall clinical trial protocol approval process without compromising patient safety or research integrity. At the cessation of this report, a further analysis may be conducted using its findings to determine whether or not these time delays in approving a study protocol are consistent with approval processes encountered at other institutions and academic health center settings like the Vanderbilt-Ingram Cancer Center and the Simmons Comprehensive Cancer Center.

Table 1

Term	Abbreviation
Simmons Comprehensive Cancer Center	SCCC
Clinical Research Office	CRO*
Protocol Review and Monitoring Committee	PRMC
Institutional Review Board	IRB
Disease Oriented Team	DOT
Data Safety Monitoring Board	DSMB
Central Review Board	CRB
Western IRB	WIRB
Department of Clinical Sciences	DCS
Clinical Research Coordinator	CRC
UT Southwestern	UTSW
International Conference of Harmonization	ICH
Federalwide Assurance	FWA
Good Clinical Practice	GCP
Principal Investigator	PI
Case Report Form	CRF
Code of Federal Regulation	CFR
Serious Adverse Event	SAE
International Conference of Harmonization Good Clinical Practice	ICH GCP
World Health Organization	WHO
Vanderbilt-Ingram Cancer Center	VICC
VICC Affiliate Network	VICCAN
US Food & Drug Administration	FDA
National Cancer Institute	NCI
NCI Cancer Therapy Evaluation Program	CTEP
Clinical Trials Office	CTO
Office for Human Research Protections	OHRP
Department of Health & Human Services	DHHS
Radiation Safety Committee	RSC
Sub-Committee for Human Use of Radiation	SHUR
Radiation Drug Research Committee	RDRC
Research Compliance Committee	RCC
University Hospitals	UH
Parkland Health & Hospital System	PHHS

Institutional Abbreviation (Not Contract Research Organization)

CHAPTER II

THE PROTOCOL APPROVAL PROCESS

Background

The protocol approval process is a multifaceted and complex process that is not uniform across all institutions. Numerous steps must be taken from the time a protocol is developed to the time a clinical trial can open and start accruing patients. Thus, every institution imposes its own regulatory steps and procedures in addition to those outlined by the U.S. Food and Drug Administration (FDA). The approval process becomes even more complex and convoluted when many institutions are integrated into a matrix system like that of the SCCC at UT Southwestern.

Before a new study can begin accruing patients at the SCCC, its protocol must go through a network of approval processes under the watchful eye of the Clinical Research Office (CRO). The CRO has many functions. One of these functions is to manage new protocols from the time of their inception or receipt to the time a study opens for patient enrollment. The CRO also monitors and provides communication within the necessary departments and institutional components that play a role in the many protocol approval processes.

Clinical trials conducted at the SCCC via the CRO recruit and perform patient care at Parkland Health & Hospital System, University Hospital Zale-Lipshy, University Hospital St. Paul, the Aston Ambulatory Care Center, the Dallas VA Medical Center, Children's Medical Center, and the SCCC Seay oncology clinic. By utilizing each one of

these institutions and their resources, the SCCC can collaborate on ground-breaking discoveries that impact our basic understanding of cancer and lead to advancements in clinical care.[4] Furthermore, it is these advancements and the continual development of new cytostatic cancer therapeutics that create an even greater need for clinical trials that study these targeted therapeutic effects.[5]

Disease Oriented Team Meeting

A new study protocol begins the approval process by first being discussed at a Disease Oriented Team (DOT) meeting. Currently, the SCCC is broken up into ten disease groups. Each DOT meets once a month and is composed of medical, surgical, and radiation oncologists, basic scientists, and research coordinators. During a DOT meeting, committee members discuss trials that are currently open, adverse events, accrual, and any other study related items (see Appendix B).

Disease Groups:

- Breast
- Lung
- Gynecology Oncology
- Radiation Oncology*
- Gastrointestinal
- Gastrourinary
- Melanoma
- Brain
- Hematology Oncology
- Head and Neck

*Radiation Oncology is a treatment modality but for administrative purposes is organized like a DOT

One of the DOTs responsibilities is to review new studies and discuss each disease group's interest in the protocols. It is also determined at the DOT meeting whether or not there are currently open protocols that would compete for the same patient population. Furthermore, it is the DOTs job to consider whether or not a new study under review coincides with the future direction and current status of the disease group in upholding the overall mission of the cancer center. By this, each disease group seeks to maintain a study portfolio with a proportionate number of investigator-initiated, cooperative group, and industry sponsored studies. Investigator-initiated and cooperative group studies are the priority and are important because they can provide financial resources and access to pharmaceutical drugs for further institutional research projects.

When a study is denied DOT approval, the study's sponsor is notified as to why the study was not approved. Studies are regularly denied approval because of inadequate staffing needed to meet the demands of the new study while continuing to provide excellent care to existing research patients. It is not uncommon for a study to be denied initial DOT approval, but be approved at a later date. This often happens after a study sponsor provides more information or scientific data regarding the protocol.

Protocol Review and Monitoring Committee

Once a protocol has been approved by the appropriate DOT, it is then submitted to the Protocol Review and Monitoring Committee (PRMC) for review. Gaining the PRMCs approval is the next Cancer Center hurdle that a protocol must clear prior to Institutional Review Board (IRB) submission. It is the PRMCs job to discuss and review the scientific merit and conceptual basis of a new study protocol. This is to ensure that the study is scientifically justified and clearly described in the protocol. For a study to be scientifically justified and gain PRMC approval it must be statistically and scientifically sound in order to answer the questions the study is asking.[6]

The PRMC meets on the second Wednesday of each month to review all cancer-related protocols that are conducted at UT Southwestern, Parkland, Children's Medical Center, and the Dallas VA Medical Center. This includes all investigator-initiated, cooperative group, other peer-reviewed, and industry-sponsored cancer studies. Cancer-related clinical protocols are specifically defined by the UT Southwestern Medical Center as "Any study that includes cancer patients or their relatives, cancer prevention trials, and studies assessing epidemiologic, imaging or biological markers for early detection or risk information."

The PRMC conducts two different types of review, an administrative review and a full committee review. All studies, except cooperative group and other studies that have undergone rigorous external scientific review are subject to full committee review.[7] For example, if a study was externally reviewed by the NCI's Cancer Therapy Evaluation Program (CTEP) prior to PRMC submission then it would likely undergo an

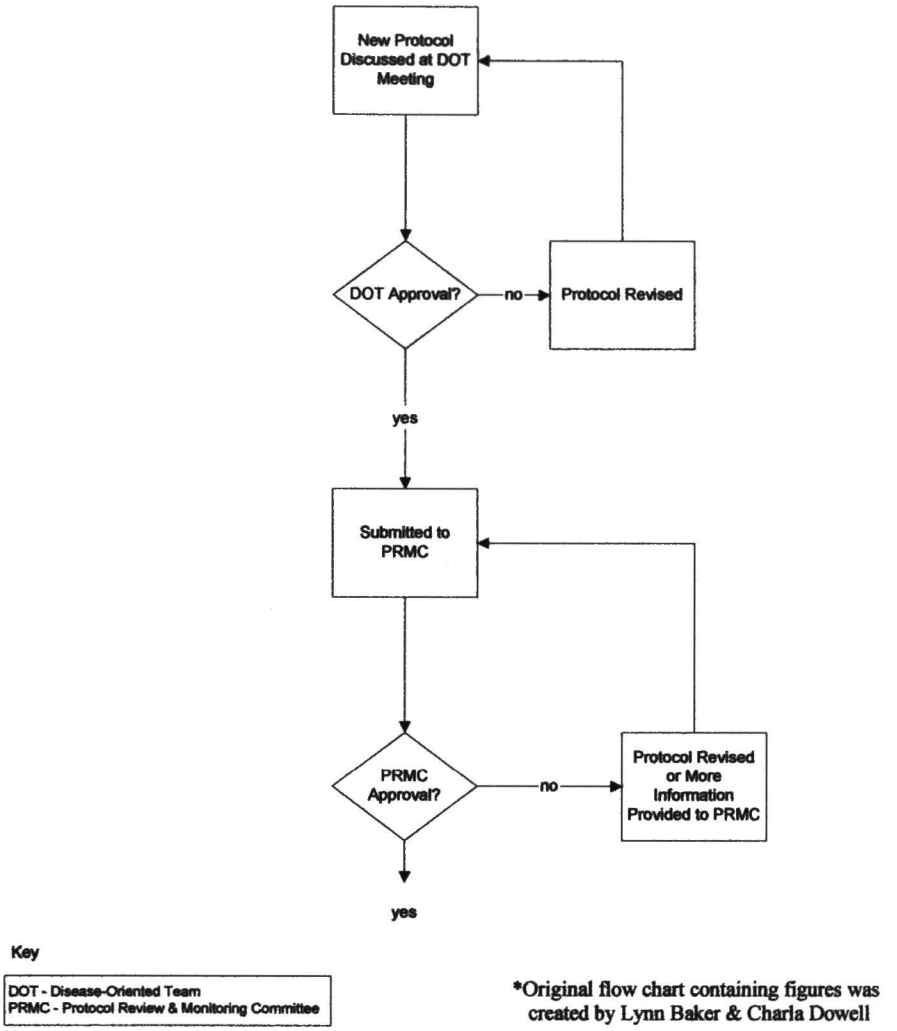
administrative review and not a full committee review. This is because protocols reviewed by CTEP are reviewed by a committee consisting of one or more oncologists, a biostatistician, a pharmacist, and a regulatory affairs professional, all of whom review protocols for scientific merit, patient safety, adequacy of regulatory and human subject protection, and any duplication of existing studies.[8] The CTEP protocol review committee is comprised of the same professional staff as UT Southwestern's PRMC. However, UT Southwestern's PRMC includes a research nurse as one of its standing members in lieu of a regulatory affairs professional.

At the end of an administrative review or a full committee review, a protocol is either approved, approved pending response, or deferred (See Appendix C). When the PRMC approves a study then no responses are required. If the PRMC approves a study pending response, then the PRMC would like for the sponsor or investigator of the trial to address some concerns or questions that the committee has about the protocol. These concerns or questions are called stipulations. Stipulations are required changes that need to be made to a study protocol within 60 days after notification.[7] A stipulation may involve something as simple as defining what is considered a "high value" during a routine blood draw. On the other hand, a stipulation may involve a more complex issue such as drug dosing or inclusion and exclusion criteria. Once all stipulations have been sufficiently answered and approved, then a study is granted PRMC approval. If stipulations are addressed and returned to the PRMC within the 60 day window, then the study is re-scheduled after all necessary information has been received for another full committee review. When the committee defers a protocol, then that protocol must be revised or

more information must be provided to the committee within 90 days. Studies that are deferred may then be re-scheduled again for full committee review if all questions and concerns as to why the study was deferred are sufficiently answered.

When a protocol is submitted to the PRMC, a resource review is conducted in parallel with the PRMC review by the CRO to ensure that adequate resources are available to effectively conduct the trial at the SCCC.[9] It must first be determined by the CRO coordinating staff that there is an adequate staffing capacity to meet the needs of the study. The research and clinical budget are then prepared and all standard of care and non-research costs are identified. A protocol is then reviewed to determine whether or not the required services and resources to conduct the study are available. For example, it must be determined if the ancillary services (laboratory, imaging, pathology), the Medical/Surgical Oncology Clinic resources, and the BMT/Malignant Hematology Clinic resources (if applicable) are available to support the study. This would include an analysis of the availability of all chemotherapy infusion areas in both clinics. Lastly, a study protocol is reviewed by a pharmacist to ensure that all pharmacy services and staff can support the study. If it is determined that the adequate resources are not available to support the study protocol, then study approval is delayed until appropriate resources are identified or the study is terminated and denied PRMC approval. If all of the adequate resources are available, then the study is granted approval by the Assistant Director of the CRO.

Figure 1



Pre-Review

Pre-review is inherently a "pre-review" to an IRB review and a consultative service provided by the Department of Clinical Sciences (DCS).[10] Pre-review documentation and the protocol are submitted to the DCS while the study is being reviewed by the PRMC for approval. However, there is no institutional or regulatory relationship

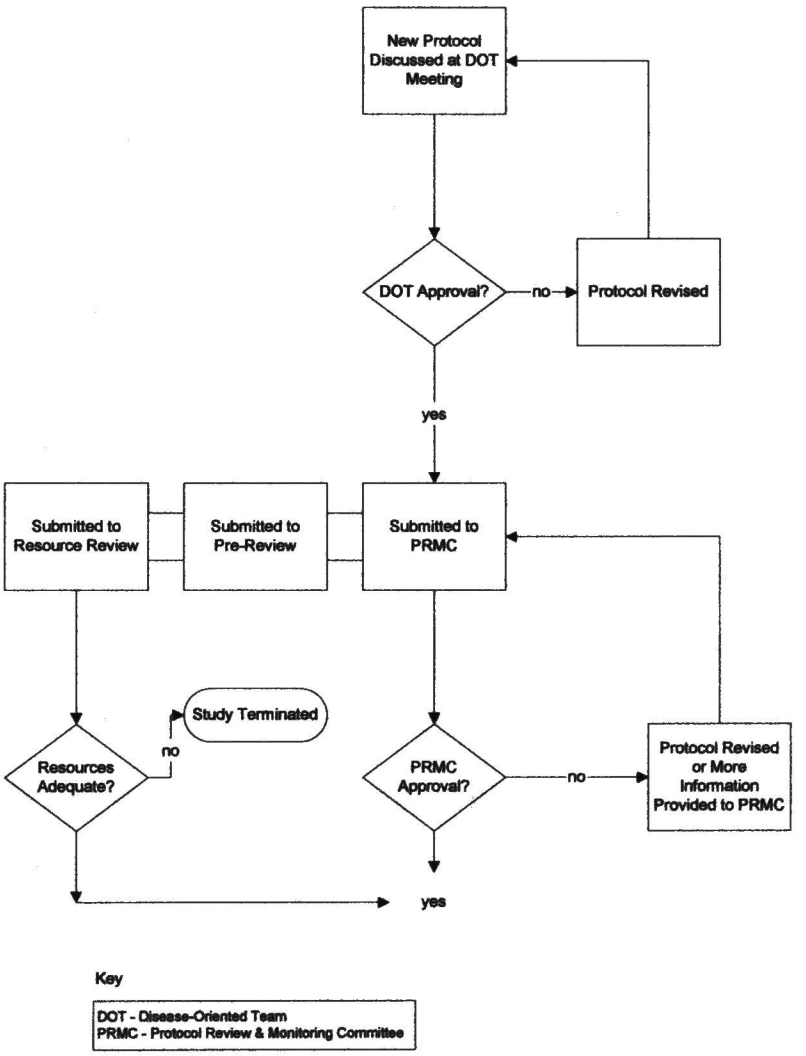
between the PRMC and pre-review. The purpose for submitting a protocol to pre-review is to allow DCS regulatory specialists to quickly look for errors that may assist investigators in preparing complete, accurate, and thorough IRB applications prior to submission for IRB full board review. [10] The entire protocol is not fully examined, but a superficial review is done to make suggested corrections and recommendations available to investigators within a few days time. This noninvasive review includes an inspection of the following:[10]

- Analysis of the research question(s)
- Background information (previous work, literature references)
- Use of a study drug or device
- Use of a placebo
- Comparison of standard of care
- Exclusion and inclusion criteria
- Recruitment procedures
- Data collection
- Safety precautions
- Risks
- Protection of confidentiality
- Biostatistical analysis
- Potential benefits

All DCS pre-review draft documents are also reviewed to assure that they have been completed correctly and that all the required information is consistently presented between all study documents. [10] Any recommendations that are made by the DCS are suggestions and not stipulations. Some, all, or none of them may be implemented at the discretion of the investigator. However, each suggestion made by the DCS should be carefully considered because the objective of each suggestion is to refine and improve the

IRB application documents so that IRB approval may be obtained in the timeliest manner. [10]

Figure 2



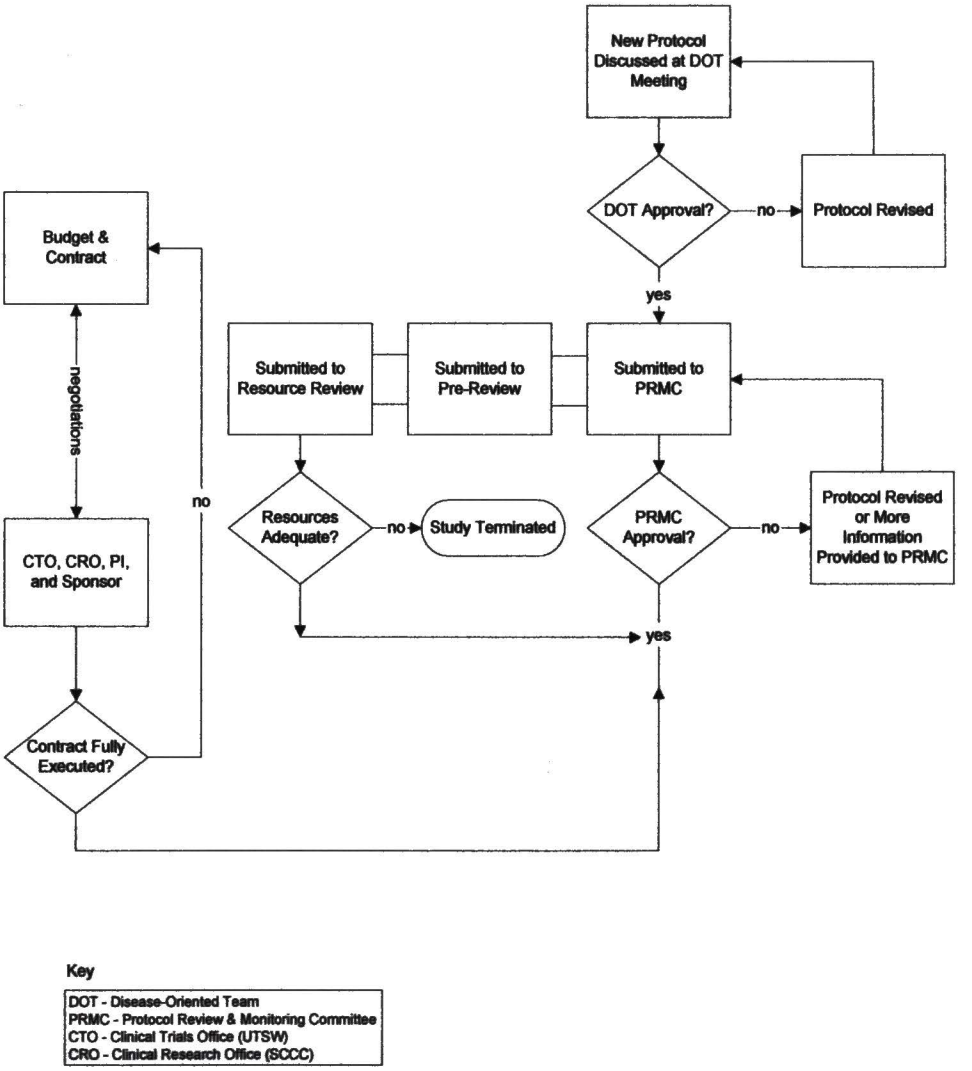
Budget and Contract

The budget and contract component of the protocol approval process exhibits a large degree of variability in its order and conduct. Some sponsors send new study budgets and contracts before any other protocol approval processes have been executed, while other sponsors complete the budget and contract process after a study has received a pre-defined level of approval (e.g. IRB, PRMC). Both the contract and budget may be approved independently. No other approval, except a study's final approval to open a clinical trial for patient enrollment, is contingent on the contract and budget approvals.

The Clinical Trials Office contract specialists, along with CRO personnel, are responsible for ensuring that each study contract is thoroughly written and covers any liability, patent and technology rights, and indemnification issues. While a contract is being prepared and gaining approval, a study's budget is concurrently prepared and negotiated. Many sponsors have a fixed budget that they deem efficient in conducting a study. However, the CRO often times finds that the sponsor's budget does not cover all research costs. Therefore, the CRO accountant performs a preliminary review and cost analysis of all potential new studies using the protocol to prepare a budget. After a budget has been prepared it is then reviewed by a research coordinator to ensure that no extraneous items were left out and the standard of care costs are separated from research-related costs. The budget is then reviewed by the clinic manager, the Revenue Cycle Manager, and the PI. Once all parties are in agreement, the CRO accountant begins the negotiations. Budget and contract negotiations can be lengthy and time-consuming,

sometimes taking months to complete before both the CRO and a sponsor can come to agreeable terms and a budget and contract are approved.

Figure 3



Institutional Review Board

Once a protocol has been approved by the PRMC, returned from the DCS pre-review, and undergone the CRO resource review, a study is then submitted to the Institutional Review Board (IRB). It is the IRBs job to ensure that the risks to human research subjects have been minimized to the greatest extent possible.[11] Making sure that any risks involved are reasonable in relation to the anticipated benefits and protecting research subjects' private health information are also responsibilities of the IRB.[11,12] The IRB approval process is the critical element in making sure that the patients' rights are protected with regard to their participation in research protocols. [13,14]

The IRB at UTSW meets every Monday and Wednesday of each month. There are four review boards that make up the IRB at UTSW. Individual boards meet once every two weeks and generally consist of 10-12 members. During an IRB meeting, members review both new research studies and conduct continuing reviews for ongoing research. Six new studies and eight continuing review studies are reviewed at each meeting. [15]

The IRB is responsible for reviewing all clinical and translational research conducted at all of the respective institutions that make up the matrix cancer center at UT Southwestern. Consequently and in accordance with the Federalwide Assurance (FWA) on file with the Department of Health and Human Services, UTSWs IRB reviews and approves research conducted at Children's Medical Center, Parkland Health and Hospital System, Texas Scottish Rite Hospital for Children, the University of Texas Southwestern Medical Center at Dallas, the Retina Foundation of the Southwest, and the Richardson Regional Medical Center. [15] The FWA is an "...assurance of compliance with the federal

regulations for the protection of human subjects in research" and is "...approved by the Office for Human Research Protections (OHRP) for all human subject research conducted or supported by the Department of Health and Human Services (HHS)."[16] The IRB must also approve any grant supported research involving humans that is conducted at the Dallas Veterans Affairs Medical Center or the Presbyterian Hospital of Dallas when the PI of the research is a faculty member at UT Southwestern.[15]

Once a study protocol is submitted, it must first be determined by the IRB if the study elicits a full board review or an expedited review. An expedited review, as outlined by 45 CFR 46.110 and 21 CFR 56.110, may be conducted when the research and any procedure involves no more than minimal risk to the research subjects. Moreover, minimal risk, as defined by 45 CFR 46.102i, means that "...the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests."[15] An IRB chair or one of the IRBs designated voting members conducts an expedited review rather than the entire twelve member IRB.[15] Expedited reviews are also periodically conducted for minor changes in approved research. For example, if a study employs a procedure that affects a study subject's mental or physical health, then the study is not eligible for expedited review.[15] This includes any surgical procedures, use of medications, radiation exposing diagnostics studies, and using DNA for DNA libraries, cells banks, and germline studies.[15] When a study involves research and procedures that are considered to be "more than minimal risk" then the study must undergo an IRB full board review. A

thorough examination of a study protocol and informed consent(s) is conducted during a full board review. As an ethics committee, IRB members debate issues and make difficult determinations that are required to ensure protection of research subjects during a full board review. [17] Stipulations are generated, similar to those generated during a PRMC review, with questions or concerns that the IRB has with a study. Stipulations arise during continuing, expedited, and full board reviews. However, full board review stipulations far out-number continuing review or expedited study stipulations and must be answered in a timely manner to move forward with the approval process.

An IRB approval of research expires after one year. [15] Studies therefore must undergo a continuing review annually and prior to the initial review expiration date. During a continuing review the IRB must determine if a study under review should remain open and if any changes have been made to the protocol or informed consent then the IRB discusses the implications of those changes and the impact they have on the protection and welfare of the research patients.

After a new study protocol is submitted to the IRB and it is determined what type of review the study must undergo, the study is then assigned to one of the four boards. Typically, studies are sent to the first available IRB meeting that is accepting studies. [15] However, there are some factors that may necessitate the study to be reviewed by a different board. For example, if a board member is an expert in a particular field of medicine that the study protocol involves, then the IRB may assign the new protocol to be reviewed at the next available time that particular board member's board accepts new studies for review. Another factor that may elicit a study to be reviewed by a different

board includes a conflict of interest with the PI or Sponsor of a study and a residing board member. In regards to continuing reviews, the date of study expiration may also determine what particular board will review that study as continuing reviews are periodically scheduled for continuing review by date of expiration. Continuing reviews are also normally assigned to the board that initially reviewed the study.

Radiation Safety

When a study protocol requires its subjects to be exposed to any ionizing radiation then it must be submitted to the Radiation Safety Committee (RSC) for review.[18] The RSC conducts a new study protocol review concurrently with the IRB. The committee's final approval is contingent upon IRB approval of the study. To oversee that radiation is safely monitored at UTSW, the RSC has assembled three separate sub-committees: the Radiation Drug Research Committee (RDRC) as mandated by 21 CFR 361.1, the Sub-Committee for Non-Human Use of Radiation in Research, and the Sub-Committee for Human Use of Radiation in Research (SHUR). It is the SHUR of the RSC that assists the IRB in reviewing new protocols that involve radiation.

Radiation exposure may occur through diagnostic X-rays, radiation therapy, nuclear medicine exams, fluoroscopy, CT, and interventional procedures.[18] When a protocol includes any of the exams listed above or the interpretation of one of the exams then it must be submitted to the RSC for review. The SHUR reviews the appropriate use, suitability, and frequency of radiation to evaluate the relative risks of the radiation against

the potential benefits. [18] The radiation risk statement in the informed consent is also evaluated to ensure relevance and accuracy.

Compliance Committees

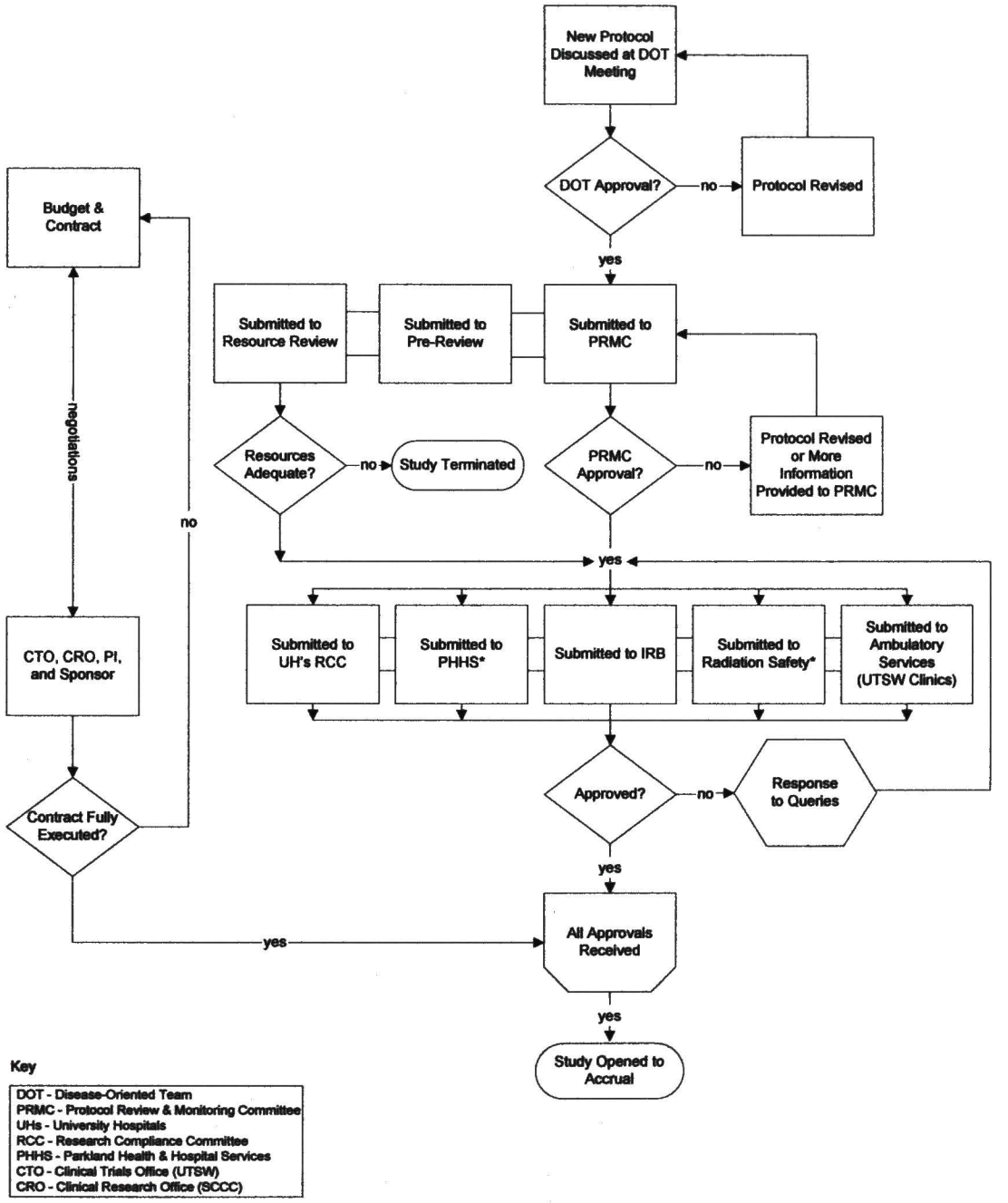
A protocol must also gain approval from the St. Paul and Zale Lipshy University Hospitals' Research Compliance Committee (UH RCC). Protocols are submitted to the UH RCC for review at the same time they are submitted for review by the IRB and Radiation Safety. Just like Radiation Safety's approval, the RCCs approval is contingent upon the IRBs approval. The RCC meets twice a month and consists of approximately 12 members. The committee's job is to review study protocols that will use any of the University Hospital's resources. Thus, studies that are conducted at the SCCC implicitly need RCC approval. This is because every study conducted at the SCCC utilizes the University Hospital's resources in some way or another. For example, if a study uses the University Hospital's laboratory for routine blood chemistries or other hematology panels, then the study would need to gain the RCCs approval. Another example would be if a study intends for some form of patient treatment to be conducted at one of the University Hospitals. Patient treatment includes, but is not limited to, pathology, radiography, or any other diagnostic imaging. Moreover, many studies require their study subjects to maintain a regular chemotherapy cycle schedule. This may constitute a patient to receive treatment over the weekend at one of the University Hospitals since the SCCC is not open. Such a study would therefore require the RCCs approval.

Parkland Health & Hospital System, Ambulatory Services, and Final Approvals

Just like University Hospitals' Compliance Committee, a protocol that calls for a study to utilize any resources at the Parkland Health & Hospital System (PHHS) must gain PHHS approval. PHHS final approval is contingent upon IRB approval. PHHS must determine if the adequate resources are available to conduct a new study with an objective similar to the UH RCCs resource review. However, pharmacy logistics are incorporated into a PHHS review. Because many of the SCCC's patients receive their medications through the PHHS, a PHHS pharmacist must review all new studies to determine if the PHHS pharmacy can provide the necessary medications and handle the increased workload of the study. PHHS approval is also necessary if a study intends to enroll patients who may currently be receiving treatment at Parkland Memorial Hospital.

Ambulatory Services' approval is also required by all new studies and is the fourth and final approval that is contingent upon IRB approval. UTSW requires that all studies conducted through the SCCC gain both UH RCC and Ambulatory Services approval. Ambulatory Services approval is necessary to ensure that all other UTSW outpatient treatment clinics are documented as possible treatment sites. Once a study has gained Ambulatory Services, Radiation Safety, IRB, PHHS, and UH RCC approval and the budget and contract have been approved and filed, then a study may begin enrolling patients.

Figure 4


New Protocol Discussed at DOT Meeting
DOT Approval?
no
Protocol Revised
yes
Budget & Contract
Submitted to Resource Review
Submitted to Pre-Review
Submitted to PRMC
Resources Adequate?
no
Study Terminated
PRMC Approval?
no
Protocol Revised or More Information Provided to PRMC
negotiations
no
yes
CTO, CRO, PI, and Sponsor
Submitted to UH's RCC
Submitted to PHHS*
Submitted to IRB
Submitted to Radiation Safety*
Submitted to Ambulatory Services (UTSW Clinics)
Approved?
no
Response to Queries
Contract Fully Executed?
yes
yes
All Approvals Received
yes
Study Opened to Accrual
Key
DOT - Disease-Oriented Team
PRMC - Protocol Review & Monitoring Committee
UHs - University Hospitals
RCC - Research Compliance Committee
PHHS - Parkland Health & Hospital Services
CTO - Clinical Trials Office (UTSW)
CRO - Clinical Research Office (SCCC)

Specific Aims

SPECIFIC AIM #1: Document and map the institutional components involved in the protocol approval process at the Harold C. Simmons Comprehensive Cancer Center at UT Southwestern Medical Center.

SPECIFIC AIM #2: Analyze and discuss the various segments of the protocol approval process at the SCCC and identify at least one issue that increases the time to open a clinical trial to patient enrollment.

SPECIFIC AIM #3: Propose suggestions and possible resolutions to the issues that create time delays and impairs the clinical trials approval process' efficiency.

Significance

There is very little documentation and research involving the protocol approval process before opening an oncology clinical trial.[3] This Internship Practicum Report will help to build upon this dearth of literature and further identify administrative barriers that protocols encounter while undergoing the various approval processes.

Moreover, this report is significant in that its findings may be utilized to help streamline the protocol approval process at the SCCC at UT Southwestern. This will in turn expedite the translational approach in bringing cancer patients new treatment options. Furthermore, its findings may be used to conduct a broad-based view analysis in

conjunction with findings at similar institutions and academic health care settings to help present general trends in identified time delays pertaining to study protocol approvals.

Materials and Methods

Microsoft Office Visio® was used to systematically map and document the institutional components involved in the protocol approval process at the Harold C. Simmons Comprehensive Cancer Center at UT Southwestern Medical Center. Various modes of research were also employed to analyze and discuss the various segments of the protocol approval process. The first mode of research involved sampling numerous in-stage protocols and evaluating the length of time each protocol spent at each approval process. This helped to identify major issues that directly and indirectly increased the time delay to open a clinical trial. Secondly, numerous interviews were conducted with the employees at the Clinical Research Office and other regulatory departments to further analyze and discuss the various segments of the protocol approval process. This further gave way to possible resolutions to be proposed to the identified issues that create unnecessary or excessive time delays and impairs the clinical trials approval process' efficiency. Lastly, Oncore®, a translational research database created by PercipEnz, was used to retrospectively evaluate industry sponsored protocols approved and opened to accrual at the SCCC for the year 2006. By retrospectively evaluating each study using Oncore®, the number of calendar days that each industry sponsored protocol spent obtaining PRMC and IRB approval were calculated.

Results and Discussion

Results

After documenting each step of the protocol approval process it soon became apparent that the IRB approval process was the most time consuming. This was further confirmed by utilizing Oncore® to track all industry sponsored studies for 2006 that went before UTSWs IRB for review. PercipEnz's translational research database, Oncore®, allowed the number of calendar days that each industry sponsored protocol spent at both the PRMC and IRB to be calculated by entering in specific date parameters. Oncore® has the ability to track all other review processes, but submission dates, review dates, and action dates are rarely entered into the database for non-IRB or PRMC related approvals. After entering in search parameter dates January 1, 2006 and December 31, 2006, a list of studies was generated for the year. The list included the four different types of sponsor trials conducted at the SCCC, and only those studies that were submitted to the PRMC and eventually approved by the IRB. However, not all sponsor type trials were examined. Only the industry sponsored trials were analyzed.

Industry sponsored studies were specifically targeted and not cooperative group studies, investigator initiated studies, or other externally peer-reviewed studies for a number of reasons. Cooperative group studies were ignored because they are sponsored by the NCI and their protocols are written by a group of researchers, community doctors, and other individuals at cancer centers who are involved in studying new cancer treatments, cancer prevention, early detection, rehabilitation, and quality of life.[19] Thus,

because these studies are NCI sponsored and involve a large number of patients participating at different NCI designated institutions and other locations, UTSWs IRB almost always approves cooperative group studies without any unnecessary time delays. Furthermore, cooperative group studies are not homogenous to the course and time that they spend in the protocol approval process. Cooperative group studies often take a circuitous pathway in their approval and do not exhibit any uniformity in their approvals. For example, cooperative group studies undergo administrative PRMC reviews instead of full committee reviews because they are externally reviewed. Secondly, many of the approval components, such as the budget and contract component, yield minimal consistency in their order of approval. Some cooperative groups send both their budget and contract to the SCCC before it has even been planned to be discussed at a DOT meeting. Other cooperative group studies fail to gain institutional approval because budget and contract negotiations continue for many months before UTSW and a sponsor can reach an agreement.

Investigator initiated studies and other peer-reviewed studies were also not examined. An investigator initiated, or PI initiated, study is a study that is funded by a NIH grant, internally reviewed, and includes any collaborative studies that are conducted with an industry sponsorship.[7] Other externally peer-reviewed studies are those studies that are supported by grant mechanisms such as R01s or P01s and utilize an external peer-review like the American Cancer Society.[7] Both investigator initiated and other externally peer reviewed studies were ignored because only a few of these types of sponsored trials are submitted to the IRB for review each year. Their analysis would not give a good

generalized and comprehensive statistical overview of the length of time that it takes for these trials to gain approval. The problems associated with the small sample size of investigator initiated and other externally peer reviewed studies for the year 2006 might have been addressed by extending the Oncore® search parameter date to include those studies reviewed over the past five years. However, the entire protocol approval process at UTSW has evolved to meet the growing demands and increased needs of clinical trials. The entire process has become much more organized and efficient than it was five years ago. Thus, the data would then disproportionately illustrate much longer approval times for studies reviewed five years ago compared to those studies reviewed one year to two years ago. Industry sponsored studies were therefore selected because of their large sample size in relation to the other three types of sponsored trials and their uniformity in the course that is taken by these studies to gain the necessary approvals.

A total of sixteen industry sponsored trials under-went PRMC review between January 1, 2006 and December 31, 2006. These sixteen industry sponsored trials were examined using Oncore® and the amount of time exhausted before a study gained PRMC, IRB Initial Review, Full Board IRB Continuing Review, and Expedited IRB Continuing Review approval was determined. PRMC approval had a mean of 19.5625 calendar days and a median of 15 calendar days. IRB Initial Review had a mean of 58.26667 calendar days and a median of 56 calendar days. Three of the sixteen studies have since undergone IRB Full Board Continuing Review. Their approval times were 21, 43, and 47 calendar days. Moreover, one of the sixteen studies underwent IRB Expedited Continuing Review with an approval time of 17 calendar days.

Figure 5

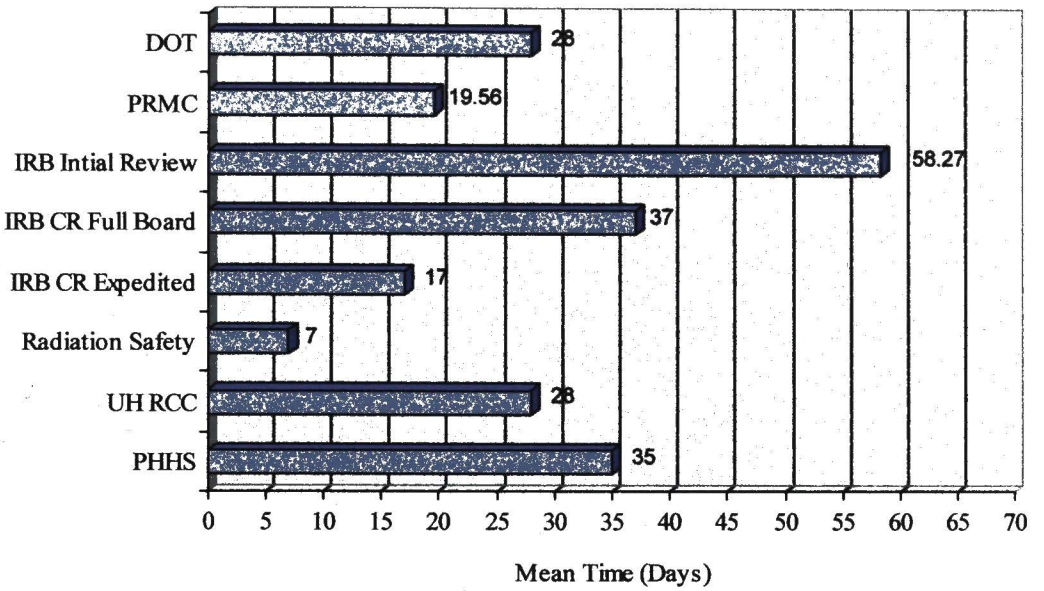
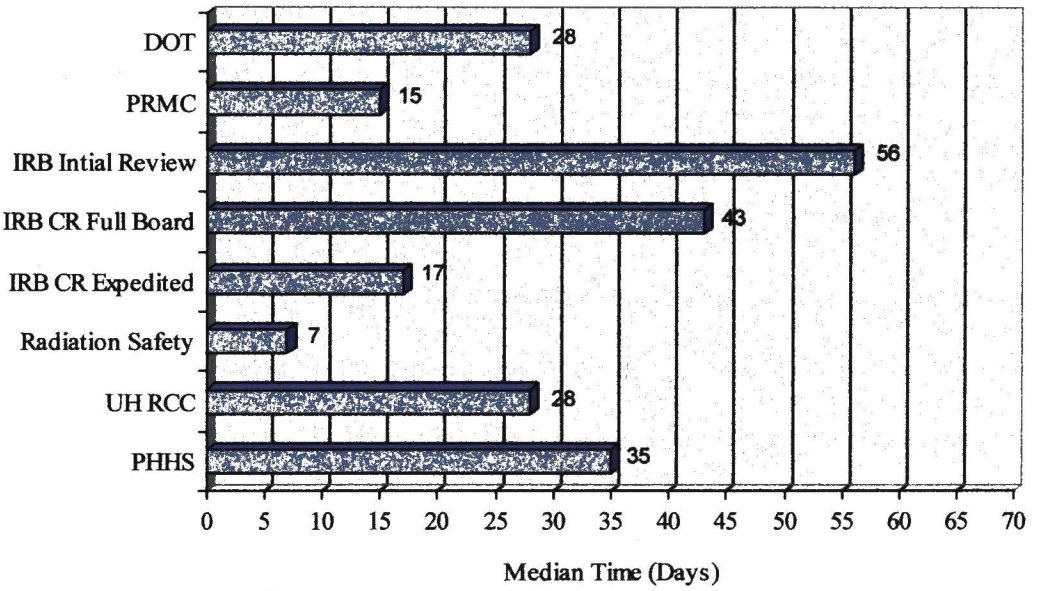


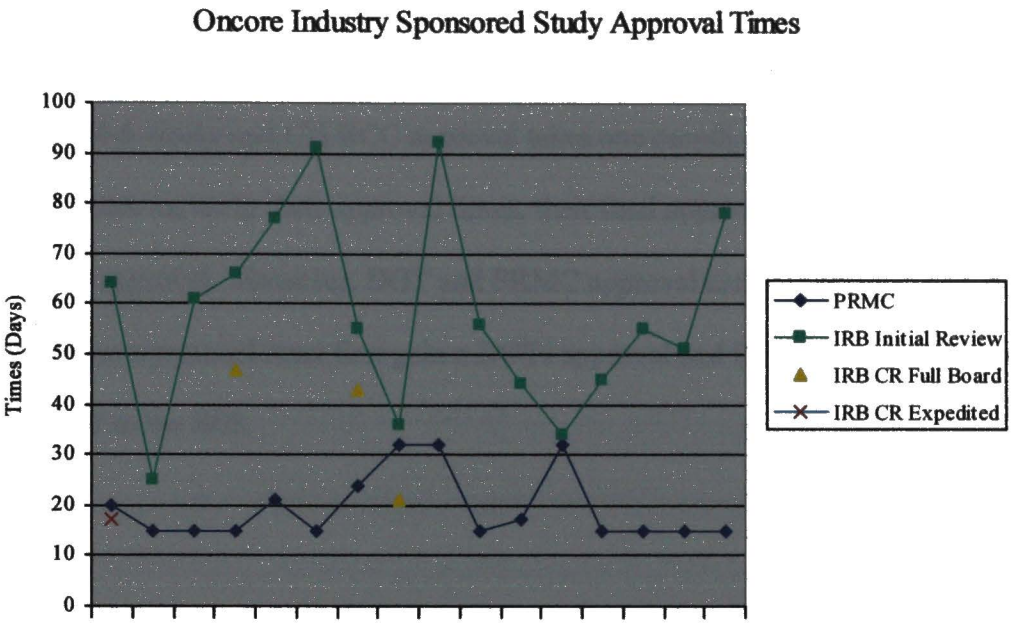
Figure 6



Key

DOT - Disease Oriented Team
PRMC - Protocol Review and Monitoring Committee
IRB - Institutional Review Board
CR - Continuing Review
UH RCC - University Hospitals Research Compliance Committee
PHHS - Parkland Health & Hospital System

Figure 7



The remaining protocol approval processes documented are more standardized in the amount of time that is exhausted before a protocol gains their approval. These approvals include, but are not limited to, the DOTs, Radiation Safety, PHHS, and the UH RCC approvals. Precise numerical data could not be acquired since these approvals are not regularly tracked by Oncore®, but approval averages were obtained after interviewing and discussing approval times for the remaining processes with the regulatory coordinators within the CRO. It takes approximately one month for a DOT to approve a study. DOT teams meet once a month and in order for a new study protocol to be presented at that month's meeting the DOT must have enough information about the trial, the drug, and be able to thoroughly discuss all aspects of the study. Some sponsors require confidentiality agreements before they can release enough information which can prolong the DOT

approval process, but assuming that enough information is provided, a study will usually be placed on the agenda for the next available meeting. Radiation Safety usually reviews and approves, when applicable, studies within a week. PHHS approval generally takes approximately 4-6 weeks and UH RCC approval takes one month. While each of these approval processes varies in their approval times, their final approvals are all contingent upon IRB final approval. However, DOT and PRMC approval are not contingent on IRB approval because a protocol must first gain a DOTs approval and PRMC approval before being submitted to the IRB.

Discussion

There are several issues of concern associated with the IRB that create unnecessary time delays, increase the time to open a clinical trial to patient enrollment, and impair the clinical trials approval process' efficiency. These issues can particularly be attributed to the staffing inadequacies that cannot meet the demands of the increasing amount of industry sponsored trials that needed to be reviewed.[20] The four separate boards that review studies every two weeks and the maximum review limits of six new studies and eight continuing review studies they have imposed for each meeting have created a backlog of studies that need to be reviewed. More boards need to be created to meet this demand. As of August 17th, any study that was submitted to the IRB would not undergo a full board or expedited review until September 19, 2007. This is assuming that all the necessary study documentation was properly filled out, filed with the IRB, and does not request a specific board's review. The evident and obvious need to create more review

boards is more complex than soliciting 10-12 new ad hoc reviewers. Board members must be properly and thoroughly trained to ensure the protection of the rights and welfare of future research subjects.[23]

The IRB approval process affects many of the other protocol approval processes both preceding and following the IRB. Many of these approvals processes are contingent upon IRB approval. Currently, an industry sponsored clinical trial takes an average of 28 calendar days to gain DOT approval and 19.56 calendar days to gain PRMC approval. By meeting more than once a month, the PRMC may be able to reduce the number of calendar days before a new study protocol is granted PRMC approval. However, there is no pressure for the PRMC to do so because of the backlog of studies that need to be reviewed by the IRB. If the PRMC were to increase the number of its reviews it conducts per month, there would not be a direct reduction in the number of calendar days that a new study takes before it can enroll patients, but instead, an increase in the workload and additional backlog of studies that the IRB is currently faced with. Thus, those issues of concern associated with the IRB must first be addressed.

The second issue of concern that creates time delays and increases the time to open a clinical trial to patient enrollment is the number of stipulations generated by the IRB. A study is rarely approved by a board without a number of stipulations. Whether the stipulations pertain to a study's protocol or its informed consent is dependent on both the sponsor of the study and the phase of clinical trial. Until stipulations are answered and approved a study is not granted approval. After interviewing many CRO and IRB regulatory staff it was concluded that many of the stipulations generated by the various

IRBs are neither necessary nor relevant to the protection of the rights and welfare of research subjects. For example, if a board member has a concern with some irrelevant usage of language within the protocol then a stipulation will be generated.

Once a stipulation is generated an IRB coordinator must then type up the stipulation and send it to a regulatory coordinator at the CRO. The regulatory coordinator then makes the necessary corrections, has the PI sign and approve the stipulation response, and then sends it back to the IRB coordinator. The IRB coordinator makes sure that the appropriate corrections have been made to the protocol and the regulatory coordinator's response sufficiently addresses the stipulation. After all stipulations have been addressed then a study may then be granted IRB approval. When many stipulations are generated by a board for a single study then the time before that study gains IRB approval is significantly increased. Regulatory coordinators do not have the scientific or technical expertise to address many of the stipulations. They must then turn to the sponsor or PI for assistance which in turn creates more delays.

A reasonable solution to the address the arising issues that create time delays in the IRB approval process for industry sponsored trials would be to investigate the possibility of using a Central Review Board (CRB) for these studies and forgo UTSWs local IRB review. A CRB is an independent for-profit organization that performs IRB reviews for a fee.[20] A CRBs responsibilities are identical to those based at academic or medical institutions and are governed by the same federal regulations as local IRBs.[21] Western IRB (WIRB), a CRB, was chosen as the model of comparison for this report to exemplify

how a CRB might expedite the protocol approval process by eliminating those issues that create unnecessary time delays.

WIRB was selected because it was the first independent IRB to be accredited by the Association for Accreditation of Human Research Protection Programs (AAHRPP) and is considered by many as the "gold standard" for CRBs.[21] WIRB was founded in 1968, incorporated in 1977, and began offering institutional review services in 1996.[21] They currently provides review services for more than 100 academic centers, hospitals, biotech research companies, and individual investigators in every state and internationally.[21] Furthermore, they have worked with all major device and pharmaceutical companies, CROs, and the biotech industry. Analogous to UTSWs IRB, WIRB conducts its reviews in accordance with three standards:[15,21]

- The International Conference on Harmonization (ICH) "Guidance for Industry—E6 Good Clinical Practice: Consolidated Guideline"
- The Food and Drug Administration (FDA) Regulations on research with human beings (21 CFR 50 and 56)
- The Health and Human Services (HHS) Regulations on research with human beings (45 CFR 46 Subparts A, B, C, and D)

Using a CRB like WIRB could eliminate the time delays in the protocol approval process by addressing the staffing inadequacies that UTSWs IRB is currently faced with and potentially reduce the number of stipulations. WIRB is composed of thirteen individual review panels, while UTSW has only four review boards. Each WIRB panel

consists of nine standing members with numerous designated alternates. Just like UTSW, new protocols are assigned to review panels based on specialty and the next available panel meeting.[21] However, because WIRB has thirteen review panels, protocols are generally reviewed the week following their receipt by WIRB. This immediately eliminates one month wait time that protocols normally incur before being reviewed at UTSWs IRB.

Table 2

Western IRB:

Monday	Tuesday	Wednesday	Thursday	Friday
Panel 1	Panel 2	Panel 3	Panel 4	Panel 6
Panel 7	Panel 5	Panel 11	Panel 12	Panel 8
-	-	-	Panel 10, 13**	-

*Panel 9 meets as needed
**Canadian Panel

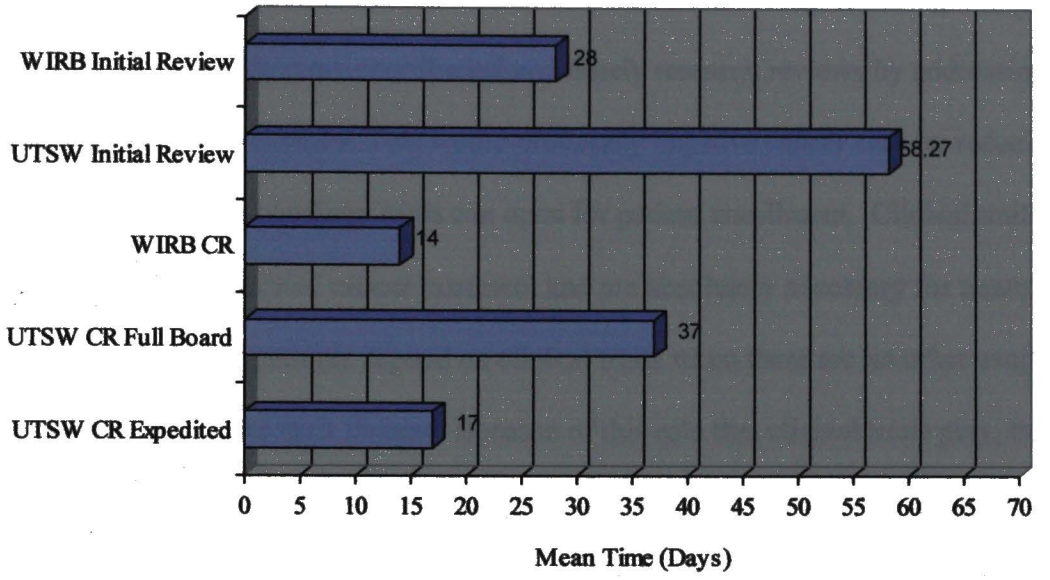
Table 3

UTSW IRB:

Monday	Tuesday	Wednesday	Thursday	Friday
Board 1	-	Board 2	-	-
Board 3	-	Board 4	-	-

The other issue of concern that a CRB like WIRB could address is the number of stipulations that are generated during an IRB review. When a board at UTSW has one or more stipulations about a study protocol then the time before that study gains IRB approval is considerably increased. There is no internal measure of review of the stipulations that the IRB generates to ensure that each stipulation is necessary and is associated with patient protection and safety. A CRB like WIRB could reduce the number of stipulations and decrease the IRB approval time because of the monetary fees that are incurred every time there is a change made to a research protocol or its informed consent. Currently, UTSWs IRB does not charge for the number of stipulations generated. There is no incentive for a sponsor to ensure that their protocol or informed consent sufficiently addresses the protection and safety of its study subjects. When a study is reviewed by UTSWs IRB and there are subject protection and safety deficiencies in the study's protocol or informed consent the sponsor is not penalized. Because WIRB charges sponsors $250 to any "change in research" associated with a review, sponsors are more inclined to thoroughly review their study protocol and informed consent and avoid this $250 fine. This fee imposed by WIRB would directly help to eliminate the number of stipulations or changes in research that a study reviewed by UTSW would normally incur. The reduction in the number of stipulations and changes to research translates into a quicker IRB approval time and a reduction in the number of calendar days before a study can ultimately start enrolling patients.

Figure 8



Summary and Conclusions

This practicum report examined the protocol approval process at a matrix cancer center. Sixteen industry sponsored trials were analyzed and it was found that the IRB approval process took the longest. The mean IRB approval time was 56.27 calendar days. A possible resolution to reduce this approval time would be to outsource all IRB reviews for industry sponsored trials to a Central Review Board like Western IRB. Utilizing a CRB would potentially cut down on the IRB approval time by decreasing the amount of time that studies incurs before being reviewed and the number of stipulations that are generated after studies are reviewed.

The recent increases in industry sponsored clinical trials conducted at academic institutions like UT Southwestern has left IRBs overwhelmed and unable to carry out their duties because of insufficient institutional resources.[22] Implementing a centralized review could provide more coordinated and timely research reviews by addressing these institutional insufficiencies. This would ultimately improve cancer care by reducing the overall time before oncology trials can open for patient enrollment. Clinical trails define the standards for optimal cancer treatment and are absolutely necessary for treatment advances.[23] Many patients depend on clinical trials when there are no other available treatment options for their disease. Because of this role that clinical trials play, they should be reviewed in a timely and efficient manner to ensure that they maintain the highest degree of ethical standards.[23] Any delays in this review leads to in an increased time before a study is approved and can begin defining the standards for current cancer treatments and provide patients with additional treatment options.

Limitations

There are a few key factors which will limit the interpretation of the data collected or arguments presented. All of them are associated with the length of time of the internship. It would be ideal to sample a far greater number of protocols and retrospectively gather all dates to statistically analyze the exact times the protocols spent at each component of the approval process. However, due to limited man-power and the limited amount of time spent at the internship before this practicum's defense, it is not feasible to achieve this tedious task. It would also be ideal to follow one particular protocol from the time of

inception to the time the study opens for enrollment. However, this is also not feasible because the overall protocol approval process takes longer than the internship itself, and following one particular protocol would only allow for analysis of a few components out of the many protocol approval processes involved.

CHAPTER III

INTERNSHIP EXPERIENCE

Internship Site Description

In fulfillment of the curriculum requirements for a Master of Science in Clinical Research Management, I interned at the Harold C. Simmons Comprehensive Cancer Center at UT Southwestern Medical Center in Dallas, Texas. My internship specifically took place within the Clinical Research Office (CRO) at the Cancer Center under the supervision of the Assistant Director of the CRO, Lynn Baker, MBA. The comprehensive cancer center is aimed a providing a wide range of patient cancer care services through a broad-based collection of cancer programs.[4] They provide state-of-the art therapeutic and diagnostic procedures tailored to the specific needs of their patients.[4] Furthermore, it is the SCCC's mission to foster multidisciplinary collaborations and increase the cancer focus of premiere investigators in basic science, translational, and clinical research to bring new knowledge and technology into the fight against cancer.[4]

The following staff and research persons significantly contributed to my internship learning experience:

- Lynn Baker, MBA
- Jean Ann Haag

- Lonnie Sorrells
- Tracee Rainey, RN
- Vicki Bigelaitis
- Candice Penn, RN
- Irina Fuller, MS
- Erin Fenske, MBA
- Helen Davis, RN
- Flo Kempmeier, ARNP
- Vanessa Tagoe, MA
- Ashley Dowell
- Charla Dowell, MPH
- Shirley Martin
- Thomas Stuenzi
- Diadria Thomas
- Arlene Thomas
- Antoinete Gonzales, RN
- Janis Brendle
- Rosalie Serrano, RN
- Anthony Zuniga, RN

Specific Aims of Internship

My duties as an intern encompassed those as someone with a position title of Clinical Research Coordinator and the duties as someone with a position title of Clinical Data Specialist. At the beginning of my internship, I worked with the Breast Cancer Program and then was later reassigned to the Bone Marrow Transplantation (BMT) Program. The reason for this was because two of the BMT coordinators went on maternity leave. My detailed day to day activities are located in the Appendix of this report.

Lab Shipments and Supplies

While working with BMT, I took over the responsibility of being in charge of shipping all patients' labs and samples to their necessary destinations. In order to coordinate when samples are drawn in the clinic, where they are stored, and when they need to be shipped, a calendar system was developed using the computer program Calendar Creator. Calendar creator allows the BMT staff to continuously update what duties needed to be performed for a specific month. This is further achieved by storing all calendars like the master patient visit calendar, monitoring visit calendar, and the lab shipment calendar on a network drive that can be accessed by all CRO staff.

Making sure that all the patients' samples are drawn, collected, and properly sent are the BMT coordinator's job. They must also make sure that any lab that must be sent to an off-site location or central lab must be recorded on the lab shipment calendar. This is so that I or any other BMT staff could track a lab or sample. For example, some studies required that plasma be sent to an off-site location for analysis. So once a blood draw

was done in the clinic I would take the sample and spin it down, extract the plasma, then store it in the necessary degree freezer. This is all outlined by each particular study's protocol and lab shipment manual. Something as simple as a calendar made things very simple to manage all labs and samples. This especially became apparent when a lab needed to be spun, frozen down using a -20 degree refrigerator and then transferred to a -80 degree refrigerator for storage. This is because the centrifuge and -20 and -80 degree refrigerators are all located on different floors and separate locations at UTSW.

Once a lab was marked to be shipped on a specified date on the calendar, it was my duty to ensure that they then make it to their destination. Some studies require their labs and samples to be shipped the same day or next day, while other studies require that their labs be sent every two weeks or once a month. Each sponsor provides their study site with all of the proper supplies to conduct the study. This even includes all shipping supplies and air bills. However, one thing that constantly created problems when shipping samples was whether a particular sponsor paid for any dry ice that was needed. Almost all labs need to be sent either at ambient temperature or frozen. When they need to be shipped frozen, then dry ice is required. However, if dry ice is not included in a study's budget or contract then they assume that the research site will provide it. This is where problems ensued and whether or not to bill the sponsor for any dry ice that the CRO supplied. Because the CRO no longer stores dry ice within its laboratory, the dry ice must be obtained from the Shipping and Receiving docks at UTSW. The CRO then incurs the cost of the dry ice after being billed by Shipping and Receiving. This problem has been brought to the attention of our Budget and Contracts coordinator who is now ensuring that any new studies that require their labs to be shipped frozen include the costs

of dry ice in their budget. One particular study that BMT is currently conducting has the delivery service provide the dry ice when picking up any packages for shipment.

Almost all of the studies that BMT conducts have very thorough lab shipment manuals that outline what shipping containers to use, how to package each particular sample, what carrier to use, and how to fill out the necessary air bills. Once a lab was packaged and ready for pick up it, was my duty to call the carrier and track the package until arriving at its destination. Once a package was shipped, then that particular lab or sample was highlighted in red on the master lab shipment calendar to notify all CRO and BMT research personnel that that lab had been sent.

Adverse Events and Serious Adverse Event Reporting

Adverse Events (AE) and Serious Adverse Events (SAE) are required to be reported to UTSWs IRB through the Electronic Research Grant Organizer (ERGO). Each adverse event sent to the CRO is sent as an Investigation New Drug Safety Report (INDSR). Coordinators must thoroughly read through INDSRs received each week and summarize and the events into the ERGO database. Each INDSR takes approximately 15 minutes to input into ERGO. Many disease groups within the CRO receive 10-15 INDSRs each which. INDSRs quickly become very burdensome to coordinators if they are not routinely entered into ERGO.

Monitoring Visits

After completing CRFs and eCRFs for the Breast Cancer Disease group and the BMT Disease group, I met with three separate monitors to ensure that my data entry was correct. The Breast study that I worked on (SEDE) utilized paper CRFs unlike the two other BMT studies that utilized eCRFs. All three monitors answered all questions that I had, and pointed out consistent errors I was making when filing out CRFs.

Maintaining Regulatory Binder and Study Files

At the beginning of my internship I was asked to organize a regulatory binder for a BMT study. The regulatory binder maintains all regulatory documents for a study. The regulatory binder documents detail all necessary information and events about the study. The five main regulatory binder tabs that organized the documentation within the binder included:

- Correspondence Between Investigator, Sponsor, and Coordinator
- IRB/Independent Ethics Committee Documentation
- Financial Disclosure
- Electronic Case Report Forms
- Protocol and Amendments, etc.

IRB Interactions and Communications

After thoroughly reviewing the protocol approval process, I spent a great deal of time investigating UTSWs IRB. The CRO is unique in that it there are regulatory coordinators that work within the CRO. It is the CRO regulatory coordinators' responsibility to ensure that all documentation is properly submitted to the IRB for Initial Review and Continuing

Review. Any modifications that are made to a research study are also the regulatory coordinator's responsibility.

The CRO regulatory coordinators work closely with the IRB coordinators. This is to ensure that pre-IRB review documentation is properly completed and filed to avoid any delays before a new potential study is assigned to a review board. Oncore® is used to track the status of all IRB documentation.

Data Collection, Case Report Forms, Electronic Data Capture

Data collection and reporting became a major component of my internship when I worked with both the Breast Cancer Disease group and BMT Disease Group. It allowed for me to become experienced with Case Report Forms (CRF) and Electronic Data Capture (EDC).

Source Document Creation

An opportunity arose to create a lab requisition form for a Geron Study (GRN163L CP04-151). In order to obtain all of the necessary information I thoroughly read the Geron study protocol. I also compiled all the necessary information using the study's NR3. Once I had gathered all the pertinent information needed, I contacted Qiana Jones so that a lab requisition form and lab account could be created. Some of the information included the estimated amount of specimens for the study, tests requested, and special instructions for the account.

Another opportunity arose where I had the opportunity to create some source documents for the BMS 044 and E1905 study. Study flow sheets needed to be created for the research nurses. The flow sheets outlined what procedures and tests needed to be conducted at each subject visit. I created the flow sheets by reading both the protocol for the BMS 044 and E1905 study and made sure that my flow sheets mirrored the study's schedule of events and relevant procedures.

APPENDIX A

INTERNSHIP JOURNAL

June 11, 2007 – October 26, 2007

Monday 6.11.07

- Begin Internship

- Completed all necessary paper work required for the Office of Human Resources before beginning new employee training
  -Degree plan
  -Proof of medical insurance coverage for the period worked

Tuesday 6.12.07

- Office of Human Resources Orientation: HIPAA, security, confidentiality, sexual harassment, etc. training
  -Also received ID badge, parking information

- Read Clinical Research Office Orientation Manual

Wednesday 6.13.07

- Office staff introductions

- Obtained computer log-in, network log-in, and email address

- Read *Cancer Clinical Trials: The In-Depth Program*
  -Published by NCI (National Cancer Institute) & NIH (National Institutes of Health)

- Sat in on Protocol Review and Monitoring Committee (PRMC) meeting

Committee brought up concerns about various portions of several protocols to be approved for new study trials. All of the protocols, but one, were "Approved Pending Response." The remaining protocol was directly "Approved." Some examples of concern involved the background of one study protocol, the definition of a high value in another, and the implementation of a Data Safety Monitoring Board pertaining to a third protocol.

Thursday 6.14.07

- ERGO (Electronic Research Grant Organizer) Training

  ERGO is an online system designed to allow the creation and approval of internal and external forms relating to research administration. ERGO also serves as an electronic filing system for the research administration process. For example, I learned how to file IND (Investigational New Drug) Safety Reports describing SAEs (Serious Adverse Events) of a study drug currently being investigated in a trial at UT Southwestern. However, the SAEs reported were from a separate study/location and were being reported to inform the IRB (Institutional Review Board) and PIs (Principal Investigators) of the SAEs that have occurred in other trials using the drug in question.

- Attended Hematology Oncology Conference
  -Speaker: Francisco Esteva, MD, PhD
  -Topic: Molecular Mechanism of Resistance of HER2-Targeted Therapy in Breast Cancer

- Organized Regulatory Binder (The Vaccine Company, i3 Research)

  Added documentation regarding Correspondence Between Investigator, Sponsor, and Coordinator, IRB/Independent Ethics Committee Documentation, Financial Disclosure, Electronic Case Report Forms, Protocol and Amendments, etc.

Friday 6.15.07

- Meeting with Charla

  Learned about New Study Approval Processes: Contracts and Budget, Documentation Preparation, PI and Sponsor Approval, Protocol Review and Monitoring Committee (PRMC), Data Safety and Monitoring Committee (DSMC), Submission of Documents, IRB, Radiation Safety, Certificate of Confidentiality, and Site Approvals including Clinical Trials Support Unit (CTSU). Also learned about Policy & Procedures for Data and Safety Monitoring.

- Meeting with Lynn

  Discussed possible ways to go about obtaining Internship Practicum Report topics and expectations for the coming weeks. Also discussed Clinical Research Office (CRO) Departmental Organization.

Monday 6.18.07

- Chemotherapy class for Cancer Center's clinical research staff
  -Instructor: Gail Kwarciany
  -In conjunction with American Association of Critical-Care Nurses

- Assisted Vanessa in preparing patient files/folders for Monitor visit concerning SEDE study: Serial Evaluation of Ductal Epithelium and Breast Health Outcomes in women at high risk for Breast Cancer

  Organized plates (Case Report Forms) for patient visit numbers accordingly in patient files/folders. Case Report Forms (CRFs) included Clinical Breast Exam form, Screening Mammography form, Screening Mammography Report Shuttle form, Right & Left Ductal Lavage forms, Device Accountability form, Recommended Follow-up form, Interval Medical History form, and Adverse Event forms.

Tuesday 6.19.07

- Continued assisting Vanessa prepare patient files/folders for Monitor visit

  Organized CRFs for patient visit numbers accordingly in patient files/folders. Also determined which patients where past due on their visit number. Then decided whether or not the visit should be rescheduled or if they were out of window and needed to be scheduled for the next consecutive visit number.

Wednesday 6.20.07

- Read protocol for:

  Phase II Study of Preoperative Radiation with Concurrent Capecitabine, Oxaliplatin and Bevacizumab Followed by Surgery and Postoperative 5-FU, Leucovorin, Oxaliplatin (FOLFOX) and Bevacizumab in Patients with locally advanced rectal Cancer

- Shadowed Anthony while he conducted a patient consultation and follow-up visit for the study listed above

- Organized GlaxoSmithKline clinical trial Investigational New Drug Safety Reports (INDSR) by Database Number, Date, and SAE

- Separated incoming INDSRs for two clinical trials and filed them accordingly for the month of June

Thursday 6.21.07

- Sat in on Clinical Research Coordinator's Meeting

- Research Matters Lecture Series: Tips for Reducing Stipulations to Studies
  -Lecturer: Kim Batchelor, M.P.H.

  Informational lecture on IRB approval processes and documentation. Lecture covered Exempt and Expedited studies, NR-1's (a statement of assurance signed by all study staff containing important study-specific information), Project Summaries, Consent Forms, HIPAA Authorization, HIPAA waivers, Continuing Review, and Modifications.

- Breast Program group meeting

  Discussed goals and expectations relevant to the future of the Breast Group and its new members & manager.

- Met with Monitors and was instructed on how to document various aspects of CRFs and pointed out corrections that needed to be made to previous documents filled out

Friday 6.22.07

- Traveled to UNTHSC to get required signatures for Designation of Advisory Committee form and Degree Plan form

- Reviewed previous students' internship practicum reports to get ideas on research problem title

- Talked with Dr. Gwirtz about internship practicum and research proposal

- Looked over PowerPoint covering general regulatory unit information

Monday 6.25.07

- Scanned GlaxoSmithKline clinical trial Investigational New Drug Safety Reports to be sent via email and entered into ERGO for the months of May and June
  -Protocol No: VEG20007
  A Phase II, Open-Label, Randomized, Multicenter Trial of GW786034 (Pazopanib) in Combination with Lapatinib (GW572016) Compared to Lapatinib Alone as First Line Therapy in Subjects with Advanced or Metastatic Breast Cancer with ErbB2 Fluorescence In Situ Hybridization (FISH) Positive Tumors

- Made Copies of Protocols: FCB-301, ML18530, Z0010, Z0011, and NSABP Protocol P-2

Tuesday 6.26.07

- Organized Investigational New Drug Safety Report binders for studies VEG20007 & EGF 30008

- Talked with Lynn about possible Internship Practicum Report ideas and approach to Research Proposal

Wednesday 6.27.07

- UT Southwestern Medical Center at Dallas Good Clinical Practices Training
  -PowerPoint Module and Post Test

- Assisted Florence organize newly received June Investigational New Drug Safety Reports for studies VEG20007 & EGF 30008

- Performed literature search for Research Proposal

Thursday 6.28.07

- Met with the monitor to make corrections to various case report forms (CRF's) pertaining to the SEDE study

Also made sure that there was appropriate documentation in the source documents (patient medical records) that properly paralleled all documentation and information contained in the CRF's.

-SEDE study:
Serial Evaluation of Ductal Epithelium and Breast Health Outcomes in Women at High-Risk for Breast Cancer

Friday 6.29.07

- Breast Group Meeting

Discussed what needed to be done and completed before Deena's departure from the Cancer Center. Juliet also discussed the problems she was facing with data-entry into various data-bases that the Clinical Research Office uses. Made a plan to enter all necessary IND Safety Reports into ERGO that were past due.

- Filed Case Report Forms (CRF) documenting patient postoperative follow-up visits for the Roche Xeloda® Study (XENA Trial)

-XENA Trial:
An Open-Label Study of Capecitabine and Docetaxel as Neoadjuvant Treatment for Patients with Recently Diagnosed HER2-NEU Negative Breast Cancer Plus Trastuzumab for HER2-NEU Positive Breast Cancer

- Meeting with Lynn to further discuss specific aims of my Internship Practicum Report since she was going to be out of the office the following week

Monday 7.2.07

- Read Study Coordinator GCP: Fundamentals
-Written by MedTrials Inc.

- Additional ERGO (Electronic Research Grant Organizer) Training with Deena

- Started entering in IND Safety Data Reports (INDSR) describing SAEs into ERGO database for studies VEG 20007 & EGF 30008

- Cancer Center Town Hall Meeting

Tuesday 7.3.07

- Continued to enter GlaxoSmithKline Protocol No.s: VEG20007 & EGF 3008 INDSRs detailing SAEs for the month of May into ERGO for IRB approval

Wednesday 7.4.07

- Holiday
- Worked on Research Proposal

Thursday 7.5.07

- Holiday
- Worked on Research Proposal

Friday 7.6.07

- Continued to enter GlaxoSmithKline Protocol No.s: VEG20007 & EGF 3008 INDSRs detailing SAEs for the month of May into ERGO for IRB approval

Monday 7.9.07

- Entered GlaxoSmithKline Protocol No: VEG20007 INDSRs detailing SAEs for the month of May into ERGO for IRB approval

Tuesday 7.10.07

- Continued to enter GlaxoSmithKline Protocol No: VEG20007 INDSRs detailing SAEs for the month of May ERGO for IRB approval

Wednesday 7.11.07

- Breast Group Meeting

- Continued to enter GlaxoSmithKline Protocol No: VEG20007 INDSRs detailing SAEs for the month of May into ERGO for IRB approval

- UT Southwestern Library Class for Clinical Researchers; Selected Electronic Resources

  Course provided information pertaining to important Databases, Science References, Drug & Pharmacology Resources, and Publication Support.

Thursday 7.12.07

- Continued to enter GlaxoSmithKline Protocol No: VEG20007 INDSRs detailing SAEs for the month of June into ERGO for IRB approval

- Attended Protocol Review and Monitoring Committee (PRMC) meeting

  Four protocols were "Approved Pending Response." Also listened to a presentation over ePRMS Implementation Planning and Roll-out.

- Read Oncore Tutorial: Reviewer's Guide to Conducting Paperless Scientific Reviews

  The tutorial described the ePRMS functionality of Oncore that is relevant to the Reviewer. Oncore = **ON**cology **CO**llaborative **R**esearch **E**nvironment

Friday 7.13.07

- Continued to enter GlaxoSmithKline Protocol No: VEG20007 INDSRs detailing SAEs for the month of June into ERGO for IRB approval

- Helped Vanessa organize patient folders for the SEDE study and prepare for next week's monitor visit

  Made sure that all CRFs paralleled all appropriate source documentation in medical records and all CRF plate fields were filled out and filed accordingly.

Monday 7.16.07

- Information Security Awareness training

  As a new employee at UT Southwestern you are required by the HIPAA Security Rule and Texas Administrative Code, Section 202 to complete information security awareness training. UT Southwestern Information Security Policy 200-10, Information Security Awareness and Training, establishes this program for the university. The information security training course is text-based and delivered using the Medelearn system. This is the same Computer Based Training (CBT) program used for the HIPAA Privacy and Privacy Refresher training courses.

- Meeting with Lynn to discuss research proposal modifications and corrections. Was also asked to develop a calendar of events to use as a template for important future internship activities

Tuesday 7.17.07

- Adverse Event Expedited Reporting System (AdEERS) web-based training

  System for all National Cancer Institute (NCI) collaborators providing electronic acquisition, exchange, submission, and analysis of Expedited Reports for Serious and/or Unexpected Adverse Events. Also reviewed Common Terminology Criteria for Adverse Events (CTCAE) provided through the Cancer Therapy Evaluation Program (CTEP) on the NCI website.

- Met with the monitor and assisted Vanessa in making corrections to various case report forms (CRFs) pertaining to the SEDE study

  Also made sure that there was appropriate documentation in the source documents that properly paralleled all documentation and information contained in the CRFs.

  -SEDE study:
  Serial Evaluation of Ductal Epithelium and Breast Health Outcomes in Women at High-Risk for Breast Cancer

Wednesday 7.18.07

- Continued to meet with monitor and assisted Vanessa with SEDE CRFs

Thursday 7.19.07

- Clinical Research Office (CRO) Staff Meeting

  Discussed CRO remodeling changes to occur August 8-9th. Also discussed future Oncore® training scheduled to be conducted by PrecipEnz during the office remodeling period. Oncore® is a computer integrated database "…platform for key operational functions including regulatory, administrative, and financials while also integrating with local laboratory and hospital information systems and data warehouses." Lastly, we discussed recent CRO staff changes.

- Sat in on Clinical Research Coordinator meeting that discussed maintaining and continually updating a recently generated list of all SCCC Open Accruing Studies

- Met with monitor again and continued to assist Vanessa with SEDE study CRFs

Friday 7.20.07

- Entered GlaxoSmithKline Protocol No: VEG20007 INDSRs detailing SAEs for the month of June into ERGO for IRB approval

- Meeting with Lynn to discuss IRB Presentation

  Asked to assist her in putting together a PowerPoint presentation about "Using a Central IRB in the Cancer Center." Also went over developed calendar of events template and discussed future pertinent internship activities relevant to my Internship Practicum Report.

Monday 7.23.07

- Literature Search for IRB presentation

- Gathered additional research material for IRB presentation

- Contacted Western IRB (WIRB) for a schedule of fees to be incorporated in presentation

Tuesday 7.24.07

- Worked on IRB presentation

Wednesday 7.25.07

- Worked on IRB presentation

Thursday 7.26.07

- Medical School Interview

Friday 7.27.07

- Meeting with Dee to discuss IRB full board and simple modifications as well as continuing reviews
- Helped Vicki box up EKG machines to be returned to sponsor for BMT study
- Meeting with Lynn to discuss progress of IRB presentation, regulatory affairs, and schedule of activities for coming week

Monday 7.30.07

- Worked Research Proposal after receiving all committee members' suggested revisions and corrections

Tuesday 7.31.07

- Finalized Research Proposal and traveled to UNTHSC to turn proposal into the Graduate School

Wednesday 8.1.07

- UTSW Clinical Researchers' Group Meeting
  Title: Match.com "Are we compatible?? (Sponsor vs. Research Site)"
  Speaker: DeLea Piechel
  From: Advanced Neuromodulation Systems (ANS), a medical device company in McKinney, TX

Thursday 8.2.07

- Started to pack up CRO for remodeling

Friday 8.3.07

- Medical School Interview

Monday 8.6.07

- Attended IRB Full Board Meeting

  Sat in on an IRB panel that reviewed 6 new studies and 8 continuing review studies. All studies were approved pending stipulations but one that was deferred.

- Started to help pack up the CRO for remodeling

Tuesday 8.7.07

- Continued to pack up CRO for remodeling

Wednesday 8.8.07

- Medical School Interview

Thursday 8.9.07

- Oncore Training

  Learned about the Oncore Financials Console that involved parameters, SOC and research items, budgets, invoice creation, and payment receipts. Also learned about the Oncore CRA Console and its capability to track subject visits and its ability to complete electronic forms.

Friday 8.10.07

- Unpacked CRO
- Remodeling finished and reassigned to Bone Marrow Transport (BMT) disease group

Monday 8.13.07

- Researched NCI CIRB Initiative for WIRB Presentation
- Helped Tracee centrifuge and store blood samples for Bone Marrow Transplant (BMT) study

Tuesday 8.14.07

- National Cancer Institute Human Participant Protections Education for Research Teams Training

  Web-based course presents information about the rights and welfare of human participants in research. The tutorial is designed for those involved in conducting research involving human participants. It satisfies the NIH human subjects training requirement for obtaining Federal Funds.

- Read Protocol for Bristol-Myers Squibb Study CA180034
- Helped Tracee prepare for BMT patient visit on Wednesday

  Prepared all necessarily documentation and orders for 18 month patient follow-up visit.

Wednesday 8.15.07

- Meeting with Lynn to finalize WIRB Presentation

  "Using a Central Review Board in the Cancer Center"

- Helped Tracee centrifuge and store blood samples for Bone Marrow Transplant (BMT) study

- Complete INDSRs

Thursday 8.16.07

- CRO Staff Meeting
- Coordinators Meeting
- Meeting with Lynn to gain final approval of WIRB presentation
- Made corrections to WIRB presentation suggested by Lynn

Friday 8.17.07

- Continued making corrections and finalized WIRB presentation
- Shadowed Vicki Martin at IRB (approval process)

  Learned about each step that a protocol must undergo once it is received by the IRB until it goes to full board or expedited review and then eventually approved pending all stipulations brought into question and answered.

Monday 8.20.07

- Medical School Interview

Tuesday 8.21.07

- Western IRB presentation "Using a Central Review Board (CRB) in the Cancer Center"

  -Presented to Dr. Wilson, Dr. Schiller, and Kim Pallock

- Researched follow up questions and literature search inquires requested by Dr. Schiller and Dr. Wilson

Wednesday 8.22.07

- Prepared Blood samples for Tracee
- Learned how to clone INDSRs using ERGO
- Cloned and filled out INDSRs for Merck Studies & other studies

Thursday 8.23.07

- Finished cloning and filling out INDSRs
- Entered lab normals for UTSW ZLUH
- Genzyme InForm Tutorial and training
- Genzyme InForm 4.5 Integrated Trial Management CRC Certification for Merck Studies

Friday 8.24.07

- Completed Genzyme InForm 4.5 Integrated Trial Management CRC Certification

Monday 8.27.07

- Shadowed Irina and learned how to ship all BMT labs for Covance IRIS study, BMS 180013 & 180034 studies, Novartis 2202 & 2211 studies, and Merck MV7 study
- Entered in normal lab ranges for six patients for Aston and Zale Lipshy laboratories into Genzyme's InForm Integrated Trial Management (Phase Forward) System

  The Genzyme InForm system is a data collection and trial management tool that harnesses the power of the Internet to provide access to clinical trial data and control of the clinical trial process.

Tuesday 8.28.07

- Finished entering in lab normals
- Read Protocols for BMS 044 and E1905 and made sure visit flow sheets mirrored all scheduled of events and relevant procedures
- Entered in INDSR's for Merck Study

Wednesday 8.29.07

- Continued to entered in INDSR's for Merck Study

Thursday 8.30.07

- Medical School Interview

Friday 8.31.07

- PACT Luncheon Honoring All Cancer Center Clinic Staff, Clinical Research Office Staff, and Physicians
- Merck Study Training

Monday 9.3.07

- Holiday

Tuesday 9.4.07

- Entered in Hematology, Chemistry, and other lab normals for Merck Study

Wednesday 9.5.07

- Continued to enter in Hematology, Chemistry, and other lab normals for Merck Study

- Began entering in corresponding lab values for Screening, Baseline, and Cycle 1 visit lab results in

- Meeting with Mary, Tracee, and Vicki to discuss any new issues with patients that both the clinic and CRO should be informed about and updated on

Thursday 9.6.07

- Meeting with Lynn to discuss progress of thesis

- MedNet Solutions training for National Lymphocare Study

Friday 9.7.07

- Attended Cancer Grand Rounds
  Title: "Genomic Strategies for Personalized Cancer Therapy
  Speaker: Joseph R. Nevins, PhD
  Director, Center for Applied Genomics and Technology
  From: Duke Institute for Genome Sciences and Policy
  Duke University Medical center

- Thoracic Malignancy Conference

Monday 9.10.07

- Worked with Shirley and gathered relevant information to put together a lab requisition form by looking through various study's NR3s

Tuesday 9.11.07

- Dentist appointment

- Traveled to UNTHSC to confirm date of defense and meeting with Jan in the Biomedical Science office to reserve a room for defense

Wednesday 9.12.07

- Attended PRMC meeting

  Five studies were reviewed and all approved pending stipulations but one due to reviewing PI's absence.

- Meeting with Mary to discuss upcoming BMT events associated with Tracee and Mary's vacation absence

- Worked on INDSRs for BMS and Novartis studies

Thursday 9.13.07

- Entered in eCRF information for Merck study

Friday 9.14.07

- Continued filling out eCRFs for Merck study

Monday 9.17.07

- Entered in lab values for a patient in the Merck's InForm electronic CRF database

- Reviewed all BMT studies to ensure that a lab requisition form had been created for each study

  A lab requisition form for a Geron Study (GRN163L CP04-151) had yet to be completed. Thus, I compiled all the necessary information using the study's NR3 and various other documents to be sent to Qiana Jones so that a lab requisition form and lab account created. Some of the information included the estimated amount of specimens for the study, tests requested, and special instructions for the account.

Tuesday 9.18.07

- Shipping Class 6.2 Dangerous Good Compliance Training

Wednesday 9.19.07

- Worked on INDSRs for Merck and Novartis studies

Thursday 9.20.07

- Finished filling out INDSRs for Merck and Novartis studies

Friday 9.21.07

- Funeral

Monday 9.24.07

- Addressed queries for Merck-0457 study that were both autogenerated by InForm and opened by the sponsor
- Shipped PK (pharmacokinetic) samples for LBH 2211 study
- Lung Cancer Disease Oriented Team Meeting

  -Lung physicians reviewed enrollment of all open trials and discussed new potential studies as well as pending studies.

Tuesday 9.25.07

- Entered in concomitant medications for patient enrolled in Merck Trial
- Updated Survival Status and Response assessment for a Quarterly update for Genetech National LymphoCare Study®

Wednesday 9.26.07

- EPIC Chart Tracking Training

  The Epic Chart Tacking system is the primary database and source for tracking the movement of patients' medical records between departments and providers at UT Southwestern Medical Center and the Parkland Health & Hospital System.

- Entered in SAEs & EKG's into InForm for Merck-0457 study
- Worked on INDSRs for Merck and Novartis PPR AMN107

Thursday 9.27.07

- Finished submitting INDSRs for Merck and Novartis PPR AMN107 through ERGO
- Filled out other eCRFs for Merck-0457 study

Friday 9.28.07

- Thoracic Malignancy Conference
- Weekly BMT meeting
- Meeting with BMS 013/034 Medical Special Liaison to discuss upcoming potential BMS studies that Dr. Collins could be interested in that involve current drugs under study but are being studied in combination with a new drug

Monday 10.1.07

- Prepared for Merck-0457 Monitor visit

  Double checked all lab normals, lab values, EKG values, vitals, AEs, concomitant medications, medical histories, prior oncologic treatments, and dosing schedules for each cycle for a patient on study.

- Shipped labs for Merck-0457 study, LBH 2211, and BMS 22111

Tuesday 10.2.07

- Continued to prepare for Merck monitor visit on Wednesday
- Worked on INDSRs for Merck-0457 study

Wednesday 10.3.07

- Monitor visit

Thursday 10.4.07

- Monitor visit

Friday 10.5.07

- Weekly BMT meeting
- Attended Cancer Center Grand Rounds

  Title: "Targeting the HER Network for the Treatment of Breast Cancer"
  Speaker: C. Kent Osborne, MD
  Director, Dan L. Duncan Cancer Center
  From: Baylor College of Medicine, Houston, TX

- Thoracic Malignancy Conference

Monday 10.8.07

- Shipped Labs for PR-1 Vaccine Trial
- Began to work on thesis

Tuesday 10.9.07

- Worked on thesis

Wednesday 10.10.07

- Completed LymphoCare Observational Study eCRFs

  Determined if study patients were past due for their next visit update and entered in previous study visit eCRFs into LymphoCare's EDC system

- Worked on thesis

Thursday 10.11.07

- Worked on thesis

Friday 10.12.07

- Traveled out of town to attend a wedding

Monday 10.15.07 – 10.26.07

- Worked on thesis

APPENDIX B

LUNG DISEASE ORIENTED TEAM MEETING MINUTES

September 24, 2007

Lung Cancer Clinical Research Meeting Minutes
Monday, September 24, 2007 4:00PM CST Rm #NF3.102

Topic	Details	Discussion
Open Trials	Review of Enrollment Adverse Event Review (See attached running log) Open Study Cheat Sheets	Reviewed. Of note, study is closed to enrollment and will be removed from the open study list. The trial is no longer on hold, and this will also be noted on the open study list. Adverse Event Review – see attached for discussion notes. Will consolidate descriptions of adverse events at updated meetings once events have been discussed and closed out by the committee. Open Study Cheat Sheets were not updated this month.
New Potential Studies	1st line: A feasibility Study Investigating Translational Science in Chemotherapy-Naïve Patients with Stage IIIB/IV NSCLC 2nd Line: X versus Y plus Placebo in Previously Treated Patients with Locally Advanced or Metastatic NSCLC 3rd Line: Single arm study of Z in Subjects with Advanced NSCLC 1st or 2nd line: A Phase II, Multi-Center, Open-Label, Trial of X in Treatment Naïve and Sensitive-relapse SCLC	Discussed briefly with the committee. There are concerns regarding the required biopsy procedure as well as whether physicians would be willing to treat 1st line patients. Additionally, we do have other first line studies open. Further discussion for this trial will be initiated either online or at the next meeting to determine whether we will participate. Dr. X would like to present more detail before a final decision is made. Discussion of other

		studies was tabled for the next meeting. Dr. X would like to review the study drugs in more detail prior to the presentation.
Pending Studies	Updates on pending study status.	Reviewed status of pending studies. Discussion was initiated as to whether or not enrollment to sub-sites in multi-institutional investigator-initiated studies will be counted toward NCI designation. We can enter this enrollment information in Oncore, and will be able to separate out enrollment from our institutions from that of sub-sites for reporting purposes.
Care Pathways	Dr. X	Cancer center has asked disease oriented teams to put together "Care Pathways." The purpose is two-fold: 1) Consistency in treatment of pts 2) This will provide pharmacy with info. regarding the volume of drugs needed to keep in house. Dr. X has gathered all of the order sets for advanced disease lung cancer to start. Mrs. X will assist in putting together the info. Care pathways will include information on supportive care drugs, such as antiemetics, and will eventually be set for all stages of disease.

SAE/ Related Grade 3 Adverse Events Lung Studies

IRB # Phase I/II Study of X and Z Stage IIIA/B NCSLC		
Pt. HAC #9001	*1. Dysphagia & Esophagitis Grade 3 SAE; Pt. hospitalized from 8/16/07-8/20/07 w/ PEG Placement on 8/17/07 Discussion 9/24/07-Resolved*	*2. Anemia Grade 3; Hgb 7.6g/dL – pt. infused w/ 1 unit of RBC on 9/14/07 and 1 unit on 9/17/07 as an outpt. Discussion 9/24/07 – Event resolved.*
Pt. D-W #1013	1. ANC Grade 3 – Treatment related but not dose-limiting	
Pt. M-D #1015	1. Fatigue Grade 3 – ECOG PS 3	
Pt. K-R #1011	1. Fatigue/increased cough/possible radiation pneumonitis SAE; Not enough evidence to determine radiation pneumonitis. If this did occur, it was no more than grade 2; F/U that patient struggled w/ dehydration and fatigue throughout his study participation.	
IRB # Phase I/II Study of X & Z in Locally-Advanced NSCLC		
Pt. BJG #114	1. Renal failure, dehydration, possible pneumonia SAE – Pt. had immediate constipation following dose 3/week 2 of X w/ no bowel movements for 1 week. Pt. was instructed to take a fleets enema and complained of being severely tired and had a fever. Pt. dosed w/ xrt and X the next day, and later presented to ER w/ symptoms as described above. Discussion that this may be treatment related possibly to anzemet as constipation can be a side effect. WBCs were normal upon admission. F/U discussion – this was a DLT. Pt. in hospital for 7 days.	
Pt. J-C #115	1. Elevated liver enzymes Grade 3; Drug was interrupted, and liver enzymes appear to be recovering. Pt to be re-evaluated on 5/21/07. If liver enzymes still elevated at that time, this would be a DLT. This was determined to be a DLT.	
IRB # Phase III Study of X as 1st Line for Patients with Advanced NSCLC		
Pt. E-M #12581001	1. May 2007 Worsening Chest Pain SAE; Pt. hospitalized – unrelated to study drug	*2. 8/9/07 Myocardial Infarction SAE; Pt. hospitalized – unrelated to study drug. Discussion 9/24/07-No comments, related to underlying cardiac disease.*
IRB # Ph I/II Study of Oral X In Combo w/ Z In Pts w/Relapsed/Refractory NSCL Cancer		
Pt. J-T #0014002	1. Chest Pain SAE – Pt. hospitalized – related to disease progression	
Pt. W-C #0014003	1. Hyperglycemia Grade 3 – possibly related. Pt. asymptomatic and diabetic at baseline	
SCCC-02507 Ph I Study of GRN163L in Combo w/ X & Z in Pts w/Advanced or Metastatic NSCLC		
Pt. L-C #001	*1. 8/6/07-8/13/07 Grade 3 Thrombocytopenia – Possibly related Discussion 9/24/07-Study on hold for protocol amendment. Events occurred on starting dose.*	*2. 8/20/07-8/28/07 Grade 3 Neutropenia – Possibly related Discussion 9/24/07-Study on hold for protocol amendment. Events occurred on starting dose of dose-escalation study.*

APPENDIX C

PRMC MEETING MINUTES

July 13, 2007

UT SOUTHWESTERN
MEDICAL CENTER

HAROLD C. SIMMONS COMPREHENSIVE CANCER CENTER
PROTOCOL REVIEW AND MONITORING COMMITTEE

June 13, 2007

Minutes

Meeting called to order at 4:04 pm.

I. PI:
Sponsor: Wyeth Research
Title: A Phase I/II Study in Pediatric Subjects with Relapsed/Refractory Solid Tumors

PRMC Decision: Approve Pending Response

A. This study is described as a Phase I/II however, the protocol states that phase I has already been completed. "The data from phase I should be presented in order to justify the use of the dose pf 75mg/m^2."

B. Although the protocol states that there will be a medical monitor, no Data Safety and Monitoring Committee (DSMC) has been mentioned. Please contact CRO for details and about the UTSW DSMC and for the DSMC template.

C. On page 1 of the consent form under the section *Why am I being asked to take part in this research study*, please change the word have to has in the sentence "which have come back or for which there is no standard therapy."

II. PI:
Sponsor: UTSW
Title: Pilot Study in Relapsed/Refractory Cutaneous T-Cell Lymphoma

PRMC Decision: Approve Pending Response

A. Section 16.1 of the protocol, please specify the method to be used for the confidence interval construction.

B. In the section "Special Precautions" of the project summary it states that Bevacizumab and Cetuximab will be provided to the subjects at no cost to them. Are these drugs part of the study?

C. Section 8.2 of the protocol; please clarify if "Patients will be observed in the GCRC for 24-48 hrs post infusion on days 1, 3 and 5..." is considered to be hospitalization. If so, please describe the inpatient stay in the project summary.

D. The consent form and project summary list Vascular Leak Syndrome (VLS) as a likely side effect and difficulty breathing as a less likely side effect. "Does VLS commonly cause significant fluid retention and difficulty breathing?" If so, should difficulty breathing be in the likely side effect section? Please clarify.

E. "No rationale for the dose is provided in the project summary. As detailed in the protocol, the dose selected is 60% less than the established MTD. The rationale for this dose is based upon the findings that grade 3 or 4 toxicities are not observed among patients treated at doses of 5-10mg/m^2 and the suggestion that T-reg cells might be sensitive to RFT5-dgA at lower doses.

Blood and tissue samples are requested (frequently) for assessment of changes in the immunophenotype or peripheral blood lymphocytes and suppression assays are described; designed to measure T-reg activity *in vitro*. One of the exploratory analysis, (section 16.2) states the following: Logistic regression on response and Cox regression on progression-free survival will be explored with multiple exploratory variables including the $CD25^+$ expression of the CTCL tumor and the changes in the pre-and post-treatment levels of $CD4^+25^+$ T-reg cells. The association of response with other demographic baseline characteristics will be explored. At the conclusion of a cycle of IMTOX-25 (day 5), blood will be drawn and Foxp3 protein levels will be evaluated using FACS analysis. Greater than 50% decreases in Foxp3 protein levels in $CD4^+$ T cells after IMTOX-25 administration, compared to pre-treatment, will be considered a successful reduction.

Given the ability to determine a biologic endpoint(s); in the face of the dramatic dose reduction, would it be reasonable to plan a dose escalation in the absence of a DLT and the absence of a measurable change in CD24+25+ T-reg cells, etc; either on an individual basis or by protocol design if there are no DLT's among the first 3-6 patients and no significant biologic effect..."

III. PI:
Sponsor: Merck
Title: A Study in Patients with Myelodysplastic Syndromes

PRMC Decision: Approve Pending Response

A. Please indicate how many bone marrow aspirates are being done in the consent.

B. No Data Safety and Monitoring Committee (DSMC) has been mentioned. Please contact CRO for details about the UTSW DSMC and for the DSMC template. Please include the template within your documents.

C. The consent states that you anticipate enrolling 20 patients which includes screen failures. Is this feasible?

D. On page 48 of the protocol, "The null hypothesis will be rejected if either arm's posterior probability of having >10% ORR is very high." Please clarify what "very high" is defined as. "Also, for the Bayesian design, it will be much clearer if the prior distributions are specified in the main protocol instead of in the appendix."

IV. PI: .
Sponsor: Department of Defense
Title: Classification of DNA in Benign and Malignant Breast Epithelium

PRMC Decision: Approve Pending Response

A. Please clarify what the asterisks in figure 2 mean.

B. Please define all the acronyms.

C. The protocol states that objective #2 has been completed; please include the data within the protocol. Since the objective has been completed please remove objective #2 from the protocol.

D. On page 3 of the protocol, is 15% methylation considered rare?

E. "On page 2 of the project summary, under both "Marker Identification Phase" and "Panel Validation Phase", one of the risk groups specified are women with untreated primary breast cancer. Another bullet point says that the women must have a clinical breast exam at the time of enrollment with no suspicious findings." Please clarify.

F. "Will it be problematic to define performance status as that with restricted normal activity for a significant portion of the day? Is there a standard definition for "significant" in this context?"

G. "Will there be an incentive for women with lower risk of developing breast cancer to undergo the fine needle aspirate?"

H. "If I understand the consent form correctly the implication is that a women being enrolled on study as part of the low-risk control group is being enrolled because her demographics and breast cancer risk profile match a woman, despite having been at low-risk, has developed breast cancer." Please Clarify.

I. If the objective is to identify the methylation markers, please clarify why expression array is being used when methylation array seems to be more direct.

J. "Will CGH array be done for the experiments?"

K. On page 12 of the protocol, please give justification for the statement "producing an FDR of about 15% would, at most, identify 1000 genes that are differentially expressed."

L. "Which classification methods will be used to discriminate between high and low risk groups?"

V. PI:
Sponsor: Genentech
Title: A Phase II Trial in Patients with Platinum-Sensitive Recurrent Ovary, Primary Peritoneal or Fallopian Tube Carcinoma

PRMC Decision: Approved

APPENDIX D

FULL BOARD IRB 1 MEETING MINUTES

August 6, 2007

The University of Texas Southwestern Medical Center at Dallas
Minutes of Full Board IRB 1 Meeting Held on August 6, 2007
Conference Room – B5

Board Members Present:

Internal Medicine – Chairperson
Internal Medicine
Pediatrics
Biostatistics
Surgery
IRB Staff
Cardiology

Internal Medicine – Vice Chairperson
Psychiatry
IRB Manager
St. Paul/Pharmacist
Neurology

*Alternate Voting Member

Members Absent:

Obstetrics and Gynecology
Community Representative/non-affiliated
Psychiatry
Parkland/Pharmacist/ non-affiliated
Internal Medicine
Pathology
Pediatrics

Ex-officio Attendees:

Total Members Present: 13

Total Number Required for Quorum: 8

Visitor(s): Tyler Bloomer, Intern from CRO

A quorum being assembled and a non-scientist member being present, David R. Karp, MD, PhD called the meeting to order at 1:35 pm. The Minutes from the July 16, 2007 meeting were approved as circulated.

Conflict of Interest:

IRB members required to abstain from voting due to financial relationships with sponsors of clinical research:

Member	Agenda # / Protocol #	Principal Investigator	Sponsor
	#4 072007-058		*F Hoffman-LaRoche*
	#10 092004-028		*AstraZeneca*

Verification from Conflict of Interest Office that all investigators listed on agenda have submitted Statements of Financial Interests:

_____ **Yes** ___X___ **No**

Exceptions: (IRB# 102004-018; Agenda #9)
(IRB# 072006-037; Agenda #12)

Date statement requested: July 30, 2007

List all investigators who have a financial relationship with sponsors of reviewed research.

Investigator	Principal Investigator	Agenda # / Protocol #	Sponsor	Amount of Annual Compensation	Type of Compensation
		#5 072007-059	MedImmune	<$10,000	Scientific Advisory Board
		#5 072007-059	MedImmune	<$10,000	Scientific Advisory Board
		#5 072007-059	MedImmune	<$10,000	Speakers Bureau
		#10 092004-028	AstraZeneca	<$10,000	Consulting

Comments:
disclosed their financial relationships with MedImmune in the consent form for IRB 072007-059 (Agenda #5) and should continue to do so.

disclosed his financial relationship with AstraZeneca in the consent form for IRB 092004-028 (Agenda #10) and should continue to do so.

Continuing Education: N/A

Agenda Item: 01 - **Deferral**

PI:

IRB File Number: 052007-021
Title: A Prospective Clinical Study for GreenLight HPS in the Treatment of Obstructive Benign Prostatic Hyperplasia (BPH)

Reviewer:

Protocol Summary: The purpose of this study is to document the advantages of the GreenLight HPS in a long-term clinical trial.

Prior IRB Action: The study was reviewed and deferred at the May 21, 2007 meeting.

Current Submission: The study is being re-submitted for review and approval.

Discussion: The IRB recommended deferral of this protocol:

Reason(s) for deferral: This resubmission is substantially different from the original study, and did not address, in a point-by-point manner, the original concerns. This made it very difficult for the Board to understand what was being proposed. The combination of the two submissions ends up without a clear study hypothesis and data analysis plan. In the end the Board was uncertain whether this clinical intervention was standard of care or not, whether the decision to use the HPS system was made outside the context of the study, and how much follow up data were being collected purely for research purposes.

1) PROJECT SUMMARY CHANGES:
   a) Under "Concise Summary of Project", information has been added to this section that is not part of the study procedures. For example, the surgical procedure is not for research and should not be included in this section.
   b) Under "Special Precautions", information regarding the DSMB was deleted, but an explanation was not provided for this change. Please clarify, and provide more specific information about how often the sponsor will review the data.

2) CONSENT FORM CHANGES:
   a) Under "Why is this study being done?" please state how the laser treatment and procedures in this study with the GreenLight HPS laser differs from standard of care with the GreenLight HPS laser.

b) Under "Why is this considered research?" please delete references to possible outcomes compared to TURP and state what the research procedures are. State clearly whether patients will be randomized to the stated comparison treatment or not (i.e.TURP).
c) Please answer the question "Why am I being asked to take part in this research study?"
d) Under "How many people will take part in this study?" a total of 40 patients locally was stated in the Project Summary, but 25 are mentioned here, please clarify.
e) Under "Screening Procedures", please state which procedures are standard of care and which are being done solely for the purpose of this study. The standard of care procedures could be placed in an appendix to the consent form.
f) Under "What are the risks of the study?" please state only the risks of the research procedures, other risks of standard of care could be placed in an appendix to the consent form.
g) Under "Will my insurance provider or I be charged for the costs of any part of this research study?" please state clearly which of the procedures are research and which are standard of care.

Controverted Issues: none

IRB Decision(s) and Vote: The Protocol was recommended for deferral.

Vote: For = 11, Abstained = 0, Opposed = 0

Agenda Item: 02

PI:

IRB File Number: 072007-051
Title: Interagency Registry of Mechanically Assisted Circulatory Support

Reviewer:

Protocol Summary: The purpose of this study is to create a national registry of subjects receiving a mechanical circulatory support device (MCSD) to treat end-stage heart failure. Both pediatric and adult subjects will be eligible and DNA samples will be collected.

Discussion: The IRB recommended approval of this protocol with the following stipulations:

1) NR1 FORM CHANGES:
   a) Please provide a copy of the Certificate of Confidentiality.

2) PROJECT SUMMARY CHANGES:
   a)
   b) Please provide copies of the quality of life questionnaire and Trail Making neurocognitive test.
   c) Under "Data to be Collected", please list the specific demographic information that will be collected.
   d) Under "Last 5 Digits of SSN for Database Identification", it is unclear why the last 5 digits of the SSN needs to be collected when there is already a mechanism in place to assign generic ID's, please clarify.

3) CONSENT FORM CHANGES:
   a) Please provide a telephone number that study doctors and research personnel can be reached after regular office hours (both consents).

4) OPTIONAL BLOOD AND TISSUE DONATION TO NHLBI REPOSITORY CONSENT FORM CHANGES:
   a) Please delete the yes/no questions on page 9 of 11, as the purpose of the consent form is to obtain permission to use test a subject's DNA. By checking "no" and then signing the consent form would be a conflict and raise questions about whether subjects are fully informed.

5) HIPAA AUTHORIZATION FORM CHANGES:
   a) Under "What health information will be collected, used and shared (disclosed)?" please include the collection of DNA information.

Other: The Board determined that future reviews of this study should be done on an expedited basis.

IRB Decision(s) and Vote: The Protocol was recommended for approval with stipulations.

The IRB determined that the Chair or designee may approve the research protocol on behalf of the IRB under expedited review procedure after the investigator has complied with the conditions for approval.

Vote: For = 11, Abstained =0, Opposed = 0
Review Interval: 12 months

Findings: The research involves children and was therefore examined against provisions of Subpart D of 45 CFR 46, particularly 46.404 and 46.408. The IRB found the research to be of minimal risk to the child, and adequate provisions are made for soliciting the assent of the child and permission of the parent or guardian. All children under the age of 10 are asked to verbalize their assent/dissent to participate. Children age 10-18 must indicate their assent in writing. The IRB evaluated the degree of risk and found a 12-month review interval is appropriate.

Dr. joined the meeting in progress at 2:15 pm.

Agenda Item: 03

PI:

IRB File Number: 072007-057
Title: Validation of Somatic and Cerebral Near Infared Spectroscopy During Cardiopulmonary Bypass in Pediatric Pateints: A Prospective Clinical Study

Reviewer:

Protocol Summary: The purpose of this study is to validate cerebral and somatic oximetry data presented by a near infrared spectroscopy (NIRS) monitor while on cardiopulmonary bypass (CPB).

Discussion: The IRB recommended approval of this protocol with the following stipulations:

1) PROJECT SUMMARY CHANGES:
   a) The data analysis will be quite challenging and an initial attempt should be made sooner rather than later in the project. The Board was particularly concerned about the proposed subject number. It seems more reasonable to do an interim analysis with data from the first ten subjects. That, accurate numbers can be used for power calculations. This analysis should be made in collaboration with any of the biostatisticians on campus. The results of that analysis must be reported to the Board. before proceeding with additional subjects. Our concern is that a total of fifty may be far too little and we will need to determine if more subjects can safetly and reasonably be studied
   b) The Project Summary and consent form must clearly distinguish between what will be done for patient care, and what is research. Please make it absolutely clear how much blood will be drawn ONLY for research purposes (it says 1-2 ml in some places and 2-3 teaspoons (10-15 ml) in others). The same is true for the risks section. Please describe and discuss ONLY the risks associated with the research project, not anything to do with routine patient care.

2) CONSENT FORM CHANGES:
   a) The consent form needs to be substantially re-written. As it is, it mixes routine clinical care of these complex patients, with what the patient needs to consent to for research purposes. Please remove everything related to standard of care (except for perhaps a brief overview with a clear statement about routine care). As it is written, it is not clear to the patient or family what they are volunteering for. For example, on page 6 of 11, it discusses what the medical team will do if the central catheter is pulled out before the last sample and suggests that the patient might get a needle stick that they might not otherwise get just for research. If this is not true, then remove it. If all that is being done is to draw some extra blood when routine bloods are drawn, then remove the language about bruising, discomfort, infection, excess bleeding, fainting, etc.,

since these are not risks of the research study. The only risks associated with this study are the risk of hypovolemia from drawing a small additional amount of blood, and the minor risk of positioning the catheter in the inferior vena cava. Since this is done under direct visualization in the OR, this risk is quite small.

b) Please delete the "Treatment" section on page 3, as there is no treatment associated with this research.

c) Under "Will my insurance provider or I be charged for the costs of any part of this research study?" please revise the language to read, "No. Neither you, nor your insurance provider will be charged for anything done only for this research study (i.e. screening procedures, experimental procedures, or monitoring/follow-up procedures described above).

Controverted Issues: none

IRB Decision(s) and Vote: The Protocol was recommended for approval with stipulations.

The IRB determined that the Chair or designee may approve the research protocol on behalf of the IRB under expedited review procedure after the investigator has complied with the conditions for approval.

Vote: For = 12, Abstained = 0, Opposed = 0
Review Interval: 12 months

Findings: The research involves children and was therefore examined against provisions of Subpart D of 45 CFR 46, particularly 46.406 and 46.408, as well as the current guidelines for inclusion of children in research. The IRB found the research involves more than minimal risk to the child and presents no reasonable prospect for direct benefit to the child, but is likely to yield generalizable knowledge about the child's disorder or condition. The IRB also found the risks represented a minor increase over minimal risk, the research procedures were reasonably commensurate with experiences inherent in their actual or expected medical, dental, psychological, social, or educational situations, the research is likely to yield generalizable knowledge of vital importance for the understanding or treatment of the child's disorder or condition. Also, adequate provisions are made for soliciting the assent of the child and permission of both the parents or guardian (unless one parent is deceased, unknown, incompetent, not reasonable available, or when only one parent has legal responsibility for the care and custody of the child). All children under the age of 10 are asked to verbalize their assent/dissent to participate. Children age 10-18 must indicate their assent in writing.

Agenda Item: 04

PI:

IRB File Number: 072007-058
Title: A Multi-Center, Randomized, Double-Blind, Placebo-Controlled Phase III Trial Comparing the Efficacy of

Bevacizumab in Combination with Rituximab and CHOP (RA-CHOP) Versus Rituximab and CHOP (R-CHOP) in Previously Untreated Patients With CD20-Positive Diffuse Large B-Cell Lymphoma (DLBCL)

Reviewer:

Protocol Summary: The purpose of this study is to compare bevacizumab in combination with rituximab and cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) (RA-CHOP) versus rituximab and CHOP (R-CHOP) for the treatment of diffuse large B cell lymphoma.

Discussion: The IRB recommended approval of this protocol with the following stipulations:

1) NR1 FORM CHANGES:
   a) Regarding Item #16, please provide a copy of the RSC approval letter.
   b) Regarding Item #19, please provide copies of the recruitment materials that will be used to recruit other patients and the letters being sent to physicians in the Metroplex.
   c) Item 29a, page 13 of 31, Please correct spelling of Riruxin - Rituxan

2) PROJECT SUMMARY CHANGES:
   a) Under "Screening Procedures", please delete the 12th bullet regarding subjects being continuously asked about medication changes, as this information is covered in the last paragraph of this section with the statement, "At every visit subjects will be asked....."
   b) Under "Special Precautions", please clarify if clofarabine and cytarabine are being administered in this study. Please modify this paragraph to reflect medications being administered according to the protocol. Also, prednisone is not being dosed based on body surface area.

3) CONSENT FORM CHANGES:
   a) Please include "Parkland Health and Hospital System" in the header on <u>all</u> consent forms since PHHS has been identified as a resource site on the NR-1.
   b) Under "Will my insurance provider or I be charged for the costs of any part of this research study?" please relocate the second, fourth and fifth paragraphs, to the section "What will happen if I am harmed....." In addition, please clearly outline which medications will be paid for by the study. Specifically, will R-CHOP medications be provided at no cost to the subjects?
   c) Under "What will happen if I am harmed.....", please replace the phrase "free of charge" with "at no cost to you" and relocate this same sentence to the "Will my insurance provider or I be charged....." section. In addition, please delete the sentence beginning "If you develop a problem....." to the end of the paragraph and replace it with, "Compensation for an injury resulting from your participation in this research is not available from the University of Texas Southwestern Medical Center at Dallas or Parkland Health and Hospital System. The sponsor has expressed a willingness to help pay the medical

expenses necessary to treat such injury." Pursuant to University policy all references to third party payorship must be deleted because it produces a detriment to research subjects who do not have insurance coverage. Most health plans have lifetime caps on the amount that they will pay out for a subscriber. Thus, with the inclusion of the third party payor language, injured subjects who have third party insurance would be required to make claims, which would count against their lifetime caps. This, in turn, results in an unacceptable disparity in the treatment of subjects who have third party insurance as opposed to those who do not.

d) Under "Will I be paid...? please clarify if subjects will be reimbursed for travel expenses. The NR-1, Item 17 indicates subjects will not receive incentive. If subjects will be reimbursed for travel expenses, please indicate the amount and method of reimbursement in the Informed Consent and Project Summary.

4) CONSENT FOR BIOMARKER RESEARCH TESTING:
   a) Under "Will I be contacted in the future?" the first sentence will need to be revised in one of two ways. The first option is to state, "You have the option to be contacted in the future in order to obtain follow-up information or have your de-identified specimens kept for use in future research." The other option is to state, "You have the option to be contacted in the future in order to obtain follow-up information or have your specimens kept for use in future research (state specific research areas).
   b) Page 10 of 10 is blank.

5) CONSENT FOR ROCHE SAMPLE REPOSITORY RESEARCH PROJECT:
   a) Under "Why is this study being done?" please spell out "RSR".
   b) Under "Will I be contacted in the future?" the first sentence will need to be revised in one of two ways. The first option is to state, "You have the option to be contacted in the future in order to obtain follow-up information or have your de-identified specimens kept for use in future research." The other option is to state, "You have the option to be contacted in the future in order to obtain follow-up information or have your specimens kept for use in future research (state specific research areas).
   c) Under "How will my samples be identified", in the second paragraph it reads "see the picture below", but there is no picture, please correct.
   d) Page 9 of 9 is blank.

6) PARTNER CONSENT:
   a) This consent form should not be used unless a pregnancy occurs.

7) HIPAA AUTHORIZATION FORM CHANGES:
   a) Please complete and submit a HIPAA Authorization to be used in tandem with the Partner Consent Form.

8) HIPAA REQUEST FOR WAIVER FORM CHANGES:
   a) Regarding item 2, please revise to outline only the information which will be collected to determine eligibility. Currently some of the information listed will

be obtained after the prospective subject's signs the Consent Form and HIPAA Authorization.

Controverted Issues: none

IRB Decision(s) and Vote: The Protocol was recommended for approval with stipulations.

The IRB determined that the Chair or designee may approve the research protocol on behalf of the IRB under expedited review procedure after the investigator has complied with the conditions for approval.

Vote: For = 12, Abstained = 0, Opposed = 0
Review Interval: 12 months

Findings: The IRB found that the risks to the subjects are minimized and are reasonable in relation to the anticipated benefits. The selection of subjects is equitable and adequate provisions are made to protect the privacy of the subjects and to maintain the confidentiality of data. The IRB evaluated the degree of risk and found a 12-month review interval is appropriate.

Dr. joined the meeting in progress at 2:35 pm

Agenda Item: 05

PI:

IRB File Number: 072007-059
Title: A Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Immunogenicity of MEDI-524, A Humanized Enhanced Potency Monoclonal Antibody Against Respiratory Syncytial Virus (RSV), In Children with Hemodynamically Significant Congenital Heart Disease. Protocol MI-CP124-S2.

Reviewer:

Protocol Summary: The purpose of this study is to determine the safety and tolerability of motavizumab (MEDI-524) when given as prophylaxis against serious respiratory synctial virus infection in children with hemodynamically significant congenital heart disease.

Discussion: The IRB recommended approval of this protocol with the following stipulations:

1) NR1 FORM CHANGES:

a) Regarding Item #29, please complete this section for each of the medications (motavizumab and palivizumab) being used in this study (do not combine the information).

2) PROJECT SUMMARY CHANGES:
   a) Under "Concise Summary of Project", please describe the randomization process. In addition, the Consent Form indicates that subjects will not be allowed to take certain medications while participating in the study. Please indicate what these medications are.
   b) Under "Study Day 0 (Study Visit 1):" please clarify as it is indicated that blood will be drawn for study drug levels prior to receiving the study drug.

3) CONSENT FORM CHANGES:
   a) Please review the IRB Consent Form template, the names listed on the consent form should be those of the investigators and those individuals who will obtain consent. Information about contacting research should be stated, "You may call these study doctors or research personnel during regular office hours at [insert phone number]. At other times, you may call them at [insert after hour's phone number]. Following this statement, please add the statement, "If you are a parent or guardian of a minor and have been asked to read and sign this form, the "you" in this document refers to the minor" and revise the consent form accordingly.
   b) In general, the informed consent document should be written in language understandable to an average middle-school reading level (8th grade level). Please provide the definition(s) or lay language term(s) for the following word(s): "chronic lung disease", "difficult congenital heart disease", "safety profile", "measurements of immune response", "medically-attended lower respiratory tract infections", "complicated CHD", "respiratory secretions", "redosed", and "abnormal blood test result", etc. Please note, that definitions only need to be written when the word(s) is initially mentioned in the consent form.
   c) Under "Instructions", please delete the second paragraph as this information is found elsewhere in the consent form.
   d) Please delete the section "Do I have to take part in this research study?" as this information is found elsewhere in the consent form.
   e) Under "Study Medication" in the third paragraph please revise "new antibody" to read "investigational antibody". Please delete the second sentence regarding studies in animals, as subjects do not normally have the background information to decide whether this information is relevant. The rest of the paragraph should be relocated to the "Why is this study being done?" section.
   f) Under "Screening Procedures", please describe how the mucous sample will be collected from the child's nose.
   g) Under "Procedures and Evaluations during the Research", please clearly indicate what medications should not be taken during the study.
   h) At the top of page 8 of 16, the statement "I agree that my child's leftover blood sample....." will need to be revised in one of two ways. The first option is to state, "I agree that my child's de-identified leftover blood and nasal mucous specimens may be kept for use in future research." The other option is to

state, "I agree that my child's leftover blood and nasal mucous specimens may be kept for use in future research regarding (state specific research areas).

i) Under "What will happen if my child is harmed as a result of taking part in this study?" please delete the second sentence beginning, "While your child is taking....." through the end of the paragraph. Pursuant to University policy all references to third party payorship must be deleted because it produces a detriment to research subjects who do not have insurance coverage. Most health plans have lifetime caps on the amount that they will pay out for a subscriber. Thus, with the inclusion of the third party payor language, injured subjects who have third party insurance would be required to make claims, which would count against their lifetime caps. This, in turn, results in an unacceptable disparity in the treatment of subjects who have third party insurance as opposed to those who do not. The language "acted negligently, or has engaged in willful misconduct" sends a very unfavorable and inflammatory message to our patients/subjects. Instead, we prefer "all study procedures and instructions were followed" or similar language. This language accomplishes the same thing, as you can't follow all study procedures and instructions while engaged in willful misconduct or acting in a negligent way.

4) HIPAA AUTHORIZATION FORM CHANGES:
   a) Under "What health information will be collected, used and shared (disclosed)?", Regarding Item #4, the information listed in this item should be consistent with the information listed in the Project Summary, and Consent Form that will be collected as part of the screening process and subjects' participation in the study. Please compare this information with the other documents and revise as needed.

Controverted Issues: The Board considered the conflict of interest posed by the fact that the investigators have financial relationships with Medimmune, the sponsor of the study. It was noted that the level of compensation for Scientific Advisory Boards and Speakers Bureaus was below the University threshold in all cases. Moreover, both drugs being tested in this study are made by Medimmune, negating a rationale to bias the study. By consensus, the Board agreed that the conflict was not significant and did not affect patient safety or contradict Good Clinical Practices.

IRB Decision(s) and Vote: The Protocol was recommended for approval with stipulations.

The IRB determined that the Chair or designee may approve the research protocol on behalf of the IRB under expedited review procedure after the investigator has complied with the conditions for approval.

Vote: For = 13, Abstained = 0, Opposed = 0
Review Interval: 12 months

Findings: The research involves children and was therefore examined against provisions of Subpart D of 45 CFR 46, particularly 46.405 and 46.408, as well as the

current guidelines for inclusion of children in research. The IRB found the research involves more than minimal risk to the child but presents reasonable prospect for direct benefit to the child. The IRB also found the research risks to be justified by the anticipated benefits to the child, and the risk/benefit analysis to be at least as favorable as that presented by available alternative approaches. Also, adequate provisions are made for soliciting the assent of the child and permission of the parent or guardian. All children under the age of 10 are asked to verbalize their assent/dissent to participate. Children age 10-18 must indicate their assent in writing.

Agenda Item: 06 - **Continuing Review**

PI:

IRB File Number: 082006-021
Title: Randomized, Blinded, Multicenter Study of Proteinase 3 PR1 Peptide Mixed with Montanide ISA-51 VG Adjuvant and Administered with GM-CSF in Elderly Patients with AML in First Complete Remission or Adults in Second Complete RemissionL: A Pivotal Study

Reviewer:

Expiration Date August 20

Protocol Summary: The purpose of this study is to determine if 4 subcutaneous injections of Proteinase 3 PR1 Peptide emulsified in Montanide ISA 51 VG Adjuvant (PR1 Vaccine) followed by granulocyte macrophage-colony stimulating factor (GM-CSF) in elderly subjects with AML in first complete remission or adults in second complete remission.

Prior IRB Action: The study received continuing review approval in October 2006.

Current Submission: The study is being submitted for continuing review approval. In addition a modification is being submitted to update study personnel.

Discussion: The IRB recommended approval of this protocol with the following stipulations:

1) CR FORM CHANGES:
   a) Question #19, should be "yes" since there are personnel changes.

2) CONSENT FORM CHANGES:
   a) On page 3 of 15, placebo is described as a pill which could be confusing since this is an injected vaccine. It does clarify this later in the same section in the next two paragraphs, so this is a minor detail.

Controverted Issues: none

IRB Decision(s) and Vote: The Protocol was recommended for approval with stipulations.

The IRB determined that the Chair or designee may approve the research protocol on behalf of the IRB under expedited review procedure after the investigator has complied with the conditions for approval.

Vote: For = 13, Abstained = 0, Opposed =0
Review Interval: 12 months

Findings: The IRB found that the risks to the subjects are minimized and are reasonable in relation to the anticipated benefits. The selection of subjects is equitable and adequate provisions are made to protect the privacy of the subjects and to maintain the confidentiality of data. The IRB evaluated the degree of risk and found a 12-month review interval is appropriate.

Agenda Item: 07 – **Continuing Review**

PI:

IRB File Number: 092005-006
Title: ADVL0416: A Phase I Study of SAHA in Pediatric Patients with Recurrent or Refractory Solid Tumors (including Lymphomas) and Leukemia Followed by a Phase I Study of SAHA in Combination with Cis-Retinoic Acid with Selected Recurrent/Refractory Solid Tumors

Reviewer:

Expiration Date August 22

Protocol Summary: The purpose of this study is to estimate the maximum tolerated dose (MTD) of suberoylanilide hydroxamic acid (SAHA) administered orally once daily for 28 days, and administered once daily for 28 days in combination with 13-cis retinoic acid in pediatric subjects with recurrent or refractory solid tumors and Leukemia.

Prior IRB Action: The study received continuing review approval in August 2006.

Current Submission: The study is being submitted for continuing review.

Discussion: The IRB recommended approval of this continuing review as submitted.

Controverted Issues: none

IRB Decision(s) and Vote: The protocol was recommended for approval as submitted.

Vote: For = 13, Abstained = 0, Opposed = 0
Review Interval: 12 months

Agenda Item: 08 – **Continuing Review**

PI:

IRB File Number: 092005-019
Title: Effectiveness of Switching Antipsychotic Medications: Polypharmacy to Monotherapy

Reviewer:

Expiration Date September 18

Protocol Summary: The purpose of this study is to determine the risks and benefits to subjects with schizophrenia or schizoaffective disorder of taking two antipsychotic medications vs one antipsychotic medication.

Prior IRB Action: The study received continuing review approval in September 2006.

Current Submission: The study is being submitted for continuing review and approval. In addition a modification has been submitted to increase the number of subjects from 18 to 44 and to add study personnel.

Discussion: The IRB recommended continuing review approval of this protocol as submitted.

Controverted Issues: none

IRB Decision(s) and Vote: The protocol was recommended for approval as submitted.

Vote: For =13, Abstained = 0, Opposed = 0
Review Interval: 12 months

Findings: The IRB found that the risks to the subjects are minimized and are reasonable in relation to the anticipated benefits. The selection of subjects is equitable, and adequate provisions are made to protect the privacy of the subjects and to maintain the confidentiality of data. The progress report is complete. The consent forms are appropriate. Renewal of this protocol is approved with stipulations.

Agenda Item: 09– **Continuing Review**

PI:

IRB File Number: 092004-028
Title: A Randomized, Double-Blind, Placebo Controlled Add-On Trial of Quetiapine in Patients with Bipolar Disorder and Cocaine Dependence

Reviewer:

Expiration Date September 19

Protocol Summary: The purpose of this study is to determine whether Quetiapine add-on therapy is associated with decrease in cocaine use and cravings and/or decrease in mood symptoms in subjects with bipolar disorder.

Prior IRB Action: The study received continuing review approval in September 2006.

Current Submission: The study is being submitted for continuing review. Nine subjects are receiving the study medication and one subject has completed the study. A modification has been submitted to revise the phone number listed on the Spanish recruitment flyer.

Discussion: The IRB recommended approval of this protocol with the following stipulations:

1) PROGRESS REPORT:
   a) The Progress Report indicates that 9 subjects have been enrolled in the study, but the CR form indicates that 34 subjects have been enrolled. Please note, that everyone that fills out a consent form is a participant including screening failures. Please clarify.
   b) The AE report shows that on June 11, 2007, a 41 year old male experienced a possible MI, has there been any additional information regarding whether the subject is continuing to participate in the study?

Controverted Issues: none

IRB Decision(s) and Vote: The Protocol was recommended for approval with stipulations.

The IRB determined that the Chair or designee may approve the research protocol on behalf of the IRB under expedited review procedure after the investigator has complied with the conditions for approval.

Vote: For = 13, Abstained = 0, Opposed = 0
Review Interval: 12 months

Findings: The IRB found that the risks to the subjects are minimized and are reasonable in relation to the anticipated benefits. The selection of subjects is equitable, and adequate provisions are made to protect the privacy of the subjects and to maintain

the confidentiality of data. The progress report is complete. The consent forms are appropriate. Renewal of this protocol is approved with stipulations.

Agenda Item: 10 – **Continuing Review**

PI:

IRB File Number: 082005-057
Title: INTACS Prescription Inserts Used to Treat Patients with Keratoconus as a Humanitarian Use Device

Reviewer:

Expiration Date August 28

Protocol Summary: The purpose of this study is to use INTACS® prescription inserts as a Humanitarian Use Device as an ophthalmic medical device designed for the reduction or elimination of myopia and astigmatism in subjects with keratoconus.

Prior IRB Action: The study received continuing review approval in August 2006.

Current Submission: The study is being submitted for continuing review.

Discussion: The IRB recommended continuing review approval of this protocol as submitted.

Controverted Issues: none

IRB Decision(s) and Vote: The protocol was recommended for approval as submitted.

Vote: For = 13, Abstained = 0, Opposed =0
Review Interval: 12 months

Agenda Item: 11 – **Continuing Review**

PI:

IRB File Number: 072006-037
Title: Determination of Hepatic Energetics by Stable Isotope Tracers and MR Spectroscopy

Reviewer:

Expiration Date September 16

Protocol Summary: The purpose of this study is to determine hepatic ketogenesis, TCA cycle flux, B-oxidation and gluconeogenesis after a 4-hour fast, after an overnight fast and after a 36-hour fast.

Prior IRB Action: The study received initial approval in September 2007.

Current Submission: The study is being submitted for continuing review. A modification to the Project Summary has been submitted to include phenylacetate or phenylbutyrate, compounds (very similar to acetaminophen) will be used as a non-invasive way to measure liver function. **No subjects have been enrolled.**

Discussion: The IRB recommended continuing review approval of this protocol as submitted.

Controverted Issues: none

IRB Decision(s) and Vote: The protocol was recommended for approval as submitted.

Vote:	For = 13, Abstained = 0, Opposed = 0
Review Interval:	12 months

Findings: The IRB found that the risks to the subjects are minimized and are reasonable in relation to the anticipated benefits. The selection of subjects is equitable, and adequate provisions are made to protect the privacy of the subjects and to maintain the confidentiality of data. The progress report is complete. The consent forms are appropriate. Renewal of this protocol is approved with stipulations.

Recorder: Denise Landers, Program Coordinator

REFERENCES

1. National Cancer Institute. Cancer Clinical Trials: The In-Depth Program. Bethesda, MD. 2005.

2. American Cancer Society. Cancer Facts and Figures. 2006. http://www.cancer.org

3. Dilts DM, Sandler AB. Invisible barriers to clinical trials: The impact of structural, infrastructural, and procedural barriers to opening oncology clinical trials. J Clin Oncol. 2006 Oct 1;24(28):4545-52.

4. Simmons Comprehensive Cancer Center: UT Southwestern Medical Center. 2007. http://www.utsouthwestern.edu/utsw/home/simmons/index.html

5. Gray R, Manola J, Saxman S, Wright J, Dutcher J, Atkins M, Carducci M, See W, Sweeney C, Liu G, Stein M, Dreicer R, Wilding G, DiPaola RS. Phase II clinical trial design: methods in translational research from the Genitourinary Committee at the Eastern Cooperative Oncology Group. Clin Cancer Res. 2006 Apr 1;12(7 Pt 1): 1949-50.

6. World Health Organization. Handbook for Good Clinical Research Practice. http://www.who.int/medicines/areas/quality_safety/safety_efficacy/gcp1.pdf

7. Simmons Cancer Center Protocol Review Form: UT Southwestern Medical Center. 2006. http://www8.utsouthwestern.edu/vgn/images/portal/cit_56417/9/5/267249PRMC_Form.pdf

8. National Cancer Institute. CTEP. The Investigators Handbook: A Manual for Participants in Clinical Trials of Investigational Agents. 2007. http://ctep.cancer.gov/handbook/hndbk_toc.html

9. Clinical Research Office Policy & Procedure Manual: UT Southwestern Medical Center. 2007.

10. Pre-Review: UT Southwestern Medical Center. 2007. http://www8.utsouthwestern.edu/utsw/cda/dept27777/files/68732.html

11. Cohen JJ, Siegel EK. Academic medical centers and medical research: the challenges ahead. JAMA. 2005 Sep 21;294(11):1367-72.

12. Mansbach J, Acholonu U, Clark S, Camargo CA. Variation in institutional review board responses to a standard, observational, pediatric research protocol. Acad Emerg Med. 2007 Apr;14(4):377-80. Epub 2007 Feb 20.

13. Jones JS, White LJ, Pool LC, Dougherty JM. Structure and practice of institutional review boards in the United States. Acad Emerg Med. 1996 Aug;3(8):804-9.

14. Dziak K, Anderson R, Sevick MA, Weisman CS, Levine DW, Scholle SH. Variations among Institutional Review Board reviews in a multisite health services research study. Health Serv Res. 2005 Feb;40(1):279-90.

15. Institutional Review Board: UT Southwestern Medical Center. 2007. http://www8.utsouthwestern.edu/utsw/cda/dept31018/files/41623.html

16. The Federalwide Assurance: U.S. Department of Health and Human Services Office for Human Research Protections. 2007. http://www.hhs.gov/ohrp/humansubjects/assurance/filasuri.htm

17. Amdur, Robert. Institutional Review Board Member Handbook. Sudbury, MA. Jones and Bartlet. 2003.

18. Radiation Safety: UT Southwestern Medical Center. 2007. http://www8.utsouthwestern.edu/utsw/cda/dept145569/files/146385.html

19. Institutional Review Board Investigators' Manual: UT Southwestern Medical Center. 2007. http://www8.utsouthwestern.edu/vgn/images/portal/cit_56417/16/5/89959im.pdf

20. Levine RJ, Lasagna L. Demystifying central review boards: current options and future directions. IRB. 2000 Nov-Dec;22(6):1-9.

21. Western Institutional Review Board. Investigator Handbook: A Guide for Researchers. Olympia, WA. 2006. http://www.wirb.com/download/Guide%20for%20Researchers%20090605.doc

22. Wechsler, Jill. Central vs. Local: Rethinking IRBs. Applied Clinical Trials. 2007. http://www.actmagazine.com/appliedclinicaltrials/article/articleDetail.jsp?id=401619

23. American Society of Clinical Oncology. American Society of Clinical Oncology Policy Statement: Oversight of Clinical Research. J Clin Oncol. 2003 Jun 15;21(12);2377-2386.

24. Dilts DM, Sandler AB, Baker M, Cheng SK, George SL, Karas KS, McGuire S, Menon GS, Reusch J, Sawyer D, Scoggins M, Wu A, Zhou K, Schilsky RL; Case of Cancer and Leukemia Group B. Processes to activate phase III clinical trials in a Cooperative Oncology Group: the Case of Cancer and Leukemia Group B. J Clin Oncol. 2006 Oct 1;24(28):4553-7.

25. McNeil C. Central IRBs: why are some institutions reluctant to sign on?. J Natl Cancer Inst. 2005 Jul 6;97(13):953-5.