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Abstract

The debate on the flaws and challenges faced by the Institutional Review Board (IRB) has been going on from its inception. The Office of Inspector General (OIG) in the department of Health and Human Services along with the FDA have reported on the current situation calling upon experts to find solutions to the laborious and inefficient human subject protection protocol review system. In spite of the emergence of thousands of IRB's and newer proposed models of review systems, the current system still remains inefficient. This is a problem faced in all countries and there is an overwhelming need for an efficient, ethically equipped, and standard system to review, regulate and monitor clinical research. A national standardized clinical research review board (CRRB) would enable in safely securing research and its subjects and advance science and ethics.

Gaining New Insights on Improving the Current System of Institutional Review Boards Research Site Interaction: A Novel Approach

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CHAPTER I

Introduction

Clinical research is an important aspect of scientific research and is carried out on a multi-national basis at institutions around the globe. It has become an integral aspect of universities, medical institutions, and hospitals. Conducting clinical research is not only a source of revenue but also imparts prestige to the institutions and investigators.

In 1747, James Lind, a pioneer physician of the British Royal Navy, conducted what was perhaps the first ever clinical trial; he proved that citrus fruits cure scurvy. The disease is known to be caused by a Vitamin C deficiency causing ulcers of the lower legs and feet, bleeding, loss of teeth and hair, opening of old wounds, depression, hallucinations, blindness and, eventually, death. In his experiment, he divided twelve scorbutic sailors into six groups. They all received the same diet, and in addition, group one was given a quart of cider daily, group two received twenty-five drops of elixir of vitriol, group three received six spoonful vinegar, group four received half a pint of sea water, group five received two oranges and one lemon and, the last group received a spicy paste plus a drink of barley water. Treatment group five stopped after six days when they ran out of fruits, but by that time one sailor was fit for duty and the other had almost

recovered. This clearly led to the establishment of citrus fruits over other remedies for treating scurvy. Although it established the importance of citrus fruits for treating scurvy it took forty years for the Navy admiral officials to supply lemon juice to ships. (www.bbc.co.uk). Since then, clinical research has developed into a vital experimental tool to test hypotheses, but there are still many issues that need to be clarified and refined.

Government agencies and sponsors have amended the way research is conducted due to misuse of subjects, conflict of interest, financial conflicts, and experimenter's biases. The Nuremberg Code, Belmont Report, and International Conference on Harmonization (ICH) guidelines have all been adopted to standardize and correct the flaws in the clinical research process. The first public law in United States calling for establishment of the National Commission for the Protection of Human Subjects in biomedical and behavioral research came about in 1974 as a result of the abuse of 300 rural black men over a period of forty years in the Tuskegee Syphilis Study (Katz et al, 2006). Further revisions of these laws by National Institutes of Health (NIH) and the United States Public Health Service (USPHS) lead to the establishment of the Institutional Review Boards (IRB) through out the United States in 1974. Today these laws and regulations are described in Codes of Federal Regulation (CFR), title 45, part 46 (www.fda.gov, OIG-HHS, 1998).

The number of research protocols submitted to the IRB for review has increased dramatically over the last two decades (McWilliams et al, 2003). The Food and Drug Administration (FDA) and Office of Human Research Protection (OHRP) have approved a system of independent IRBs by granting Federal-wide Project Assurances (FWAs) to review and approve federally funded or industry sponsored research projects. Currently, local institutionally based IRBs and central IRBs are doing the job of reviewing, approving and regulating the local research sites carrying out human subject research protocols; however, the system of local institutional IRB and independent IRBs often fall short of meeting today's needs (DHHS - Office of Inspector General, 1998; Dyrbye et al., 2007; Nowak et al., 2006; www.FDA.gov).

The need for changes in the current local and independent central IRB review-approval process has been debated for decades. In countries such as Tasmania, a common centralized IRB system for all fields of research has been adopted. In Great Britain and New Zealand a dual system using both central and local IRBs is utilized (Fitzgerald and Phillips, 2006). The United States and Canada have a decentralized IRB system, having local institutional IRB such as hospital and university IRBs, independent IRBs, and centralized IRBs depending on the research site preference and institutional policies that use them (www.fda.gov, www.hhs.gov). All these countries face similar problems reflecting the flaws of the current IRB system (Fitzgerald and Phillips, 2006). An

ideal solution for the IRB review process has yet to be developed and problems such as laborious and inefficient review and approval process on most of the research protocols as well as failing to apply the codes of federal regulations (CFR) in human subject protection still presents a challenge. Some of the common issues that need to be addressed include: 1) the differences in the review process between IRB committees, 2) differences in the intra-IRB committees, 3) delays in the initiation of a protocol, 4) problems associated with submitting a protocol to multiple IRB committees for review and 5) the ongoing process of reporting new adverse events to multiple IRBs (Dyrbye et al., 2007).

Table 1: Countries and Their Adopted IRB Review System. (Fitzgerald and Phillips, 2006)

Primary IRB System	Country
Centralized	Tasmania
Dual System	United Kingdom, New Zealand
Decentralized System	USA, Canada and Australia

CHAPTER II

Gaining New Insights on Improving the Current System of Institutional Review Boards Research Site Interaction: A Novel Approach

Specific Aims

The aim of my internship project is to examine the process of IRB review-approval and the ongoing communication between research sites and IRBs involving human subject research protocols. The day-to-day challenges associated with IRBs, especially involving multiple IRB committee review of the same multisite research protocol will be assessed after reviewing the literature. The following specific aims will be addressed:

Specific Aim 1: Examine and evaluate challenges associated with IRB review process of research protocol.

Specific Aim 2: Propose a new model of an ethics review committee (Human Subject Protection Panel) to improve the current IRB review-approval system and develop a research protocol to evaluate the proposed model.

Materials and Methods

A literature search using PubMed database, Ovid, World Wide Web internet, Wikipedia, Google search engine, journals at UNTHSC library, review of references cited by other publications, and the reports from the Office of Inspector General (OIG) department of HHS and FDA on the current system of IRB were used to examine the specific areas of weakness in the current protocol review system and discuss suggestions for improvements.

Background and Significance

During the Second World War, Nazi physicians conducted painful and deadly human experimentations on thousands of war prisoners. These experiments were aimed to facilitate the survival of German military personnel and were divided into three categories according to the United States Holocaust Memorial museum.

The first category included high altitude experiments using a low-pressure chamber to determine the maximum altitude from which crews of damaged aircraft could land safely with parachutes. Freezing experiments in which naked subjects were forced to endure water temperatures below freezing for up to three hours were designed to test various rewarming techniques. They also tested various methods of making seawater potable by giving prisoners only chemically-processed seawater to drink (www.ushmm.org).

The second category of experimentation was aimed at developing and testing pharmaceuticals and treatment methods for injuries and illness which German military and occupation personnel encountered. Scientist tested sera and immunization products in the treatment of diseases, including typhoid, yellow fever, tuberculosis and infectious hepatitis. Malaria experiments where conducted on more than a thousand prisoners. Men and women were infected with malaria

by injecting extracts of the mucous glands of mosquitoes and then treated with various agents to test the relative efficiency of drugs. To test pharmaceutical agents, fresh wounds were inflicted and infected with bacteria such as streptococcus, gas gangrene, and tetanus and then treated with sulfonamide and other drugs to determine the effectiveness of these drugs. Prisoners were also subjected to phosgene and mustard gas to test antidotes for these criminal weapons (www.ushmm.org).

The third category of experiments was aimed at determining the racial differences to various contagious diseases and were sought to advance ideological tenets of Nazi worldview. Experiments on twins, Roma Gypsies and Jews were conducted to establish the racial inferiority. Sterilization experiments and experiments with poison and incendiary bombs were also included in their brutal research (www.ushmm.org).

As a result of these experimentations, twenty-three Nazi doctors and scientists were tried in what has become known as the ***Doctors' Trial***. Of the twenty-three professionals tried at Nuremberg, fifteen were convicted, seven of them were condemned to death by hanging and eight received prison sentences of ten years to life. Eight professionals were acquitted. These experiments gave rise to the development of the Nuremberg Code of medical ethics, which includes, stressing the need for informed consent and preclinical animal studies before

doing any human research, all research is to be conducted by qualified scientists to keep any risks such as mental and physical sufferings to a bear minimum, to inform the subjects about the risks and benefits as well standard treatments available before starting the procedures, and any research leading to disability or death must not be conducted (Paul Weindling, 2001).

Food, Drug and Cosmetic Act

In 1937, the pharmaceutical company, Massengill Co, created ***Elixir Sulfanilamide*** a preparation of sulfanilamide using diethylene glycol (DEG) as a solvent. The company's chief pharmacist was not aware of the poisonous effect of DEG and marketed the preparation which lead to death of more than a hundred people who consumed it (www.wikipedia.org). At that time there were no regulations requiring pre-market safety testing of new drugs which led to US government passing the 1938 **Federal Food, Drug, and Cosmetic Act** (FFDCA, FDCA, or FD&C). This required companies to perform safety tests on their proposed new drugs and submit the data to the FDA before being allowed to market their product in the United States (www.fda.gov).

Thalidomide Tragedy

Thalidomide (2-(2, 6-dioxo-3-piperidyl) isoindole-1, 3-dione), is a sedative, hypnotic, and multiple myeloma medication developed by German

pharmaceutical company Grünenthal. It was sold from 1957 to 1961 in almost 50 countries under at least 40 names, including Distaval, Talimol, Nibrol, Sedimide, Quietoplex, Contergan, Neurosedyn, and Softenon. Thalidomide was chiefly sold and prescribed during the late 1950s and early 1960s to pregnant women, as an antiemetic to combat morning sickness and as an aid to help them sleep (Linda Bren, 2001). Inadequate tests to assess the safety during pregnancy were performed prior to marketing thalidomide. From 1956 to 1962, approximately 10,000 children were born with severe limb malformations known as phocomelia, because their mothers had taken thalidomide during pregnancy. The FDA rejected the application for marketing thalidomide six times after the sponsor company continually failed to provide safety data on pregnant women even though it was widely used in Europe and many other countries. In reaction to the tragedy, the United States Congress amended the food Drug and Cosmetic act in 1962 requiring tests for safety during pregnancy before a drug can receive approval for sale in the U.S., other countries enacted similar legislation. The Thalidomide tragedy led to the framing of ICH Declaration of Helsinki in 1964. Thalidomide was not prescribed or sold for decades and was banned completely from use for many years but recently it has been re-discovered to be of use in the treatment of skin lesions of leprosy and Crohn's disease (Linda Bren, 2001, www.fda.gov; www.wikipedia.org).

Tuskegee Study 1932-1972

The Tuskegee Study of Untreated Syphilis in the Negro Male, also known as the Tuskegee Syphilis Study, was conducted between 1932 and 1972 in Tuskegee, Alabama. In this study, more than three hundred and fifty poor and illiterate black sharecroppers were denied treatment for syphilis (Katz et al, 2006).

This was a notorious study because it was conducted without due care to its subjects, and led to major changes in how patients are protected in clinical studies. Individuals enrolled in the Tuskegee Syphilis Study did not give informed consent and were not informed of their diagnosis; instead they were told they had "bad blood" and would receive free medical treatment, rides to the clinic, meals and burial insurance in case of death in return for participating (Katz et al, 2006).

When the study started in 1932, standard treatments for syphilis were toxic, dangerous and of questionable effectiveness. Part of the original goal of the study was to determine if patients were better off not being treated with these toxic remedies. By 1947, penicillin had become the standard treatment for syphilis. Prior to this discovery, syphilis frequently led to a chronic, painful and fatal multi-system disease. Rather than treat all syphilitic subjects with penicillin and close the study, or split off a control group for testing penicillin, the Tuskegee scientists withheld penicillin and information about penicillin, purely to continue to study how the disease spreads and kills. Participants were also prevented from

accessing syphilis treatment programs that were available to other people in the area. The data from these experiments was collected from the autopsies. These subjects were deliberately left to degenerate to tertiary syphilis and its complications and to die. As a consequence of withholding the information of a diagnosis of syphilis, twenty-eight subjects died directly due to syphilis, one hundred died due to its complications, forty of their wives were infected and nineteen of their children were born with congenital syphilis (Borgna Burnner, www.infoplease.com). The study continued until 1972, when a leak to the press resulted in its termination.

The Tuskegee Study was flawed and unethical in many aspects and it was referred by media as "the experiment that used human beings as laboratory animals in a long and inefficient study of how long it takes syphilis to kill someone" (Katz et al, 2006). It has been cited as "arguably the most infamous biomedical research study in U.S. history (Katz et al, 2006). The Tuskegee Study led to the first public law 93-348 in 1974, The National Research Act. This act called for the establishment of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research to develop principles and boundaries for conducting ethical research and also establishing the Institutional Review Boards (IRBs) at all institutions receiving federal grants.

Because of the abuses and exploitation of human research subjects earlier, the human subject protection panel was established in 1970's. Research during

this time was, for the most part, conducted at a single site in large university or academic medical centers settings. This era called for a local body to govern, monitor and protect the research subjects lending to the creation of the current system of Human Subject Protection Panel established at local institutions.

The National Research Act 1974 (Public Laws: 93-348)

The National Research Act (Pub. L. 93-348), established in July 12, 1974, the law framed the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research that provides us with the pillars of basic ethical principles. These principles underlie the conduct of biomedical and behavioral research involving human subjects and develop guidelines which should be followed by all institutions conducting research. In order to carryout this task, the Commission considered the following clauses: (1) Boundaries to delineate research and routine practice of medicine, (2) Assessment of risk-benefit ratio in research involving human subjects, (3) Guidelines for the selection of human subjects for participation in such research and (4) Aspects and dimensions for framing informed consent in various research settings (www.wikipedia.org, www.fda.gov).

The Belmont Report- 1979

Based on the work of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (1974-1978), the

Belmont Report provides us with the definite ethical principles and guidelines for research involving human subjects and even today stands as the foundation for all the research activities. The main principles of this report are the following (Belmont Report, www.hhs.gov).

A. Boundaries Between Practice and Research

In order to know what activities should undergo review from the human subject protection panel, it is important to distinguish between biomedical and behavioral research from the standard practice. Any activity designed to test a hypothesis, allow conclusions to be drawn, and develop knowledge should be considered research and undergo risk benefit review before being conducted (Belmont Report, www.hhs.gov).

B. Basic Ethical Principles

1. Respect for Persons: Respect for persons incorporates first, individuals should be treated as autonomous agents and second, persons with decreased or compromised autonomy are entitled to protection. These are the two most important ethical convictions of the principle of respect for persons.

2. Beneficence: The term "beneficence" is referred to the expressions of complementary beneficent actions such as (1) do not harm and (2) maximize possible benefits and minimize possible harms.

3. Justice: Justice is equality, who is equal and who is unequal? And in what respects should people be treated equally. The pillars of justice are (1) to each person an equal share, (2) to each person according to individual need, (3) to

each person according to individual effort, (4) to each person according to societal contribution, and (5) to each person according to merit. It should assure fairness in distribution (Belmont Report, www.hhs.gov).

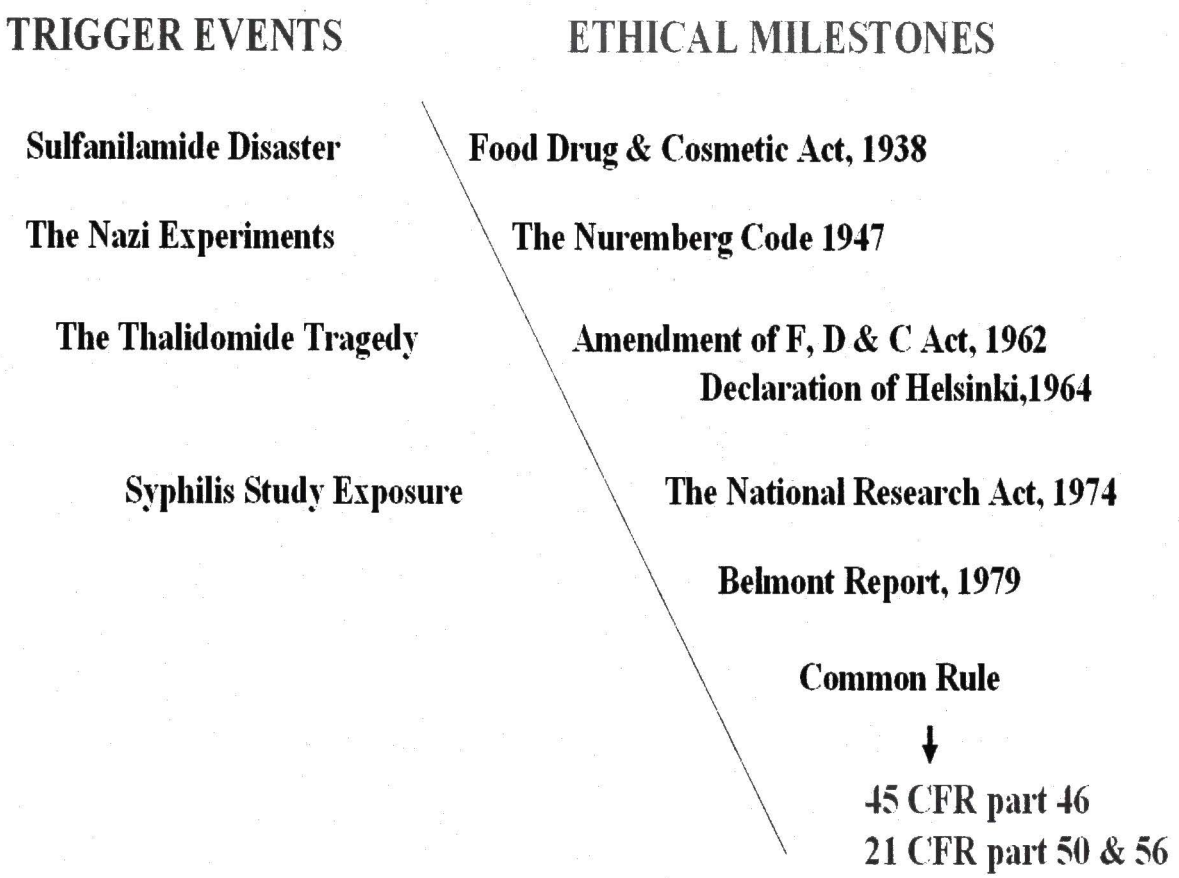
C. Applications

1. Informed Consent: Respect for persons requires that subjects to agree and, given the opportunity, to choose what shall or shall not happen to them in case of research and what is the standard method of treatment. This is a voluntary decision made by the research subject completely willing to be involved in the research after knowing the benefits and risks about the study.

2. Assessment of Risk and Benefits: The study subjects would be presented with all the foreseeable and anticipated risks and benefits which is reviewed and already approved by the human subject protection panel which is presented to the research subject who later voluntarily decides to consent or dissent enrollment.

3. Selection of Subjects: Justice in the selection of subjects would require researcher's to exhibit fairness that is they should not offer potentially beneficial research only to some patients who are in their favor or select only "undesirable" persons for risky research. Today we have randomization of patients and blinding of studies to make justice to subject selections. These principles of the Belmont Report and Common Rule are main guidelines for IRB and research regulatory authorities to oversee all research (Belmont Report, www.hhs.gov).

Figure 1: Milestones Achieved in Protection of Human Subjects.



Institutional Review Board

The role of the IRB is to protect the rights and welfare of human research subjects (Rozovsky and Adams, 2003). Regulations require IRB review and approval for research involving human subjects if it is funded or regulated by the federal government. Research institutions, professional organizations, and journals apply the same requirements to all human research. The Codes for IRB's

functions are listed in title 45 CFR 46.

The Composition of the IRB must include at least five members of both genders from varied professional backgrounds (Rozovsky and Adams, 2003). One of the members must have expertise in the area of the protocol being reviewed and at least one member must be a nonscientist whose interest should be concerned with the lay public. The IRB is authorized to verify, approve, disapprove, amend and observe the research protocols. They can at times even observe the consent process and research procedures of all the protocols submitted to them. In case of any violations and adverse events they are able to suspend or terminate a research study (Rozovsky and Adams, 2003).

An IRB review can be of three types: full board review, expedited review, and exempt review. Each type of IRB review has been described in the CFR and it is the soul discretion of the IRB to determine what kind of review and the frequency of continuing review a protocol undergoes and not the investigators (Rozovsky and Adams, 2003).

Full committee review is the standard type of IRB review where all members receive basic information about the research application. A "primary reviewer" with expertise in the study area is assigned to conduct a thorough review of the IRB application and any accompanying documentation (e.g., an

Investigator's Brochure, protocol, informed consent or grant application). The "primary reviewer" will then report his/her findings for discussion at a convened meeting of the full board. Reviewers may contact the investigator with questions or suggestions prior to the meeting. The IRB may ask that investigators attend the IRB meeting or be available by phone to answer questions that may arise. The review must be conducted at a convened meeting of the IRB with a majority of members present. All of the requirements specified in code of federal regulation, 45 CFR part 46 and 21 CFR part 56 should be satisfied and approved by a majority of the members. IRB members who have a conflict of interest to the protocol being reviewed cannot participate in the review (Rozovsky and Adams, 2003).

The information the expedited reviewer(s) is (are) required to consider is the same as if the submission were receiving Full Committee Review. Federal regulations permit the IRB chairperson or one or more experienced members to do an expedited review, if the following two criteria are established. First, the research may not involve more than "minimal risk" meaning 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 (Oki and Zaia, 2006). Second, clinical studies involving drugs or medical devices for which an investigational new drug (IND) or an investigational device exemption (IDE)

application is *not* required and, a study with a cleared/approved medical device that is being used in accordance with its cleared or approved labeling (Oki and Zaia, 2006).

Federal guidance indicates that applying exempt status to a project is a decision to be made by the IRB. The following categories of research are eligible for exemption status: (1) research conducted in established or commonly accepted educational settings, involving normal educational practices; (2) research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior; (3) research involving the collection or study of freely available de-identified existing data, documents, records, pathological specimens, or diagnostic specimens; (4) research and demonstration projects conducted by heads of government departments or agencies which are designed to evaluate public programs; and (5) taste and food quality evaluation and consumer acceptance studies (Prentice and Oki, 2006).

The current system of IRB, its functions and regulations have been in debate for decades (Wood et al, 2004, Fitzgerald and Phillips, 2006, McWilliams et al, 2006, Dyrbye et al, 2007). In order to protect human subjects and oversee scientific investigators and pharmaceutical companies, the current IRB system was established at all the research sites, but there still remain serious flaws within

the IRB system. Today, not only is it necessary to inspect research sites, investigators and sponsors but also the IRBs, which were created to oversee the research sites and support investigators.

Code of Federal Regulation 45 CFR part 46

Currently, the IRBs in the United States are governed by Title 45 CFR (Code of Federal Regulations) Part 46. The Research Act of 1974 defines IRBs and requires them to review and approve all research that receives funding, directly or indirectly, from the Department of Health and Human Services (HHS). (www.fda.gov) IRBs are regulated by the Office for Human Research Protections (OHRP). IRBs were developed as a result of research abuses earlier in the twentieth century. Two of the most notorious of these abuses were The Nazi Experiments, that became a focus of the post-World War II Nuremberg Trials in Germany, and The Tuskegee Syphilis Study in US.

Maintaining research integrity and protecting human subjects due to lack of standard operating procedures and inability to apply and maintain the common rule have remained flawed and we have seen most recently disasters such as the Vioxx and TGN1412 studies.

Rofecoxib is a nonsteroidal anti-inflammatory drug (NSAID) which was developed by Merck & Co, to treat osteoarthritis, acute pain conditions, and

dysmenorrhoea (Bombardier et al, 2000). Rofecoxib was approved as safe and effective by the Food and Drug Administration (FDA) on May 20, 1999 and marketed under the brand names Vioxx, Ceoxx and Ceeoxx. Rofecoxib gained widespread acceptance among physicians treating patients with arthritis and other conditions causing chronic or acute pain. Worldwide, over 80 million people were prescribed rofecoxib at some time. In 2000 the VIGOR (Vioxx GI Outcomes Research) study, conducted by Bombardier and coworkers compared the efficacy and adverse effect profiles of rofecoxib and naproxen, had indicated a significant 4-fold increased risk of acute *myocardial infarction* (heart attack) in rofecoxib patients when compared with *naproxen* patients over the 12-month span of the study (Bombardier et al, 2000). The difference in overall risk was accounted for by the patients at higher risk of heart attack, i.e., those meeting the criteria for low-dose aspirin prophylaxis of secondary cardiovascular events (previous myocardial infarction, angina, *cerebrovascular accident*, *transient ischemic attack*, or *coronary artery bypass*). The results of the VIGOR study were submitted to the US FDA in February 2001, which led to the introduction, in April, 2002, of warnings on Vioxx labeling concerning the increased risk of cardiovascular events (Bombardier et al, 2000).

TGN1412, also known as CD28-SuperMAB, is a humanized monoclonal immunomodulatory drug, intended for the treatment of B cell chronic lymphocytic leukemia (B-CLL) and rheumatoid arthritis (Lin et al, 2004). It is a

strong agonist for the CD28 receptor of the T cells (Lin et al, 2004). In its first human clinical trials, in March, 2006, it caused catastrophic systemic failure in the volunteer subjects, despite being administered at a supposed sub-clinical dose of 0.1 mg per kg. This dose was approximately 500 times lower than the dose found safe in animals and resulted in the hospitalization of six volunteers in March, 2006. At least four subjects suffered multiple organ dysfunctions, and one trial volunteer is said to be showing signs of developing cancer (Suntharalingam et al, 2006). The developing company, TeGenero Immuno Therapeutics, entered into insolvency proceedings later in 2006. Opinions from an as-yet uncompleted inquiry suggest that the problems arose due to "unforeseen biological action in humans", rather than breach of trial protocols, and the case therefore has had important ramifications for future trials of potentially powerful clinical agents (www.wikipedia.org).

Emergence of Independent IRB & Assurances

In order to cope with the job of reviewing the voluminous number of the research projects and clinical trial protocols, there has been the emergence of independent IRBs (OIG-HHS report, 1998). Independent IRBs help in reviewing the protocols for many local investigators and large institutions. This has become one of the most acceptable ways of reviewing the protocols. Pharmaceutical companies and the private clinic physicians have the advantage of having their protocols reviewed and put into operation in a more efficient manner (OIG report,

Emergence of Independent IRB, 1998).

In the early 1990s, independent IRBs reviewed only industry or private investigator sponsored research protocols, but the FDA and the OHRP later approved the system of independent IRBs to review the federal funded research along with industry sponsored protocols by giving single project assurances (SPA), multiple project assurances (MPA) and cooperative project assurances (CPA) (www.fda.gov, OIG-HHS, 1998). By these Federal-wide assurances the independent IRBs could review federally funded human research projects along with private industry sponsored and investigator initiated protocols. Some institutions now have independent IRBs as the IRB of record for their institutions to review research protocol for them.

Independent IRBs charge a substantial fee for reviewing protocols which provides them a good source of income. These costs are added to the cost of research leading to higher cost of drugs and devices. An independent IRB can act as the IRB of record for many university and institutions. One of the well established independent IRB, reviews 1000 initial protocols and over 2500 continuing review of protocols annually (OIG report, Emergence of Independent IRB, 1998).

Western Institutional Review Board (WIRB)

One of the oldest and best established independent IRB is the Western

IRB, which has extensive experience of working in the USA and internationally and has been the standard model for all the independent IRBs to follow. The WIRB is made up of more than 10 committee panel boards and approximately 300 or more employees. In spite of having 110 voluntary board members, the fee charged by them for reviewing the protocol is debatably high (www.wirb.com).

The various wings of this WIRB include the IRB Review committee, Training Group, Institutional Biosafety Committee Services (IBC), Data and Safety Monitoring Services and consultations. The WIRB act as IRB of records for many institutions under the Federal Wide Assurance (FWA) from OHRP. They also train many sponsors and principle investigators in human subject research nationally and internationally (www.wirb.com).

Apart from the independent IRBs, there are a cluster of satellite-organizations, alliances among institutions which provide scope for improvement on the current laborious, inefficient and burdensome IRB protocol review process. Such organizations help overcome the time delay in research initiation and attract research to their institutions. This is one of the situations where many of the institutions come under the umbrella of one single IRB leading to more timely and efficient protocol review system and having standard operating procedures (SOP) and standard forms for all research sites (www.wirb.com).

Biomedical Research Alliance of New York- BRANY

BRANY is an alliance of research communities in northeast USA. They offer IRB and Independent Biosafety Committee (IBC) services to the sponsors and all institutions on request and they also provide various other services like identifying the research sites, educating the staff and assisting in setting up the research organization. They have many specialty boards and cater to many research fields on various types of clinical trials. They have IBC services to review recombinant DNA/gene transfer research. Biosafety officers provide scrupulous oversight safety involving a recombinant DNA/gene research. This group even offer "very competitive pricing (fees available upon request)", which is mentioned on their websites (www.brany.com).

Multicenter Academic Clinical Research Organization- MACRO

MACRO is a partnership among four well known institutions including the University of Pennsylvania School of Medicine, University of Alabama at Birmingham, Vanderbilt University and Washington University School of Medicine. MACRO is able to expedite the review of clinical trial protocols. Through this sponsor, CROs (contract research organization) and SMOs (site management organization) can have access to investigators and have their protocols reviewed and approved by this collaboration. The IRB services provided by MACRO are accepted by all the affiliate institutions. Each institution acts on a rotating basis to take responsibility of reviewing the protocol. They

participate in phase II, III and IV trials.

The advantages of MACRO are that it consists of four premier institutions with a single IRB reviewing and processing the protocols for all the four sites and its affiliate institutions. Once approved, it can be put into operation at all four sites and it involves standard operating procedures, quality control and reporting to one single IRB saving time and cost from multiple submissions to four IRBs (http://ccs.wustl.edu/macro/aboutmacro.htm).

Colorado Multiple Institutional Review Board- COMIRB

COMIRB is an alliance of health care facilities in Colorado consisting of the University of Colorado Health Sciences Center, Colorado Prevention Center, Denver Health Medical Center, Denver Veterans Affairs Medical Center, The Children's Hospital and University of Colorado Hospital. COMIRB provides the IRB service to review biomedical and behavioral research involving human subjects conducted at these institutions or supported institutions. This alliance also has many advantages such as many research sites under the umbrella of one single IRB, which makes standard submission forms, standard operating procedures, saving time and cost and making research site –IRB interaction more efficient (http://comirbweb.uchsc.edu/portal/).

IRBNet[tm]

IRBNet was developed under the funding of National Institutes of Health program for Human Subjects Research Enhancement Awards as a cooperative venture of Dartmouth College and The Children's Hospital of Philadelphia. IRBNet is a service-based solution for the research community. IRBNet is a web hosted toolset that is secure and accessible from anywhere, at anytime with an internet connection. IRBNet provides a flexible data architecture, allowing one to quickly change the data from anywhere. IRBNet's supports institutions of all categories. IRBNet also supports Institutional Animal care and Use Committee (IACUC), IBC, and other boards (https://www.irbnet.org).

Regional Ethics Organizations

Wood and Emanuel (2004) proposed a Regional Ethics Organization (REO) as a solution to the current decentralized IRB system in USA. Currently there is no such system adopted in US. They propose that 20 REOs should be formed in the US instead of having 4000-6000 IRBs across the country. According to Wood and Emanuel, five major responsibilities would be undertaken by REOs: (1) ethical reviewing of protocol in its geographic area; (2) monitoring of adverse event and adhering to protocol; (3) training of research teams to conduct ethical research; (4) developing and refining policies; and (5) collecting performance data. Each REO would be comprised of 20 boards having 400 committee boards. In such a model, clinical research is not separated from

other human research and propose to eliminate the current institutionally based IRBs (Wood et al, 2004). This REO system raises issues such as, will the institutions accept to relegate authority and turf of their institution into other hands, worries of not addressing local issues and complaints and volume of the protocol reviewed would be a huge burden on REOs (Wood et al, 2004).

Discussion

Over the last two centuries as human research has increased, the need for human subject protection (safety and privacy) has evolved. Though it is often difficult to differentiate between standard practice and research, the research community needs to balance this delicate line in order to maintain safety of human subjects and to maintain the integrity of research. Research advances knowledge and understanding of science, but at the same time safety and privacy of subjects' presents a challenge. By balancing ethics and safety, a smooth and ethical progression in science is made without harming any human subjects.

Clinical research today is not limited to academic centers; it is multi-faceted, involving private clinics, hospitals and large universities. Most of the protocols are carried out at multiple sites globally which creates a large subject pool and takes research to many different geographic areas. Conducting studies worldwide lends an opportunity for a multi-racial population to participate in research bringing access to newer therapies to many in deprived areas. In contrast,

research indirectly benefits from a large subject pool by allowing researchers to better validate studies (power of study) and apply research conclusions and results universally.

Studies regarding the role and function of the IRBs over the past decade have shown that there is a national and international crisis requiring a change in the current system of the IRB review process for human subject research protocols. (OIG-HHS, 1998). It has been proposed that the use of a centralized IRB over the use of multiple local IRBs be implemented to meet the current needs of research and avoid unnecessary delays and human exploitation. These delays may be due to administrative deficiency or delays in the review and approval of research protocol by IRB committees (Fitzgerald and Phillips, 2006; Dziak et al., 2005).

An eight-year study among five nations conducted by Fitzgerald and Phillips (2006) on the IRB review process clearly showed the flaws involved within IRBs. There is a need for expertise in the review of specific research, although not all IRBs are equipped with these tools. Fields such as stem cell research, genetic research, device implants and nanotechnology are areas of research in which most IRBs lack adequate expertise to review a protocol (Fitzgerald and Phillips, 2006). Biomedical research personnel dominate the composition IRB committees and are reviewing protocols in their own perspective

of ethics. This biomedical perspective of reviewing protocols in cases involving the social sciences or educational research may cause delays in the initiation of research and also limit the subject pool for this type of research (Silverman et al., 2001; Church et al., 2002). In contrast, a social scientist reviewing biomedical research protocols may lead to similar problems for protocols in these areas. Along with administrative ineptness, lack of staffing and research being carried out internationally there are problems specific to research and to local geographic areas. To address these issues, an expert panel is required which can recognize the problems and arrive at ethical answers that suit individual research areas, which are accepted universally. Some countries use a centralized IRB system and others use dual IRB systems (Fitzgerald and Phillips, 2006); however, these systems still do not solve all the issues and have been inefficient in keeping up with the CFR and Common Rule and review process (Morahan et al., 2006). Studies have determined that having a local IRB or having a centralized IRB is just not sufficient. A report form the Office of the Inspector General (OIG) Department of Health and Human Services (HHS), 1998 stated that "There is a call for a complete reform in the entire system, instead of piece meal amendments to the present system – A Time for Reform".

Recent studies have examined the specific details of IRB review process. The information has been collected in detail by surveying and recording various types of communication between principle investigators (PI) or research site

personnel and IRBs from the submission to approval of the protocol by IRBs.

Dyrbye and coworkers (2007), found that information requested by different IRBs at the time of initial protocol submission can vary from the content of informed consent, recruitment methods and specimen storage to something as insignificant as details of a thank you letter to patients (Dyrbye et al, 2007). After obtaining the required information from the research sites, amendments and changes made in the submission forms and informed consent can vary according to the different IRBs that the protocols have been submitted. This has lead to insufficient content, ambiguous language (variability of reading grade levels of informed consent) and even missing basic elements of informed consents, Silverman and coworkers (2001) found within a multicenter trial, IRBs reviewing a common protocol varied in several of their approved research practices to the extent to which the basic elements of informed consent included in their consent forms. This clearly showed the inconsistencies of the information requested from the research sites are more of random requests than a standard regulatory requirement (Silverman et al, 2001).

Mc Williams and coworkers (2006) found that issues such as data storage and DNA specimen banking were handled differently by individual IRBs. Even when the combined response of all IRBs was more ethical and acceptable none of the individual IRB did a complete job which leaves a threat to research integrity

and patient data (Mc Williams et al, 2006). This clearly shows that all local issues related to conducting a clinical research trial need to be addressed nationally by changing policies and developing standardized universal ethical principles to safeguard research integrity and patient confidentiality.

A protocol can undergo a full board review, expedited review or an exempt review depending on the nature of the risk benefit associated with the study and on the IRB. The type of review a common protocol undergoes and the reason given by the local IRB for such a review varies from IRB to IRB. The reason given by IRBs for a particular type of review does not reflect any regulatory requirement; rather it seems to be a random judgment call, questioning whether it should be followed or is it just a requirement of that particular IRB (Dziak et al, 2005). Examples of reasons cited why a single protocol undergoes different types of review include: (1) all new projects have to undergo a full board review; (2) initially submitted as expedited review but later resubmitted for expedited review as patient was contacted; (3) initially submitted as expedited but later resubmitted for full board review as protocol had questions on illegal drug or physical abuse; and (4) initially submitted as exempt review but later required a full board review as the subject complained. In some cases the type of review decided at the initial submission of the protocol and the type of review undergone later were completely different making the review process an extra long time or even twice the time required resulting in delay initiating the protocol (Dziak et al, 2005).

Good clinical practice requires clinical trail investigators to report any adverse events (untoward medical occurrence in patient during clinical trial which does not have to have causal relationship) and serious adverse events (any untoward medical occurrence that results in hospitalization, prolongation of hospitalization or is life-threatening or death or significant disability or birth defect) to clinical trail sponsors (Liauw and Day, 2003). These requirements have evolved over the years, and have led to a substantial increase in the interactions between sponsors, investigators, IRBs, clinical monitors, and regulatory agencies, often leading to multiple interactions related to one adverse event. In effect, a costly paper trail provides data rather than information, creating a situation in which there is a real danger of losing the "needle" (important adverse reaction to drugs) in the "haystack" of all the adverse event reports (Liauw and Day, 2003). Reporting a single adverse event to multiple agencies and multiple local IRBs further compounds the issue.

The IRB review process is a lengthy communication between the IRB and the research sites. Indirect communication between the local IRB and sponsor through the PI can also lead to further delay and lengthening the approval time. Researchers recommend a six-month-lead time for initiation of a study and attribute this time to the IRB review process (Morahan et al., 2006). This can account for delay in study initiation up to several months, which in turn can lead to forfeiting of selected research sites from participating in research (Dyrbye et

al., 2007). Unfortunately, even with all the modern electronic media and satellite technology, loss of research studies at large institutions due to these issues is still being reported (McWilliams et al., 2006).

Table 2: Range of Time Taken by IRBs to Approve Different Research Protocols (Dyrbye et al, 2007)

No	Number of IRBs Used	Type of Research Study	Range of Time to Review-Approve the Protocol (days)
1	6	Educational survey-Medical students	6-216
2	31	Genetic epidemiology study	9-252
3	15	Health service research study	5-172
4	44	Clinical Trials	26-62
5	3	Minimal risk survey study	12-77

In some instances, the investigators have not been educated as to when to seek IRB approval for their research projects (Tomkowiak and Gunderson, 2004). In educational research, such as case reports, chart reviews and opinion-based student surveys, investigators sometimes feel that there are no risks involving

their research and forget to obtain IRB approval and informed consents. Later when investigators published the data and implemented the research conclusions for the benefit of the public, they had a significant problem. Human research conducted without IRB approval lead to the retrieval of published data and destruction of all the data obtained from such research (Tomkowiak and Gunderson, 2004). This situation demonstrates the need for regular education of investigators on CRF and norms in conducting ethical research.

The OHRP and FDA regularly conducts inspections of IRB, This inspection can be a self-initiated or as a result of any complaints against IRB. The action taken after inspections can vary from a simple warning letter to complete shut down of the IRB. In 1996, the IRB at the University of Rochester was shut down by the OHRP and FDA as a result of the death of a student enrolled in one of the research studies conducted at the university (Jordan Cohen, AAMC report, 2000). After the close down, they had to approach the independent IRB for review of their research protocols and it took more than five years for them to re-establish their own IRB (Jordan Cohen, AAMC report, 2000). During 1999, the inspections of IRBs conducted by OHRP and FDA led to regulatory actions on many grounds such as inadequate documentation, inadequate continuing review, deficient informed consent, inadequate safety review and inadequate training of IRB members. This clearly shows the lack of commitment to maintain research integrity (Burman et al, 2001).

Apart from all the above inconsistencies in the review process which is between IRB and research sites, there is another side of review process known as intra-IRB issues which are seldom discussed (Bankert and Amdur, 2006). Intra-IRB conflict-of-interest kindles serious doubts in minds about maintaining the integrity of common rule while reviewing protocols and can come from various aspects such as sponsors, investigator, institution, IRB/IEC members and governmental agencies. Conflict of interest includes financial, institutional, national advantage or suppressing a colleague and IRB member's research interests (Bankert and Amdur, 2006). Included in this are the following: (1) research by members: direct conflict while reviewing research conducted by one of the members of IRB and, secondly, indirect conflict, this is hard to define but can be negative or positive approving, delaying or even disapproving the protocol. Of the two, indirect is very difficult to manage; (2) financial interest: IRB members holding equity in the study drug or device or the pharmaceutical company carrying out the research or if IRB members conducting research with large grants and benefits are reviewing the protocol; (3) loyalty to colleagues: members may be inclined or biased to approve their peers' protocols. Peers can be superiors, subordinates or colleagues. They can be lenient over continuing review and would persuade the other IRB members for the approval of the study; (4) members' area of expertise: if the submitting investigator is a competitor or rival there can be proprietary information sold when reviewing the protocol called as "insider trading". They can also be overly lenient or overly critical while

reviewing protocol of their expertise; and lastly (5) impact of decisions: if the decision taken is going to affect his/her research interests, then they are going to act in opposite way. This is a personnel agenda or a preconceived thought of the IRB members. Personal agendas can be positive or negative towards reviewing protocols. Sources for such aspects can be personal, peer pressure, departmental pressure or institutional interests they weigh them against the liability and economic gains (Nelson, 2006).

Within the last four decades of establishing the IRB we have come to accept the burdensome and inefficiency of current IRB protocol review system. The system was adopted to support and police research sites, but today we are in a state to frame policies and laws for policing the current IRB system (OIG-HHS, 1998, www.fda.gov). Due to the presence of thousands of IRBs, there is IRB shopping by the research community with absolutely no communication if the protocol has been already reviewed by other IRBs. Today's IRBs have many flaws and these maladies need to be addressed. Research being reviewed by multiple local boards in different places and people has proven ineffective (OIG-HHS, 1998). In order to reduce these conflicts of interests, laborious, burdensome and inefficient review process a new system has to be developed.

After an extensive literature search, it is clear that the current system of the IRB, whether independent or institutional, have no standard operating

procedures, standard forms, required expertise and have substantial limitations in resources and all of them are over burdened with tremendous work loads. There are many new and old issues which are not addressed leading to many ill-effects on research and its participants. The task given to the IRB is compromised in many ways, the purpose is unaccomplished, and the current IRB-research site interaction is laborious, time consuming and inefficient.

There is a need for more ethical answers from experts in their domain to develop standard-operating procedures to support the future of research which can be applied universally. This way we can make smooth progress in science and maintain integrity of research and avoid such future disasters.

Proposed Model - Clinical Research Review Board (CRRB)

A solution for the burdensome and inefficient current IRB system and to maintain the integrity of the research and common rule would be the creation of a separate expert Clinical Research Review Board (CRRB). This would be a national standardized central system where all the clinical research protocols and its issues would be reviewed and approved. Continous review of these protocols would also be done from its inception to the end phase of all clinical research protocols in a timely manner. Over 20,000 clinical research protocols are currently flooding all level of institutions, from private clinics to big university hospitals which are being reviewed by thousands of local IRBs.

A CRRB would be an expert organization like the NIH or FDA having multiple wings with all the tools to support the organization. This would allow a smooth process of review and continued review of the clinical research protocols but also addresses all the issues like serious adverse events, conflict of interest and all the ethical issues. The local issues of concern by the investigators, institutions, research subjects and public would be addressed nationally so that any local problems and events requiring new laws would be looked and addressed by specialized wings within the CRRB.

Description of CRRB - Wings or Departments of CRRB:

Administrative wing: Includes different individual administrative staff for all the individual departments in the organization and a common staff to integrate and coordinate the departments and the other overseeing organizations such as NIH, FDA, HHS, OHRP and CBE.

Board of Directors: This would include the members from governmental agencies, regulatory agencies, universities and private sponsors who would help oversee the organization and its functions. They would help select the committee members and other appointments.

Pre-review Committee: This would include both scientific and non scientific members who make the initial corrections of the submitted forms for review and it would be assisted by a committee member who would be reviewing the protocol along with the complete board.

Protocol Development Assistance Wing: Triangle of FDA-Sponsor-OHRP assisted by CRRB to develop protocol and assess the risk-benefit and other aspects of research.

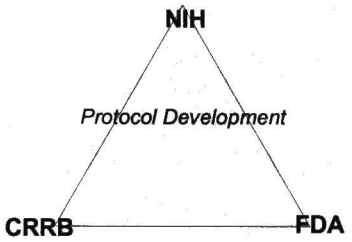


Figure 2. Protocol Development Assistance

Scientific Review Committee/Protocol Review Committee: As many as 100-500 boards with expert committees would be established. Each specific research field would have many expert and specialized boards tailored to review protocols of that particular field of science. Each field of science would have as many boards as possible to cope with the large number of protocols. This can be spread in many different parts of states across the nation.

Data Safety and Monitoring Board: This provides the expertise and knowledge for clinical trial design, conduct, and interpretation of data and safety of all the study. It would also help in committee member selection and training, and administrative support and in scheduling of meetings.

Specialized SAE/AE Board: This panel addresses adverse events and assists all the other departments in CRRB. This board would determine whether to suspend

or terminate the study and make recommendations to committee boards reviewing the study protocol. An online interface created will help the coordinators submit the SAEs to both CRRB and local IRBs which helps in reducing the work load on SAE reporting thus saving time and cost on SAE reporting.

Monitoring Board: This board conducts site visits and examine the integrity of research (Already FDA & OHRP conducts inspections when ever required)

Ethics Advisory Boards: This would be a group of scientific, legal and constitutional experts who looks at the ethical issues and provide ethical answers. They would be assisted by SAE board, DSMB, Monitoring Board and Complaint Cell. They would look into all the conflict of interest matters from investigator-research site, Institutions, IRB and sponsors.

Database Development Board: This board would develop a database of all physicians and their subject pool which can be used for future research. This would also help allocate the research to different geographic locations where the research and new therapies have not yet been taken. This data base would be made accessible upon request to authorized personel. This database can also be used as an epidemiologic tool, to learn demographics of disease and in the practice of evidence based medicine.

Education Department: Educating the research personnel would be one of the key goals of the CRRB and all the personnel involved in research would be educated about the current methods and SOPs, bioethics and medico-legal aspect and new developments in research. Some of the issues would also be imparted in

the medical and other educational program curriculum. This way an educated environment where everyone clearly knows his or her individual roles as research personal is inculcated.

Research Subject Support / Public Complaint Cell: This cell would address all the complaints received from patients/public, investigators/research Staff and IRB and assist other department in the CRRB and other monitory agencies to address these complaints and to take necessary actions.

This would be a virtual CRRB and there would be integration and coordination among all its departments with the institutions carrying out research. This organization would be overseen by NIH, FDA, OHRP, CBE and HHS. This organization would take the liability of reviewing and providing the ethical answers to protocol and would sign a contract with the participating institution. The institution would still remain liable for implementing the protocol, just like Form 1572 between sponsor and principle investigator. When multiple review boards review the same protocol over time much of the bias would be eliminated.

One way to solve the current problems is to streamline and segregate research fields. The load of clinical trial protocols can be dealt with on a nationalized review system CRRB under the direct guidance of FDA, HHS, OPHS, NIH and CBE. This would unify the clinical trial process and reduce the burden for local IRBs. Federal agencies with expert committees would directly

oversee the integrity of applying "Common Rule" in protecting human subjects as research candidates. This would address all the local issues and lead to a uniform national policy. A national standardized central CRRB would have multiple boards so that one board can hold one meeting at a time on a rotating schedule allowing other committee members to pursue other professional interests. This would be assisted by a single administrative wing which would assist all the boards, hence create expert committees that could provide the required knowledge and expertise supported by an efficient administrative staff leading to standardization of research and protecting human subjects, which is the primary goal of the CFR.

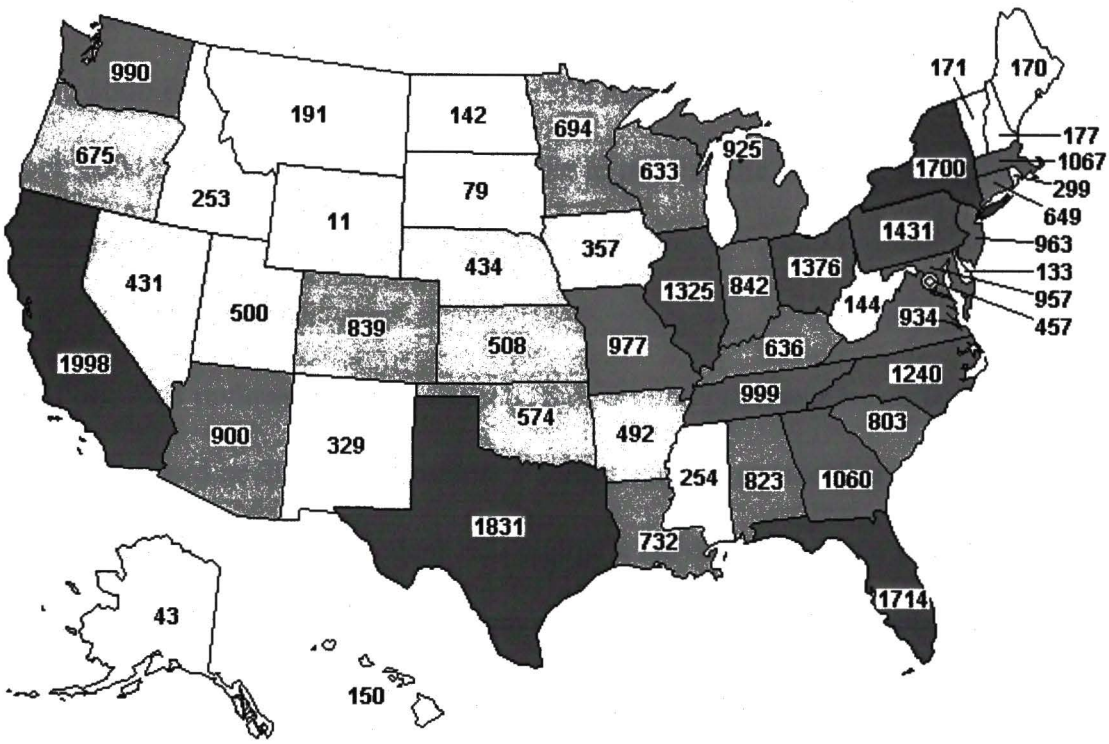


Figure 3: Clinical Trials in Each State of US (www.clinicaltrials.gov. app 27,000 clinical trials)

Today there are approximately 20,000 ongoing trials in USA, Most of which are multisite clinical research protocols. Some of these trials have more than 200 sites participating. All these sites have to undergo the same IRB review process. A fee is charged by IRB to review the protocol for research sites submitting the protocol. Without the approval of the IRB, the research cannot be conducted. There are approximately 5,000-6,000 IRBs in U.S., but in spite of this

there still appears to be many unresolved issues, burden of loads of protocol and no standardized operating procedures in IRBs. Currently the approximate budget of an individual IRB varies from $ 75,000 – 2 million and the overall budget in sustaining 5000-6000 IRBs is approximately 500 million dollars (Wood and Emanuel, 2004). Despite this, IRBs are not able to provide the required service to the community.

If one IRB reviews 20,000 protocols, the revenue generated by an IRB on initial review would be 20,000 (protocols) x $ 2800 (fee for protocol review) = $ 56,062,000 (based on the independent IRB charge a fee of 2800). If the protocols undergo review at three such IRBs, the amount spent on such a review process will sum up to be approximately $ 168,000,000 and this is the cost for the initial review by only three IRBs per protocol. It is up to local IRBs to decide how often a protocol should undergo continuing review depending on the risk to the research subjects, sometimes a protocol may undergo continuing review quarterly or once in six months, but all protocols have to undergo annual review. Thus, the cost of continuing review by single IRB for reviewing partial number of protocols would approximately be 15000 (protocols) x $ 1500 = $ 22,500,000 in the same year (based on the independent IRB charge a fee of $ 1500). If three IRBs were used to conduct the continuing review for only a partial number of protocols, it would create revenue of approximately $ 65 million. Left alone, the monetary charges for amendments, change in principal investigator, additional sites would add extra

costs and generate more funds. Thus, just for the initial and partial continuing review, this CRRB would generate revenue of approximately 200-250 million dollars per year, by charging what only three IRB would charge. With other grants from the government CRRB would support itself as an independent organization and provide best service and assist all the research sites, investigators and sponsors to conduct ethical research and also address all the issues and SAEs nationally in a more efficient manner. This would stream line all research and reduce the burden on institutionally based IRBs and research sites and most of all there would be an efficient research site and regulatory authority interactions.

The future of research is going to be more challenging. There is a trend of growth of number of protocols and in the coming years the numbers of protocols can rise to 100,000 per year. The research community needs to prepare for the future not only to manage the process of protocol review but to ethically assist them. In areas such as genetics, nanotechnology, DNA computers, radio frequency identification (RFID), robotics, artificial intelligence, various thought processor equipped gadgets used on humans and many newer fields; we need to equip ourselves with tools for good conduct of research and provide ethical answers for protecting patient privacy and confidentiality. Along with good clinical practice (GCP), good research practices (GRP) we need to develop ethical research practice (ERP) or ethical codes for clinical research (ECCR).

By having an expert organization such as a CRRB and a well-developed database system we can foresee and prevent many disasters, including addressing issues such as protection of human subjects ethically, maintaining research and common rule integrity, educating the research community and tackling the loads of research protocol in a better way. By streamlining the protocol review process, this model can also reduce the unnecessary cost and reduce the cost of medication to some extent.

Table 2. McWilliams and coworkers (2006)

Multi-center Epidemiology and Genetic Studies listed in PubMed.

	Frequency of Multicenter Studies in PubMed, 1979-2002 Genetic and Epidemiology Studies	
1	1974-79	385
2	1980-84	990
3	1985-89	3016
4	1990-94	5541
5	1995-99	8632
6	2000-02	6521
7	2000-04 (Projected)	1087

Table 3: Range of Time for Reviewing Research Protocols, (Dyrbye et al, 2007)

No	Number of IRBs Used	Type of Research Field	Range of Time (days)
1	6	Educational Survey	6-216
2	31	Genetic epidemiologic study	9-252
3	15	Health service study	5-172
4	44	Clinical trials	26-62
5	3	Minimal risk survey	12-77

Recommendations for Improvements in Investigators/Coordinators Meetings

The best place to educate and learn about the research and implementation of clinical trial protocol would be the investigators/coordinators meetings. There can be cooperation among all agencies in the investigator meetings leading to a better ways in carrying out ethical research.

The presentation made at the investigator meeting would include presentations by the sponsor, FDA, NIH-OHRP and CRRB. All standard operating procedures would be taught and charts, CD's and other educational materials would be dealt in detail. The ethical and regulatory issues concerns would be spoken by government agencies.

These meeting should involve all the staff who is likely to be part of research such as nurses, pharmacist or people and hospital ward authorities, by these practices the protocol deviations could be completely avoided. (protocol violations are an entirely different situation).

Conclusion

An expert streamlined national standardized clinical research review board would reduce a major portion of the burden on local IRBs. By reviewing clinical research protocols, the CRRB will be liable for human research protection and the institutions taking part in research will be liable for implementing the protocols. The institutional IRB would still be in place and would be given more responsibility regarding other aspects of human research subjects, patients and public protection in the local areas of their jurisdictions. These local IRB would be called the Human Subject Protection Cell (HSPC) rather than an IRB. The local IRB or HSPC would assist the CRRB and look into the concerns of the local public and research sites and make recommendations to the CRRB. By this, the CRRB would eliminate the independent IRBs, IRB shopping by sponsors, and would streamline the research review process. Instead of having 4000-6000 IRBs and not addressing the issues and delaying research initiation, this model will streamline the process and eliminate the ill-effects of research and maintain research integrity in a much better way by having a separate clinical research review board. Along with such advantages, this model would reduce the paper work and time spent on research site communication with multiple local IRBs and this would also reduce the cost and man-power.

Another advantage of this system would be that the CRRB can groom research from phase I thru phase IV of a clinical trial and can have a clear idea of

what exactly is going on in the research and know in advance the ill effects of research and stop the ones which are proving to be harmful. There can be better coordination of all the sites participating in research and the FDA, OHRP and other regulatory authorities would have a better coordination and insight about the research, research sites and the sponsors and they can work more efficiently.

To test this novel system of a separate expert national standardized clinical research review board the CRRB model, I propose the following protocol with specific aims and required tools to research its feasibility. This protocol is entitled "A national standardized central clinical research review board (CRRB) is more efficient than multiple local IRBs when processing a multisite clinical research protocol and it would reduce the burden on local IRB and eliminate the ill-effects on research"

A standardized central clinical research review board would create a positive effect on the timeliness, cost-effectiveness and the processing of paperwork for clinical trials by expediting the review and approval process, minimizing the latency for initiation of research protocols and making ongoing communication between clinical sites and regulatory authorities more efficient. In addition, a centralized IRB would be able to develop a database that would identify all the potential physician scientists capable of doing research and their patient pool that may be useful for future research.

Table4: Comparison of current system and CRRB

	Current IRB system	CRRB
1	Designed for single site protocol	Multisite protocol-clinical research
2	Address local issues	Address local issues
3	Review is generic and random	Focused leading to policy change
4	Conflict of interest and biased review	Less conflict of interests and unbiased
5	Delay in protocol initiation	No delays or minimal delay
6	Repetitive review of same protocol	Standardized review and clear follow up of protocol
7	Conflict of interest at local IRB	No conflict of interest or minimal
8	Volume burden of many protocol	Capable of handling the thousands of protocol
9	Complaints partially addressed	Complaints from subjects, investigators, local IRB and sponsors addressed
10	No streamline of clinical research	Streamlined research with grooming of phase I through phase IV trial
11	No expert boards	Expert boards
12	No database developed	Database development for future research and evidence based medicine
13	Not all IRBs have special SAE monitoring board	Specialized SAE/AE monitoring-knows when to stop a protocol before disaster
14	Wide variation in fee charged Lot of IRB shopping	Standard fee No IRB shopping
15	Not all IRBs impart training to IRB members	Assistance and education to physicians and research staff

CHAPTER III.

PROTOCOL INFORMATION

Title of Project: ***A national standardized central clinical research review board (CRRB) may be more efficient than multiple local institutional review boards (IRB) in processing a single multisite clinical research protocol.***

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Collaborating Investigators: Albert O'Yurvati, D.O.

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Hypothesis

A standardized central clinical research review board is more efficient than multiple local IRBs when processing a multisite clinical research protocol.

A standardized central clinical research Review Board will create a positive effect on the timeliness, cost-effectiveness and the processing of paperwork for clinical trials by expediting the review and approval process, minimizing the latency for initiation of research protocols and making ongoing

communication between clinical sites and regulatory authorities more efficient. In addition, CRRB will be able to develop a database that would identify all the potential physician scientists capable of doing research and their patient pool that may be useful for future research.

Specific Aims

The aim of this investigation is to test the hypothesis that a centralized CRRB is more efficient than multiple local IRBs following analysis of a questionnaire that would target all personnel involved in the clinical research.

1. To determine the time delay between submission and initiation of a research protocol involving multiple local IRBs.

2. To determine the advantages and disadvantages of having a local IRB compared to a centralized IRB.

3. A central review board can develop a database of physicians and their patient pool which can be used in the future research.

4. To determine the cost burden for review, approval and per-subject charges by multiple local IRB submission.

5. To determine the time and money spent by reporting a single event to multiple local IRBs.

6. To determine the need for having a standardized submission forms involving all the components required by the Federal Regulators.

Introduction

Clinical Research **is an important stage in scientific research.** It is carried out on a multi-national basis at many institutions around the globe. It has become an integral part of medical and educational institutions as well a source of income. The first recorded clinical research dates back to the mid 18th century when physicians used citrus fruits in the treatment of scurvy. Since then, clinical research has developed as an excellent experimental design to test hypotheses, but there are some issues that have yet to be clarified and refined. In the past misuse of subjects, conflict of interests, financial conflicts and experimenter biases, has lead sponsors and government agencies to amend the way we carryout research. These changes brought about The Belmont Report, International Conference on Harmonization (ICH) and many other guidelines have been adopted to standardize and correct the flaws of clinical research (www.fordhamethics.org). During this process progress has been made in the system that meets the requirements of the modern day research, however, these changes have always lagged behind and often fall short of meeting today's needs (DHHS - Office of Inspector General; 1998; Dyrbye et al., 2007; Nowak et al., 2006; Office of Inspector General Department of HHS; www.*FDA.gov*).

The need for a centralized IRB system has been debated for decades. Some countries have adopted a common centralized IRB system for all fields of research but this system also remains flawed. On the other hand, a few countries

have a dual system using both central and local IRBs (Fitzgerald and Phillips, 2006). An ideal solution for the IRB review process has yet to be developed and we continue to face the same problems such as laborious and inefficient review and approval process on most of the clinical research protocols as well as failing to apply the codes of federal regulations (CFR) in human subject protection. Some of the common issues that need to be addressed include the differences in the review process, differences in the intra-IRB committees, delays in the initiation of protocol, problems submitting to multiple IRB and the ongoing process of reporting new adverse events to multiple IRBs (Dyrbye et al., 2007).

This study will test the hypothesis that clinical research is an entirely different sub-specialty of research and needs its own identity and a different system of approach to deal with the day-to-day challenges of IRB's review-approval and ongoing communication process with the clinical research sites. In the past, the idea of a centralized CRRB has meant that the same IRB had to deal with all kinds of research, such as basic science research, behavioral research, public health research and other fields of research. **A nationalized system of a standardized clinical research review board (CRRB) with specialized boards and the required expertise to oversee only clinical research would make a positive difference in applying the CFR.**

Background and Significance

The protection of human subjects participating in clinical research is the number one priority of educational institutions and researchers. The Nazi experiment that led to the Nuremberg Code of 1945 was the first step towards protecting human subjects; this was followed by International Conference on harmonization (ICH) Declaration of Helsinki in 1964. The abuse of 300 rural black men in Tuskegee Syphilis Study for over 30 years lead to the first public law in 1972, calling for the establishment of the National Commission for the Protection of Human Subjects in biomedical and behavioral research. Further revision of these laws by National Institutes of Health (NIH) and the United States Public Health Service (USPHS), lead to the establishment of the Institutional Review Boards through out the United States in 1974. Today these laws and regulations are described in Codes of Federal Regulation (CFR) 45 part 46 (http://fordhamethics.org).

Studies on IRB over the past decade have shown that there is a national crisis requiring a change in the current system. Many researchers have proposed a centralized IRB over multiple local IRBs in order to meet the current needs of research and avoid unnecessary human exploitation and delays in research. Many studies have clearly shown the delay in initiation of research because of the inefficiency in the IRB review process (Dyrbye et al., 2007; Edgar and Rothman, 1995; Fitzgerald and Phillips, 2006; Dziak, et al., 2005). These delays can be due

to administrative deficiency or delays in the review and approval of research protocol by IRB committees (Fitzgerald and Phillips, 2006; Dziak et al., 2005).

An eight-year study among five nations conducted by Fitzgerald and Phillips (2006) on the IRB review process clearly shows the flaws of IRBs and delays in the review of protocol. There is a need for expertise in review of specific research fields, although not all IRBs are equipped with the tools to review all areas of research. Fields such as stem cell research, genetics research, device implants and nanotechnology are the areas of research in which most of the IRBs lack adequate expertise. On the other hand, biomedical research personnel dominate the IRB and reviewing protocols with their perspective of ethics while also reviewing social science or educational research protocols and in some cases causes delay in educational and social science research and limits the subject pool (Silverman et al., 2001; Church et al., 2002). Along with administrative ineptness, lack of staffing and research being carried out internationally there are problems specific to research and to local geographic areas. To address these issues an expert panel is required which recognizes the problems and arrive at ethical answers that suit individual research areas which are accepted universally. Some countries have centralized IRBs and few others have a dual IRB systems (Fitzgerald and Phillips, 2006), but this still does not solve all the issues and has been inefficient to keep up with the CFR and Common Rule (Morahan et al., 2006; 45CFR46.102 (d)) of federal guidelines. Studies being conducted have

identified that having a local IRB or having a centralized IRB is not sufficient. There needs to be a change in the entire system, instead of piece meal amendments to the present system (Office of Inspector General Department of HHS, 1998).

Considering previous studies and referring to the current system, we need to have a standardized central IRB with all the necessary expertise and resources to handle thousands of clinical research protocols. This will not only provide an efficient, smooth review process, but an expert committee with years of experience in a specific field that can oversee the needs of the ethical issues of research. This system would establish itself as the highest governing body specific to research and would be guided by governmental agencies including the Food and Drug Administration (FDA), Office of Human Subject Protection (OPHS), National Institute of Health (NIH), Council of Bio-health (CBE), and Health and Human Services (HHS).

Studies have examined the specific details of the IRB review process. This information has been collected in detail by surveying and recording various types of communication between principle investigators (PI) and IRBs. The types of requests from IRBs includes corrections and amendments in a wide variety of aspects including informed consent, protocol, demographics, sample size, funding, recruitment details, information and education materials for the lay public and types of review involving different IRB amendments (Dyrbye et al., 2007; Nowak et al., 2006). It is a long process of communication between the IRB

and the research sites. Indirect communication between the local IRB and sponsor through the PI can also lead to further delay and lengthening the approval process. Researchers recommend a six-month-lead time for initiation of a study and attribute this time to the IRB review process (Morahan et al., 2006). This can account for months of delay and in some cases the study initiation can be delayed up to several months in some multi-institutional studies. This in turn can lead to the selected research sites forfeiting studies since IRB delays lead to exclusion of sites by the investigator or sponsors (Dyrbye et al., 2007). Unfortunately, even with all the modern electronic media and satellite technology, we still see this kind of loss of research studies at large institutions due to these issues (McWilliams et al., 2006).

In some instances, the investigators have not been educated as to when to seek IRB approval for their research projects. In educational research such as case reports, chart reviews and opinion-based student surveys, investigators sometimes feel that there are no risks involving their research. Later when researchers published the data and implemented the research conclusions for benefit of public, they had a huge problem, as this research became invalid due to lack of IRB review and approval leading to the retrieval and destruction of all data (Tomkowiak and Gunderson, 2004). There is need for regular education of the investigators on CRF and how to conduct research.

Discussion

The issue of concern for all institution is (1) protecting human subjects (2) avoiding litigation (3) negative publicity and (4) loss of federal and private grant funds for the entire institution. Institutions and all their departments must make sure that common rule and CFR is maintained with the utmost integrity. The IRB and OPHS at all institutions have become over-burdened and strained reviewing all possible aspects for keeping the integrity of CFR. Most of the IRBs are not equipped with expertise in all research areas and resources necessary to deal with the current loads of research protocols. One institution in the United States has approximately 3000 protocols operating concurrently (Fitzgerald and Phillips, 2006; Nowak et al., 2006). These large protocol numbers creates a huge workload for reviewing and re-reviewing protocols from a multitude of research fields.

Clinical trials are a major portion of multisite research projects and it involves institutions, hospitals, nursing homes and even small units such as private clinics. With such a broad range of institutions, all are approaching IRBs either central or local, for protocol review and approval of a single protocol by many different local IRBs. This kind of process is not only expensive and laborious but affects the application of CFR and common rule in human subject protection. An advantage of having multiple local IRBs is that we can identify the local issues in applying CFR; however these issues are not discussed and addressed nationally. By creating various review systems to deal with the

numerous research protocols, the integrity of the common rule and CFR is compromised (Mann et al., 2005; Mann and Shamoo, 2006).

One way to solve these problems is to streamline and segregate the research fields. The load of clinical trial protocols can be dealt with on a nationalized review system under the direct guidance of FDA, HHS, OPHS, NIH and CBE. This will unify the clinical trial process and reduce the burden for local IRBs. Federal agencies with expert committees would directly oversee the integrity of applying "Common Rule" in protecting human subjects as research candidates. This would address all the local issues and lead to a uniform national policy. A national standardized central IRB would have multiple boards so that one board can hold one meeting at a time on a rotating schedule allowing other committee members to pursue other professional interests. This would be assisted by a single administrative wing which will assist all the boards, hence create expert committees that could provide the required knowledge and expertise supported by an efficient administrative staff leading to standardization of research and protecting human subjects, which is the primary goal of CFR.

Experimental Design and Methods

1) Methods and Procedures

Questionnaires will be distributed to specific clinical research personnel and IRB committee members after signing an informed consent form. No personal

identifiers of any kind or health information will be required to be involved in this research. This is a qualitative research requiring an opinion of the working aspect of IRB within areas research sites. Participants will spend 10 to 20 minutes filling out the questionnaire, which will be returned either by mail or by fax.

A web site will also be used and the survey links will be sent to the research and IRB personnel. This link (survey site like surveymonkey.com) will have all the information about the study and committee members. There will be a consent form the participants must sign prior to answering the questionnaire survey. A one-on-one conversation or a telephone interview may also be implemented using the same questions and an interview will be recorded. The interview will be analyzed by Kiran Bangalore or a third party to eliminate any bias. There will be no personal identifiers collected in the interview.

Participating subjects may call for any questions regarding the questionnaire or the research study and necessary clarification or assistance will be provided by Kiran Bangalore. The procedural flowchart at the end of this document outlines the order of the protocol steps.

2) Data Storage and Confidentiality

All participant response sheets will be stored separately from the informed consent forms. All documents will be stored in a locked file cabinet and the interview recorded information in a computer folder inside Kiran Bangalore's office at 855 Montgomery, UNTHSC-PCC, Room 597. Only Don Peska, D.O.

and Christopher Hayes, PA-C will have access to these records.

3) Data Analysis and Data Monitoring

Questionnaires will be analyzed to determine whether the factor favors the proposed hypothesis or if it nullifies the hypothesis. Each answered question will be graphed into bar and pie charts and will be concluded in the percentage format. The content analysis of recorded interview will be done at the same time. The final analysis will be drawn by discussing all the answers to questionnaire and analysis of interview by Don Peska, D.O., Christopher Hayes, PA-C and Kiran Bangalore, M.D.,

4) Estimated Period of Time to Complete the Study

The expected total time will be approximately 10 to 20 minutes to complete the questionnaire or interview including the consent form. The time period to complete collecting data for the desired sample size is expected to be two to three months.

Human Subjects

1) Description of research sample

Professionals who have experience in Clinical Research and IRB work will be involved in the research project. There can be a wide variety of professionals from the sponsor, research site, IRBs and contract research

organizations (CROs) are eligible for the study.

2) Sample Size

This initial study will be a pilot project thus, a minimum of 20 and a maximum of 50 subjects will studied during this period.

3) Inclusion / Exclusion Criteria

Inclusion Criteria

1. Clinical research staff with more than one year of experience in initiation, communication and completion of the paper work required for IRB will be eligible for this study.

2. IRB staff and committee members who have more than one year of experience in both administrative and ethics review will be eligible.

3. Staff at CRO is involved in communicating with research site, IRB and monitoring with more that one year work experience will be eligible for the study.

Exclusion Criteria

1. Any person who has less than one year of experience in any clinical research, IRB, regulatory affairs, CRO and sponsor site will not be eligible to participate in the survey.

G. Risk/Benefit Assessment

There are no foreseeable risks for participating in the study. The study investigators will take all precautions necessary to protect the confidentiality of a research study participant. No personal identifying information, such as name or health information will be collected on this survey

The investigation will provide information about the working perspective of the IRB and the research sites. These results will chart out the pros and cons of having multiple local IRB and the idea of central IRB for clinical research. This will give the exact opinion of the research staff making the rapport between IRB and research sites better.

Payment/Compensation:– Subjects will not receive any compensation for their participation.

Subject Costs: There is no cost involved to be in the study


IRB Approval
Finding the target sites for sending questionnaire
Identifying key personnel for interview
Data collection and improving upon the questionnaire and interview skills
Communication with IRB
Analyzing the data
Thesis Defense
Test CRRB and publish the research.

INFORMED CONSENT AUTHORIZATION TO PARTICIPATE

IN A RESEARCH PROJECT

TITLE: ***A* national standardized *central clinical research review board (CRRB) is more efficient than multiple local IRB involving a single multisite clinical research protocol.***

PRINCIPAL INVESTIGATOR: Kiran Bangalore, MD

CO-PRINCIPLE INVESTIGATOR: Don Peska, DO, FACOS

INSTITUTION: University of North Texas Health Science Center at Fort Worth

SUBJECT NAME (please print):

_____

I. STUDY PURPOSE

The purpose of this study is to evaluate the present disadvantages in the review, approval and ongoing submission process between sites and IRB involving multiple IRBs and also to chart a path to make this process systematic. By identifying the focus group we can give an opportunity for everyone to be a part of research.

II. STUDY PROCEDURES

A questionnaire is administered to Principal Investigators, IRB Members, IRB staff, Clinical Research Coordinators, Clinical Research Associates, Monitors and Sponsor company personnel involved in research management process. A set of approximately 25-30 questions will be asked to complete about the day to day situation and your personal judgments/opinions on how you would deal with them. The survey should take approximately 20 minutes. You do not need to answer any question that you are uncomfortable with. You can also correspond your quires with the author.

III. RISKS AND DISCOMFORTS OF THE STUDY

There is no foreseeable risk to you for participating in the study. The study

investigators will take all precautions necessary to protect your confidentiality as a research study participant. No personal identifying information, such as name or health information will be collected on this survey.

IV. CONTACTS

If you have any question at any time about the study, you may contact Kiran Bangalore, M.D., at (817) 735-0512 or Fax: (817) 735-5120. If you have any questions about your rights as a participant in this study, you may contact Dr. Brain Galdue, Chairman of the Institutional Review Board, University of North Texas Health Science Center at Fort Worth at (817) 735-0409.

V. BENEFITS

You may receive no direct benefit from participating in this study. The information gained from this research may lead to the development of better system for conducting the research and gives an opportunity for everybody to participate in the research.

VI. CONFIDENTIALITY

Your survey answers will be kept as confidential as possible under current local, state and federal laws. However, the Office for Human Research Protections, possibly other federal regulatory agencies, and the Institutional Review Board may examine your survey responses and the study data. In case the final results of this study should be published, your name will not appear in any published material.

VII. COMPENSATION FOR INJURY

There is no sponsor and it is a qualitative research, a questionnaire study.
We, at the University of North Texas health Science Center at Fort Worth, have not set aside any funds for financial compensation or costs of medical treatment should you be harmed or injured as a result of your participation in this research. We are unable to offer financial compensation nor absorb the costs of treatment should you be harmed as a result of your participation in this research. You should understand that by signing this form you are neither waiving any of your legal rights against nor releasing the principal investigator, the University of North Texas Health Science Center at Fort Worth or any of their respective agents from liability for negligence with respect to the conduct of this study

VIII. LEAVING THE STUDY

You can choose not to be in the study or leave it at any time without penalty or loss of benefits that you are otherwise entitled. If you are a student or employee of the University of North Texas Health Science Center, your participation will in no way affect your academic standing or employment status.

IX. CONSENT

Your participation in this research study should be completely voluntary. You

should ask the study investigators any questions you have regarding this study before you agree to participate.

PLEASE KEEP A COPY OF THIS INFORMED CONSENT AGREEMENT FOR YOUR RECORDS.

Name (print) Signature Date

Witness Name (print) Signature Date

Survey for the PI's, Research site personnel, Monitors and Sponsors.

Your Job Title: (circle one of the following)

1) PI 2) CRC 3) Monitor 4) Sponsor-CRA 5) Regulatory Affairs personnel

1. Your IRB is: (circle all related)

1. Commercial IRB
2. University IRB
3. Community Service IRB
4. Centralized IRB
5. Specify if others _____

2. Your IRB serves:

1. One institution
2. Two Institutions
3. If more, please mention_____

3. Please give the average range of time it took for your IRB to approve a protocol. (Please mention for the last 5 protocols and please give a separate estimate if using more than one IRB). For example XX- ZZ days (submission-approval days):

	PROTOCOL1	PROTOCOL2	PROTOCOL3	PROTOCOL4	PROTOCOL5
IRB -1					
IRB -2					
IRB -3					
IRB -4					

4. If your site is dealing with more than one IRB, Does this involve multiple reporting with different submission forms and different IRB numbers for a same protocol?

1. Yes
2. No
3. Don't know/not sure

5. How satisfied do you think that researchers are with the IRB review in general?

1. Very satisfied
2. Somewhat satisfied
3. Neutral

4. Somewhat unsatisfied

5. Very unsatisfied

6. In your opinion, describe the three main reasons for your answer to question 5:

1.

2.

3.

7. Does your IRB currently have standardized forms, guidance material, consent forms, adverse event forms developed to assist specific research fields like public health research, basic science research, clinical research and qualitative research or do you use general forms for all the IRB submission process?

1. We have specific standardized form for individual research fields
2. We have same general form for all research fields
3. Don't know
4. Others, please specify

8. If no, do you plan to request for a standardized forms for each field of research?

1. Yes
2. No
3. Don't know/not sure

9. In your opinion, is the review process is more efficient involving: (Circle one of the following)

1. Multiple local IRB
2. Central IRB
3. It is same
4. Don't know

10. Please list three advantages & disadvantages of having multiple local IRBs:

***Advantages*:** 1.

2.

3.

***Disadvantages*:** 1.

2.

3.

To answer questions **11-16** *please use the following* ***hypothetical situation*** *encountered in an IRB and sites carrying out same multisite research protocol in one of the major cities at their hospitals associated in the clinical research.* ***If you were involved in a similar situation, please explain which of the following options would you chose from.***

A clinical research protocol is being conducted in 4 hospitals in a major city had to be reviewed by each hospitals IRB for initiation at their sites. The trial being carried out by same physician as principle investigator at all the 4 hospitals. As the trial went on, a single adverse event occurring at another site other than these 4 hospitals had to be reported to all the IRBs by the study coordinators each time by faxing different submission forms to all 4 hospitals with different IRB approval numbers. Each event submitted had to have signatures of PI and CRC along with other submissions to governmental agencies.

11. Would standardized submission form for all four hospitals lessen the burden of paper work and time?

1. Yes
2. No
3. Don't know/not sure
4. Specify any other reasons _____

12. In your opinion, would submission to one central IRB be more time and monetary efficient than submitting to all 4 hospital IRBs?

1. Yes
2. No
3. Don't know/not sure

13. If your IRB were not the one directly overseeing the research site, in what time period would you like to be notified of serious adverse events?

1. ≤ 24 hours
2. > 24 hours
3. Don't know

14. Can the paper work submitted to multiple local IRB be minimized by any of the following? (Circle all that related)

1. Centralized IRB
2. Standardized forms
3. Individual IRB committee Boards for specific research fields
4. Multiple local IRBs

15. Are there cost saving advantages of having single central IRB rather than an individual IRB for all the four hospitals?

1. Yes
2. No
3. Don't know/not sure

16. In your opinion, would it be any better if all four hospital IRB boards had some understanding in approval of a same protocol that could be conducted at all 4 hospital?

1. Yes
2. No
3. Don't know/not sure

17. Are you satisfied by the current system of IRB review-approval process for clinical research management?

Local IRB System	*Central IRB System*
1. Yes	1. Yes
2. No	2. No
3. Don't know	3. Don't know

18. What are your thoughts on the IRB review-approval process involving clinical research? Please comment

19. Would you please give the following details of the number of sites used to the number of IRB used to review the same protocol for recent five ongoing or completed trials?

Study	Number of Sites	Number of IRB reviewing/reviewed the protocol
1		
2		
3		
4		
5		

Thank you very much for your participation and we appreciate your time.

Please do forward any quarries or please return the survey via email to Dr Kiran Bangalore: kirank@hsc.unt.edu or fax it to 817-735-5120

Kiran Bangalore, MD

Intern, Dept of Surgery

University of North Texas, Health Science Center

3500 Camp Bowie Blvd

Fort Worth, Texas-76107

Ph: 817-735-0512, Fax: 817-735-5120

Survey for the IRB committee members and IRB administrative staff

Job Title-Circle one: 1) *IRB committee members*

2) IRB administrative staff

1. Your IRB is: (circle one of the following)

a. Commercial IRB

b. University IRB

c. Community Service IRB

d. Centralized IRB

e. Others please specify:

2. Are all members certified by any accredited or certification programs?

a. Yes

b. No

If yes, please specify the certification standard used:

3. How many fully established boards are currently serving?

a. 1

b. 2

c. 3 or more please specify _____

4. Your IRB serves:

a. One institution

b. Two Institutions

c. If more, please mention _____

5. What percentages of the protocols are? Please specify:

a. Clinical Trials Drugs/Devices -

b. Basic Science Research -

c. Public Health Research -

d. Behavioral Research -

e. Others -

6. Please give a range of the number of days from submission to final IRB approval; please give a range for the last five protocols reviewed: For example XX- ZZ days (submission-approval days):

a. Protocol-1
b. Protocol-2
c. Protocol-3
d. Protocol-4
e. Protocol-5

7. Would you please attach an organizational chart that reflects the IRB office structure and its functional aspect with all the sites at the end?

a. Yes, Attached.
b. No, we don't have a standard organizational system.

8. Does your IRB currently have standardized guidance material, consent forms, adverse event forms developed to assist specific research fields like public health research, basic science research, clinical research and qualitative research or do you use general forms for all the IRB submission process?

a. We have specific standardized form for individual research fields

b. We have same general form for all research fields

c. Don't know

d. Others, please specify

9. If no, do you plan to create standardized forms for each field of research?

a. Yes

b. No

c. Don't know/not sure

Please comment future on plans:

10. What is the approximate budget of your IRB?

11. How much do you charge for review-approval of?

a. Clinical research protocol:
b. Other research protocol:

12. Are the IRB consultation hours paid?

a. Yes

b. No

c. Don't know/not sure

Specify any other mode of compensation: (Traveling, accommodation etc. ,)

_

_

13. If no, will the IRB review-approval process be better if the consultation hours are paid?

a. Yes

b. No

c. Don't know/not sure

d. Specify any other reasons

14. What types of changes or amendments are made in the submission forms by IRBs?

(Circle all that related)

a. Minor Grammatical changes

b. Addition and deletion of an element of informed consent

c. Funding and Grant information

d. Cover letter

e. Others please specify –

15. Are these amendments consistent to all research projects?

a. Yes

b. No

c. Don't know

16. In your opinion, what do you think would improve the IRB's review-approval and ongoing communication process? (Circle all that related)

a. Centralized IRB

b. Standardized forms

c. Individual IRB committee Boards for specific research fields

d. Multiple local IRBs

e. Certification for IRB members

f. Others, please specify

17. In your opinion, would any of the following improve the clinical research-IRB process?

a. Multiple local IRB

b. Central IRB

c. Better with both

d. Don't know

18. How can the paper work submitted to multiple IRB be minimized? (Circle all that related)

a. Centralized IRB

b. Multiple Local IRB

c. Standardized forms

d. Don't know

e. Others please specify

To answer questions **19-24** *please use the following* ***hypothetical situation*** *encountered in an IRB and sites carrying out a research protocol in one of the major cities at their hospitals associated in the clinical research.* ***If you were involved in a similar situation, please explain which of the following options would you chose from.***

A clinical research protocol is being conducted in 4 hospitals in a city had to be reviewed by each hospitals IRB for initiation at their sites. The trial being carried out by the same physician as principle investigator at all 4 hospitals. As the trial went on, a single adverse event occurring at another site other than these 4 hospitals had to be reported to all the IRBs by the study coordinators each time by

faxing different submission forms to all 4 hospitals. Each event submitted had to have signatures of PI and Coordinators along with other submissions to governmental agencies.

19. Would standardized submission form for all four hospitals lessen the burden of paper work and time?

1. Yes
2. No
3. Don't know/not sure
4. Specify any other reasons

_____

20. In your opinion, would submission to one central IRB be time and monetary efficient than submitting to all 4 hospital IRBs?

1. Yes
2. No
3. Don't know/not sure

21. If your IRB were not the one directly overseeing the research site, would you like to be notified of the adverse event in:

1. ≤ 24 hours
2. > 24 hours
3. Don't know

22. Can the paper work submitted to multiple local IRB be minimized by any of the following (Circle all that related)

1. Individual IRB committee Boards for specific research fields
2. Centralized IRB
3. Standardized forms
4. Certification for IRB members
5. Others. Please specify:

23. Are there cost saving advantages of having single central IRB over four individual IRB for all the four hospitals?

1. Yes
2. No
3. Don't know/not sure
4. Specify, if other reasons

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24. In your opinion, Would it be any better if all four hospital IRB boards had some understanding in approval of a same protocol that could be conducted at all 4 hospital

1. Yes
2. No
3. Don't know/not sure
4. Specify any other reasons

25. Are the adverse events discussed in the IRB board meetings?

1. Yes, discussed
2. No, not discussed
3. Don't know/not sure

26. Is there any specialist who looks into the adverse event?

1. Yes
2. No

27. If you were an IRB committee member sitting on two of the boards of different hospitals, would either of the boards expedite the review of a research protocol already reviewed by other board?

a. Yes

b. No

c. Don't know/not sure

d. Specify any other reasons

28. If you were sitting on two boards, what would be the there main challenges you face?

1.

2.

3.

29. Would you please attach copies of the IRB forms that an investigator at your institution would complete for this research?

a. Yes

b. Web links, please print here:

30. Are you satisfied by the current system of IRB's review-approval process for clinical research protocols?

1. Yes
2. No
3. Don't know

31. What are your thoughts on the IRB review-approval process involving clinical research? Please comment.

Thank you very much for your participation and we appreciate your time. Please do forward any quarries or please return the survey via email to Dr Kiran Bangalore: kirank@hsc.unt.edu or fax it to 817-735-5120

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CHAPTER IV

My Internship Experience

I enrolled in the Clinical Research Management program at UNTHSC because my interests lay in both practicing medicine and conducting clinical research. My internship experience has expanded my understanding of how clinical trials run from start to finish

I was given the choice of which department I could complete my internship, and I choose the Department of Surgery. It was not only exciting but it was a great opportunity for me to work with Dr. Peska and Mr. Christopher Hayes they made me feel comfortable and they gave me an opportunity to work with them in all aspects of clinical trials. I was given an office for the duration of my internship (room #597, 5th floor, PCC Department of Vascular Surgery) and since my career goal is to be a physician scientist, this was a right place to start. Because of my medical background I had the added advantage of working in this clinical department.

The Department of Surgery is located in the 5th floor of the patient care center. It is one the best established department at UNTHSC seeing almost 500-1000 patients per year. There are three general surgeons, one vascular and thoracic surgeon and one cardiovascular surgeon. Dr A Yurvati is the chair of the

department. Most of the patients seen here have there surgeries performed at Plaza Medical Center of Fort Worth, John Peter Smith hospital, Baylor All Saints or Harris Methodist Hospitals.

During my first committee meeting, the committee decided that I would work on the role of the IRB and its integration as the current system of IRB was in debate. My focus was narrowed down within the first four weeks I worked hard in developing a proposed hypothesis which was discussed and approved in the committee meeting. Once approved, I developed a protocol and a set of two questionnaires, to test my hypothesis. These questionnaires included eighty questions regarding the IRB process. I also developed and built a website to conduct the research online. In order to finalize and approve the research proposal, protocol and the questionnaires, the committee met four times.

The aim of my research was to evaluate the IRB protocol review approval process and develop a new more efficient model. By the end of internship I proposed a new model, a separate clinical research review board (CRRB) which may be a more efficient, cost effective and a timely in the review and approval of the multisite clinical research protocols. I believe by having a separate nationalized standard clinical review board the local IRBs would be relieved of the burden of reviewing large numbers of protocols and help streamline all fields of clinical research.

During my internship I had the great opportunity to work with Mr. Christopher Hayes who is certified physician assistant with great deal of clinical experience. As I had worked in the department of Endocrinology and Metabolism, M S Ramaiah Hospital, Bangalore, India as a research associate and sub-investigator I had a great advantage to work in clinical trials here in the department of Surgery, University of North Texas Health Science Center.

At the start of my internship I underwent all the necessary training for me to be a clinical research coordinator and a research associate in the department. During the first week I trained and became certified in:

HIPPA Training

OSHA Blood Borne Pathogens Training

NIH Training for IRB member

NCI training for Human subject Protection

CITI course training for Biomedical and Human subject research

With all the above training, I was then able to meet with patients, obtain informed consent, observe and take past medical histories. As I am not board certified physician in the United States, I was not allowed to perform a physical examination.

In the initial days of my internship I became familiar with the IRB at both Plaza Medical Center and the UNTHSC as the trials in the department were concerned with both the IRBs. Mr. Hayes introduced me to Regan Wilson, IRB coordinator for plaza.

During my internship I gained insight of the difference between the surgery trials and other non-surgical trials. The closure of OMCT had a greatest impact on the surgery trials than trials in other departments. Since the closure of OMCT there has been a decrease in the number of trials in spite of having an experienced coordinator. This is because most of the surgery trials are in-patients compared to out-patient trials. Currently 12 studies are being conducted in the department and one upcoming trial by King Pharmaceutical is in process of initiation. Of the 12 studies, 3 are closing out as the sponsor had achieved the target number of trial subjects and others are open for patient recruitment.

As a daily routine, I was able to discharge all the duties of a clinical research associate which included:

Administering and obtaining informed consent

Study implementation like collecting the specimen and processing the specimen, following the reports and communicating and discussing them with the consultants and investigators.

Study visits: document and record all the subsequent study visits by patients while

on research study

Exit procedures: Following the subjects and completing the case report forms and source documents and help them complete the final study visit.

Additional visits and Unexpected visits: Attending patients for any unexpected visits while enrolled in the study.

Terminating patients: Any of the patients who falls out of the study for any exclusion criteria would be called in and explained the reasons for his/her inability to participate in the study.

Monitoring Visits: Assist monitors from sponsor to correcting the CRFs and Regulatory binders

Study Close out visit: Assist Monitors from sponsors for close out visit, helping them in study log, regulatory binder log, IND log, shipping any remaining investigational devise and drug and regulatory binders.

Study initiation visit: Assist the study site initiation meeting and recording the equipment log, examination rooms required for conducting the trials.

SAE reporting to both plaza and UNTHSC IRBs

Filing and Maintaining of CRFs, Regulatory Binders and Source Documents.

Along with this I was able to work on my thesis.

CHAPTER V

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VI. DAILY JOURNAL

"Department of Surgery Internship UNTHSC PCC"

Aug 20th

Met Dr Gwirtz, went over the Internship activities.

Scheduled Meetings with Dr Peska and Chris Hayes.

Aug 21st

Scheduled meeting with Dr Harold Sheedlo

Assisted Dr Mallet with Pig experiment

Aug 22nd

Met Chris Hayes, spoke about the on going trials and took the names of persons who previously had done Internship in the same department and referred their thesis book in library

Met Dr Harold Sheedlo

Finalized the meeting date for 24th august 2007.

Aug 23rd

Met Dr Gwirtz talked about the degree plan, committee forms and research proposal forms.

Met Chris and collected the protocols of the ongoing trials.

Met Dr Peska, Introduced my self and gave a brief picture about myself, my interest in his department and my future carrier interest.

Aug 24th

First Committee Meeting at 12:00-12:45 pm, Surgery conference room, UNTHSC.

Decided to work on **IRB INTEGRATION** as specific aim on all the ongoing trials in the department, since the approval of many IRB are necessary for a single trial to be operational and approval and coordination all the IRB's will help trials and patient better perform. Further proposals will be built on this.

27th August

Went over the studies being conducted in department of Surgery

Collected and reviewed the protocols

28th August

Protocol reviewing for research proposal

Discussed with Dr Yurvati about Atrium study as a thesis topic

29th August

Meeting with Dr Gwirtz and borrowed some thesis books for over view of research proposals

Underwent blood Bourne pathogen training in HR department

30th August

Meeting with Dr Sheedlo and borrowed books for research proposal

Alcon study monitor was at the site, Chris introduced me to Berrie Galberth, study monitor from Alcon

31st August

Alcon monitor was at the site, assisted her in maintaining CRF and Regulatory binder

3rd September

Meeting with Dr Gladue to discuss about IRB

Went over to Plaza Medical Center with Chris for SAE submission

Chris introduced me to Regan Wilson, IRB coordinator at Plaza

4th September

NIH Training on human research members for IRB

Worked on updating regulatory binders

5th September

Discussed the hypothesis with Dr Peska and Chris

Worked on hypothesis

6th September

Discussed hypothesis with Dr Yurvati

Work on research proposal

10th September 2007

Followed up with Alcon Clear study patient

Assisted monitor from Wyeth with monitoring needs, all CRFs, ADE, SAE and other documents

Final visit of patient for Alcon clear study followed the exit procedure for the etrials.

11th September

Preparation for the Alcon Clear study monitoring on Thursday and Friday.

Prepared data base of doctors to send letters describing the Alcon study

12th September

Meeting with Dr Brain Gladue, talked about the protocol development and IRB work for the project.

Reviewed the Alcon Clear study files with Chris and Megan.

13th September

Assisted Alcon monitor.

Visited plaza to collect documents and EKG of the new Wyeth patient.

Had meeting with Dr Sheedlo and discussed the protocol development, hypothesis and specific aims.

Reviewed the patient for Alcon Clear study: 3rd visit.

14th September

Monitor from Alcon Clear study was at the site. Assisted with monitoring all CRFs, ADE, SAE and other documents.

17th September

Met with Dr. Peska & Dr Yurvati, Discussed the hypothesis and specific aims.

Meeting with Dr Gwirtz

Screened Wyeth study subject. Subject did not qualify for the study as her Creatinine clearance was high.

Reported SAE's to the IRB for the Pfizer study of Linezolid in MRSA pneumonia.

18th September

Nuvelo study closure letter signed by Dr Peska and submitted to Plaza IRB

Enrolled a patient for Alcon clear study.

Screened a subject for the Accentia study for chronic sinusitis patients, but he declined to be in study.

Meeting with Dr Yurvati regarding a Grant or an Intramural Research Proposal.

19th September

Wyeth monitor was at the site, assisted him with case files.

Alcon clear study patient was followed.

HIPPAA training

20th September

Meeting with Graduate advisor

Meeting with Dr Peska and discussed the hypothesis and specific aims.

Meeting with Dr Gladue, went over the cost effective issue.

21st September

Continued literature search for questionnaire development.

Reviewed Accentia CRF's for monitoring on Tuesday.

24th September

Orientation at Plaza medical center

Preparation for Accentia study monitoring on Wednesday and Thursday

25th September

Alcon clear study patient for visit 3

King Pharmaceutical representative for the site selection meeting with the representative and site personnel.

Questionnaire preparation.

26th September

Monitor from Accentia pharmaceutical Dominica was at the site. Assisted her with CRF's and source documents.

27th September

Managed subject for Alcon clear study scheduled visit

Meet Dr Gwirtz

Questionnaire development.

28th September

Arranged meeting on October 3rd

Attended seminar on "No Reflow" in Lib-110

1st October

Observed procedure at plaza- subclavian femoral bypass.

Questionnaire development.

2nd October

Meeting wit Dr Peska

Managed Alcon Clear study patient scheduled return visit

IRB work.

3rd October

Committee meeting

Discussed protocol submissions with final corrections to be completed by 13th Oct.

4th October

Managed Alcon clear study patient.

Alcon CRF completion work

Library class on refworks

5th October

Working on revised questions and research paper

Discussed the questions with Chris

Eliminated many questions so that the total number of questions would be less than 30.

8th October

Discussed questions and reframed few of questions after discussing with Chris

Working on research proposal

9th October

Working on research proposal

Meet Dr Sheedlo and discussed the questionnaire

10th October

Working on research proposal

Managed Accentia study patient

11th October

Working on research proposal

Accentia CRF completion work

12th October

Committee meeting

Finalized the protocol, Informed consent and two set of questionnaire after discussion with Dr Peska, Dr Yurvati, Dr Gwirtz, Dr Sheedlo and Chris.

Chris made some final corrections

Committee authorized me to be principal investigator for the study

15th October

IRB work, filling the UNTHSC IRB forms for protocol review. Chris helped me

fill the IRB forms.

Called Ms Sharon Tobola and arranged a meeting. Submitted all the research documents for UNTHSC IRB with Ms Sharon. She explained and confirmed it would be expedited review and it would take 2-3 weeks for approval.

16th October

Discussed the budgeting aspect of clinical trials in surgery department, learned how the fees are negotiated for surgery trials and at UNTHSC.

Regulatory binder completion and updating.

17th October

Meeting with Dr Peska, Asked him to write a letter to UNTHSC IRB stating that the department of surgery is permitting me to be principal investigator for my research proposal.

Monitor at site from Alcon, assisted monitor with CRFs and regulatory binders.

Obtained signatures from Dr. Phillips

18th October

Website building, discussed with Dr Peska about the different domain names which we could use to conduct the research.

Discussed with Chris and told him about Dr. Peska's opinion. Later decided a domain name of:

www.ncrrb.com would be registered and will be used for our research.

19th October

Inauguration ceremony

Website work, created a blue print of how the website would look when completed. Discussed with Dr Peska and he mentioned before completely finishing the website he would go over all the pages and give his comments.

22nd October

Meeting with Dr Gwirtz

Alcon Clear ear study monitoring work

Wyeth patient SAE reporting

23rd October

Alcon study patient

Alcon Clear ear study monitoring work

Wyeth SAE reporting

Meeting with Ms Sharon Tobola, discussed about my protocol.

24th October

Meeting with Dr Gwirtz and Chris Hayes, discussed problems of the research project. Concluded not to do the project at the University or in the North Texas metroplex area as per Dr Brain Gladue and Dr Glenn Dillon.

Plaza hospital IRB work.

25th October

Alcon clear study new patient

Plaza Wyeth study SAE patient

Meeting Dr Gwirtz and Dr Peska regarding research proposal.

26th October

The proposal was dropped due to IRB disapproval (conflict of interest from institution point of view) as Dr Brain Gladue, Acting Chairman of UNTHSC, IRB would not give his approval for the proposed research project and all other research materials.

29th October

Alcon clear study patient was at the site, completed CRF for Alcon study.

Pfizer study closure preparations were performed

Informed Dr. Yurvati about the IRB denial of protocol approval.

Informed Dr. Sheedlo about the IRB denial of protocol approval.

Scheduled meeting with graduate adviser, Dr J Vishwanatha on 30th October, But meeting was cancelled and Carolyn Polk, His secretary called and asked me to meet with dr Gwirtz, as He was not be able to guide on the research proposal and IRB disapproval of project.

30th October

Pfizer monitor was here and helped in close-out of study A5951001

Plaza drug dispensing and accountability work.

31st October

Work on new research proposal

"Literature search for IRB review of human subject research".

1st November

Working on new proposal

Wyeth patient rounds subject was discharged after colostomy and exploratory laprotomy- SAE

Called Dr. Fikkert and informed about the Wyeth patient as Dr. Buchanan was out of town.

2nd November

Literature search for new proposal

Alcon clear study patient and paper work, completion of CRF.

5th November

Plaza IRB SAE submissions

UNTHSC IRB SAE submissions

6th November

Alcon Clear Study

Filing

Assisted with Wyeth Monitor

Submission to graduate office

Meeting with Dr Sheedlo

7th November

Pfizer A5951001 linezolid study close out

8th November

Assisted with PfizerA5951001 linezolid study close out visit by Monitor Jennifer Fretz.

Pfizer study closure work

Plaza pharmacy binder work

Drug log and return

9th November

Assisted with Pfizer A5951001Llinezolid study close out visit by Monitor Jennifer Fretz.

12th November

Assisted with Pfizer A5951001Llinezolid study close out visit by Monitor

Jennifer Fretz.

Shipped the investigational drug back to sponsor

Wyeth monitoring visit

Wyeth SAE- patient work

13th November

Medical record work – Wyeth study

Wyeth Source documents work

14th November

Alcon study- patient disqualification

Lab report – fungus in culture, study subject excluded

15th November

Filing of documents

Regulatory binder updates

16th November

Regulatory binder updates

SAE reporting from other sites

19th November

Wyeth study SAE reporting (SAE at our site) and faxing of medical records to Wyeth sponsors

20th November

SAE and Medical records work for Wyeth study

21st November

Source document completions and corrections for the Wyeth study

Thanks giving holiday!!!

22nd & 23rd November

26th November

Completed case report forms from patient medical records

Made copies of some records for the source documents

27th November

Answered fax quires regarding CRF corrections

Completion of CRF work

28th November

Met Dr. Sheedlo and discussed thesis work.

Worked on thesis the whole day.

29th November

Worked on SAE from other sites and submitted to Plaza Hospital IRB and UNTHSC IRB

Attended clinics with Dr Peska

3rd December- 10th December

Worked on my thesis all day

Went over and corrected thesis with Chris

Extra articles were obtained from internet search and cited

11th December

Finalized thesis and printed out a copy for Dr Sheedlo

Submitted thesis to Dr Sheedlo and he asked a week to make his corrections.

12th December

Chris gone to California 12th thru 18th

Worked on my reference section of thesis

13th December

Worked on SAE and made copies and submitted SAEs to both Plaza Medical Center and UNTHSC IRBs

14th December

Patient here for Accentia study, visit 4

Patient was late and had to call him

Collected the used investigational product and dispensed the new box of drug

Called Chris and briefed him about the patient.

Scheduled the next visit 5 for patient

15th December

Completed the CRF for visit four, Accentia study.

Worked on my thesis

17th December

Plaza SAE work, received SAEs from other sites and filled them according to

Plaza IRB SAE reporting forms.

18th December

Assisted with patient for Accentia study

Regulatory binder work

19th December – 1st January

Holiday, Christmas and Winter Break

2nd January 2008

Completed the thesis work and got corrections from Dr Sheedlo.

3rd January

Met Dr Peska and discussed the thesis.

4th January

Worked on thesis

7th January

Assisted Wyeth study monitor with CRF corrections and Regulatory documents

8th January

Assisted Wyeth study monitor with CRF corrections and Regulatory documents

9th January

Worked on PowerPoint presentation

Discussed with presentation with Chris

10th January

Worked on PowerPoint presentation

11th Jan

Worked on PowerPoint presentation

Alcon Clear ear Study work

14th January

Assisted with Alcon clear ear study, worked on CRF and Regulatory binders

15th January

Mock Presentation with Dr Gwirtz, Dr Sheedlo and Mr. Christopher Hayes

Alcon study monitor was at the site; Chris took off for an hour for presentation

16th January

Assisted Alcon Clear Ear Study monitor in maintaining CRF and Regulatory binder.

Submitted the final copy of my thesis to all committee members.

Scheduled two mock presentations 17th January and 1st February.

CHAPTER VII

LIST OF ABBREVIATION

AAMC: American Association of Medical Council

B-CLL: B cell chronic lymphocytic leukemia

BRANY: Biomedical Research Alliance of New York

CBE: Council of Bioethics

CFR: Code of Federal Regulations

COMIRB: Colorado Multiple Institutional Review Board

CPA: Cooperative Project Assurances

CRO: Contract Research Organization

CRRB: Clinical Research Review Board

DEG: Diethylene Glycol

DSMB: Data and Safety Monitoring Board

ERP: Ethical Research practice

ECCR: Ethical Codes for Clinical Research

FDA: Food and Drug Administration

FDC: Federal Food Drug and Cosmetic Act (FFDCA, FD&C)

FWA: Federal Wide Assurances

GCP: Good Clinical Practice

GEP: Good Ethical Practice

GRP: Good Research Practice

HHS: Health and Human Services

HSPC: Human Subject Protection Cell

ICH: International Conference on Harmonization

IDE: investigational Device Exemption

IND: Investigational New Drug

IRB: Institutional Review Board

MACRO: Multicenter Academic Clinical Research Organization

MPA: Multiple Protocol Assurances

NIH: National Institute of Health

OHRP: Office of Human Research Protections

OIG: Office of Inspector General

OPRR: Office of Protection of Research Risks

REO: Regional Ethics Organization

RFID: Radio Frequency Identification

SAE: Serious Adverse Events

SMO: Site Management Organization

SOP: Standard Operating Procedures

SPA: Single Protocol Assurances

USPHS: united States Public Health Services

WIRB: Western Institutional Review Board

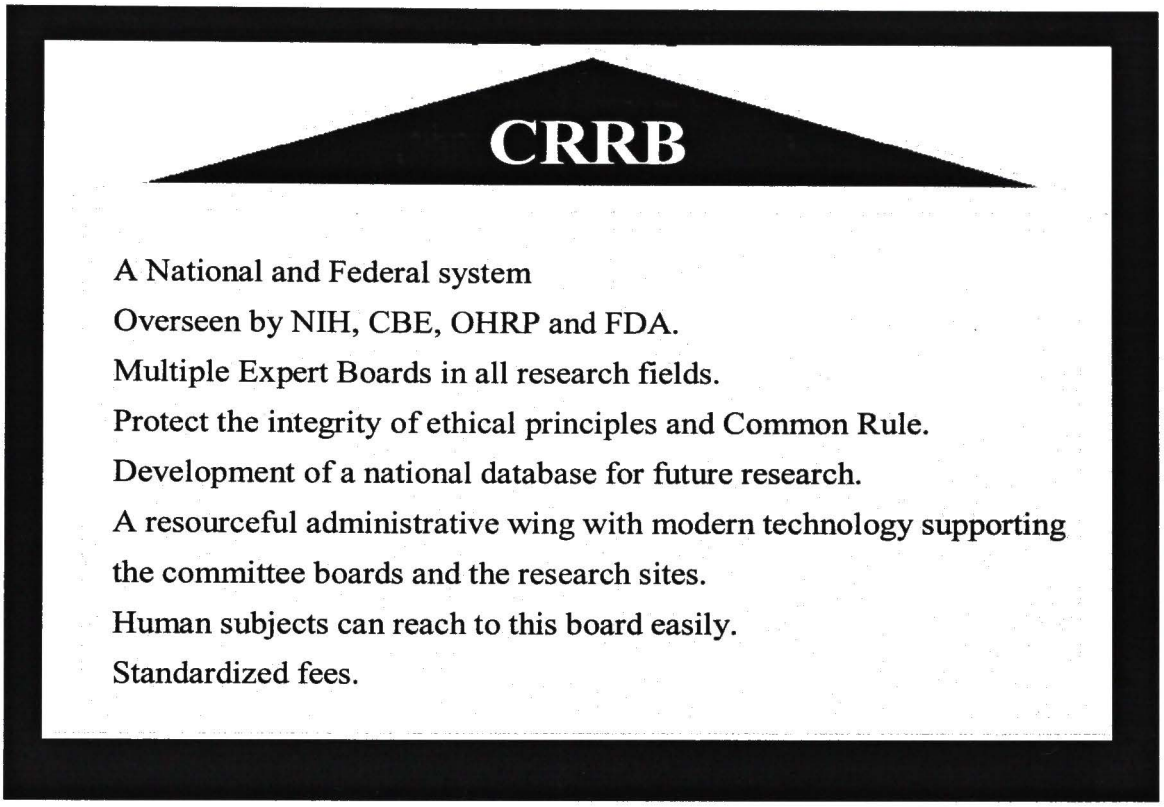

Figure 4: CRRB structure

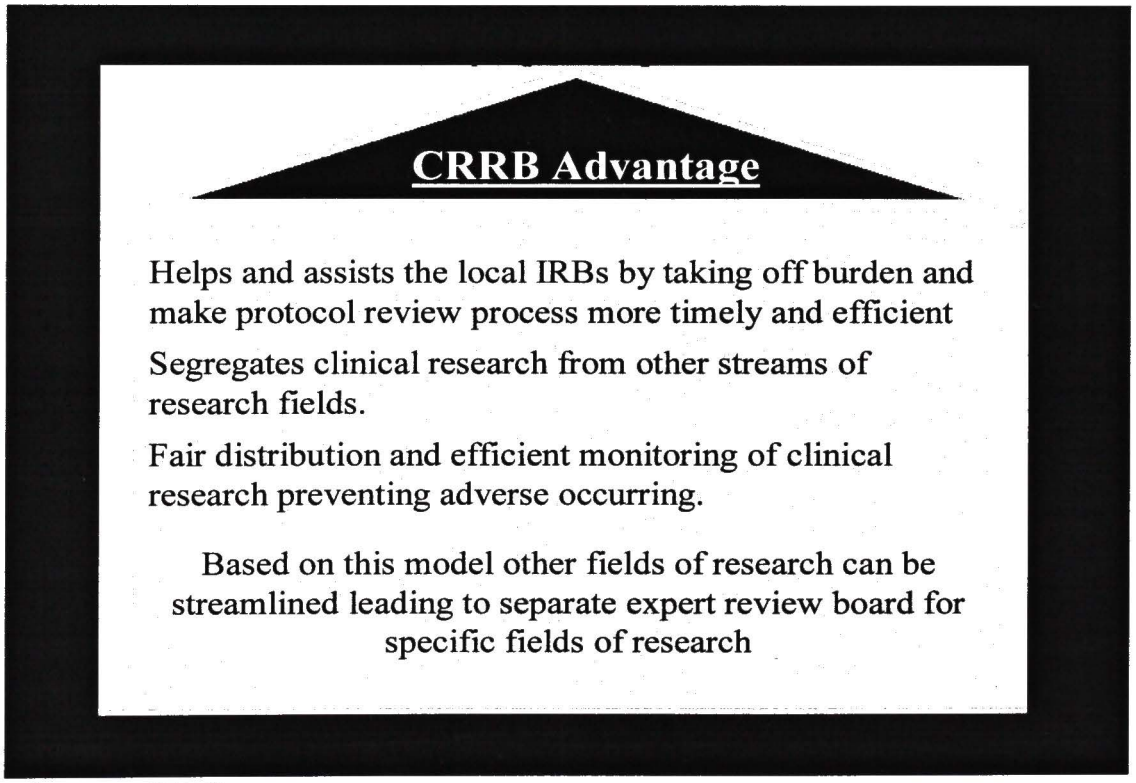

Figure 5: CRRB structure

Figure 6: Balancing Research Streams, CRRB advantage.