ESTABLISHING A QUALITY MANAGEMENT SYSTEM FOR A BIOMEDICAL ACADEMIC INSTITUTION THAT PERFORMS CLINICAL RESEARCH IN COMPLIANCE WITH GOOD CLINICAL PRACTICES

by

KELLY ANNE WINN

(Under the Direction of David W. Mullis)

ABSTRACT

The focus of this research was to establish a Quality Management System for a biomedical academic institution that performs clinical research in compliance with Good Clinical Practices. The research incorporated a retrospective review of FDA warning letters to establish the most common deficiencies among academic biomedical clinical research institutions and compared these results against a survey used as verification in order to answer the following research questions:

What are the challenges of implementing a GCP/Quality Management System?

What are the most common GCP violations issued by the FDA?

What areas of GCPs should be concentrated on the most in developing a GCP Quality Management System?

It was from this qualitative comparative analysis results that a comprehensive process based quality management system standard operating procedure was established.

INDEX WORDS: Good Clinical Practices; 21 CFR 50; 21 CFR 54, 21 CFR 56, 21 CFR 312; 21 CFR 812; 21 CFR 11; ISO 9001:2008; ICH E6; Belmont Report; Quality Systems, Quality Management System

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DEDICATION

This thesis is dedicated to Barbara S. Henry who without her continued support, mentorship, and friendship, none of this would have been possible. A big thank you to Barbara, my friends and family for all their support, patience and understanding during this journey into the next chapter of my life.

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TABLE OF CONTENTS

Page

LIST OF GRAPHS

Page

LIST OF FIGURES

Page

CHAPTER 1

OVERVIEW

1.1 Introduction

Biomedical academic institutions in the United States consistently engage in research to test the safety and efficacy of the investigational drugs, devices and biologics that they invent. In order to effectively test these products, humans are used as volunteer test subjects in research experiments, known as clinical trials. Clinical trials consist of several stages of testing product from the very first in human trials which are known as Phase I and then continuing on to Phase II, Phase III and Phase IV. In biomedical academic clinical research, most clinical testing is done as a Phase I or Phase II clinical research trial. A Phase I clinical trial is a first in-human research trial of a drug, biologic or medical device product and consists of testing the safety and efficacy, and the pharmacokinetics and biocompatibility of the product are tested on a very small sample of volunteer subjects. Phase II is a continuation of a Phase I clinical trial and may consist of a slightly larger cohort of volunteer subjects. Phase III clinical trials usually have established baseline safety and efficacy testing; and therefore, are performed on an extremely large population of subjects, and the product is used as a treatment for the disease or the medical condition for which it is intended. Phase IV clinical trials are usually known as the post-marketing phase of testing. Both of the latter phases of clinical trials (Phase III and Phase IV) are usually performed by major pharmaceutical /medical device companies or startups that obtain products from academic research institutions that initially tested them. [1]

Clinical trials performed by pharmaceutical and medical device companies follow Good Manufacturing Practices or cGMPs (clinical Good Manufacturing Practices). As specified by the Food and Drug Administration (FDA), good manufacturing practices require a "central objective: to create a system of programs, policies, processes, and facilities that prevent errors and defects." [2] This practice is incorporated into the Quality System. "Quality systems and risk management approaches that meet the requirements of the Agency's current good manufacturing practice (CGMP) regulations are found in 2l CFR parts 210 and 211" [3] and 21 CFR part 820 for medical devices. [4] A quality system is organized in a way that dictates responsibilities, standard operating procedures, process, and resources in implementing a systematic management framework that delegates responsibilities and complies with good manufacturing practices and the Food, Drug and Cosmetic Act.

Since most biomedical academic institutions are innovators of product but not manufacturers of product, these institutions usually do not follow cGMP guidelines, but, instead, follow Good *Clinical* Practices (GCPs). Unlike GMPs which focus on both production and quality, "Good *Clinical* Practices is an internationally recognized ethical and scientific quality standard for the design, conduct, recording and reporting of clinical research trials that involve the participation of volunteer human subjects." [1] Compliance with GCPs provides assurance that the rights, safety and well-being of volunteer subjects are protected, consistent with the principles of the Declaration of Helsinki and that the resulting data are credible. [5] Good Clinical Practices have been adopted as an international standard by the International Conference on Harmonization as ICH GCP (E6). [6]

1.2 History of Good Clinical Practices

Historically, human subjects have too often been treated unethically as participants in clinical trials. Perhaps the most egregious examples are the atrocities committed by the Nazis during World War II in the name of science. These unspeakable acts of human experimentation were fully documented and exposed during the military tribunals held in Nuremberg, West Germany in the mid- to late-1940s. The Nuremberg Trials resulted in the writing of one of the first ethical codes to undergird research with human subjects, the Nuremberg Code, "and it was from these instructions that the foundations of GCP were formed. The key points of this code identified and prioritized the rights of the individual and included, for the first time in an international document, such principles as voluntary participation, informed consent and allowing the participant to withdraw from the experiment at any time. It also suggested that measures should be taken in order to minimize any risk to the participant, and that the benefits of the research should outweigh the potential risks." [1]

In 1964, the World Medical Association produced its first *Declaration of Helsinki*- another set of ethical principles governing human experimentation but specifically developed for the medical community. This cornerstone document on human research ethics has been amended several times, and the final and official version of this document was produced in October 2013. [7]

The Common Rule is federal United States policy that was adopted from the amended versions of the Declaration of Helsinki and harmonizes the requirements across nearly two dozen federal agencies. The Common Rule concentrates on "compliance by research institutions, the informed consent process, Institutional Review Board (IRB) regulations and additional protections for vulnerable populations." [8]

Despite the proliferation of ethical guidelines, unprincipled practices in human research continued in the mid- to late-twentieth century. It was the exposure in 1976 of the infamous 40-year syphilis study in rural Tuskegee, AL that prompted Congress to establish the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. In 1979, the Commission published its timeless "Belmont Report" which culminated from a four-year deliberation over serious research misconduct cases and the resulting public outrage. The Belmont Report established three important ethical principles as a guide for conducting human subjects research: 1) respect for persons, 2) beneficence, and 3) justice. Respect for persons establishes a human being as an autonomous agent. The second ethical principle, beneficence, says that benefits must outweigh the risks in research to the human subject. The third principle, justice, mandates equality among populations in research. No population should be targeted in research if unlikely to be the beneficiary of the research outcome. [8]

It was these and similar historical events that formed the basis *in ethics* for what we know as Good *Clinical* Practices. The World Health Organization (WHO) handbook similarly consists of international guidelines that address the justification for "clinical trial and protocol development, protection of human subjects, responsibilities of investigators, sponsors and monitors, assurance of data integrity and product accountability and the roles and responsibilities of regulatory authorities." [8]

In contrast to good laboratory practices or good manufacturing practices which have their own entitled sections within title 21 of the Code of Federal Regulations (CFR), good clinical practices do not. GCPs are dispersed throughout the CFR and through FDA guidance documents. GCPs found within the CFR are enforceable within the United States while the accompanying FDA guidance documents represent the current non-binding thinking of the

FDA's best practices. The FDA's official guidance was established from ICH GCP (E6), which is a universal standard between the European Union, Japan and the United States. The other official FDA guidance documents for GCPs are the Information Sheets for Clinical Investigators and IRB's.

Title 21 CFR is the United States version of GCP principles and regulations. GCPs are found in the Code of Federal Regulations as follows: [8]

- 21 CFR 11: Electronic records and signatures [8]
- 21 CFR 50: Protection of human subjects (Informed consent: requirements, exceptions, elements and documentation) [8]
- 21 CFR 54: Financial disclosure [8]
- 21 CFR 56: Institutional Review Boards (General provisions: scope, IRB review, exemptions, Organization and Personnel: membership, IRB functions: IRB operations, criteria for IRB approval, suspension/termination of IRB approval, Records and Reports: documentation, Action for noncompliance: Disqualification of an IRB) [8]
- 21 CFR 312: Investigational new drug applications (Responsibilities of: Principal Investigator, sponsor [8]
- 21 CFR 812: Investigational device exemptions (Responsibilities of: Principal Investigator, sponsor) [8]

The FDA's GCP regulations and the ICH GCP E6 are very much alike and almost parallel each other, especially when it comes to investigator responsibilities and the process of informed consent. However, the FDA regulations tend to be more precise when it comes to Institutional Review Boards and their functions. On the other hand, the ICH GCP E6 provides more explicit detail regarding sponsor and monitoring responsibilities. [9] The ICH GCP E6

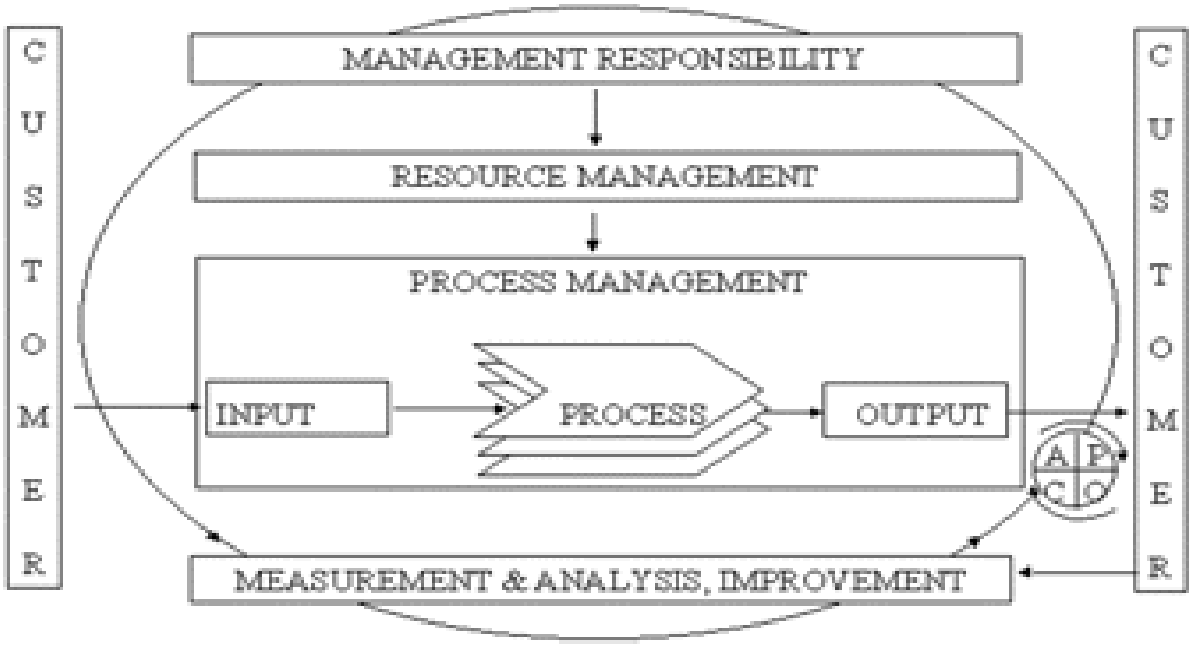
consists of thirteen guiding principles of good clinical practice. These thirteen principles can be organized into five major areas: 1) conduct clinical trials ethically, 2) subject protection is the paramount priority, 3) have a well-designed plan, 4) select qualified study staff, and 5) documentation. [8]

1.3 Quality Systems Model

Clinical investigators, sponsors, monitors, contract research organizations and institutional review boards are all responsible for adherence to Good Clinical Practices in clinical trials research. This leads us to the Quality System approach. There is a need for incorporating quality into the clinical trial process. This systematic approach will lead to obtaining quality data during the clinical trial without compromising the safety and welfare of human subjects.

Historically, clinical research has initiated quality assurance processes reactively after a serious problem has occurred instead of proactively as part of a quality management system. Today, innovation is accelerating at such a rapid pace that results in more complex research needs and increasing the demand for quality resources and quality product while protecting the rights and welfare of the clinical trial participants. This requires the development and implementation of standards for each part of the clinical research process. [10]

Figure 1 presents the international standards organization for the quality approach. The four key areas of concern are management responsibility (policy, objectives, planning, quality management system, and management review), resource management (human resources, information, and facilities), process management (customer satisfaction, design, purchasing, and production), and measurement, analysis, and improvement (audit, process control, and continual improvement). [10]



2015 Infectious Diseases Society of America

Figure 1.1 International Standards Organization for Quality Framework

This research paper will focus on the implementation of a quality management system as a subset of management responsibility of the quality framework to be applied to a biomedical academic institution performing clinical research. The initial research method was partially informed by the methodological approach described in Naran Patel's "Developing a Comprehensive CGMP/Quality System Implementation Plan to Meet FDA Regulations for Class II Medical Devices". [4] The researcher initially analyzed five + years (January 2010 to June 2015) of FDA warning letters for Good Clinical Practice citations issued by the FDA's Bioresearch Monitoring (BIMO) program. A warning letter is the result of a FDA observational Form 483. A FDA observational Form 483 is issued during an inspection or audit by the FDA for violation of the regulations. Usually, these violations are rectified with a corrective action plan and satisfactory response to the FDA within a fifteen day time period. However, observational

violations that are not corrected may result in a FDA warning letter being issued. The purpose for the collection and analysis of Good Clinical Practice citations was to identify the types of non-compliance violations that the FDA issued relative to Good Clinical Practices. The individual citations were tallied within each of the following categories in order to perform a trend analysis of GCP citations per category over the 5+ years: Clinical Investigator, Institutional Review Board, and Sponsor/Monitor/CRO. Then the five+ year total citations per category were tallied to reveal the number of violations per quality management system area. This analysis will reveal which areas of the quality management system were most frequently cited over the last 5+ years and which areas must be focused on while establishing a quality management system for a biomedical academic institution. [4]

1.4. Research Methodology

As stated above, for phase I the researcher initially used the model of methodology presented in Naran Patel's "Developing a Comprehensive CGMP/Quality System Implementation Plan to Meet FDA Regulations for Class II Medical Devices". [4] Naran Patel's model was based on a qualitative evaluation of FDA warning letters resulting in a trend analysis. The research presented here expands on Patel's model by obtaining and analyzing FDA warning letters for Good Clinical Practice issued citations issued by the FDA's Bioresearch Monitoring (BIMO) program from January 2010 through June 2015. The individual citations were tallied by their Title 21 Code from the CFR within each of the following groups to perform a trend analysis of GCP citations per group over 5+ years: clinical investigator, institutional review board, and sponsor/monitor/contract research organization (CRO). The five+ year total citations per group were tallied to reveal the number of violations per quality management system area. This will show which areas of the quality management system were cited the most over the last 5+ years

and which areas must be focused on while establishing a quality management system for a biomedical academic institution. [4]

For phase II, the researcher submitted a human subject research application to the University of Georgia's Institutional Review Board (#IRB00000063) under Federalwide Assurance #FWA00003901. [11] The human subject research application consisted of the protocol description, the targeted population, subject recruitment number, the recruitment plan, and the consent process. The email recruitment, consent form, and survey material were uploaded and approved with the IRB application prior to any human subject research being conducted.

Once the human subject IRB application was approved, the research involved surveying professional and expert subjects in the field of quality assurance and regulatory compliance from the top 50 National Institutes of Health (NIH) funded academic biomedical institutions; the NIH is the largest funder of biomedical research in the world. The recruitment plan involved sending an email invitation, with a link to the survey material on Survey Monkey®, to the quality assurance and regulatory compliance departments of the top 50 NIH funded academic biomedical institutions. The body of the email invitation included the elements of consent found in the University of Georgia (UGA) informed consent template with an option to click on the link to access the survey. When clicking on the link to the survey, human subjects imply their voluntary consent for participation in the survey and the research study. A waiver of documentation of consent was approved by the UGA IRB in accordance with 45 CFR 46.117(c) part 2. Per 45CFR46.117(c) an IRB may waive the requirement for the investigator to obtain a signed consent form for some or all subjects if it finds either: [12]

(1) That the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each

subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern; or

(2) That the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.

The survey questions were designed to validate the results found from the analysis of the FDA warning letters from Phase I of the research. Continuing with Naran Patel's approach, these survey results were compiled and summarized in a table using comparative analysis. [4] Common gaps from the survey results were identified and used as the foundation for determining majors concerns for violation of the different areas of the GCP quality system.[4] Subsequent to performance of the gap analysis, gaps were addressed by including them in the implementation plan to establish a GCP quality management system for biomedical academic institution. [4]

1.5. Research Questions

A quality management systems approach is proactive about protecting the rights and welfare of human subjects while ensuring data validity for viable research results. In clinical research, this may be achieved through combined oversight by the clinical investigator, sponsor, IRB, monitor and/or CRO. Since FDA inspections and audits use a risk based approach, implementation of a risk based approach is encouraged in biomedical research and should focus on the critical areas of the quality management system in order to protect human subjects and data validity in clinical research. The focus of this research was to design a quality management system for a biomedical academic institution that performs clinical research in compliance with Good Clinical Practices. This research study carried out a retrospective review of FDA warning letters for good clinical practice citations during the last 5+ years and a survey of compliance professionals from the top 50 NIH funded biomedical institutions. This survey was used to verify

and validate the results from the retrospective review analysis in order to answer the following research questions:

What are the most common GCP violations issued by the FDA?

Are there areas of GCPs that should be concentrated on more than others in developing a Quality Management System?

Are there challenges of implementing a GCP/Quality Management System in an academic biomedical institution?

These results were used to establish a robust comprehensive quality management system in compliance with Good *Clinical* Practices. This risk based approach ensures that all areas of the quality management system are in compliance with the regulations at all times and that human subject protection is a priority.

CHAPTER 2

QUALITY SYSTEMS: A CONTROLLED APPROACH FOR COMPLIANCE WITH GOOD CLINICAL PRACTICES

2.1 Quality Systems Overview

While quality systems were first implemented in manufacturing for Good Manufacturing Practices compliance, the application of similar systems to clinical research is critical to ensure a quality product. The quality system model consists of 7 subsystems as seen below in figure 1.2 and is based on the Quality System Inspection Technique or QSIT. [13]

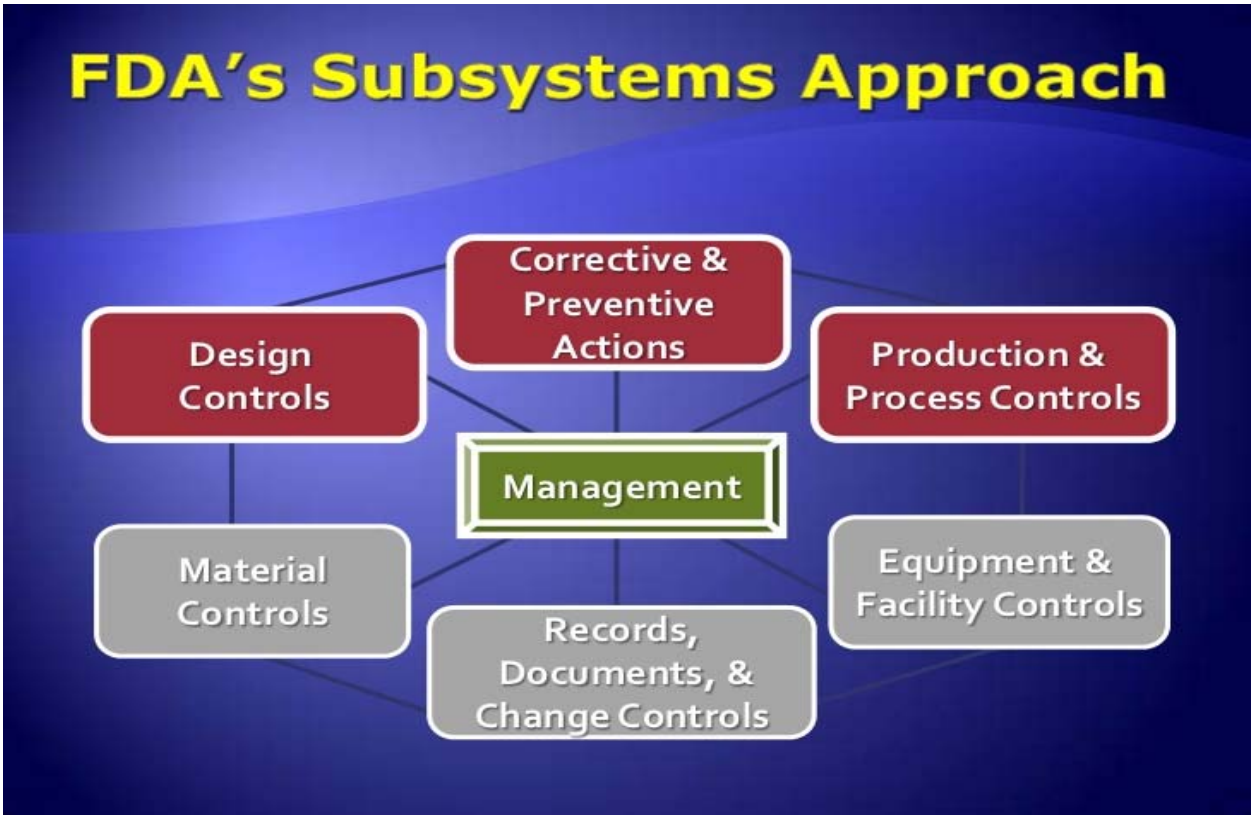


Figure 2.1 Seven Subsystems by Raul Soto [13]

The Quality Systems regulations are found in ISO 9001:1994, ISO 13485:2003 and within Title 21 CFR 820 and are written for manufacturers of medical device products. This research will expand on the medical device Quality Systems model and will examine the Quality System as an applicable framework in clinical research.

What is quality? “Quality is a measurement of the ability of a product, process, or service to satisfy stated or implied needs. A high quality product readily meets those needs.” [14] This relates to the International Standards Organization for quality framework model that is seen in figure 1.1 under process management. By implementing quality into the process as an input, the output is a high quality product that meets customer needs.

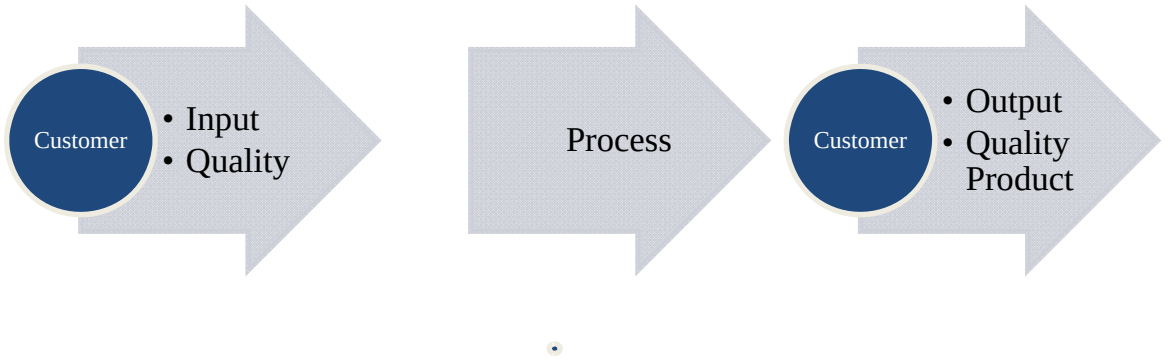


Figure 2.2 Quality Framework Model

In clinical research, quality is applied to the processes of research, such as: the data being obtained, protocol adherence, GCP compliance, process of informed consent, data handling, documentation and records (keeping, reporting and retention). [14] Components of quality also include a quality scientific design of the study protocol, assessment of clinical investigator qualifications, IRB/ethics review, regulatory, personnel training, monitoring and auditing. [15]

In order to achieve and maintain compliance, standard operating procedures, also called SOPs, are developed and followed. SOPs provide guidance in the implementation and execution

of a clinical research study. SOPs are a step by step guide that is put in place in order for the clinical research study to maintain quality throughout the lifetime of the research study. SOPs combined with close supervision of sponsors, clinical research organizations (CRO), monitors and clinical investigators, create a framework for assuring quality in generating accurate and reliable data as well as protecting human subjects participating in the clinical research study.[14, 15]

A Quality System is a systematic approach that produces a quality outcome. A Quality System is defined as "the organizational structure, responsibilities, procedures, processes and resources for implementing quality management." [16] Quality systems include monitoring and audit programs, complaint handling, adverse events and any other formal practice in order to maintain data and process quality. [14]

2.2. Fundamentals of Quality Systems

Within GCPs, there are three fundamental parts of a quality system in clinical research: quality assurance, quality control and quality improvement. [14] These integral parts fall under the management subsystem of the quality system. Each component is described below per the *Handbook for Good Clinical Research Practice*: [14]

Quality Control

"Quality control is the steps taken during the generation of a product or service to ensure product/service quality. For a clinical trial, "quality control" encompasses steps taken during the clinical trial (e.g., investigator supervision, sponsor monitoring, and any ongoing review by regulatory authorities) to ensure that the trial meets protocol and procedural requirements and is reproducible." [14]

Quality Assurance

"Quality assurance refers to a systematic process to determine whether the quality control system is working and effective. Most often, quality assurance in clinical trials is implemented by the sponsor through independent auditing of quality control activities and, where applicable, by regulatory authorities through inspection of quality control systems and activities. Quality assurance audits may be performed during the course of the clinical trial and/or upon trial completion." [14]

"The purpose of a sponsor's audit, which is independent of and separate from routine monitoring or quality control functions, should be to evaluate trial conduct and compliance with the protocol, SOPs, GCPs, and the applicable regulatory requirements (ICH E6, section 5.19)." [14]

To ensure that quality is maintained throughout the entire clinical research process, the Shewhart Model is often used as a best practice. Walter Shewhart was known as the father of quality control and set many precedents in the importance of distribution of information among quality managers and personnel. These precedents include statistical quality control (SQC), the Six Sigma approach for quality assurance and the total quality management (TQM) philosophy.[17]

Figure 2.3 Shewhart Model of Quality Assurance [17]

In Shewhart's model, the plan is to create processes that are necessary to produce the expected output. "Do" is to put the plan into action, carry out the process and produce the product. The next step is to "check" the outcome of the product and compare against the accepted outcome of product. The last step is to "act". If the "check" plan shows that there is improvement in product,

then the new “do” becomes the new standard for how the organization should “act”. If there is no improvement shown, then the previous standard will resume. [18]

Quality Improvement

“Quality improvement refers to a systematic process for taking the knowledge gained through quality assurance audits and activities and using this knowledge to make changes in systems and activities in order to increase the ability to fulfill quality requirements then and for the future.” [14] Since the standard level of quality is not passive due to differences in customer quality acceptability, there is an increased focus on quality improvement during the entire clinical research process in order to produce a quality output. [10]

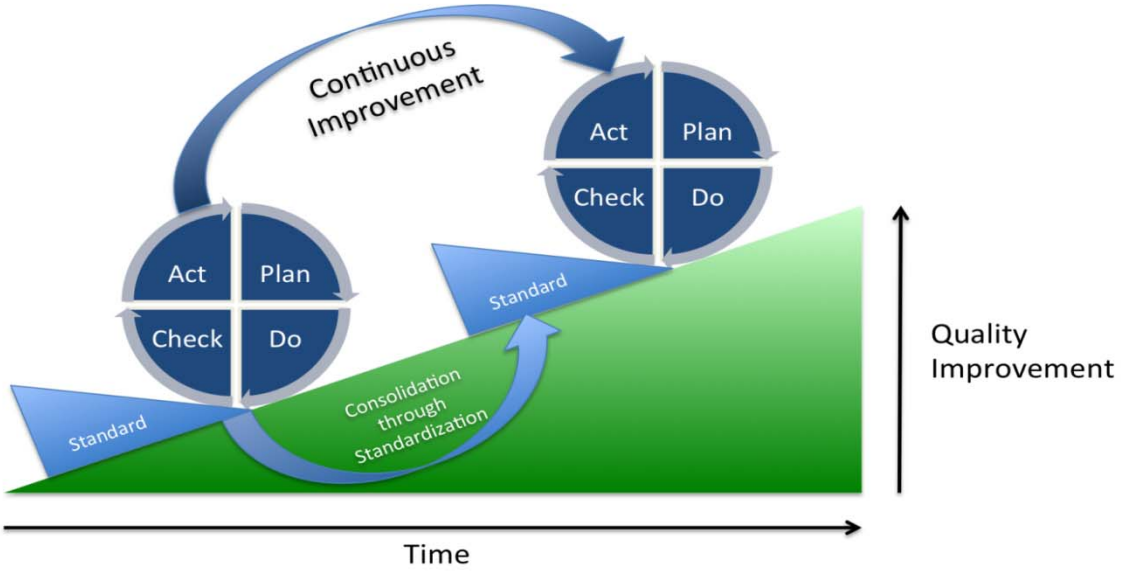


Figure 2.4 Continuous Quality Improvement with PDCA [18]

2.3 Monitoring, Auditing and Inspecting

The following excerpt from the *Handbook for Good Clinical Research Practice* describes the differences between monitoring, auditing and inspecting: [14]

“Monitoring is a quality control activity conducted by the sponsor or a representative of the sponsor to ensure that the research is conducted in accordance with the study protocol, GCP, and

applicable regulatory requirements and that research data are accurate, complete, and verifiable from source documents. Monitors generally compare source documents with case report forms and seek to resolve any discrepancies. Monitors also try to verify that activities related to protecting the rights and welfare of study subjects (e.g., prior approval of the IEC/IRB, obtaining legally effective informed consent from all study subjects) were appropriately carried out." [14]

"Auditing is an independent quality assurance activity used by the sponsor to evaluate the effectiveness of a monitoring program and/or specific monitoring activities. Auditing is distinguished from monitoring by the fact that monitoring is carried out while the study is in progress whereas auditing can occur anytime during or after the study." [14]

"An inspection is "[t]he act by a regulatory authority(ies) of conducting an official review of documents, facilities, records, and any other resources that are deemed by the authority(ies) to be related to the clinical trial and that may be located at the site of the trial, at the sponsor's and/or contract research organizations (CROs) facilities or at other establishments deemed appropriate by the regulatory authority(ies)." [6] The purpose of such inspection is to determine whether research was conducted in compliance with national/local laws and regulations for the conduct of research and the protection of human subjects." [14]

In summary, the components of the Quality System in clinical research are implemented by management in order to comply with Good Clinical Practices. It is through these tactics that quality is incorporated throughout the entire research process. Ensuring that quality is built in from implementation and throughout the processes will result in quality data and a quality product for the customer while protecting the health and welfare of human subjects. Implementing quality into all processes will also result in a decrease in costs and prevent unnecessary repeats or loss of data.

CHAPTER 3

RESEARCH METHODOLOGIES

3.1 Risk Assessment

Quality is built into every aspect of the clinical trial process from the very beginning from protocol development through the recruitment of subjects, informed consent process, experimental (or research) procedures, data attainment, analysis and reporting of quality results. The quality process consists of initiation and implementation of standard operating procedures (SOPs), protocol design, investigator qualification and selection, research location, institutional review board/ethics committee approvals, informed consent process, records and data integrity, monitoring, audits, and personnel training. [15] These processes combined with sufficient clinical trial and management oversight, create a framework to ensure that quality is built into the entire clinical trial process. It is under this systematic approach that all parts of the framework endure a risk based assessment. During the risk assessment, each risk is prioritized based on severity, occurrence and detectability. [15] This allows for management to prioritize corrective and preventive action (CAPA) measures based on the risk assessment and any gaps or differences found in the quality system. Problems in the quality system should be anticipated and corrective steps should be taken to avoid potential problems. The detection of any problem should initiate corrective action and amelioration of a plan to prevent occurrences.

Phase I of this qualitative research study consisted of a risk based analysis of warning letters issued by the FDA's Bioresearch Monitoring (BIMO) program for Good Clinical Practice violations over a five + year period (January 2010 to June 2015). The objectives of the FDA's

Bioresearch Monitoring (BIMO) program are to protect the safety and welfare of volunteer human subjects in clinical trials, determine data validity in research reports submitted to the FDA or marketing applications, and to evaluate compliance with the federal regulations and Good Clinical Practices. The FDA's BIMO program addresses all FDA regulated products. BIMO inspections are limited to available resources and are usually conducted after studies have concluded; however, BIMO's latest trend is to apply more resources to inspection during in-process clinical trials. Usually, BIMO findings are centered at one inspection site; therefore, compliance deficiencies may not apply to the entire clinical trial. [19]

In order to develop and implement an effective quality system, it was necessary to pinpoint common deficiency areas by citation analysis. The citation analysis aided in the risk assessment that was used to determine the most violated quality system areas. The citation analysis also actualized current trends in common compliance deficiencies in addition to the FDA's current areas of concentration during quality system inspections. The results from this analysis helped to generate the survey questions that were sent to the top 50 NIH funded biomedical institutions in order to facilitate validation of the FDA's findings and to support analysis of any resulting gaps. This risk assessment was comprised of three different analyses:

1) A literature review of recent GCP enforcement trends
2) A thorough analysis of FDA warning letters from 2010 to 2015 resulting in trends of non-compliance, and
3) A survey of experts in the field to validate the trend analysis results and ascertain best practices for a quality systems approach.

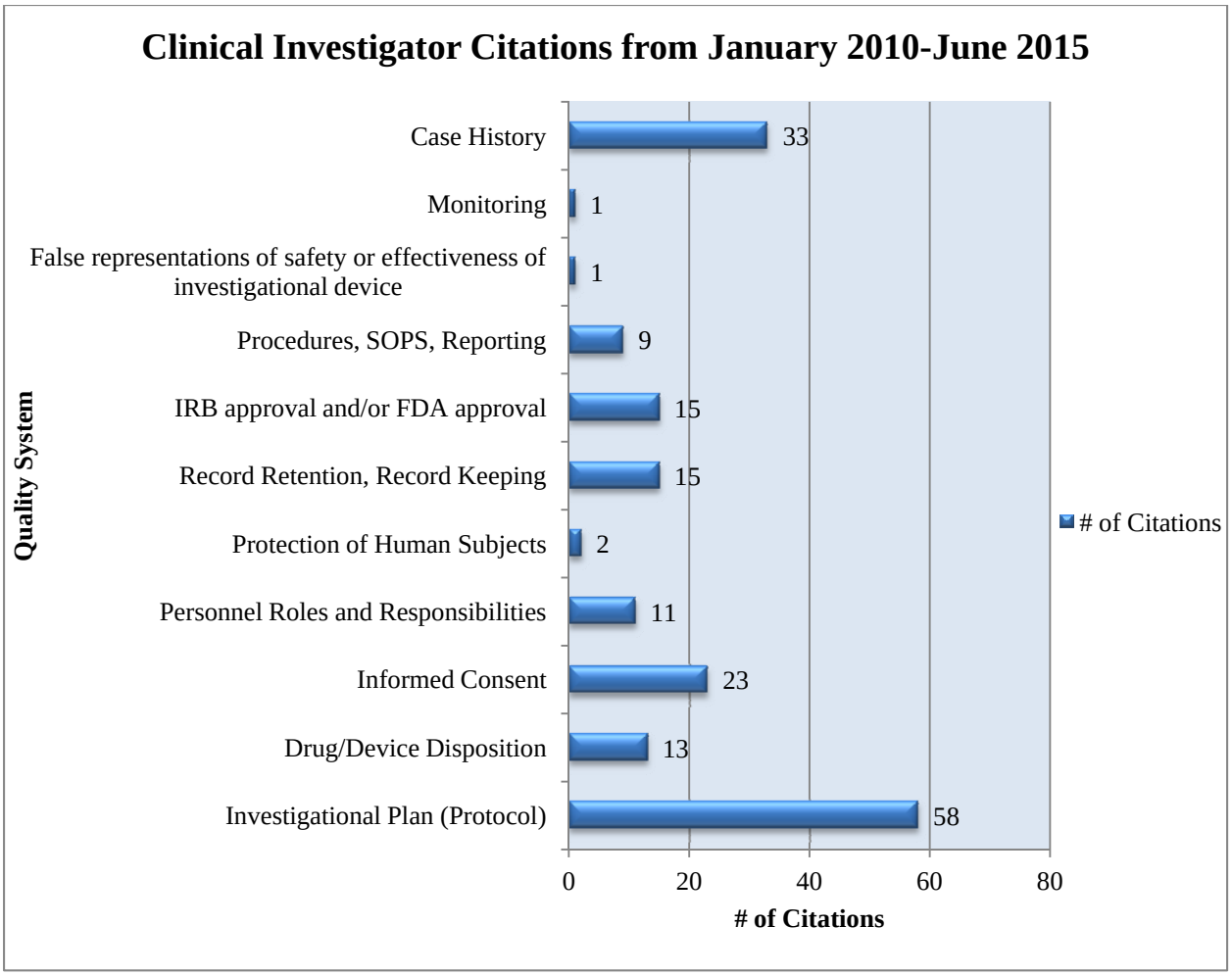
The data obtained from the results of the risk assessments were analyzed and used to create a comprehensive quality management system for an academic biomedical institution in compliance with Good Clinical Practices.

3.2 FDA Warning Letter and Citation Review

To obtain the warning letters issued by the FDA's Bioresearch Monitoring Program, the FDA home webpage was accessed at www.FDA.gov and a search for warning letters was conducted. From the *FDA's Electronic Reading Room - Warning Letters*, the researcher then searched under bioresearch monitoring and all publicly available warning letters under that category were displayed. The warning letters were then sorted by issue date, and the researcher obtained the warning letters from January 6, 2010 through June 29, 2015. [20] The warning letter deficiencies were compiled per year, entity, day and month of letter issuance and citation in table form and are located in appendix A. Each citation deficiency was assigned to its corresponding Code of Federal Regulation (CFR) and arranged by the number of deficiencies per quality system per year. The individual citations were summed within each of the following three groups to perform a trend analysis of GCP citations per group over the years 2010-2015: Clinical Investigator, Institutional Review Board, and Sponsor/Monitor/CRO. The research further categorized the five+ year total citations per group and summed them to determine the number of violations per quality system area (appendix C). This table shows which areas of the quality management system were cited the most over the last 5+ years and which areas must be focused on while establishing a quality management system for a biomedical academic institution.[4]

Analysis of the FDA warning letters issued by BIMO revealed the most common deficiencies of GCP quality systems. FDA issued 116 warning letters for GCP non-compliance during January 2010 to June 2015 and 371 citations. The citations were grouped by number of

citations per GCP quality system per targeted group: clinical investigator, institutional review board, and sponsor/monitor/CRO. To illustrate the data in a visual manner, the number of citations per quality system per group is presented in the following bar graphs. The number of citations was entered on the x-axis against the quality system on the y-axis per targeted grouping (clinical investigator, IRB, sponsor/monitor/CRO).

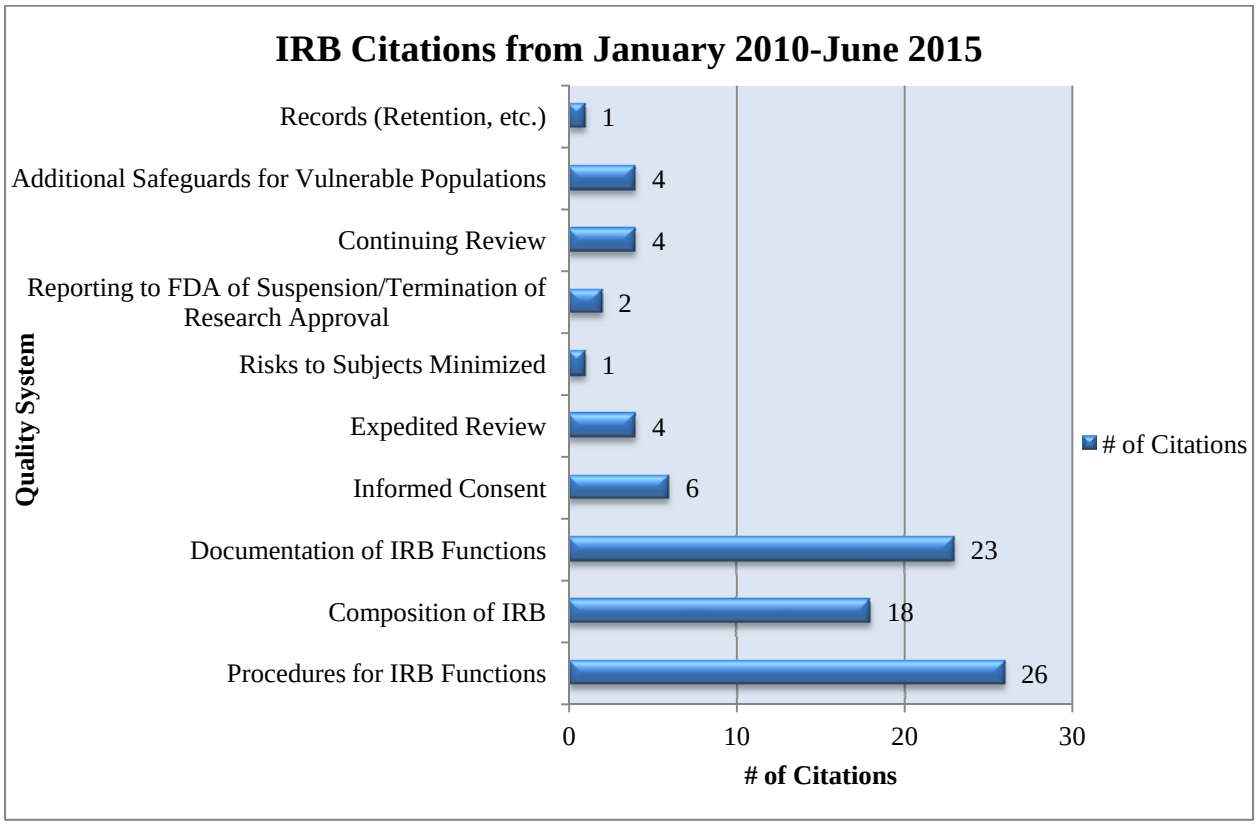


Graph 3-1 Number of Citations for CI from January 2010 - June 2015

Graph 3-1 represents the risk assessment for clinical investigator citations issued from January 2010 through June 2015. This risk assessment identified the most frequently identified citations during this period of time under the FDA's risk based approach for clinical research auditing. The citations were then grouped into the appropriate quality system and the results

presented above in graph 3-1. For the clinical investigator group, the top three most cited quality systems violations were: 1) the investigational plan, 2) case history records, and 3) informed consent.

Other quality system areas that were the most cited for the clinical investigator were IRB and/or FDA approval, record retention and record keeping, drug and/or device disposition, personnel roles and responsibilities, procedures, SOPs and reporting procedures. For clinical investigators, the least cited quality system areas were the protection of human subjects, monitoring and the false representation of safety or effectiveness of an investigational device.



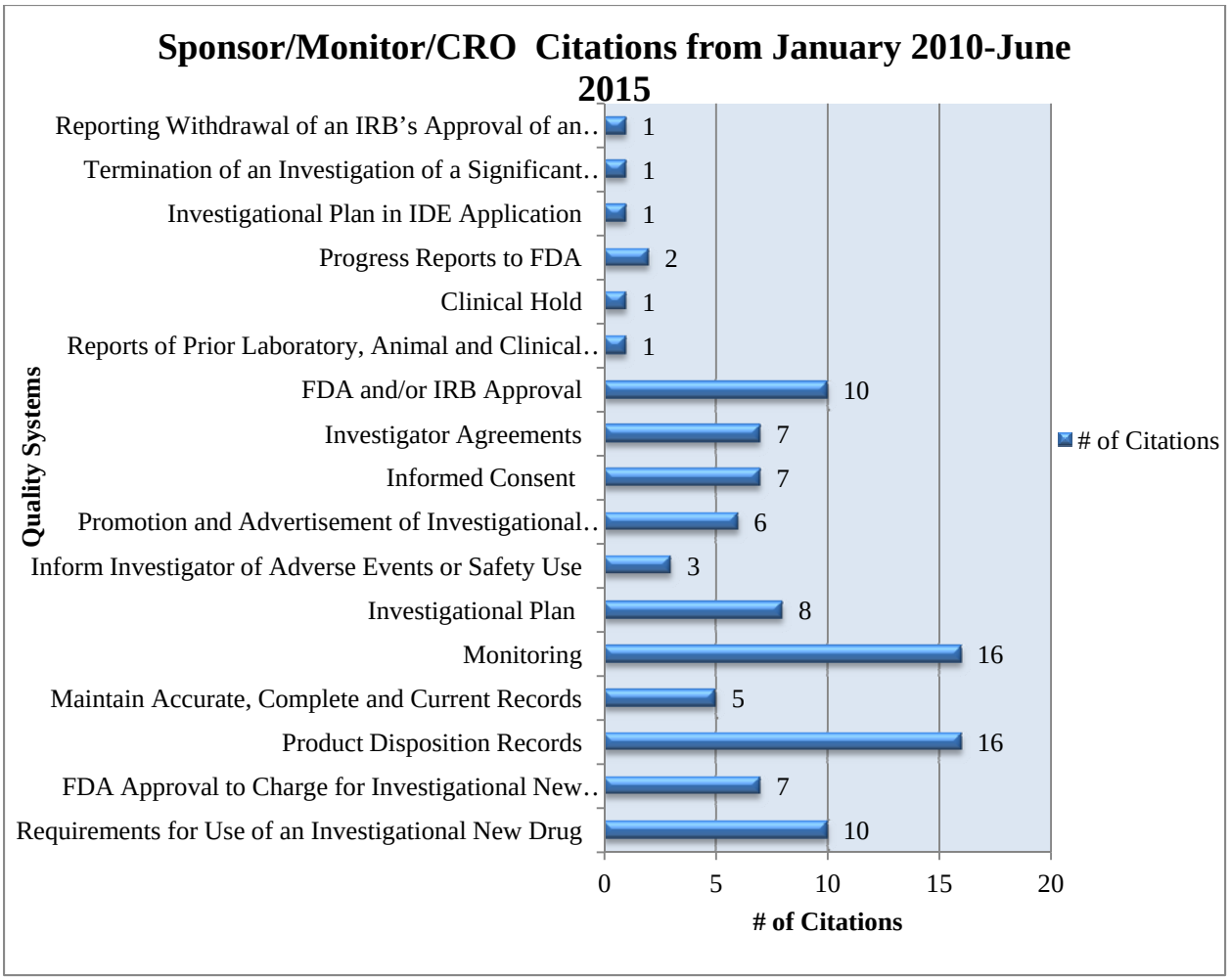
Graph 3-2 Number of Citations for IRB from January 2010 - June 2015

Graph 3-2 represents the risk assessment for Investigational Review Board (IRB) citations issued from January 2010 through June 2015. This risk assessment identified the most frequent citations during this period of time under the FDA's risk based approach while auditing

IRB's that review clinical research. The citations were then grouped into the appropriate quality system and the results presented in graph 3-2. The top three most cited quality systems violations for IRB's were: 1) procedures, 2) documentation of IRB function, and 3) composition of the IRB.

Other quality system areas for IRB's that followed the top three cited quality system areas were informed consent, expedited review, continuing review and making sure that additional safeguards were in place for vulnerable populations. The least cited quality system areas for IRB's were reporting suspension and/or termination of research approval to the FDA, records/record keeping/record retention and ensuring that risk to subjects are minimized.

Graph 3-3 (below) represents the risk assessment for sponsor/monitor and CRO citations issued from January 2010 through June 2015. This risk assessment identified the citations that were most common during this period of time under the FDA's risk based approach auditing for sponsors/monitors and CRO's that perform clinical research. The citations were then grouped into the appropriate quality system and the results presented in graph 3-3. The top most cited quality systems violations for sponsors/monitors and CRO's were: 1) product disposition records, 2) monitoring, 3) FDA and/or IRB approval, and 4) requirements for use of an investigational new drug. Other citations involving quality system areas that for sponsors/monitors and CRO's were the investigational plan, investigator agreements, informed consent, obtaining FDA approval to charge for the investigational new drug; promotion and advertisement of an investigational device as being safe and effective; maintaining accurate, complete and current records including product disposition records; and informing the investigator of adverse events or use of an investigational drug or investigational device.



Graph 3-3 Number of Citations for S/M/CRO from January 2010 - June 2015

The least cited quality system areas for sponsors/monitors and CRO's were sending progress reports to the FDA, reporting withdrawal of an IRB's approval of an investigation, informed consent, etc., termination of an investigation of a significant risk device, investigational plan in IDE application, clinical holds and reporting of prior laboratory, animal and clinical testing of an investigational device.

In summary, the findings from the risk assessment of FDA warning letters from January 2010 through June 2015 of clinical investigators, IRB's and sponsors/monitors and CRO's aided the researcher in generating the survey material for phase II of this research.

3.3 Human Subject Research

The findings from the risk assessment of FDA warning letters were the basis for generating survey material for phase II of this study.

The targeted population for this research project consisted of quality assurance and regulatory compliance professionals, aged 18 and up, from the top 50 National Institutes of Health (NIH) funded academic biomedical institutions in the United States. The recruitment process involved sending an IRB approved email invitation (see appendix D) that contained a link to the survey material (see appendix E) on Survey Monkey to the quality assurance and regulatory compliance departments of the targeted institutions (see appendix F). These email contacts were acquired by thoroughly exploring each institution's web site for the relevant contact information. The email recruitment invitation included the required elements of consent found in the UGA informed consent template with an option to click on the link at the bottom of the email to access the survey. When the volunteer human subject clicked on the link to the survey, this constituted their voluntary consent for participation in the survey and the research study. A second email invitation was sent two weeks later to those contacts who did not opt out of participating in the research study after the first email invitation was sent, but who had not yet completed the survey. Recruitment and enrollment were concluded a week after the second email reminder was sent due to time constraints for the research presentation and defense.

The human subject protocol application, STUDY00002646, was approved by the University of Georgia IRB on September 24, 2015 (see appendix G). Human subject research began immediately following approval. A waiver of documentation of consent was approved by the UGA IRB in accordance with 45 CFR 46.117(c).

The survey questions were designed to verify the results found from the risk assessment of the FDA warning letters from Phase I. By using a concurrent validation process[48], a combination of these results were used as the foundation for determining major concerns for violations of the different areas of the GCP quality system.[4] After a gap analysis was performed, the gaps were addressed by including them in the implementation plan to establish a robust GCP quality management system for a biomedical academic institution. [4]

CHAPTER 4

RESULTS AND ANALYSIS

4.1 FDA Warning Letter Results and Analysis

In addition to a literature review, this research study analysis implemented a qualitative and comparative approach by analyzing FDA warning letters issued for Good Clinical Practice violations during the years 2010 through 2015 and verified this analysis with a survey of quality and regulatory professionals in the field of clinical research from the top NIH funded academic biomedical institutions in the United States. It is from this analysis and verification of results that the researcher was able to determine the quality system areas that are most targeted during FDA inspections.

To recap the results from the risk assessment in the previous chapter (chapter 3), the top clinical investigator quality system violations issued from January 2010 through June 2015 resulted in findings regarding 1) the investigational plan, 2) case history records, and 3) informed consent and 4) IRB and/or FDA approval (graph 3-1). Other quality system areas most cited for the clinical investigator were record retention and record keeping, drug and/or device disposition, personnel roles and responsibilities, procedures, SOPs and reporting procedures. For clinical investigators, the least cited quality system areas were the protection of human subjects, monitoring and the false representation of safety or effectiveness of an investigational device.

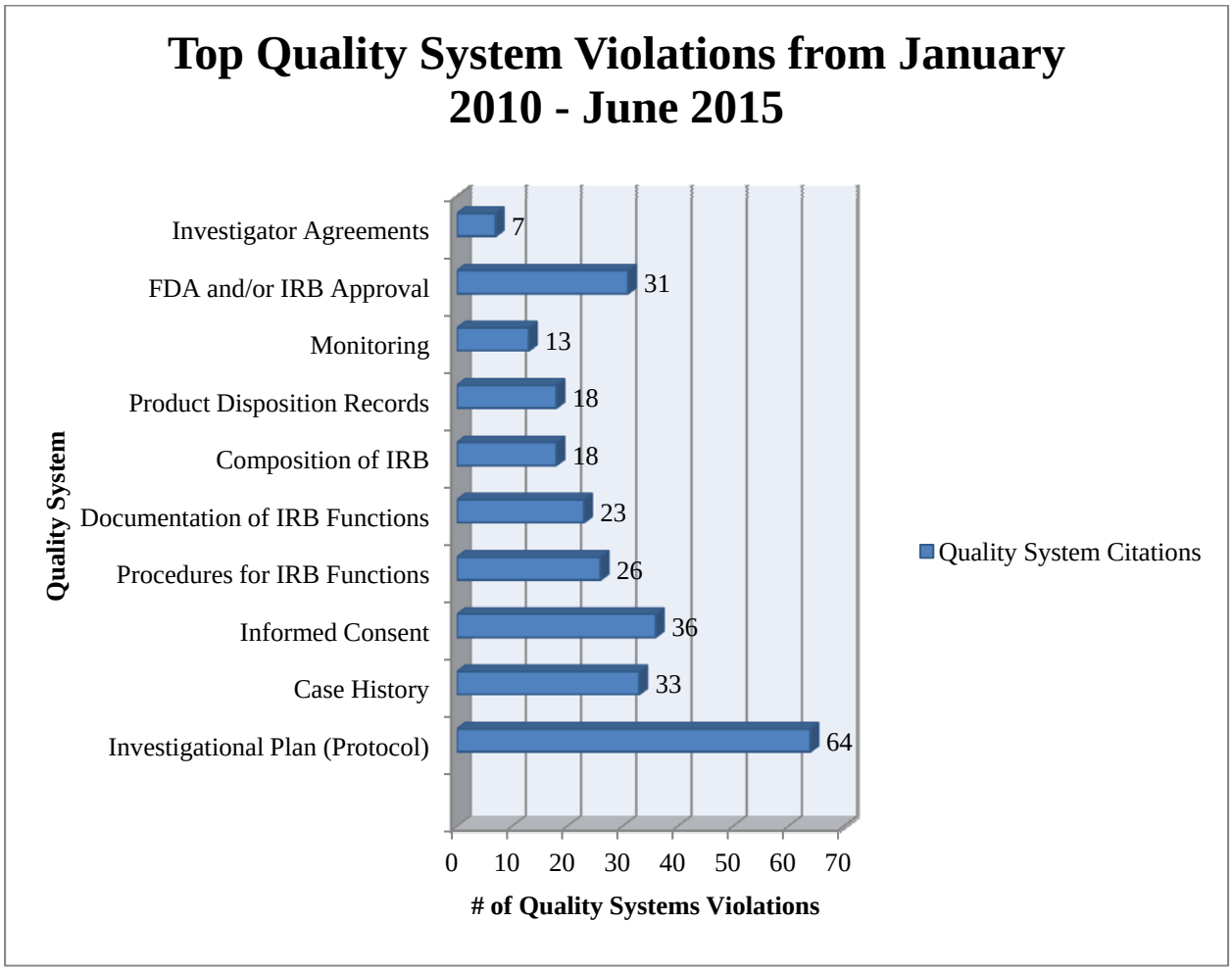
The top frequently cited quality systems violations for IRBs were: 1) IRB procedures, 2) documentation of IRB function, and 3) composition of the IRB. Other quality system areas cited for IRBs were informed consent, expedited review, continuing review and making sure that

additional safeguards were in place for vulnerable populations. The least cited quality system areas for IRB's were the reporting of suspension and/or termination of research approval to the FDA, records/record keeping/record retention and minimizing risk to subjects.

The top frequently cited quality systems violations for sponsors/monitors and CRO's were: 1) monitoring, 2) FDA and/or IRB approval, 3) investigational plan, and 4) investigator agreements. Other cited areas for sponsors/monitors and CRO's were obtaining FDA approval to charge for the investigational new drug, promotion and advertisement of an investigational device as being safe and effective, maintaining accurate, complete and current records, informed consent and informing the investigator of adverse events or use of an investigational drug or investigational device. The least cited quality system areas for sponsors/monitors and CROs were sending progress reports to the FDA; reporting withdrawal of an IRB's approval of an investigation; termination of an investigation of a significant risk device; investigational plan in IDE application; clinical holds and reporting of prior laboratory, animal and clinical testing of an investigational device.

The risk assessment analysis of Good Clinical Practice FDA warning letters resulted in the compilation of the most targeted quality system violations for biomedical clinical research over the last five years. The most frequent citations for the clinical investigator, IRB, sponsor/monitor/CRO groups were combined and organized together into the associated quality system. The results of the top quality system violations from January 2010 through June 2015 from the FDA warning letter analysis are in order of their significance: 1) investigational plan (protocol), 2) informed consent, 3) case history, 4) FDA and/or IRB approval 5) procedures for IRB functions, 6) documentation of IRB functions, 7) composition of IRB, 8) product disposition records, 9) monitoring, and 10) investigator agreements. These top ten quality system violation

findings are visually represented in the bar graph below (graph 4.1). The number of quality system violations per quality system is presented in the following bar graph developed in Microsoft Excel. The number of violations was entered on the x-axis against the quality system on the y-axis for all years 2010 through 2015.



Graph 4.1 Top Quality System Violations from January 2010-June 2015

These results revealed that the FDA pays specific attention to compliance with the investigational plan or protocol, case histories, informed consent and IRB and/or FDA approval during inspections. Non-compliance with any of these quality system areas significantly affects the protection of human subject rights, safety and welfare, scientific validity, ethical experimental design and also data validity. [19] In order for research to be considered as

scientifically valid, the research must have FDA review for all significant risk studies and all FDA regulated clinical research must have IRB review. [19] The most FDA warning letter violations were issued for the failure to follow the investigational plan, with 64 violations over the years 2010 through 2015. The specific Code of Federal Regulations (CFR) corresponding with identified failures to follow the investigational plan violations were Title 21 CFR 312.60, Title 21 CFR 812.100, Title 21 CFR 812.110(b), and Title 21 CFR 812.150(a)(4). All of these CFRs fall under the investigator responsibilities in clinical research. Title 21 CFR 312.60 is the investigational new drug regulation, while Title 21 CFR 812.100 is the investigational device exemption regulation. Both of these CFRs describe the responsibilities of the investigator in ensuring that the research is conducted under the signed investigator agreement, the investigational plan or protocol, other additional regulations in addition to the safety and welfare of human subjects, and for the control of the drug or the device in the investigator's care. [21, 22] Title 21 CFR Section 812.110(b) specifically defines compliance of the investigator and investigation with the investigator's agreement, the investigational plan, other applicable FDA regulations and IRB or FDA conditions of approval for investigational device exemption research.[22] Title 21 CFR 812.150(a)(4) discusses deviations from the investigational plan by requiring the investigator to notify the sponsor and the IRB of any deviation from the investigational plan in order the protect the human subject in an emergency. The investigator must give the notice no more than 5 working days from the date of occurrence. Other than in an emergency situation, any and all deviations from the investigational plan, or any deviation that may affect scientific validity and/or the safety, welfare and rights of human subjects must be approved by the FDA and the IRB prior to implementation. [23]

Following significantly behind investigational plan violations, with 36 issued violations from 2010 through 2015, the second most issued FDA warning letter violations were for non-compliance with informed consent regulations. The citations issued for informed consent violations corresponded with Title 21 CFR 50, Title 21 CFR 312.60, Title 21 CFR 50.20, Title 21 CFR 50.27(a), and Title 21 CFR 812.100. Informed consent violations are grouped under the regulations that are concerned with the rights, safety and welfare of human subjects. Specifically, Title 21 CFR 50.20 violations were for violations of the general requirements of consent. The general requirements of consent include the following: enough ample time provided to the subject or legally authorized representative to make an informed decision without any possible coercion or undue influence, the information that was provided to the subject or the legally authorized representative should be in lay language so it is comprehensible and an informed decision may be made, and no informed consent process or document shall contain any exculpatory language in which a subject or authorized representative were made or appear to be made to waive their legal rights. [24] Title 21 CFR 50.27(a) specifically discusses documentation of consent. These issued citations were in violation of the requirement to use an IRB approved written consent form that the subject or authorized representative would sign and date and receive a copy of the consent form. [25] The citation violations for Title 21 CFR 312.60 and Title 21 CFR 812.100 involve the general responsibilities of the investigator, where 21 CFR 312.60 addresses investigational new drug applications, and 21 CFR 812.100 addresses investigational device exemptions. In summary, the citations for informed consent violations directly affect the rights, safety and welfare of human subjects and are a major part of an investigator's responsibilities. [21, 22]

Case history violations were third in line for the most FDA issued violations, with 33 citation violations from January 2010 through June 2015. These case history citation violations are found under Title 21 CFR 312.62(b) and Title 21 CFR 812.140(a)(3). Title 21 CFR 312(b) and Title 21 CFR 812.140(a)(3) are very similar and both fall under the investigator responsibilities regulation requirements of records, record keeping and record retention. Title 21 CFR 312(b) sets forth the record keeping and record retention requirements under the investigational new drug application regulations while Title 21 CFR 812.140(a)(3) is the investigational device exemption regulations for investigator records and reports. Both regulations require the investigator to maintain case history records that include all observations and applicable data on individual participants who are administered the study drug or a control subject in an investigational drug study and subjects that come into contact with the investigational device. The case history records must include an approved signed and dated consent form prior to the subject's participation in the study and any relevant medical records, including physician notes. Title 21 CFR 812.140(a)(3) also requires documentation of any use of the investigational device without prior informed consent from the subject and a justification for such use. The IDE requirements under 21 CFR 812.140(a)(3) also require records of all anticipated or unanticipated adverse effects and each subjects medical condition at the same time the subject enters the study and throughout his participation in the investigation. This would include any results from diagnostic tests and previous medical history. These case history record citations result from an investigator's violations of his responsibilities.[26, 27]

The fourth most cited FDA issued violations for GCP non-compliance was the failure to obtain FDA and/or IRB approval with 31 citation violations from January 2010 through June 2015. These citations were in violation of Title 21 CFR 812.20(a)(1) and (a)(2), Title 21 CFR

812.40, Title 21 CFR 812.42, Title 21 CFR 312.20 and Title 21 CFR 312.30. These federal requirements are the designated responsibility of the sponsor of the clinical trial. Title 21 CFR 812.20(a)(1) and (a)(2), Title 21 CFR 812.40, and Title 21 CFR 812.42 are categorized under the investigational device exemption requirements. Title 21 CFR 812.20(a)(1) requires the sponsor to submit an investigational device exemption application to the FDA if the investigational device is a significant risk device. This title also requires the sponsor to submit an application to the FDA where informed consent would be exempted under Title 21 CFR 50.24 and if the sponsor is notified by the FDA that an application must be submitted for the investigation. Title 21 CFR 812.20(a)(2) under the IDE regulations requires the sponsor to have obtained FDA approval prior to initiation of the investigation if the FDA's approval of an application is required. Title 21 CFR 812.40 and Title 21 CFR 812.42 both fall under subpart C of the sponsor responsibilities under the investigational device exemptions. Title 21 CFR 812.40 sets forth the general responsibilities of the sponsor: the sponsor is required to select qualified investigators, provide those investigators with the necessary information to conduct the investigation accordingly, accurately monitor the investigation, affirm that IRB review and approval have been obtained, submit the IDE to the FDA when the device is of significant risk, and update the reviewing IRB and FDA when compelling new information regarding the investigation has been obtained. Title 21 CFR 812.42 discloses that the sponsor may not start the investigation or even part of the investigation without the proper IRB and FDA application approvals or any supplemental application approvals. Titles 21 CFR 312.20 and 21 CFR 312.30 are located within the investigational new drug application (IND) regulations. Title 21 CFR 312.20 sets forth the sponsor requirements for an investigational new drug (IND). These regulations require the sponsor to: (a) submit an IND application to the FDA for an investigational new drug that is

subject to 21 CFR 312.2(a) and is being used in an investigation, (b) may not begin the investigation until the IND is in effect if the investigation is subject to acquiring an IND (21 CFR 312.40), and (c) the sponsor must submit a separate IND to the FDA for any investigation involving an exception from consent (21 CFR 50.24), and this investigation may not commence without prior written FDA authorization. A written determination from the FDA should come within 30 days of the sponsor submitting the IND to the FDA. Title 21 CFR 312.30 enumerates the sponsor requirements for protocol amendments under the investigational new drug application regulations. When an IND has been approved, the sponsor shall modify the IND to maintain compliance with the active protocol. This section of the regulations describes the plan to which new protocols may be submitted and any modifications of existing protocols may be implemented. If the sponsor intends to conduct a clinical investigation with an exception from informed consent as set forth in Title 21 CFR 50.24, the sponsor will need to submit a separate IND for this type of investigation.[28, 29, 30, 31]

The fifth frequently cited FDA violation was for Institutional Review Boards' failures to comply with the required functional procedures with 26 citation violations from January 2010 through June 2015. These citations were in violation of Title 21 CFR 56.108(a), (b) and c, Title 21 CFR 56.115(a), and Title 21 CFR 56.109(e). Found under subpart C of Title 21 CFR 56, these regulations define IRB operations and procedures. The IRB shall follow (a) written procedures for: (1) conducting the initial and continuing review of the research and reporting the IRB's findings to the investigator and the institution; (2) determining which investigations need review more than annually and which investigations need authentication from other sources that no changes have occurred since previous IRB review and approval; (3) validating that any changes to the investigation have been reported to the IRB in a timely manner; and (4) that all

modifications to the IRB approved research have been granted IRB approval prior to initiation unless the modification is needed to eliminate any immediate hazard to the human subject. Part (b) requires the IRB to follow written procedures for the prompt reporting to the IRB, the institutional official and the FDA of: (1) any unanticipated problem that affects risk to human subjects; (2) any serious or continued non-compliance with these regulations and/or any requirements or determinations made by the IRB; or (3) suspension or termination of IRB approval. Part (c) requires that all full board studies be reviewed by an IRB where at least one member is a non-scientific representative and a majority of the members of the IRB are present. In order for the investigation to be approved, the investigation must be approved by an IRB with a majority of the members present during the meeting. Title 21 CFR 56.115(a) falls under subpart D relating to IRB records and reports. This regulation requires that an IRB must prepare and maintain sufficient documentation of IRB activities that include the following: (1) copies of research investigations reviewed, scientific evaluations, consent forms, progress reports sent in by investigators and any reports of injury to subjects; (2) IRB meeting minutes; (3) continuing review activity records; (4) all correspondence between the IRB and the investigator; (5) all IRB members and their credentials; (6) written procedures for the IRB; and (7) any significant new findings that are provided to human subjects. Title 21 CFR 56.109(e) falls under subpart C of IRB functions and operations. This regulation requires the IRB to notify the investigator and the institution in writing of the IRB's decision to approve or disapprove the investigation or any modifications required to obtain IRB approval of the investigation. If the IRB decides to disapprove the investigation, it must notify the investigator and the institution of this decision and provide the reasons for its determination of disapproval. [32, 33, 34]

The sixth most cited FDA violation was for documentation of IRB function with a total of 23 citation violations issued from January 2010 through June 2015. Documentation of IRB function citations were in violation of Title 21 CFR 56.115(a)(1), Title 21 CFR 56.115(a)(2), Title 21 CFR 56.115(a)(4) and (5). Like the fifth most cited FDA violation for failure to comply with the procedures of IRB function, these regulations fall under subpart D records and reports of an IRB. This regulation requires that an IRB must prepare and maintain sufficient documentation of IRB activities that include the following: (1) copies of research investigations reviewed, scientific evaluations, consent forms, progress reports sent in by investigators and any reports of injury to subjects; (2) IRB meeting minutes; (4) all correspondence between the IRB and the investigator; (5) all IRB members and their credentials. [33]

Issues dealing with the composition of an IRB were the seventh most cited FDA violation from January 2010 through June 2015 with a total of eighteen citation violations. Composition of an IRB is found under Title 21 CFR 56.107(d) and (e) and Title 21 CFR 56.108(c) respectively. Under Title 21 CFR 56.107, these two regulation violations require that: (d) the IRB contains at least one non-affiliated member of the institution, including an affiliation of a family member of the institution and (e) no member of the IRB should participate in any review where a conflict of interest exists; however, such members may provide information to the IRB when needed. Similar to the fifth most cited FDA violation, Title 21 CFR 56.108(c) requires that all full board studies be reviewed by an IRB where at least one member is a non-scientific representative and a majority of the members of the IRB are present. [35, 33]

Product disposition records are the eighth most cited FDA violation from January 2010 through June 2015 with a total of eighteen citation violations. These regulations are found in Title 21 CFR 312.57(a), Title 21 CFR 812.140(b)(2) and Title 21 CFR 812.140(d). Title 21 CFR

312.57(a) is found under the investigational new drug application regulations under subpart D, sponsor and investigator responsibilities for record keeping and record retention. This regulation requires the sponsor and/or investigator to keep adequate records regarding the receipt, shipment or disposition of the investigational drug. Title 21 CFR 812.140(b)(2) and Title 21 CFR 812.140(d) are found under the investigational device exemption requirements for records and reports. Title 21 CFR 812.140(b)(2) requires the sponsor to keep and maintain adequate records of shipment or disposition of an investigational device. Whereas, Title 21 CFR 812.140(d) require both the sponsor and the investigator to maintain the records required under subpart D for a period of two years after the latter of the following two dates: the termination or completed date of the investigation, or the date when records are no longer needed to support a premarket approval application (PMA) or the date of completion of a product development protocol. [27, 36]

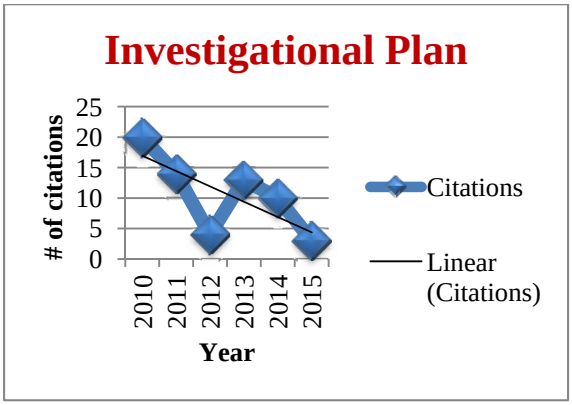
Sponsor, monitor and/or CRO monitoring was the ninth most cited FDA violation from January 2010 through June 2015. These violations are found under Title 21 CFR 312.50, Title 21 CFR 812.40 and Title 21 CFR 312.56(a). Title 21 CFR 312.50 and Title 21 CFR 312.56(a) are found under the investigational new drug application regulations under subpart D, the responsibilities for sponsors and investigators. Title 21 CFR 312.50 ensures that the sponsor provides the proper monitoring of the investigation as one of the general responsibilities of the sponsor; whereas, Title 21 CFR 312.56(a) requires the sponsor to monitor the progress of all clinical investigations under its IND as part of continued review of ongoing investigations. Title 21 CFR 812.40 has the same sponsor requirements as Title 21 CFR 312.50 except this ensures that the sponsor provides proper monitoring of the investigation under the investigational device exemption regulations. [37, 38, 39]

Investigator agreements round out the bottom of the ten most cited FDA violations from January 2010 through June 2015 with a total of seven violations. The failure to obtain signed investigator agreements is a violation of the requirements in Title 21 CFR 812.43(c)(5) and Title 21 CFR 54. The sponsor responsibility to select investigators and monitors are set forth within Title 21 CFR 812.43(c)(5) and require the sponsor to submit a complete and accurate financial disclosure statement as described under Part 54. This includes a commitment from the investigator to immediately update this information if any changes occur during the study and for a one year period after the study has ceased. This information is to be submitted with any marketing application of the device and not in the IDE. Title 21 CFR 54 sets forth the general financial disclosure requirements and financial record keeping and retention requirements of the clinical investigator. [40, 41]

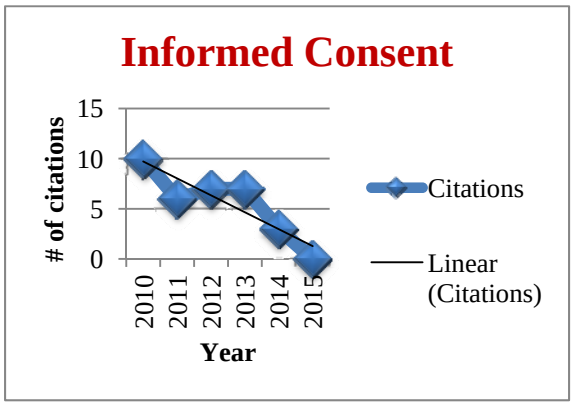
4.2 Top Ten Quality System Violations Trend Analysis

Once the total top ten quality system violation results were found from the FDA warning letter analysis over the last five plus years, the top quality system violations per year were analyzed to perform a trend analysis. The results for each of the top quality system violations were broken down per year and are shown in graphs 4.2 through 4.11 below. These graphs represent trends for the top ten FDA issued GCP quality system violations from January 2010 through June 2015. The trend analysis that was used is a type of comparative analysis in which the focus of FDA inspections was analyzed over the last five plus years. It is from this analysis that key factors were used to identify FDA's prime focus during inspections and any possible gaps when compared with the results from the human subject research study in the next section. (sec. 4.3)

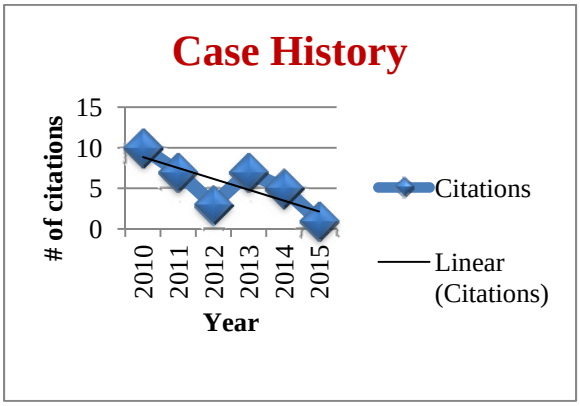
Top Ten Quality System Violations Trend Analysis Results



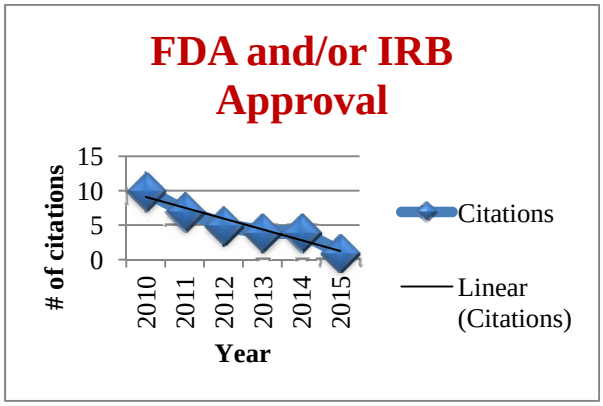
Graph 4.2 Investigational Plan



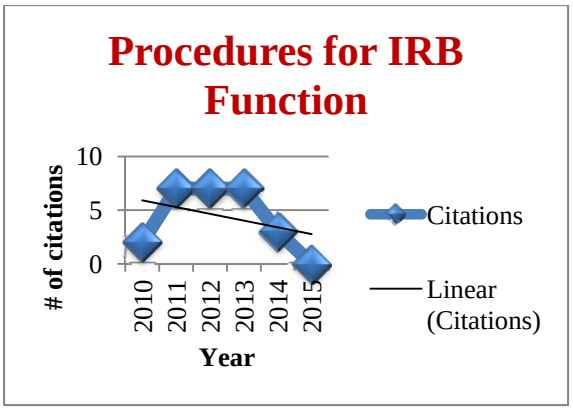
Graph 4.3 Informed Consent



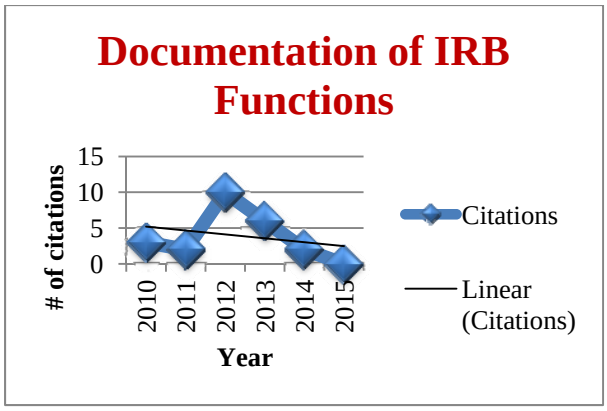
Graph 4.4 Case History



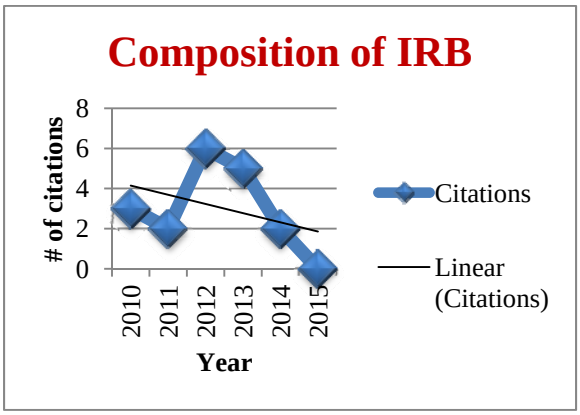
Graph 4.5 FDA and/or IRB Approval



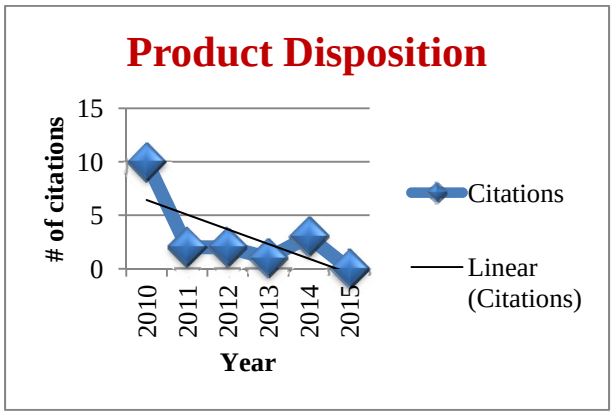
Graph 4.6 Procedures for IRB Function



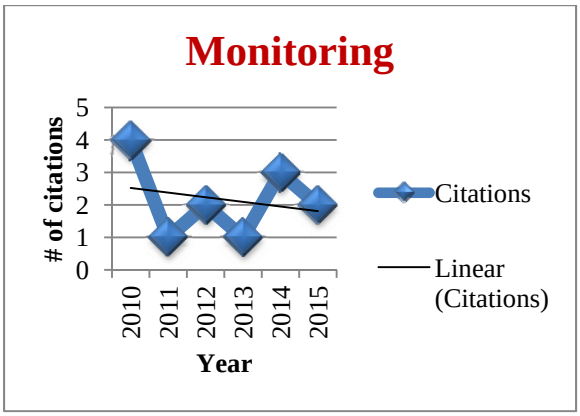
Graph 4.7 Documentation of IRB Function



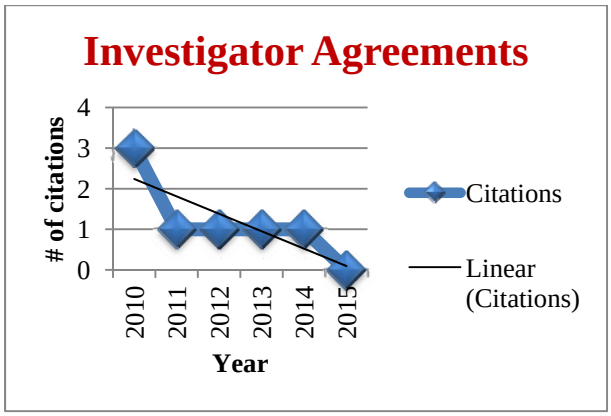
Graph 4.8 Composition of IRB



Graph 4.9 Product Disposition



Graph 4.10 Monitoring



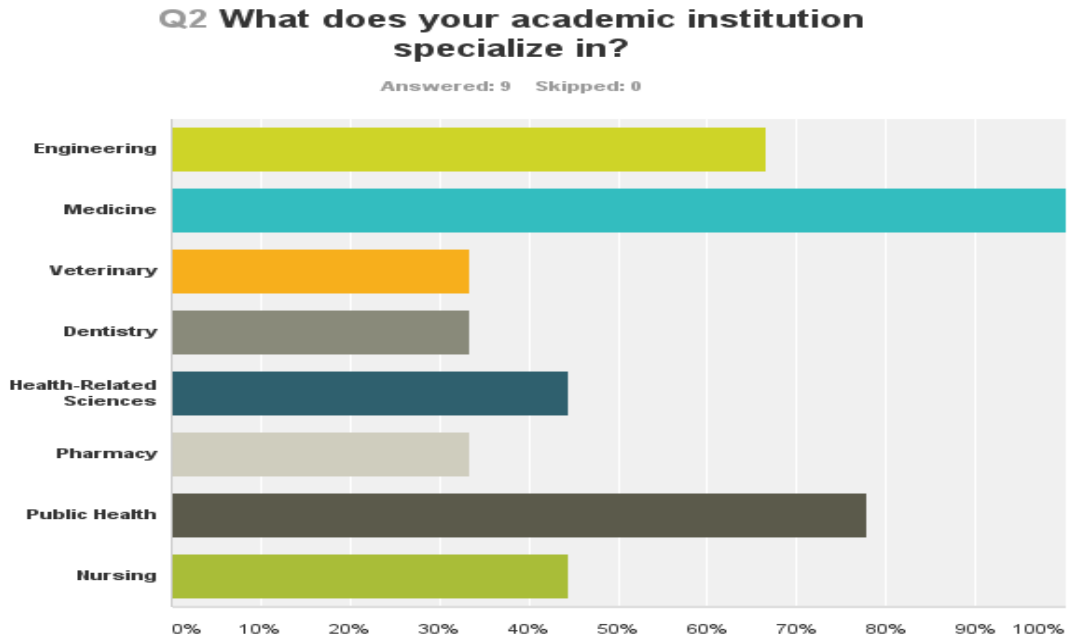
Graph 4.11 Investigator Agreements

The trend analysis revealed that quality system violations decreased in numbers over the last five plus years. This may be due to FDA's risk based approach during inspections or the

possibility that research teams as a whole are becoming better educated and informed about running their clinical trials. As a result, this may imply that more quality management systems are being implemented within clinical research investigations, therefore leading to better quality investigations, better quality data and as a result, better quality product.

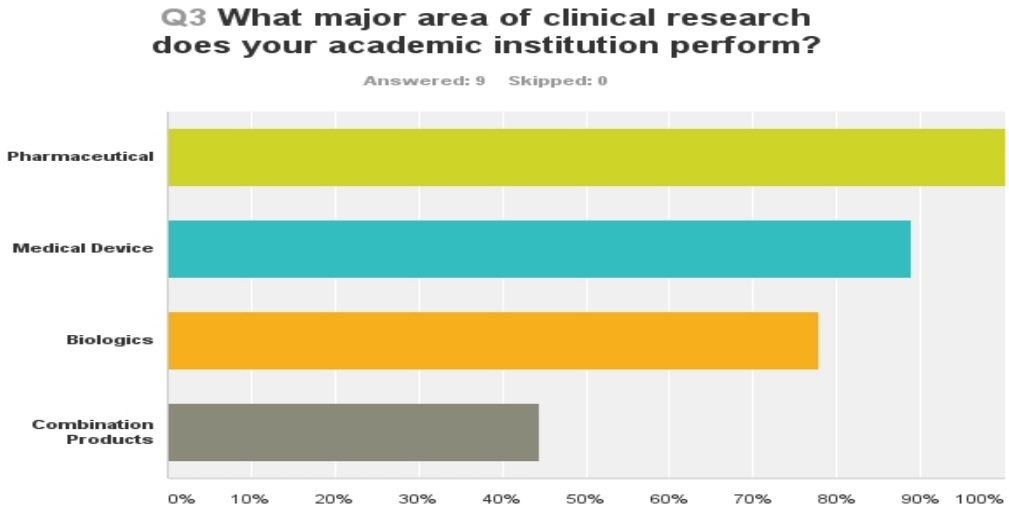
4.3 Human Subject Research Results and Analysis

As part of this research project, an email invitation was sent to regulatory and quality professionals from the top 50 NIH funded biomedical institutions in the United States. The email invitation contained a link to the survey that was housed on the SurveyMonkey® platform. Responses from the 50 NIH funded biomedical medical institutions receiving the email invitation equated a response rate of 18% or n=9. This response rate was most likely due to the lack of availability of respondents in this type of work as this is a highly demanding professional area. One hundred percent of the respondents confirmed that their institutions had a medical school. Survey respondents described their academic institutions' specializations as 100% medicine, 77.78% public health, 66.67% engineering, 44.44% health-related sciences, 44.44% nursing, 33.33% pharmacy, 33.33% dentistry, and 33.33% veterinary. The survey responses revealed that the majority of biomedical institutions participate in multiple disciplines of clinical research. These results are presented in graph 4.12. The percentage of respondents is labeled on the x-axis with the biomedical discipline labeled on the y-axis. The following graphs were all generated using the SurveyMonkey® platform.



Graph 4.12 Academic Specializations

When asked what major area of clinical research that their academic institution performed, 100% of the survey respondents identified pharmaceuticals. The results of question 3 are displayed in the graph below:



Graph 4.13 Academic Area of Research Performed

Eighty-nine percent of respondents reported medical devices as being their institution's major area of concentration in clinical research, while 77.78% reported biologics and 44.44% reported combination products. When respondents were asked which type of studies were carried out at their institutions, 100% stated academic research pilot studies, sponsor-investigator initiated clinical trials and industry sponsored studies. One respondent separately reported social behavioral, public health, health services and medical data. Another respondent reported federally funded clinical research. From the results of the FDA warning letter analysis, it was discovered that there appeared to be a lack of FDA warning letters issued directly to academic institutions. When respondents were asked if they thought this was accurate, in an open-ended question format, the respondents clearly disagreed with the results of the FDA warning letter analysis. The following are the direct respondent responses:

Subject #1: *"I work in cell therapy gene transfer and I actually don't find that to be true. I think that academic medical centers involved in truly innovative research (i.e. INDs where the product is made at the AMC as compared to one where it is obtained from another manufacturer using the cross reference mechanism) are scrutinized by the FDA both during the IND submission process but also via audits."*

Subject #2: *"I feel that it is rare for data generated from AMC sponsored trials (IITs) is used to support applications to the FDA for new products or new indications. Therefore a majority of the data sent to the FDA for approval is sponsored research (Pharma) and it is their responsibilities that are most scrutinized."*

Subject #3: *"Not sure that I would agree with this assessment."*

Subject #4: *"Warning letters are not issued directly to the institution, but instead to the clinical investigator, sponsor-investigator, sponsor, IRB director, etc. However, in general I don't think*

there are many warning letters directed to clinical investigators or sponsor-investigators. And I don't think this speaks to the fact that everyone is doing things the right way, but more along the lines of the FDA not putting their inspection efforts towards academic researchers. I'm not sure why that is."

Subject #5: *"When FDA has no findings, there is no letter published. We have an average of 6-8 FDA inspections each year with minimal findings and warning letters published rarely."*

Subject #6: *"The regulation of products is mainly for the marketing and sale of the research article. Since Academic institutions rarely do research to support marketing or sale (sic) they are less likely to be scrutinized."*

Subject #7: *"They fly 'under the radar.' There are numerous investigator-initiated studies of marketed meds that are IND exempt."*

Subject #8: *"SEE: O'Reilly EK, Holbein ME, Berglund JP, Parrish AB, Roth MT, Burnett BK. Warning Letters to Sponsor-Investigators at Academic Health Centers – The Regulatory "Canaries in a Coal Mine". Clin Invest Med. 2013 Dec 1;36(6):E290-6. 1. Lower risk studies at academic health centers 2. Most studies use approved test agents 3. Significant reliance on institutional review from IRBs and compliance offices 4. High cost of monitoring in lower risk studies (resource imitations)"*

Subject #9: *"Academic medical centers have a more robust compliance program when compared to free-standing research centers because most centers conduct research that is federal funded, which requires compliance with terms of the FWA. Moreover, a significant amount of the funding arises from NIH, which requires investigators to complete training."*

Most of the respondents agreed with the FDA warning letter analysis that academic institutions are not directly cited with FDA warning letters; however, it is the clinical

investigator, the sponsor-investigator, or the IRB from the academic institutions themselves that are cited. Some respondents also felt that most academic research institutions perform lower risk studies and that the institutions tend to "fly under the radar" with IND exempt investigations. This may explain why academic institutions tend to be less scrutinized by the FDA, as evidenced by the FDA warning letter analysis.

The next open-ended survey question asked respondents if they saw any patterns in the FDA's GCP enforcement activities during inspections. The following responses resulted:

Subject #1: *"I have been doing this a long time and I think things change over time. I personally definitely think that the bar gets higher with each review. For a number of years the focus has been on how AMCs are monitoring IIT studies internally (QA, QC and Data Safety Monitoring) and how staff (research and clinical) are trained regarding the research."*

Subject #2: *"Over the past many years I see a higher rate of 483s being issued. I think this is a direct result in the increasing scrutiny of research practices following GCP- i.e. ALCO standards and the increase in FDA inspections at AMCs."*

Subject #3: *"No"*

Subject #4: *"For FDA it's all about subject safety. We don't have too many FDA inspections."*

Subject #5: *"PI responsibility and oversight are the issues that seem to be highest on the list."*

Subject #6: *"Yes. They use the BIMO regulations which include the GCP and E6 guidelines."*

Subject #7: *"Verification of credentials and actual assessment of compliance to procedures are two different things."*

Subject #8: *"I am not in the compliance office. No 483s or Warning Letters here in the time I have been at the institution."*

Subject #9: *"The FDA follows the published manual for investigations of IRBs and clinical investigators."*

Some of the respondents felt that patterns in FDA GCP enforcement were focused on quality assurance, quality control, data safety monitoring and personnel training. There was a feeling of increased scrutiny of research practices in following GCP's. Others felt that the FDA follows the manual for investigations and felt that no patterns existed.

When respondents were asked what FDA priorities and inspection red flags do they feel that typically lead to GCP violations, the results in an open-ended question format were as follows:

Subject #1: *"Problems with consent, problems with eligibility, incomplete or sloppy CRFs or related source documents."*

Subject #2: *"I'm not sure what is being asked."*

Subject #3: *"A lack of clear documentation of the informed consent process, unclear delegation of authority, lack of adequate SOPs."*

Subject #4: *"Informed consent issues, not following the protocol."*

Subject #5: *"Delegation of authority and data management."*

Subject #6: *"No approved consents, Wrong version of the protocol being used. Not having all documentation in the regulatory binder."*

Subject #7: *"SAEs Protocol violations unreal data patterns- falsification of data."*

Subject #8: *"Research participant complaints, institutional compliance reporting, research misconduct."*

Subject #9: *"Failure to obtain and document consent in compliance with regulations. Failure to follow the protocol and inadequate case histories."*

It was clear from the analysis of these comments that most respondents indicated that issues with informed consent were a FDA inspection red flag as was the delegation of authority, inadequate case histories, lack of SOPs and failure to follow the approved protocol. These results are consistent with the FDA warning letter analysis from the previous section.

When respondents were asked whether their institutions use regulatory and/or quality assurance/quality control consultants in their clinical trial process, 66.67% responded that they do not, while 33.33% responded that their institutions do use regulatory and/or QA/QC consultants.

Question #9 from the survey asked if their institutions had a formally written quality management system in place. Fifty-six percent stated that their institution did have a formally written quality management system while 44% said their institution did not.

Question #10 was another open-ended question about what areas of a quality management system respondents would recommend concentrating on while establishing an initial QMS plan in an academic biomedical institution in compliance with Good Clinical Practices. The responses were as follows:

Subject #1: *"Training of staff Development of Standard Operating Procedures Review of patient records (consents, eligibility documentation, CRFs and source documents)."*

Subject #2: *"Education, Training - tools and templates. Most times violations occur as the result of lack of knowledge or resources."*

Subject #3: *"Training of research faculty and staff in study conduct."*

Subject #4: *"Initial mandatory training in GCP for anyone conducting clinical trials. Mandatory audits of investigator-initiated, greater than minimal risk research."*

Subject #5: *"Management and documentation of the consent process. Data capture and management."*

Subject #6: *"One central area for all clinic research to be run through. PI training that includes GCP and not just financial training."*

Subject #7: *"Protocol compliance consent/re-consent verification amendment approvals and enactments study visit window compliance AE reporting- with attention to attribution and expectedness."*

Subject #8: *"Research staff training, electronic clinical research management systems, and compliance audits."*

Subject #9: *"Investigator initiated clinical trials."*

When respondents were asked what areas of a quality management system they would suggest to concentrate on while implementing a QMS plan from question #10 above, the majority replied with the following: training of staff, SOP development, record keeping, audits, informed consent, protocol compliance, reporting, using one central area for all clinical research to run through and establishing electronic clinical research management systems.

Question #11 of the survey asked respondents to comment on whether their institutions QMS plan implemented a total management system or Six Sigma approach. Seven respondents responded no to implementing a TMS or Six Sigma approach. One respondent said that this approach is only used for finances and another committed that CTSA implements a Lean approach to process management.

Question #12 was an open-ended question about what characteristics survey respondents thought should comprise a successful quality management system. The following five survey responses resulted:

Subject #1: *"Establishing training of clinical research investigators and staff. Ensuring protocol specific training for investigators, staff, and treating physicians/personnel auditing."*

Subject #2: *"Classes and hands on competency training."*

Subject #3: *"Regular auditing, internally by research staff and an institutional monitoring operation."*

Subject #4: *"Training Education and follow up."*

Subject #5: *"Incremental improvements buy in from leadership accepting that QMS support is to promote efficiencies, not chastise nor fire/reduce staff."*

When respondents were asked in question #12 about the characteristics that a successful quality management system should possess, most replied that training and auditing were successful characteristics. A single respondent replied that leadership of the QMS should promote efficiencies and not chastise or fire/reduce staff.

Question #13 was another open-ended question about how respondents educate their faculty and students and related departments on campus in the regulatory requirements of performing clinical research. This question generated eight responses:

Subject #1: *"Most of the general education is done through lectures in various venues AMCs have an advantage in that most junior faculty have experienced mentors who are aware of the requirements to conduct clinical research and will train them and/or ensure they receive such training."*

Subject #2: *"Multifaceted approach: -Monthly education sessions 2x for coordinators -Faculty dinner series -On-going QA reviews with targeted education for found issues -Intro to clinical research series for new staff."*

Subject #3: *"Formal research conduct classes."*

Subject #4: *"Monthly staff lecture topics bi-annual 3 day course for newer staff very difficult to reach faculty."*

Subject #5: *"IRB has some required training but we need to create a better system of training for investigators."*

Subject #6: *"Group sessions: investigators and coordinators. Coordinators best as they are the 'front line troops' One-on-one sessions are best- as there is application of regs and best practices to a specific relevant context."*

Subject #7: *"Training required; multiple approaches available to meet requirements."*

Subject #8: *"Join ACRP/SOCRA/MAGI/PRIM&R and attend education offerings."*

When respondents were asked in question #13 how they educate their faculty and students and related departments on campus in the regulatory requirements of performing clinical research, they responded as follows: lectures, formal research classes, group sessions and attend educational conferences/workshops.

The final question was open-ended question and asked what recommendations they had regarding an academic biomedical institution that is just starting to perform clinical trials. This survey question resulted in the following seven responses:

Subject #1: *"Robust training is essential. No issue in clinical research is too small to address whether through policies, SOPs, or actually training. In a situation where you are just starting out you might want to outsource the training of key personnel to outside entities (i.e. send them to training courses) but after you have a key group of trained personnel use them to help distribute the information to others within the institution."*

Subject #2: *"Evaluate infrastructure needs carefully and include a QC/QA component."*

Subject #3: "*Train staff prior to allowing them to work on a clinical study."*

Subject #4: *"Follow the FDA and NIH regulations for the conduct of clinical trials. GCP E6 and training for PI's and coordinators is necessary."*

Subject #5: *"See above"*

Subject #6: *"Internal infrastructure for the clinical research enterprise should be robust."*

Subject #7: *"Obtain training and do a careful feasibility analysis before accepting a clinical trial."*

When respondents were asked about what recommendations they could provide in question #14 above, the majority of respondents stated that training and a robust infrastructure were necessary in performing successful clinical trials.

In summary, all of the participants in this research phase were from academic biomedical institutions that had a medical school. One hundred percent of participants in the survey specialized in pharmaceutical research, and a few also specialized in medical device, biologics and combination products. Respondents suggested quality management system topics that should be concentrated on while implementing a QMS plan; these included training of staff, SOP development, record keeping, audits, informed consent, protocol compliance, and reporting. One suggestion was to use one central area for all clinical research to run through and to establish an electronic clinical research management system.

The human subject research survey, in combination with the qualitative analysis of FDA warning letters, resulted in identifying the quality system areas focused on in the next chapter which addresses establishing the quality management system.

CHAPTER 5

ESTABLISHMENT OF THE QUALITY MANAGEMENT SYSTEM

5.1 Discussion

The survey results were compared with the top ten quality system violations from the FDA warning letter analysis as verification of the most frequently cited quality system violations. Any differences or gaps between the analysis and the survey results were also taken into consideration. The following table illustrates the top ten FDA quality system violations compared to the opinions of top quality and regulatory professionals from the survey results:

Top Ten Quality System Violations	
Per the FDA Warning Letter Analysis	**Per the Survey Results by Subject Number**
Investigational Plan	#4, #6, #9
Informed Consent	#1, #3, #4, #6, #9
Case History	#1, #9
FDA and/or IRB Approval	
Procedures for IRB Function	
Documentation of IRB Functions	
Composition of IRB	
Product Disposition	
Monitoring	
Investigator Agreements	

Figure 5.1 Top Quality System Violations

From the comparative analysis, the research indicated that the most common quality system violations were failure to follow the investigational plan, issues with informed consent, and poor case history record documentation. This risk based comparative approach was used for prioritizing certain areas to consider during implementation of the quality management system.

This research used the process based Quality Management System approach model from ISO 9001:2008 in figure 5.2 below. [42] Clinical investigators, sponsors, monitors, contract research organizations and institutional review boards all have responsibilities for processes within a quality management system.

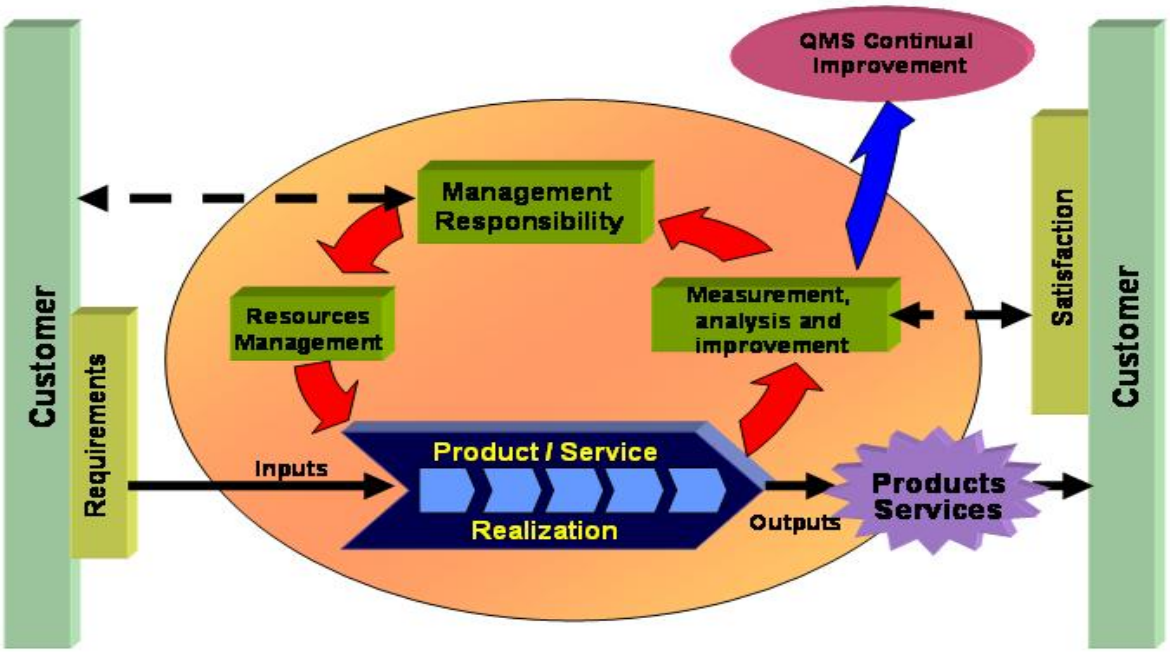


Figure 5.2 Quality Management System Model

Quality is applied to processes as a measurement of the ability of the process to satisfy stated or implied needs of the customer. [14] By implementing quality into the process as an input, the output is a high quality product that meets customer needs. The Quality Management System

was focused on implementing a quality system plan on the following processes from the research results: investigational plan, informed consent, case history, FDA and/or IRB approval, IRB functions, product disposition, monitoring and investigator agreements. This comprehensive list should be followed to establish the process requirements for quality system compliance with Good Clinical Practices and FDA regulations. [4]

5.2 Informed Consent

Informed Consent Quality System	
Checklist (include signature and date in this column from quality system management)	**Actions Required** [43, 44, 14, 45]
	Adequate reading and comprehension level of targeted population and/or legally authorized representative, adequate time allotted
	Voluntary consent free from coercion and undue influence (Consider possible vulnerable populations: subordinates, minors, educationally or economically disadvantaged, social, cultural, psychological, medical, pregnant women, fetus/embryo)
	No unjustifiable assurances of risk, benefit or inconvenience
	No exculpatory language appearing to waive rights
	Subject or legally authorized representative receives copy of consent form

Informed Consent Quality System	
Checklist (include signature and date in this column from quality system management)	**Actions Required** [43, 44, 14, 45]
	In accordance with national culture and requirements: • Designated authority of community does not replace an individual's consent
	Individual who conducts the consent process should be knowledgeable about the research and able to answer all subject questions • Investigator's responsibility to assure delegated individual is adequately trained and qualified to perform consent process
	Informed consent document contains the title of research protocol, the sponsor, clinical investigator's name and clinical investigator's institutional affiliation identity, and source of funding (if applicable)
(required elements in bold)	The consent document contains the elements of consent: • The trial involves **research** • State that participation is **voluntary** • Subject may withdraw **without penalty** • **Purpose** of the research • Trial treatment(s) and probability of random assignment • Research **procedures** • The subject's responsibilities during the research trial • Any **experimental** procedures

Informed Consent Quality System	
Checklist (include signature and date in this column from quality system management)	**Actions Required** [43, 44, 14, 45]
(con't) (required elements in bold)	The consent document contains the elements of consent: • Any **risk** or inconveniences to subject or to embryo, fetus or nursing infant • Any expected or unexpected **benefits** to subject • **Alternative** treatments • **Compensation and/or treatment available for injury** occurred during trial • Subject's participation in research • **Compensation** for participation (if any) • Any anticipated **costs** of participation • Inform subject that the monitor, auditor, IRB/Ethics committee and regulatory authorities will have **access to subject's medical records** without violating subject's confidentiality and to the extent permitted by law and regulations • **Confidentiality** of subject's records and information protected to the extent permitted by law and regulations; potential risks should there be a breach in confidentiality

Informed Consent Quality System	
Checklist (include signature and date in this column from quality system management)	**Actions Required** [43, 44, 14, 45]
(con't) (required elements in bold)	The consent document contains the elements of consent: • Subject or subject's legally authorized representative will be informed if **new information** becomes available that may influence the subject's continuing participation in the trial • **Contact instructions** for information about the research study, subject's participation rights and in case of injury contact • **Termination** of participation without regard to subject consent • **Duration** of subject participation in the research • **Number** of subjects to participate in research
	Obtain consent, signed and dated by subject or legally authorized representative and by person obtaining consent • Written, oral, action, impartial witness, short form
	Inclusion of subjects that are incapable of providing consent must be ethically and medically justifiable
	Consent must be obtained prior to subject's participation in trial • Includes any pre-screening tests
	Consent review and approval, modifications, observing consent process • Obtained by IRB/Ethics committee

Informed Consent Quality System	
Checklist (include signature and date in this column from quality system management)	**Actions Required** [43, 44, 14, 45]
(con't)	Clinical Investigators responsibility: • Delegated staff for consent process are appropriately trained • Consent form is reviewed and approved prior to use • Consent is obtained from subject or subject's legally authorized representative prior to participation in research trial
	Sponsors/Monitors/CRO responsibility: • Monitor research site to make sure that informed consent is obtained from all research study participants
	Regulatory Authorities responsibilities: • Verify consent process is in compliance with applicable laws and regulations
	Exception from informed consent requirements: • Life threatening situation or emergency research

5.3 Investigational Plan (Protocol Compliance)

Investigational Plan (Protocol Compliance) Quality System	
Checklist (include signature and date in this column from quality system management)	**Actions Required** [43, 14, 21, 22, 23]
	Perform all study related activities in the precise manner specified in the approved protocol. Research study conducted in compliance with the IRB/Ethics committee approved protocol and any conditions of approval imposed by the IRB/ethics committee or FDA • Effective monitoring
	No deviation from protocol without prior sponsor and IRB/Ethics committee approval of an amendment except where immediate hazards to subjects are apparent or administrative changes are necessary • Emergency deviations reported to sponsor and IRB within 5 working days of event occurrence
	Inform subjects fully and obtain consent
	Subjects recruited according to the approved inclusion and exclusion criteria
	Treating subjects with the investigational product as specified in the approved protocol; exception for emergency use

Investigational Plan (Protocol Compliance) Quality System	
Checklist (include signature and date in this column from quality system management)	**Actions Required** [43, 14, 21, 22, 23]
	Maintain accurate records of key safety and efficacy data
	Report all serious adverse events immediately to the sponsor; no minor events
	Well designed and clearly written protocol
	Investigator/institution and the sponsor should sign the protocol (or other contract) to confirm their agreement. This assures compliance with regulatory requirements and the approved IRB/ethics committee protocol
	Non-compliance should lead to prompt action by the sponsor to achieve compliance with the approved protocol
	Any deviation from protocol should be documented and explained
	Clinical investigator and sponsor have responsibility of protocol compliance
	If monitoring or auditing results in findings of serious non-compliance or continued non-compliance, investigator/institution's participation should be terminated; not applicable to all study sites
	Participation and/or study termination reported to regulatory authorities

5.4 Case History

Case History Quality System	
Checklist (include signature and date in this column from quality system management)	**Actions Required** [43, 14, 26, 27]
	Case histories include the case report forms and supporting data, such as signed and dated consent forms, medical records and nurses' notes
	Investigators prepare and maintain adequate records that record all observations and other data important to the study on each subject
	Investigator should ensure accuracy, legibility, completeness and timeliness of data reported to sponsor in case report forms
	Data reported in case report forms should be consistent with the source document or any discrepancies explained
	Any change or correction should be made in compliance with Good Documentation Practices (GDP) • Sponsors should provide guidance to investigators or investigator’s designated representatives on changes
	Investigator retains records of all changes and/or corrections
	Documents maintained as required by applicable regulatory requirements

Case History Quality System	
Checklist (include signature and date in this column from quality system management)	**Actions Required** [43, 14, 26, 27]
	Retained at least 2 years after approval of marketing application unless otherwise required by regulatory requirements or sponsor requirements • Sponsor should inform investigator when documents when retention period is complete
	Sample case report form located in investigator and sponsor files
	Subjects identifying information should be kept separate from the case report form
	Case report forms are compared with source documents by monitors to catch any discrepancies
	Sponsors should develop SOPs for case histories
	Case report forms should be signed, dated and fully completed by investigator or delegated member of investigator's staff to document confirmation of the observations recorded

5.5 FDA and/or IRB Approval

FDA and/or IRB Approval Quality System	
Checklist (include signature and date in this column from quality system management)	**Actions Required** [43, 14, 28, 39, 46, 30, 31]
	Sponsor responsibilities: • Ensure that IRB and FDA review and approval have been obtained by the clinical investigator • Shall not begin investigation without FDA approval for which an FDA application is required • IRB and FDA have been promptly informed of significant new information about an investigation • Shall submit an IND or IDE to the FDA • Shall submit a separate IND to the FDA involving an exception from informed consent
	Protocol should be submitted to an IRB/ethics committee that is independent of the investigator, sponsor or any other undue influencers or conflicts
	Protocol reviewed for ethical and scientific soundness
	Prior to initiating a trial, the investigator/institution should have written and dated approval from the IRB/ethics committee for the trial protocol, written informed consent form, consent form updates,

FDA and/or IRB Approval Quality System	
Checklist (include signature and date in this column from quality system management)	**Actions Required** [43, 14, 28, 39, 46, 30, 31]
(con't)	subject recruitment procedures (e.g., advertisements), and any other written information to be provided to subjects.

5.6 Procedures for IRB Function, Composition and Documentation

Procedures for IRB Function, Composition and Documentation Quality System	
Checklist (include signature and date in this column from quality system management)	**Actions Required** [43, 35, 32, 34, 33]
	IRB shall consist of qualified members with varying backgrounds: • At least five members • At least one member whose primary area of interest is in a non-scientific area • At least one member who is independent of the institution/trial site • Not gender biased
	Members with a conflict of interest with the research shall not vote
	Members should maintain qualifications
	Perform functions according to written operating procedures
	Maintain written records of its activities and meeting minutes
	Comply with applicable regulatory requirements
	Must have a member quorum when making voting decisions
	Only members who participate in the IRB review and meeting discussion should vote
	Investigators may provide information on the trial but may not participate in the deliberations or vote of the IRB
	May use non-members as consultants for expertise in certain areas

Procedures for IRB Function, Composition and Documentation Quality System	
Checklist (include signature and date in this column from quality system management)	**Actions Required** [43, 35, 32, 34, 33]
(con't)	The IRB should establish, document in writing and follow its procedures for the following: • Determining composition and the authority under which it is established • Scheduling and notification of meetings to members • Conduct initial and continuing review • Determine frequency of continuing review (at least annually) • Expedited review and approval of minor changes to research • Specify that no subject shall participate in the research without prior written approval of the research • Deviation or modification of research may not be implemented without prior IRB review/approval except in an emergency situation that affects a subjects safety and welfare • Specify to the investigator that all modifications to eliminate immediate hazards to subjects, changes affecting risk to subjects, serious adverse events, and any new information that may affect the safety of subjects should be reported to the IRB immediately

Procedures for IRB Function, Composition and Documentation Quality System	
Checklist (include signature and date in this column from quality system management)	**Actions Required** [43, 35, 32, 34, 33]
(con't)	The IRB should establish, document in writing and follow its procedures for the following: • The IRB promptly reports the following in writing to the investigator: o All trial related decisions/opinions o Reasons for the decisions/opinions o Procedures for appealing the decisions/opinions

5.7 Investigational Product Disposition

Investigational Product Disposition Quality System	
Checklist (include signature and date in this column from quality system management)	**Actions Required** [14, 43, 36, 27]
	Sponsor and/or Investigator shall maintain adequate records of investigational product receipt, shipment and disposition. Records should include name of investigator to who product is shipped, date, quantity, batch or code of each shipment, and reasons for and method of disposal
	Sponsor shall not supply investigator or institution with investigational product until all approvals and documentation have been acquired
	Sponsor responsibilities: • Ensure timely delivery of investigational product to investigator • Maintain system for documenting the retrieval of investigational product • Take steps to ensure investigational product is stable over a period of use • Maintain sufficient quantities of investigational product to reconfirm specifications if necessary

5.8 Monitoring

Monitoring Quality System	
Checklist (include signature and date in this column from quality system management)	**Actions Required** [43, 37, 38, 39]
	Records must be maintained for a period of 2 years after the latter of the two dates: • Date the investigation is terminated or completed • Date that records are no longer required to support a pre-market approval or a notice of completion of a product development protocol
	Any clinical investigations under an IND or IDE shall be monitored; monitors appointed by sponsor
	Monitors should be appropriately trained, should have scientific and/or clinical knowledge to monitor trial
	Document monitor(s) qualifications
	Monitor should be familiar with investigational product, protocol, informed consent form, and any written information provided to subjects
	Monitor should be familiar with sponsor SOPs and applicable regulatory requirements
	On- site monitoring performed before, during and post-trial

Monitoring Quality System	
Checklist (include signature and date in this column from quality system management)	**Actions Required** [43, 37, 38, 39]
	Monitor Responsibilities: • Monitor is primary contact between sponsor and investigator • Monitor verifies that investigator has appropriate qualifications and resources prior and during the trial period • Staff and facilities are adequate and appropriate to carry out trial safely and properly • Verifies investigational product: o Storage times and conditions are acceptable o Supply is sufficient throughout trial o Investigational product only supplied to subjects who qualify to receive it and at the approved specified dose o Instruction for using, handling, storing and returning investigational product are provided to subjects o Receipt, use and storage of investigational product at trial sites are controlled and documented o Disposition of unused investigational product is in compliance with applicable regulatory requirements and complies with sponsors authorized procedures

Monitoring Quality System	
Checklist (include signature and date in this column from quality system management)	**Actions Required** [43, 37, 38, 39]
(con't)	Monitor Responsibilities: • Verify that investigator follows approved protocol and amendments • Verify that informed consent was obtained prior to a subjects participation in the trial • Verify that investigator receives current Investigator's Brochure, all documents and all trial supplies to carry out trial properly and in compliance with regulatory requirements • Verify that investigator and investigator's staff are adequately informed about trial • Verify that investigator and investigator's staff are performing approved protocol procedures • Verify that investigator is only enrolling subjects who meet the inclusion/exclusion criteria • Report subject recruitment rate • Verify that source documents and other trial records are accurate, complete, updated and maintained

Monitoring Quality System	
Checklist (include signature and date in this column from quality system management)	**Actions Required** [43, 37, 38, 39]
(con't)	Monitor Responsibilities: • Verify that the investigator maintains all required reports, notifications, applications, submissions and that these documents are accurate, complete, timely, legible, dated and identify the trial • Check the accuracy of Case Report Form entries, source data and documents, and other trial records against each other for accuracy • Specifically verify: o Protocol data are recorded on the Case Report forms and consistent with source data and source documents o Dose and/or therapy modifications are well documented for each trial subject o Adverse events, concomitant medications, and inter-current illnesses are reported on the Case Report Forms in accordance with the approved protocol

Monitoring Quality System	
Checklist (include signature and date in this column from quality system management)	**Actions Required** [43, 37, 38, 39]
(con't)	• Specifically verify: o Visits that the subjects miss, tests that are not conducted and examinations that are not performed have been documented on the Case Report Form(s). o All subject withdrawals and dropouts are reported and explained on the Case Report Form(s)
(con't)	Monitor Responsibilities: • Inform the investigator of any entry error, omission or illegibility on the Case Report Form(s) • Ensure that the appropriate corrections, additions or deletions are made, dated, explained and initialed by the investigator or by the investigator's delegated official for initialing Case Report Form changes for the investigator • Determine if adverse events are reported within the required time periods • Determine if investigator is maintaining all essential documents

Monitoring Quality System	
Checklist (include signature and date in this column from quality system management)	**Actions Required** [43, 37, 38, 39]
(con't)	Monitor Responsibilities: • Informing the investigator of any deviations from the protocol, SOPs and applicable regulatory requirements and taking the appropriate action designed to prevent recurrence of the deviation(s) • Submit written report to sponsor after each site visit or trial-related communication: o Include date, site, name of monitor and name of investigator or other individual contacted o Include summary of what was reviewed and a statement concerning any significant findings, deviations, conclusions, actions to be taken or actions that have already been taken and/or actions to be recommended to bring the trial back into compliance o Review and follow-up of the monitoring report by the sponsor should be documented by the sponsor's delegated representative

5.9 Investigator Agreements

Investigator Agreements Quality System	
Checklist (include signature and date in this column from quality system management)	**Actions Required** [40, 41]
	Investigator Agreement shall include: • Investigator Curriculum Vitae • Statement of investigator's relevant experience that includes the date, location, extent and type of experience • If the investigator was ever involved in research that was terminated and an explanation of the termination • Statement of the investigator's commitment to: o Conduct investigation in accordance with agreement, investigational plan, applicable FDA regulations, and any conditions imposed by the IRB or FDA o Supervise all testing of the investigational product o Ensure the requirements for informed consent are met

Investigator Agreements Quality System	
Checklist (include signature and date in this column from quality system management)	**Actions Required** [40, 41]
	• Appropriate financial disclosure information was provided to allow the sponsor to submit a complete and accurate disclosure or certification statement o Commitment from investigator to promptly update the information if any changes occur during the investigation and for up to 1 year following completion of the study

Implementation of these quality system processes into the quality management system should aid in achieving a quality product that meets the customer needs. These results may also be used as standard operating procedures for a process approach in the quality management system for maintaining compliance with Good Clinical Practices and FDA regulations. From Shewart's model that was discussed in chapter 2, the quality system plan is to create processes that are necessary to produce the expected output. The "Do" is to put the plan into action, carry out the process and produce the product. The next step is to "Check" the outcome of the product and compare against the accepted outcome of product. The last step is to "Act". If the "Check" plan shows that there is improvement in product, then the new "Do" becomes the new standard for how the organization should "Act". If there is no improvement shown, then the previous standard will resume. [18]

Figure 5.3 Shewhart Model of Quality Assurance [17]

Biomedical research institutions using this plan should take into consideration that although this is a comprehensive quality system plan, the regulations and requirements change, so modification may be necessary for a complete and thorough implementation into the Quality Management System.

CHAPTER 6

CONCLUSION

6.1 Conclusion

Initially, the focus of this research was to design a quality management system for a biomedical academic institution that performs clinical research in compliance with Good Clinical Practices; however, at biomedical academic institutions performing clinical research, the research uncovered numerous quality system violations, as documented in FDA warning letters and as confirmed by a survey of quality and regulatory professionals across the country. Since these violations predominantly fall within the *process management* function of a Quality Management System in clinical research the implementation plan focused on this *process based* approach.

The research consisted of a retrospective analysis of FDA warning letters from January 2010 through June 2015- some five+ years- for cited violations in clinical research, as compared to survey professionals with expertise in the fields of quality assurance and regulatory compliance from the top 50 NIH (National Institutes of Health) funded academic biomedical institutions in the United States. The survey analysis of the nine anonymous respondents from the top NIH funded academic biomedical research institutions confirmed concurrence with the top quality system violations documented in the FDA warning letter analysis; there were no differences or gaps observed.

The research results identified the most frequently cited FDA quality system violations in clinical research as deficiencies in the investigational plan, informed consent, case history, FDA and/or IRB approval, IRB functions, product disposition, monitoring, and investigator agreements. Analysis of these quality system violations informed the design of an implementation plan checklist or standard operating procedure (SOP) for biomedical institutions that are engaged in clinical research. Implementation of these quality system processes into the quality management system should aid in achieving a quality product that meets the customer needs. As discussed in chapter 2 and chapter 5, Shewart's model implies that the quality system plan is to create processes necessary to produce the expected output. The "Do" is to put the quality system checklist/SOP plan into action or implementation, carry out the processes described in the plan and produce the product or results. The next step is to "Check" the outcome of the product and compare against the accepted outcome of product. This may be achieved by integrating internal and external auditing procedures into the Quality Management System. The last step is to "Act", which incorporates a corrective and preventative action plan or procedures (CAPA) to improve performance where necessary. If the "Check" plan shows improvement in the product, then the new "Do" becomes the new standard for how the organization should "Act". If no improvement is shown, then the previous standard will resume. This incorporates a risk based approach that is necessary for an effective Quality Management System. [18, 47]

Research Questions

1. *What are the most common GCP violations cited by the FDA?*

The results of this research identified the most frequently cited Good Clinical Practice violations issued by the FDA were related to the investigational plan, informed consent, case history, FDA and/or IRB approval, IRB functions, product disposition, monitoring, and

investigator agreements. A trend analysis was performed on these results to uncover any trends over the last five plus years. The downward trend over time was noted in all citation violation categories. This may be due to the FDA's risk based approach during inspections or the possibility that research teams as a whole are better educated and informed about running their clinical trials. This may imply that more quality management systems are being implemented within clinical research investigations, thus, leading to more quality investigations, quality data and as a result, quality product. Further research could be performed to conclusively validate the reasons for the decrease in citation violations.

2. *Are there areas of GCPs that should be concentrated on more than others in developing a Quality Management System?*

A comparative analysis of the FDA warning letter and survey responses indicated that areas of Good Clinical Practice quality system violations were concentrated on issues involving the investigational plan, informed consent, and case history. These results were given priority when implementing the Quality Management System plan. Clearly, training and education of research staff in these areas should be a prime focus of the Quality Management System plan.

3. *Are there challenges of implementing a GCP/Quality Management System in an academic biomedical institution?*

Yes, the research results from the survey responses indicated challenges of implementing a GCP/Quality Management System. One major challenge of implementing a GCP/Quality Management System is the training of clinical research staff. The research results indicated that training within a biomedical clinical research institution is best achieved through monthly educational lectures, formal research conduct classes, focus group sessions and attending educational conferences/workshops. The research survey results also indicated that leadership of

the Quality Management System should promote efficiencies and not chastise, fire, or reduce staff. This challenge would most likely be eliminated through effective training procedures and processes within the Quality Management System.

Although the research had resulted in answering the proposed research questions, there were some unavoidable limitations during the research process. These limitations included the sample size of the respondents to the survey, the quality of the survey, and bias and error that was introduced into the survey design. First, the sample size of respondents to the survey was small with only nine respondents out of the fifty email invitations sent. The small sample size may not be a true representation of all regulatory and compliance professionals in academic biomedical research institutions. Therefore, in order to accurately generalize the results for the majority of academic biomedical research institutions, the sample size should have involved more participants from these types of institutions. Second, the quality of the survey could have been stronger. Obtaining demographics about the survey respondents would have increased survey validity by defining and measuring the significance of the group of respondents and the population represented. Third, bias and error in the survey design could have been limited by controlling the margin of error by having the most appropriate sample size and obtaining demographics of respondents. Finally, these limitations could be overcome through future research by increasing the sample size of respondents, obtaining demographics of the population surveyed, and reducing bias and error through these additional implementations. Also adding an additional population of survey respondents from experts at the Food and Drug Administration's (FDA) Bioresearch Monitoring Program would aid in providing additional validity and stronger survey results.[49]

In conclusion, a quality management systems approach to processes proactively protects the rights and welfare of human subjects while ensuring data validity for viable research results. In clinical research, this result may be achieved through combined oversight by the clinical investigator, sponsor, IRB, and monitor and/or contract research organization (CRO). Since FDA inspections and audits take a risk based approach, the quality framework for a biomedical academic institution performing clinical research should also employ such an approach to implementing processes. By focusing on these critical areas of the quality management system, this method ensures the protections of humans, better data validity and production of a quality product that meets customer needs.

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APPENDICE A

FDA WARNING LETTER CITATIONS FOR YEARS 2010-2015

Clinical Investigators	Citation 2010
1. Cayman Chemical Company 01/19/2010	VIOLATIONS RELATED TO INVESTIGATOR RESPONSIBILITIES [21 CFR 312.60, 312.66, and 312.62(a)] 1. Failed to obtain informed consent in accordance with the provisions of 21 CFR part 50, as required by 21 CFR 312.60. 2. Failed to ensure that an IRB complying with the requirements set forth in 21 clinical study [21 CFR 312.66]. 3. Failed to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects [21 CFR 312.62(a)].
2. Samya Nasr M.D. 01/28/2010	1. Failed to obtain the informed consent of each human subject, in accordance with 21 CFR part 50 [21 CFR 312.60] 2. Failed to ensure that the investigations were conducted according to the investigational plans [21 CFR 312.60] 3. Failed to promptly report to the IRB all changes in research activities and made changes in the research without IRB approval [21 CFR 312.66].
3. Sohail S. Punjwani, M.D. 02/04/2010	1. Failed to conduct the studies or ensure they were conducted according to the investigational plans, and to protect the rights, safety and welfare of subjects [21 CFR 312.60]. 2. Failed to promptly report to the Institutional Review Board (IRB) all changes in the research activity [21 CFR 312.66].
4. Timothy Summers, M.D. 02/24/2010	1. Failed to conduct the studies or ensure they were conducted according to the signed investigator statement and the investigational plan, and to protect the rights, safety, and welfare of subjects under the investigator's care [21 CFR 312.60]. 2. Failed to maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation [21 CFR 312.62(b)]. 3. Failed to obtain informed consent of each subject in accordance with the provisions of 21 CFR Part 50 [21 CFR 312.60].

4. Failed to promptly report to the IRB all changes in the research activity and you made changes in the research without IRB approval [21 CFR 312.66].

5. Miguelangelo J. Perez-Cruet, M.D.
03/02/2010

1. Failure to ensure that informed consent is obtained in accordance with 21 CFR Part 50. [21 CFR 50.20, 21 CFR 50.27(a), and 21 CFR 812.100]
2. Failure to ensure an investigation is conducted according to the signed agreement, the investigational plan, applicable FDA regulations, and any conditions of approval imposed by an IRB or FDA. (21 CFR 812.100 and 21 CFR 812.110(b)]

6. Henry Lin, M.D.

1. Failure to ensure proper monitoring of the clinical investigations [21 CFR 312.50 and 312.56(a)].
2. Failed to obtain a signed investigator statement, Form FDA 1572, before permitting an investigator to participate in an investigation [21 CFR 312.53(c)(1)].
3. Failed to give each participating investigator an investigator brochure containing the information described in 312.23(a)(5) [21 CFR 312.55(a)].
4. Failed to review and evaluate the evidence relating to the safety and effectiveness of the drug as it is obtained from the investigator [21 CFR 312.56(c)].
5. Failed to submit to the FDA an annual report of the investigation [21 CFR 312.33 & 312.56(c)].
6. Failed to maintain adequate records showing the receipt, shipment, or other disposition of the investigational drug [21 CFR 312.57(a)].
7. Failed to maintain complete and accurate records showing any financial interests of investigators subject to 21 CFR Part 54 [21 CFR 312.57(b)].
8. Failed to retain records and reports for two years after shipment and delivery of the drug is discontinued and FDA has been so notified [21 CFR 312.57(c)].

7. Charles H. Toledo, M.D.
03/11/2010

1. Failed to ensure that the investigation was conducted according to the signed investigator statement, the investigational plan, and the applicable regulations in order to protect the rights, safety, and welfare of subjects under your care. [21 CFR § 312.60].
2. Failed to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation. [21 CFR § 312.62(b)].
3. Failed to maintain adequate records of the disposition of the investigational drug. [21 CFR § 312.62(a)].
4. Failed to retain records required to be maintained for a period of two years following the date a marketing application is approved for the indication for which the drug is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until two years after the investigation is discontinued. [21 CFR § 312.62(c)].

8. Sant P. Chawla, M.D.

1. Failed to conduct the studies or ensure they were conducted according to the investigational plans [21 CFR 312.60].

03/17/2010	2. Failed to maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation [21 CFR 312.62(b)].
9. Robert Deitz, M.D. 04/01/2010	1. Failed to maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation [21 CFR 312.62(b)]. 2. Failed to obtain informed consent in accordance with the provisions of 21 CFR part 50 [21 CFR 312.60]. 3. Failed to promptly report to the IRB all changes in the research activity [21 CFR 312.66]. 4. Failed to ensure that the investigation was conducted according to the signed investigator statement and the investigational plan [21 CFR 312.60]. 5. Failed to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects [21 CFR 312.62(a)]. 6. Failed to retain records required to be maintained under 21 CFR part 312 until 2 years after the investigation was discontinued and FDA was notified [21 CFR 312.62(c)].
10. Jason Pozner, M.D. 06/25/2010	1. Failure to adhere with the regulation that prohibits representations that an investigational device is safe or effective for the purposes for which it is being investigated. [21 CFR 812.7(d)]. 2. Failure to conduct the investigation according to the signed agreement, the investigational plan, applicable FDA regulations, and any conditions of approval imposed by an Institutional Review Board (IRB) or FDA. Also failure to adhere to the regulation that governs an investigational device to be used only with subjects under the investigator's supervision. [21 CFR 812.110(b) and (c)]. 3. Failure to maintain accurate, complete, and current records of receipt, use, or disposition of a device that relate to the type and quantity of the device and the dates of receipt. [21 CFR 812.140(a)(2)]. 4. Failure to maintain accurate, complete, and current records of each subject's case history. [21 CFR 812.140(a)(3)].
11. Patrick Nemecheck Do Pa 06/28/2010	1. You failed to ensure that the investigation was conducted according to the signed investigator statement and the investigational plan. [21 CFR § 312.60]. 2. You failed to ensure that informed consent was obtained in accordance with 21 CFR Part 50. [21 CFR § 312.60]. 3. You failed to retain records required to be maintained for the period of two years following the date a marketing application is approved for the indication for which the drug is being investigated; or, if no application is filed or if the application is not approved for such indication, until two years after the investigation is discontinued. [21 CFR § 312.62(c)].

12. Stuart Harlin, M.D. 07/21/2010	1. Failure to conduct an investigation according to the signed agreement, the investigational plan, and FDA regulations. [21 CFR 812.100 and 21 CFR 812.110(b)] 2. Failure to maintain accurate and complete records of each subject's case history and to maintain required records for a period of 2 years after the date on which the investigation was terminated. [21 CFR 812.140(a)(3) and (d)] 3. Failure to submit a timely report of withdrawal of Institutional Review Board approval to the sponsor. [21 CFR 812.150(a)(2)]
13. Sean Scully, M.D. 07/30/2010	1. Failure to conduct the investigation according to the signed agreement, the investigational plan, applicable FDA regulations, and any conditions of approval imposed by an Institutional Review Board (IRB) or FDA. [21 CFR 812.100 and 812.110(b)]. 2. Failure to maintain accurate, complete, and current records of each subject's case history and also failure to maintain complete and current protocol. [21 CFR 812.140(a)(3) and 812.140(a)(4)]. 3. Failure to submit progress reports on the investigation to the sponsor and reviewing IRB at regular intervals. [21 CFR 812.150(a)(3)].
14. Herman A. Jenkins, M.D. 08/16/2010	1. Failure to submit to the sponsor and to the reviewing IRB a report of any unanticipated adverse device effect (UADE) occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect. [21 CFR 812.150(a)(1)] 2. Failure to ensure an investigation is conducted according to the signed agreement, the investigational plan, applicable FDA regulations, and any condition of approval imposed by an IRS or FDA. [21 CFR 812.100 and 21 CFR 812.110(b)] 3. Failure to maintain accurate, complete, and current records of receipt, use, or disposition of a device. [21 CFR 812.140(a)(2)]
15. Matthew N. Songer, M.D. 08/27/2010	1. Failure to include all elements of informed consent. [21 CFR 50.25(a) and 50.25(b)] 2. Failure to conduct the investigation according to the signed agreement with the sponsor, the investigational plan, 21 CFR part 812, other applicable FDA regulations, and any conditions of approval imposed by an Institutional Review Board (IRB) or FDA. [21 CFR 812.110(b)] 3. Failure to maintain accurate, complete, and current records related to your participation in the investigation. [21 CFR 812.140(a)(1), 812.140(a)(3)(ii) and 812.140(a)(4)]
16. Joel Picus, M.D. 09/20/2010	1. You failed to personally conduct or supervise the clinical investigation [21 CFR 312.60]. 2. You failed to ensure that the investigation was conducted according to the investigational plan, and you failed to protect the rights, safety, and welfare of the subjects under your care [21 CFR 312.60]. 3. You failed to obtain informed consent in accordance with the provisions of 21

	CFR Part 50 [21 CFR 312.60]. 4. You failed to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects [21 CFR 312.62(a)].
17. Lamar L. Snow, M.D. 09/29/2010	1. You failed to ensure that the investigation was conducted according to the signed investigator statement, in that you failed to personally conduct or supervise the clinical investigation [21 CFR 312.60]. 2. You failed to maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation [21 CFR 312.62(b)]. 3. You failed to ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60].
18. Thomas Jr. O'Barr, M.D. 09/30/2010	1. You failed to ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60]. 2. You failed to maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation [21 CFR 312.62(b)]. 3. You failed to maintain adequate records of the disposition of the drug, including the dates, quantity, and use by subject [21 CFR 312.62(a)].
19. Howard Lippton, M.D. 10/20/2010	1. You failed to assure that an Institutional Review Board (IRB) that complies with the requirements set forth in part 56 was responsible for the initial review and approval of Protocol (b)(4) [21 CFR 312.66]. 2. You failed to protect the rights, safety, and welfare of the subjects under your care [21 CFR 312.60].
20. David F. Scott, M.D. 10/20/2010	1. You failed to ensure that the investigations were conducted according to the signed investigator statements and the investigational plans [21 CFR 312.60]. 2. You failed to obtain Institutional Review Board approval for changes in the research prior to implementing the changes [21 CFR 312.66]. 3. You failed to maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation [21 CFR 312.62(b)].

1. Providence Hospital IRB 01/06/2010 [21 CFR 56.108(a), (b) and (c)]	1. Failure to have adequate written procedures governing the functions and operations of the IRB 2. A majority of the members are present including at least one member whose primary concerns are in nonscientific areas. 3. Failure to include at least one member of the IRB who is not affiliated with the institution and maintain minutes of IRB meetings in sufficient detail. [21 CFR 56.107(d) and 21 CFR 56.115(a)(2)]
2. Wayne State University IRB 04/15/2010	1. Failure to prepare and maintain adequate documentation of IRB activities. Such documentation must include minutes of IRB meetings which shall be in sufficient detail to show the vote on actions taken by the IRB, including the number of members voting for, against, and abstaining Such documentation also must include a list of IRB members identified by name, earned degrees, representative capacity, indications of experience, and any employment or other relationship between each member and the institution. [21 CFR 56.115(a)(2) and 21 CFR 56.115(a)(5)] 2. Failure to review proposed research at convened meetings at which a majority of the members of the IRB are present, including at least one member whose primary concerns is in nonscientific areas. [21 CFR 56.108(c)]
3. MedCentral Health System 06/22/2010	1. Failure to follow written procedures governing the functions and operations of the IRB and to ensure that the IRB reviews proposed research at convened meetings at which a majority of the members are present including at least one member whose primary concerns are in nonscientific areas [21 CFR 56.108(a), (b), (c) and 21 CFR 812.60]. 2. Failure to prepare and maintain adequate documentation of IRB activities, including minutes of IRB meetings, which shall be in sufficient detail to show attendance at the meetings, actions taken by the IRB, the vote on these actions including the number of members voting for, against, and abstaining, the basis for requiring changes in or disapproving research, and a written summary of the discussion of controverted issues and their resolution [21 CFR 56.115(a)(2)]. 3. Failure to adopt a method for keeping all members advised of research proposals which have been approved under an expedited review procedure [21 CFR 56.110(c)].
4. Independent Review Consulting, Inc. 07/19/2010	1. Failure to use expedited review procedures only for certain kinds of research involving no more than minimal risk or for minor changes in approved research [21 CFR 56.110, 21 CFR 56.108(c)].

2. Failure to prepare and maintain adequate documentation of IRB activities, including minutes of IRB meetings, which shall be in sufficient detail to show attendance at the meetings, actions taken by the IRB, the vote on these actions including the number of members voting for, against and abstaining, the basis for requiring changes in or disapproving research, and a written summary of the discussion of controverted issues and their resolution. [21 CFR 56.115(a)(2)].
3. The IRB failed to ensure the information given to subjects as part of informed consent is in accordance with 21 CFR 50.25. [21 CFR 56.109(b)].
4. In approving research covered by the regulations, the IRB failed to determine that risks to subjects are minimized, risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may be expected to result. [21 CFR 56.111(a)(1), (a)(2)]

Sponsors/Monitor/CRO	Citation 2010
1. Cayman Chemical Company 01/19/2010	VIOLATIONS RELATED TO SPONSOR RESPONSIBILITIES [21 CFR 312.40, 312.8(a)(3), and 312.57(a)] 1. Failed to comply with the requirements for use of an investigational new drug in a clinical investigation by administering the investigational new drugs Compounds 1,2, and 3 to subjects without an IND in effect [21 CFR 312.40]. 2. Failed to obtain prior written authorization from FDA prior to charging for an investigational drug [21 CFR 312.8(a)(3)]. 3. Failed to maintain adequate records showing the receipt, shipment or other disposition of an investigational drug [21 CFR 312.57(a)].
2. Otologics LLC 03/05/2010	1. Failure to maintain accurate, complete, and current records of correspondence relating to an investigation [21 CFR 812.140(b)(1)]. 2. Failure to maintain accurate, complete, and current device shipment records [21 CFR 812.140(b)(2)]
3. Pfizer Inc. 04/09/2010	1. Failed to ensure proper monitoring of the investigation [21 CFR 312.50]. 2. Failed to ensure that the investigations were conducted in accordance with the general investigational plan and protocols contained in the IND [21 CFR 312.50]. 3. Failed to keep each participating investigator informed of new observations discovered by or reported to the sponsor on the drug, particularly with respect to adverse effects and safe use [21 CFR 312.55(b)].
4. Pioneer Surgical Technology 08/03/2010	1. Failure to comply with FDA regulation that prohibits the promotion and advertisement of an investigational device as safe and effective. [21 CFR 812.7(d)] 2. Failure to include all elements of informed consent. [21 CFR 50.25(a) and (b)] 3. Failure to ensure adequate monitoring of the investigation and failure to supply all investigators participating in the study with copies of the investigational plan. [21 CFR 812.40 and 21 CFR 812.45] 4. Failure to obtain signed investigator agreements that include sufficient accurate financial disclosure information. [21 CFR 812.43(c)(5) and 21 CFR Part 54] 5. Failure to maintain accurate, complete, and current device shipment records. [21 CFR 812.140(b)(2)]

5. Spineology, Inc. 09/22/2010	1. Failure to ensure adequate monitoring of the investigation. [21 CFR 812.40]. 2. Failure to secure the investigator's compliance with the signed investigator agreement, the investigational plan, applicable FDA regulations, and any other conditions of approval imposed by the reviewing IRB or FDA. [21 CFR 812.46(a)].

Clinical Investigators	Citation 2011
1. Judith Ratzan, M.D. 02/16/2011	1. You failed to personally conduct or supervise the clinical investigation [21 CFR 312.60]. 2. You failed to ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60]. 3. You failed to maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation [21 CFR 312.62(b)].
2. Vaughn H. Mancha Jr., M.D. 02/17/2011	1. You failed to ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60]. 2. You failed to maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation [21 CFR 312.62(b)].
3. Margaret E. Thurmond-Anderle, M.D. 02/25/2011	1. You failed to conduct the studies or ensure they were conducted according to the investigational plans, and to protect the rights, safety, and welfare of subjects [21 CFR 312.60].
4. John Griffin, M.D. 03/14/2011	1. You failed to ensure that the investigation was conducted according to the signed investigator statement, in that you failed to personally conduct or supervise the clinical investigation [21 CFR 312.60]. 2. You failed to conduct the studies or ensure they were conducted according to the investigational plan [21 CFR 312.60].
5. Jeffrey Horowitz, M.D. 03/21/2011	1. You failed to retain records required to be maintained under 21 CFR part 312 until 2 years after the investigation was discontinued and FDA was notified [21 CFR 312.62(c)]. 2. You failed to prepare and maintain adequate and accurate case histories

that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation [21 CFR 312.62(b)].
3. You failed to ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60].
4. You failed to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects [21 CFR 312.62(a)].

6. Martin N. Zaiac 03/21/2011

1. You failed to personally conduct or supervise the clinical investigation [21 CFR 312.60].
2. You failed to conduct the studies or ensure they were conducted according to the investigational plan, and failed to protect the rights, safety, and welfare of subjects under the investigator's care [21 CFR 312.60].
3. You failed to maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation [21 CFR 312.62(b)].
4. You failed to obtain informed consent of each subject in accordance with the provisions of 21 CFR part 50 [21 CFR 312.60].
5. You failed to assure that an Institutional Review Board (IRB) that complies with the requirements set forth in part 56 was responsible for the initial and continuing review and approval of Protocol (b)(4) [21 CFR 312.66].

7. Joseph B. Michelson, M.D. 07/06/2011

1. You failed to ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60].

8. Linda D. Bosserman 07/19/2011

1. You failed to ensure that the investigation was conducted according to the signed investigator statement, in that you failed to personally conduct or supervise the clinical investigation [21 CFR 312.60].
2. You failed to maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation [21 CFR 312.62(b)].
3. You failed to ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60].

9. Yale Cohen, M.D.
08/12/2011

1. You failed to ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60].
2. You failed to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation [21 CFR 312.62(b)].
3. You failed to obtain IRB approval before making changes in the research [21 CFR 312.66].

10. John Caton Jr., M.D.
08/26/2011

1. You failed to ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60].
2. You failed to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects [21 CFR 312.62(a)].
3. You failed to promptly report to the IRB all unanticipated problems involving risk to human subjects or others [21 CFR 312.66].
4. You failed to obtain informed consent in accordance with the provisions of 21 CFR part 50 [21 CFR 312.60].

11. Laura A. Teasley, M.D.
10/14/2011

1. You failed to ensure that the investigation was conducted according to the signed investigator statement, in that you failed to personally conduct or supervise the clinical investigation [21 CFR 312.60].
2. You failed to ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60].

12. Betty Tuller, Ph.D.
11/21/2011

1. You failed to obtain informed consent in accordance with the provisions of 21 CFR Part 50 [21 CFR 312.60].
2. You failed to maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation [21 CFR 312.62(b)].
3. You failed to promptly report to the IRB all unanticipated problems involving risk to human subjects or others [21 CFR 312.66].

13. Satyaprakash N. Makam, M.D.
12/19/2011

1. Failure to ensure that informed consent was obtained in accordance with 21 CFR Part 50 [21 CFR 50.20, 50.27(a), and 812.100].
2. Failure to ensure that an investigation is conducted in accordance with the signed agreement, investigational plan, applicable FDA regulations, and any conditions of approval imposed by an IRB or FDA [21 CFR 812.100 and 812.110(b)].

Clinical Investigators	Citation 2011
1. Judith Ratzan, M.D. 02/16/2011	1. You failed to personally conduct or supervise the clinical investigation [21 CFR 312.60]. 2. You failed to ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60]. 3. You failed to maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation [21 CFR 312.62(b)].
2. Vaughn H. Mancha Jr., M.D. 02/17/2011	1. You failed to ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60]. 2. You failed to maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation [21 CFR 312.62(b)].
3. Margaret E. Thurmond-Anderle, M.D. 02/25/2011	1. You failed to conduct the studies or ensure they were conducted according to the investigational plans, and to protect the rights, safety, and welfare of subjects [21 CFR 312.60].
4. John Griffin, M.D. 03/14/2011	1. You failed to ensure that the investigation was conducted according to the signed investigator statement, in that you failed to personally conduct or supervise the clinical investigation [21 CFR 312.60]. 2. You failed to conduct the studies or ensure they were conducted according to the investigational plan [21 CFR 312.60].
5. Jeffrey Horowitz, M.D. 03/21/2011	1. You failed to retain records required to be maintained under 21 CFR part 312 until 2 years after the investigation was discontinued and FDA was notified [21 CFR 312.62(c)]. 2. You failed to prepare and maintain adequate and accurate case histories

that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation [21 CFR 312.62(b)].
3. You failed to ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60].
4. You failed to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects [21 CFR 312.62(a)].

6. Martin N. Zaiac 03/21/2011

1. You failed to personally conduct or supervise the clinical investigation [21 CFR 312.60].
2. You failed to conduct the studies or ensure they were conducted according to the investigational plan, and failed to protect the rights, safety, and welfare of subjects under the investigator's care [21 CFR 312.60].
3. You failed to maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation [21 CFR 312.62(b)].
4. You failed to obtain informed consent of each subject in accordance with the provisions of 21 CFR part 50 [21 CFR 312.60].
5. You failed to assure that an Institutional Review Board (IRB) that complies with the requirements set forth in part 56 was responsible for the initial and continuing review and approval of Protocol (b)(4) [21 CFR 312.66].

7. Joseph B. Michelson, M.D. 07/06/2011

1. You failed to ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60].

8. Linda D. Bosserman 07/19/2011

1. You failed to ensure that the investigation was conducted according to the signed investigator statement, in that you failed to personally conduct or supervise the clinical investigation [21 CFR 312.60].
2. You failed to maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation [21 CFR 312.62(b)].
3. You failed to ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60].

9. Yale Cohen, M.D.
08/12/2011

1. You failed to ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60].
2. You failed to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation [21 CFR 312.62(b)].
3. You failed to obtain IRB approval before making changes in the research [21 CFR 312.66].

10. John Caton Jr., M.D.
08/26/2011

1. You failed to ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60].
2. You failed to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects [21 CFR 312.62(a)].
3. You failed to promptly report to the IRB all unanticipated problems involving risk to human subjects or others [21 CFR 312.66].
4. You failed to obtain informed consent in accordance with the provisions of 21 CFR part 50 [21 CFR 312.60].

11. Laura A. Teasley, M.D.
10/14/2011

1. You failed to ensure that the investigation was conducted according to the signed investigator statement, in that you failed to personally conduct or supervise the clinical investigation [21 CFR 312.60].
2. You failed to ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60].

12. Betty Tuller, Ph.D.
11/21/2011

1. You failed to obtain informed consent in accordance with the provisions of 21 CFR Part 50 [21 CFR 312.60].
2. You failed to maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation [21 CFR 312.62(b)].
3. You failed to promptly report to the IRB all unanticipated problems involving risk to human subjects or others [21 CFR 312.66].

13. Satyaprakash N. Makam, M.D.
12/19/2011

1. Failure to ensure that informed consent was obtained in accordance with 21 CFR Part 50 [21 CFR 50.20, 50.27(a), and 812.100].
2. Failure to ensure that an investigation is conducted in accordance with the signed agreement, investigational plan, applicable FDA regulations, and any conditions of approval imposed by an IRB or FDA [21 CFR 812.100 and 812.110(b)].

1. Marquette General Health System
IRB 01/18/2011

1. Failure to require that information given to subjects as part of informed consent is in accordance with 21 CFR 50.25. [21 CFR 56.109(b)]
2. Failure to follow written procedures for conducting its initial and continuing review of research. [21 CFR 56.108(a)(1)]
3. Failure to include at least one member whose primary concerns are in a nonscientific area when reviewing proposed research at convened meetings. [21 CFR 56.108(c)]
4. Failure to prepare and maintain adequate documentation of IRB activities, including minutes of IRB meetings. [21 CFR 56.115(a)(2)]

2. Napoli LLC 01/21/2011

1. Failure to ensure that the IRB is composed of at least five members; at least one IRB member's primary concerns are in nonscientific areas; and no IRB member participates in the initial or continuing review of any projects in which the member has a conflict of interest. [21 CFR 56.107(a), (c), and (e)]
2. Failure to have adequate written procedures governing the functions and operations of the IRB. [21 CFR 56.108(a), (b), and (c)]

3. American Association of Acupuncture and Bio-Energetic Medicine 03/24/2011

1. Failure to ensure that informed consent will be sought from each prospective subject, in accordance with 21 CFR Part 50 [21 CFR 56.111(a)(4)].
2. Failure to follow written procedures for conducting initial and continuing review of research and for reporting your findings and actions to the investigator and the institution [21 CFR 56.108(a)].
3a. Failure to follow written procedures for ensuring prompt reporting to the appropriate institutional officials and FDA of any instance of serious or continuing noncompliance with 21 CFR Part 56 or determinations of the IRB, and of any suspension or termination of IRB approval [21 CFR 56.108(b)].
b. Failure to report promptly to the FDA any suspension or termination of approval [21 CFR 56.113].

4. Centra Health Inc. IRB
06/13/2011

1. Failure to conduct continuing review of research at least annually. [21 CFR 56.109(f)]
2. Failure to prepare, maintain, and follow required written procedures governing the functions and operations of the IRB. [21 CFR 56.108(a)(1),

21 CFR 56.108(b)(1)-(3), and 21 CFR 56.115(a)(6)]

5. Mother Frances Hospital IRB
06/13/2011

1. Failure to have adequate written procedures governing the functions and operations of the IRB. [21 CFR 56.108(b)(1), (2) and (3)]
2. Failure to follow written procedures for conducting continuing review of research at least annually. [21 CFR 56.108(a)(1) and 56.109(f)]
3. Failure to prepare and maintain adequate documentation of IRB activities, including minutes of IRB meetings. [21 CFR 56.115(a)(2)]

Sponsors/Monitor/CRO Citation 2011

1. Orthocon Inc.
01/06/2011 1. Failure to secure the investigator's compliance. [21 CFR 812.46(a)]

2. Anulex Technologies, Inc. 02/11/2011
1. Failure to submit an application to the FDA and obtain approval prior to allowing subjects to participate in an investigation. [21 CFR 812.20(a)(1) and (a)(2), 21 CFR 812.40, and 21 CFR 812.42]
2. Failure to comply with FDA regulations that prohibit promotion of an investigational device until after FDA has approved the device for commercial distribution and representation that an investigational device is safe or effective for the purposes for which it is being investigated. [21 CFR 812.7(a) and (d)]
3. Failure to obtain adequate signed investigator agreements for each participating investigator. [21 CFR 812.43(c)]

3. Valor Medical Inc. 03/24/2011
1. Failure to include reports of all prior clinical, animal, and laboratory testing of the device. [21 CFR 812.27(a)]

4. LifeCell Corporation 05/05/2011
1. Failure to submit an application to the FDA and obtain approval prior to allowing subjects to participate in the investigation. [21 CFR 812.20(a)(1) and (a)(2), 21 CFR 812.40, 21 CFR 812.42]
2. Failure to submit an application to the FDA and obtain approval prior to allowing subjects to participate in the investigation. [21 CFR 812.20(a)(1) and (a)(2), 21 CFR 812.40, 21 CFR 812.42]
3. Failure to submit an application to the FDA and obtain approval prior to allowing subjects to participate in the investigation. [21 CFR 812.20(a)(1) and (a)(2), 21 CFR 812.40, 21 CFR 812.42]
4. Failure to comply with FDA regulations that prohibit promotion of an investigational device until after FDA has approved the device for commercial distribution and representation that an investigational device is safe or effective for the purposes for which it is being investigated. [21 CFR 812.7(a) and (d)]

5. TCA Cellular Therapy, LLC 08/15/2011
1. You failed to fulfill the general responsibilities of sponsors to ensure that investigations were conducted according to the investigational plan and you failed to monitor the progress of ongoing investigations. [21 CFR §§ 312.50 and 312.56(a)].
2. You initiated clinical investigations without an IND in effect. [21 CFR §§ 312.20 and 312.40].

3. You initiated clinical investigations without either submitting a protocol amendment or a new IND to FDA. [21 CFR §§ 312.20, 312.30 and 312.40].
4. You administered an investigational product in violation of a clinical hold. [21 CFR § 312.42(a) and (e)].

Clinical Investigators	Citation 2012
1. Louis G. Jenis, M.D. 02/14/2012	1. Failure to conduct the investigation according to the signed agreement, the investigational plan, applicable FDA regulations, and any conditions of approval imposed by an Institutional Review Board (IRB) or FDA [21 CFR 812.100 and 812.110(b)]. 2. Failure to maintain accurate, complete, and current records of each subject's case history [21 CFR 812.140(a)(3)]. 3. Failure to ensure that an investigation is conducted in accordance with the signed agreement, investigational plan, applicable FDA regulations, and any conditions of approval imposed by an IRB or FDA and failure to submit progress reports on the investigation to the sponsor and reviewing IRB at regular intervals [21 CFR 812.100, 812.110(b), and 21 CFR 812.150(a)(3)].
2. Vascular Group PLLC 02/21/2012	1. Failure to submit an application to the FDA and obtain IRB and FDA approval prior to allowing subjects to participate in an investigation [21 CFR 812.40 and 21 CFR 812.42]
3. Matthew Malcom, Ph.D. OTR 05/22/2012	1. Failure to ensure that informed consent was obtained in accordance with 21 CFR Part 50 [21 CFR 50.25(a)(2) and 812.100]. 2. Failure to maintain accurate, complete, and current records relating to all relevant observations, including anticipated and unanticipated adverse events [21 CFR 812.140(a)(3)(ii)]. 3. Failure to maintain accurate, complete, and current records relating to each subject's case history and all relevant observations, including records showing the dates and reasons for each deviation from the protocol [21 CFR 812.140(a)(3) and 812.140(a)(4)].
4. Elizabeth E. Houser, M.D. 05/25/2012	1. You repeatedly or deliberately submitted to FDA or to the sponsor false information in any required report [21 CFR 312.70(a)]. 2. You failed to ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60].
5. John Joseph Hewett, M.D. 09/05/2012	1. Failure to ensure that an investigation is conducted according to the signed agreement, the investigational plan, and applicable regulations. [21

CFR 812.100]

2. Failure to obtain informed consent by the use of a written consent form approved by the IRB and signed and dated by the subject or the subject's legally authorized representative at the time of the consent. [21 CFR 50.27(a)]

3. Failure to maintain accurate, complete, and current records related to your participation in the investigation. [21 CFR 812.140(a)(2) and 21 CFR 812.140(d)]

6. Synergy Health Concepts, Inc.
09/05/2012

1. Failure to ensure that informed consent was obtained in accordance with 21 CFR Part 50 [21 CFR 50.27(a)].

2. Failure to maintain accurate, complete, and current records related to your participation in the investigation [21 CFR 812.140(a)(2); 21 CFR 812.140(a)(3)(iii); and 21 CFR 812.140(d)].

7. Steven W.
Boyce, M.D.
09/28/2012

1. You failed to assure that an Institutional Review Board (IRB) that complies with the requirements set forth in part 56 was responsible for the initial and continuing review and approval of the proposed clinical study [21 CFR 312.66].

2. You failed to maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation [21 CFR 312.62(b)].

3. You failed to ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60].

4. You failed to obtain informed consent in accordance with the provisions of 21 CFR part 50 [21 CFR 312.60, 21 CFR 50.27].

IRBs

Citations 2012

1. Christian Hospital Northeast-Northwest 03/27/2012

1. The IRB failed to prepare, maintain and follow its written procedure for conducting its initial and continuing review of research. [21 CFR §§ 56.108(a) and 56.115(a)(6)].
2. The IRB failed to prepare and maintain adequate documentation of IRB activities. [21 CFR § 56.115(a)].
3. The IRB failed to review proposed research at convened meetings at which a majority of the members of the IRB were present, including at least one member whose primary concerns are in nonscientific areas. [21 CFR § 56.108(c)].

2. Biomedical Research Institute of America d/b/a BioMed IRB 03/29/2012

1. The IRB failed to fulfill membership requirements. [21 CFR § 56.107].
2. Failure to prepare, maintain, and follow adequate written procedures for conducting the review of research, including initial and continuing review. [21 CFR §§ 56.108(a) and 56.115(a)(6)]
3. Minutes of IRB meetings are not sufficient to show attendance at the meetings; actions taken by the IRB; the vote on these actions including the number of members voting for, against, and abstaining; the basis for requiring changes in or disapproving research; and a written summary of the discussion of controverted issues and their resolution. [21 CFR § 56.115(a)(2)].

3. Advocate Health Care 06/01/2012

1. The IRB failed to ensure that informed consent would be sought from each prospective subject or the subject's legally authorized representative in accordance with and to the extent required by 21 CFR Part 50, 21 CFR 56.111(a)(4).

4. Center for the Improvement of Human Functioning International, Inc. IRB 07/03/2012

1. The IRB failed to prepare, maintain, and follow required written procedures governing the functions and operations of the IRB [21 CFR 56.108(a), 21 CFR 56.108(b), and 21 CFR 56.115(a)(6)].
2. The IRB failed to prepare and maintain adequate documentation of IRB activities, including copies of all research proposals reviewed, approved consent documents, and progress reports submitted by investigators [21 CFR 56.115(a)(1)].
3. The IRB failed to prepare and maintain adequate documentation of IRB activities, including minutes of IRB meetings [21 CFR 56.115(a)(2)].

4. The IRB failed to maintain copies of all correspondence between the IRB and investigators [21 CFR 56.115(a)(4)].
5. The IRB failed to prepare and maintain a list of IRB members identified by name; earned degrees; representative capacity; indications of experience sufficient to describe each member's chief anticipated contributions to IRB deliberations; and any employment or other relationship between each member and the institution [21 CFR 56.115(a)(5)].

5. Memorial Hospital of South Bend, IRB 09/21/2012

1. The IRB failed to determine at the time of initial review that studies involving children are in compliance with 21 CFR Part 50, Subpart D, Additional Safeguards for Children in Clinical Investigations [21 CFR 56.109(h)].
2. The IRB failed to prepare, maintain, and follow required written procedures governing the functions and operations of the IRB [21 CFR 56.108(b) and 21 CFR 56.115(a)(6)].
3. The IRB failed to prepare and maintain adequate documentation of IRB activities, including minutes of IRB meetings [21 CFR 56.115(a)(2)].
4. The IRB failed to review proposed research at convened meetings at which a majority of the members of the IRB are present, including at least one member whose primary concerns are in nonscientific areas [21CFR 56.108(c)].
5. The IRB failed to ensure that no member participated in the initial or continuing review of a project in which the member had a conflicting interest, except to provide information requested by the IRB [21 CFR 56.107(e)].
6. The IRB failed to conduct continuing review of research at intervals of not less than once per year [21 CFR 56.109(f)].

6. Texas Applied Biomedical Services
09/24/2012

1. The IRB failed to ensure that no member participated in the initial or continuing review of a project in which the member had a conflicting interest. [21 CFR § 56.107(e)].
2. The IRB failed to prepare, maintain and follow its written procedures for conducting its initial and continuing review of research. [21 CFR §§ 56.108(a) and 56.115(a)(6)].
3. The IRB failed to fulfill membership requirements. [21 CFR § 56.107].
4. The IRB failed to determine that a pediatric study is in compliance with Part 50 Subpart D. [21 CFR §§ 56.109(h) and 56.111(c)].
5. The IRB failed to prepare and maintain adequate documentation of IRB activities. [21 CFR § 56.115].

7. Salem
Hospital IRB
11/29/2012

1. The IRB failed to prepare and maintain adequate documentation of IRB

activities [21 CFR 56.115(a)(1) and (4)].
2. The IRB failed to prepare and maintain adequate documentation of written procedures for the IRB, as required by 21 CFR 56.108(a) and (b) [21 CFR 56.115(a)(6)].
3. The IRB failed to prepare and maintain a list of IRB members identified by name; earned degrees; representative capacity; indications of experience sufficient to describe each member's chief anticipated contributions to IRB deliberations; and any employment or other relationship between each member and the institution [21 CFR 56.115(a)(5)].
4. The IRB failed to review proposed research at convened meetings at which a majority of the members of the IRB are present, including at least one member whose primary concerns are in nonscientific areas [21 CFR 56.108(c)].
5. The IRB failed to follow FDA regulations regarding expedited review procedures [21 CFR 56.110(b)].

Sponsors/Monitor/CRO	Citation 2012
1. Matthew Malcom, Ph.D. OTR 05/22/2012	1. Failure to prepare and submit progress reports to FDA at regular intervals and at least yearly [21 CFR 812.150(b)(5)].
2. Cardio MEMS, Inc. 06/05/2012	1. Failure to submit an accurate investigational plan in an IDE application including a written protocol describing the methodology to be used [21 CFR 812.20(b)(2) and 21 CFR 812.25(b)] 2. Failure to maintain accurate, complete, and current records of correspondence relating to an investigation [21 CFR 812.140(b)(1)] 3. Failure to provide investigators with the information they need to conduct the investigation properly [21 CFR 812.40] 4. Failure to include a complete description of the procedures to be followed in the informed consent given to subjects in the study [21 CFR 50.25(a)(1)]
3. Endogastric Solutions, Inc. 06/08/2012	1. Failure to provide investigators with the information they need to conduct the investigation properly, ensure proper monitoring of the investigation, and ensure that any reviewing IRB and FDA are promptly informed of significant new information about an investigation. [21 CFR 812.40] 2. Failure to notify FDA within 30 working days of termination of an investigation of a significant risk device. [21 CFR 812.150(b)(7)]
4. Synergy Health Concepts, Inc. 09/05/2012	1. Failure to submit an application to the FDA and obtain IRB and FDA approval prior to allowing subjects to participate in an investigation [21 CFR 812.20, 21 CFR 812.40, and 21 CFR 812.42] 2. Failure to maintain accurate, complete, and current device shipment records [21 CFR 812.140(b)(2) and 21 CFR 812.140(d)].
5. Solta Medical, Inc. 11/28/2012	1. Failure to include all appropriate elements of informed consent. [21 CFR 50.25(b)(1)] 2. Failure to provide the investigators with information needed to conduct the investigation properly and failure to ensure proper monitoring of the investigation. [21 CFR 812.40]

3. Failure to obtain signed investigator agreements and sufficient accurate financial disclosure information. [21 CFR 812.43(c) and 21 CFR Part 54]
4. Failure to maintain accurate, complete, and current device shipment and disposition records. [21 CFR 812.140(b)(2)]

Clinical Investigators	Citation 2013
1. Michael Ring, M.D. 01/14/2013	1. Failure to ensure that informed consent was obtained in accordance with 21 CFR Part 50. [21 CFR 50.25(a)(1)-(2), 21 CFR 50.20, 21 CFR 50.27(a), and 21 CFR 812.100] 2. Failure to ensure that an investigation is conducted in accordance with the signed agreement with the sponsor, the investigational plan, applicable FDA regulations, and any conditions of approval imposed by an IRB or FDA, and failure to notify the sponsor and reviewing IRB of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency within 5 working days after the emergency occurred. [21 CFR 812.100, 21 CFR 812.110(b), 21 CFR 812.150(a)(4)] 3. Failure to maintain accurate, complete, and current records relating to the investigation. [21 CFR 812.140(a)(1), (3), and (4)]
2. Mark Pinsky, M.D. 01/14/2013	1. Failure to conduct the investigation according to the signed agreement, the investigational plan, applicable FDA regulations, and any conditions of approval imposed by an Institutional Review Board (IRB) or FDA. [21 CFR 812.100 and 812.110(b)] 2. Failure to ensure that an investigation is conducted in accordance with the signed agreement, investigational plan, and applicable FDA regulations for the control of devices under investigation; and failure to maintain accurate, complete, and current records of disposition of a device. [21 CFR 812.100 and 21 CFR 812.140(a)(2)(ii-iii)] 3. Failure to properly document informed consent, to maintain accurate, complete and current records evidencing informed consent, and to conduct an investigation according to applicable FDA regulations for protecting the rights, safety, and welfare of subjects under the investigator's care. [21 CFR 50.27(a) 21 CFR 812.140(a)(3)(i), and 21 CFR 812.100] 4. Failure to maintain accurate, complete, and current records of each subject's case history and exposure to the device. [21 CFR 812.140(a)(3)]

3. Jose Joseph-Vempilly, M.D. 05/14/2013	1. You failed to ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60]. 2. You failed to maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation [21 CFR 312.62(b)].
4. Henry A. Frazer, Pharm D 06/05/2013	1. You failed to ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60]. 2. You failed to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation [21 CFR 312.62(b)].
5. Bernard H. Doft, M.D. 06/12/2013	1. You failed to ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60]. 2. You failed to maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation [21 CFR 312.62(b)]. 3. You failed to obtain informed consent in accordance with the provisions of 21 CFR part 50 [21 CFR 312.60, 21 CFR 50.20].
6. Janet K. Tillisch, M.D. 06/20/2013	1. You failed to fulfill the general responsibilities of an investigator. [21 CFR § 312.60 and Part 50]. 2. You failed to ensure that the investigation was conducted according to the signed investigator statement, the investigational plan, and the applicable regulations in order to protect the rights,

	safety, and welfare of subjects under your care. [21 CFR § 312.60]. 3. You failed to prepare and maintain adequate and accurate case histories recording all observations and other data pertinent to the investigation on each individual administered the investigational drug, including case report forms and supporting data. [21 CFR § 312.62(b)].
7. Omid Nassim, M.D. 09/03/2013	
	1. You failed to ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60]. 2. You failed to obtain Institutional Review Board (IRB) approval for changes in the research prior to implementing the changes [21 CFR 312.66].
8. Dimitri Sirakoff 09/12/2013	
	1. You failed to ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60].
9. Dennis J. Hurwitz, M.D. 09/30/2013	
	1. Failure to ensure that informed consent is obtained in accordance with 21 CFR 50.27, and failure to maintain accurate, complete and current records evidencing informed consent under 21 CFR 812.140(a)(3)(i). 2. The informed consent document lacked a description of reasonably foreseeable risks or discomforts to the subject. 21 CFR 50.25(a)(2). 3. Failure to ensure that the investigation was conducted according to the signed agreement, investigational plan, and applicable FDA regulations, and any conditions of approval imposed by an IRB or FDA. 21 CFR 812.100.
10. Sreedhar Samudrala 11/19/2013	
	1. You failed to ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60].

11. Agnes E. Ubani, M.D. 11/21/2013	1. You failed to ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60]. 2. You failed to maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation [21 CFR 312.62(b)].
12. George C. Velmahos, M.D., Ph.D. 11/29/2013	1. You failed to ensure that the investigation was conducted according to the signed investigator statement, the investigational plan, and the applicable regulations, and to protect the rights, safety, and welfare of subjects under your care. [21 CFR § 312.60]. 2. You failed to administer the drug only to subjects under the investigator's personal supervision or under the supervision of a subinvestigator responsible to the investigator. [21 C.F.R. § 312.61]. 3. You failed to prepare and maintain adequate and accurate case histories that recorded all observations and other data pertinent to the investigation on each individual administered the investigational drug. Case histories include case report forms and supporting data. [21 CFR § 312.62(b)]. 4. You failed to obtain the informed consent of each human subject to whom the drug was administered in accordance with the provisions of 21 CFR Part 50. [21 CFR § 312.60].

1. Singing River Hospital System IRB
02/01/2013

1. The IRB failed to prepare, maintain, and follow required written procedures governing the functions and operations of the IRB [21 CFR 56.108(a), 21 CFR 56.108(b), and 21 CFR 56.115(a)(6)].
2. The IRB failed to fulfill membership requirements [21 CFR 56.107].
3. The IRB failed to review proposed research at convened meetings at which a majority of the members of the IRB are present, including at least one member whose primary concerns are in nonscientific areas [21 CFR 56.108(c)].
4. The IRB failed to prepare and maintain adequate documentation of IRB activities [21 CFR 56.115(a)].

2. Agnesian
Healthcare IRB
03/25/2013

1. The IRB failed to prepare, maintain, and follow required written procedures governing the functions and operations of the IRB [21 CFR 56.108(a), 21 CFR 56.108(b), and 21 CFR 56.115(a)(6)].
2. The IRB failed to notify investigators and the institution in writing of its decision to approve or disapprove proposed research activities or of modifications required to secure IRB approval of the research activity [21 CFR 56.109(e)].
3. The IRB failed to prepare and maintain adequate documentation of IRB activities, including minutes of IRB meetings [21 CFR 56.115(a)(2)].
4. The IRB failed to ensure that basic elements of informed consent are included in the IRB-approved consent form [21 CFR 56.109(b)].
5. The IRB failed to prepare and maintain adequate documentation of IRB activities [21 CFR 56.115(a)(1) and (4)].

3. Valley Health/Winchester Medical Center IRB 05/09/2013

1. Failure to follow FDA regulations regarding the expedited review procedures. [21 CFR 56.110(b)(2)]
2. Failure to follow written procedures for conducting an initial and continuing review of research. [21 CFR 56.108(a)(1)]

4. St. Joseph Mercy Oakland IRB
08/01/2013

1. Failure to prepare, maintain, and follow written procedures for conducting initial and continuing review of research [21 CFR 56.108(a) and 56.115(a)(6)]
2. Failure to review proposed research at convened meetings at which a majority of the members of the IRB are present [21 CFR 56.108(c)]

3. Failure to report promptly to the FDA any suspension or termination of approval and failure to prepare written procedures [21 CFR 56.113 and 21 CFR 56.115(a)(6)]
4. Failure to prepare and maintain a list of IRB members identified by name, earned degree, representative capacity, and the relationship between each member and the institution [21 CFR 56.115(a)(5)]

5. Kootenai Medical Center IRB
11/15/2013

1. Failure to ensure that research involving children is in compliance with 21 CFR Part 50, Subpart D, at the time of initial review of research [21 CFR 56.111(c)]
2. Failure to notify investigators of modifications required to secure IRB approval of the research activity [21 CFR 56.109(e)]
3. Failure to review proposed research at convened meetings at which a majority of the members of the IRB are present [21 CFR 56.108(c)]
4. Failure to conduct continuing review at least annually [21 CFR 56.109(f)]
5. Failure to prepare and maintain adequate documentation of IRB activities [21 CFR 56.115(a)(2) and (5)]
6. Failure to prepare and maintain written procedures for IRB activities [21 CFR 56.115(a)(6)]

6. St. Vincent Hosp and Hlth Care
11/27/2013

1. The IRB failed to determine at the time of initial review that clinical investigations involving children were in compliance with 21 CFR part 50, subpart D, Additional Safeguards for Children in Clinical Investigations [21 CFR 56.109(h)].
2. The IRB failed to fulfill membership requirements [21 CFR 56.107].

Sponsors/Monitor/CRO Citation 2013

1. Burzynski Research Institute 12/03/2013

1. Failure to ensure proper monitoring of the investigations and failure to ensure that the investigations are conducted in accordance with the general investigational plan and protocols contained in the IND [21 CFR 312.50 and 21 CFR 312.56(a)].
2. Failure to obtain from an investigator sufficient financial information to allow the sponsor to submit complete and accurate certification or disclosure statements required under 21 CFR part 54 [21 CFR 312.53(c)(4)].

Clinical Investigators	Citation 2014
1. Ralf C. Zimmermann 02/21/2014	1. You failed to personally conduct or supervise the clinical investigations [21 CFR 312.60]. 2. You failed to obtain informed consent in accordance with the provisions of 21 CFR part 50 [21 CFR 312.60 and 21 CFR 50.20]. 3. You failed to ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60]. 4. You failed to assure that an IRB that complies with the requirements set forth in part 56 was responsible for the initial and continuing review and approval of the proposed clinical study [21 CFR 312.66].
2. Moussa C. Mansour, M.D. 03/18/2014	1. Failure to ensure that an investigation was conducted in accordance with the investigational plan. [21 CFR 812.100 and 812.110(b)] 2. Failure to maintain accurate, complete and current records regarding correspondence with the IRB [21 CFR 812.140 (a)(1)]
3. Ruemu Birhiray 04/28/2014	1. You failed to ensure that the investigations were conducted according to the investigational plan [21 CFR 312.60]. 2. You failed to maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation [21 CFR 312.62(b)].
4. Ana J. Fandino 04/30/2014	1. You failed to personally conduct or supervise the clinical investigations [21 CFR 312.60]. 2. You failed to ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60]. 3. You failed to take adequate precautions to prevent theft or diversion of an investigational drug that is subject to the Controlled Substances Act [21 CFR 312.69].

5. Michele A. Sewell, M.D. 04/30/2014

1. You failed to ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60].
2. You failed to maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. [21 CFR 312.62(b)].
3. You failed to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects [21 CFR 312.62(a)].

6. Gilbert R. Weiner 07/14/2014

1. You failed to ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60].
2. You failed to maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation [21 CFR 312.62(b)].

7. Opada Alzohalli, M.D. 07/17/2014

1. You failed to protect the rights, safety, and welfare of subjects under your care [21 CFR 312.60].
2. You failed to ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60].
3. You failed to maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation [21 CFR 312.62(b)].

8. John M. Wise, M.D. 08/12/2014

1. You failed to retain records required to be maintained under 21 CFR Part 312 for a period of two years following the date a marketing application is approved for the drug for the indication for which the drug is being investigated; or, if no application is filed or if the application is not approved for such indication, until two years after the investigation is discontinued [21 CFR 312.62(c)].

9. Keith A.
Aqua, M.D.
09/02/2014

1. You failed to ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60].

10. Louise A.
Taber, M.D.
10/09/2014

1. You failed to maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation [21 CFR 312.62(b)].
2. You failed to ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60].

1. Mercy Hospital Medical Center IRB
01/10/2014

1. Failure to follow written procedures for conducting an initial and continuing review of research. [21 CFR 56.108(a)(1)]
2. Failure to review proposed research at convened meetings at which a majority of the members of the IRB are present. [21 CFR 56.108(c)]
3. Failure to prepare and maintain required written procedures governing the function and operations of the IRB. [21 CFR 21 CFR 56.115(a)(6) and 56.108(a)(1)-(2)]
4. Failure to retain IRB records for at least 3 years after completion of the research. [21 CFR 56.115(b)]
5. Failure to prepare and maintain adequate documentation of IRB activities including minutes of IRB meetings that are of sufficient detail to show the actions taken at the meeting and the vote on these actions. [21 CFR 56.115(a)(2)]

2. Advanced Interventional Pain CTR IRB 02/07/2014

1. Failure to have adequate written procedures governing the functions and operations of the IRB. [21 CFR 56.115(a)(6)]
2. Failure to require that information given to subjects as part of informed consent is in accordance with 50.25. [21 CFR 56.109(b)]
3. Failure to ensure that no IRB member participated in the IRB's initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB. [21 CFR 56.107(e)]
4. Failure to prepare and maintain adequate documentation of IRB activities. [21 CFR 56.115(a)(1), (a)(2), and (a)(4)]

Sponsors/Monitor/CRO Citation 2014

1. Advanced Magnetic Research Institute International LLC 01/16/2014

1. Failure to obtain Institutional Review Board approval of the investigation [21 CFR 812.2(b)(1)(ii)]
2. Failure to comply with FDA regulations that prohibit promotion of an investigational device until after FDA has approved the device for commercial distribution and representation that an investigational device is safe or effective for the purposes for which it is being investigated [21 CFR 812.2(b)(1)(vii)].
3. Failure to maintain required records under § 812.140(b)(4) and make the reports required under § 812.150(b)(1) through (3) and (5) through (10) [21 CFR 812.2(b)(1)(v].

2. Impladent Ltd.
03/28/2014

1. Failure to submit an application to the FDA and obtain FDA and Institutional Review Board (IRB) approval prior to allowing subjects to participate in an investigation [21 CFR 812.20, 21 CFR 812.40 and 21 CFR 812.42].
2. Failure to ensure that the requirements for obtaining informed consent were met [21 CFR 50.20, 21 CFR 50.25(a)(4), 21 CFR 50.27(a)].
3. Failure to obtain signed agreements from participating investigators and failure to maintain accurate, complete and current records of product disposition [21 CFR 812.43(c), 21 CFR 812.140(b)(2)].

3. AMKS Time Release Lab, LLC 04/10/2014

1. Failure to submit an IND application for the conduct of clinical investigations with an investigational new drug that is subject to 21 CFR 312.2(a) [21 CFR 312.20(a) and 312.40(a)].
2. Failure to ensure proper monitoring of the investigations and failure to ensure that the investigations are conducted in accordance with the general investigational plan and protocols contained in the IND [21 CFR 312.50 and 312.56(a)].
3. Failure to maintain adequate records showing the receipt, shipment, or other disposition of the investigational drug [21 CFR 312.57(a)].

4. Rogerio Lobo, M.D.
04/18/2014

1. Failure to ensure proper monitoring of the investigation and failure to ensure that the investigation is conducted in accordance with the general investigational plan and protocols contained in the IND [21 CFR 312.50 and 312.56(a)].

5. Brava, LLC
08/28/2014

1. Failure to ensure proper monitoring of the investigation and to promptly inform the IRB and FDA of significant new information about an investigation. [21 CFR 812.40 and 21 CFR 812.46(a)]
2. Failure to prepare and submit complete, accurate, and timely reports regarding withdrawal of an IRB's approval of an investigation, informed consent, and other requested information about the investigation. [21 CFR 812.150(b)(2), 21 CFR 812.150(b)(8), and 21 CFR 812.150(b)(10)].

Clinical Investigators	Citation 2015
1. Binh Bui-Nguyen, M.D. 05/04/2015	1. You failed to ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60].
2. Howard M. Gross, M.D. 06/29/2015	1. You failed to ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60]. 2. You failed to maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation [21 CFR 312.62(b)].

Sponsors/Monitor/CRO	Citation 2015
1. CXL-USA, LLC 04/01/2015	1. Failure to submit an IND for the conduct of clinical investigations with an investigational new drug that is subject to 21 CFR 312.2(a) [21 CFR 312.20(a), (b) and 312.40(a), (b)]. 2. Failure to ensure proper monitoring of the clinical investigations [21 CFR 312.50; 312.56(a)].
2. AB Science 06/16/2015	1. Failure to ensure proper monitoring of the investigations and failure to ensure that the investigations are conducted in accordance with the general investigational plan and protocols contained in the IND [21 CFR 312.50 and 312.56(a)].

APPENDICE B

TOTALS FOR TOP CITATION VIOLATIONS FOR YEARS 2010-2015

1) Failure to follow Investigational Plan 21 CFR 312.60, 21 CFR 812.100, 21 CFR 812.110(b), 21 CFR 812.150(a)(4): 64

2) Inadequate Case History 21 CFR 312.62(b), 21 CFR 812.140(a)(3): 33

3) Informed Consent 21 CFR 50, 21 CFR 312.60, 21 CFR 50.20, 21 CFR 50.27(a), and 21 CFR 812.100: 36

4) Failure to have or follow adequate written procedures governing the functions and operations of the IRB 21 CFR 56.108(a), (b) and c, 21 CFR 56.115(a), 21 CFR 56.109(e): 26

5) Failure to prepare and maintain adequate documentation of IRB activities, including minutes of IRB meeting 21 CFR 56.115(a)(1), 21 CFR 56.115(a)(2), 21 CFR 56.115(a)(4) and (5): 23

6) Composition of IRB issues 21 CFR 56.107(d) and (e), 21 CFR 56.108(c): 18

7) Failure to maintain adequate records showing the receipt, shipment or other disposition of an investigational drug or device 21 CFR 312.57(a), 21 CFR 812.140(b)(2), 21 CFR 812.140(d): 18

8) Failure to ensure proper monitoring of the investigation 21 CFR 312.50, 21 CFR 812.40, 21 CFR 312.56(a): 13

9) Failure to submit an application to the FDA and/or IRB and obtain approval 21 CFR 812.20(a)(1) and (a)(2), 21 CFR 812.40, 21 CFR 812.42, 21 CFR 312.20, 312.30: 31

10) Failure to obtain signed investigator agreements 21 CFR 812.43(c)(5), 21 CFR Part 54: 7

APPENDICE C

EMAIL RECRUITMENT AND CONSENT LETTER

September 27th, 2015

Dear Compliance and Quality Assurance Professional:

I am a graduate student under the direction of Professor David W. Mullis in the Department of Regulatory Affairs/School of Pharmacy at The University of Georgia. I would like to invite you to participate in a research study entitled *Establishing a Quality Management System for a Biomedical Academic Institution that Performs Clinical Research in Compliance with Good Clinical Practices* that is being conducted for my graduate thesis requirement. The purpose of this study is to validate common FDA warning letter citations issued for GCP non-compliance in order to focus on certain areas of the quality management system for implementation in a biomedical academic institution. It is hoped that from these results that the following research questions will be answered:

What are the most common GCP violations issued by the FDA?

Are there areas of GCPs that should be concentrated on more than others in developing a Quality Management System?

Are there challenges of implementing a GCP/Quality Management System in an academic biomedical institution?

Inclusion criteria: Quality Assurance and regulatory compliance professionals over the age of 18 that work for academic biomedical institutions.

Your participation will involve taking a short survey about GCP and Quality Management Systems and should only take about 15-20 minutes to complete. Your involvement in the study is voluntary, and you may choose not to participate or to stop at any time without penalty or loss of benefits to which you are otherwise entitled. If you decide to stop or withdraw from the study, the information/data collected from or about you up to the point of your withdrawal will be kept as part of the study and may continue to be analyzed. This survey is confidential.

The results of the research study may be published, and your name or any identifying information will not be collected or used from this confidential survey. In fact, the published results will be presented in summary form only.

The findings from this project may provide information on implementing a quality management systems in clinical research and FDA warning letter trends for GCPs. There are no known risks or discomforts associated with this research.

If you have any questions about this research project, please feel free to call me at (678) 575-9514 or send an e-mail to kwinn@uga.edu. Questions or concerns about your rights as a research participant should be directed to The Chairperson, University of Georgia Institutional Review Board, telephone (706) 542-3199; email address irb@uga.edu.

By clicking on the link to the survey on Survey Monkey, you are agreeing to participate in the above described research project.

If you would like to opt out of further contact about this research, please contact Kelly Winn at kwinn@uga.edu with the response “opt out”.

Thank you for your consideration! Please keep this letter for your records.

Sincerely,

Kelly Winn

https://www.surveymonkey.com/r/QMS_GCP

APPENDICE D

SURVEY QUESTIONS

Survey Questions:

1) Does your academic biomedical institution have a medical school? If not, what does your academic biomedical institution specialize in? (engineering, nursing, etc.)

2) Does your institution have its own IRB or use a commercial IRB?

3) How many IRB's does your academic institution have?

4) What majority type of clinical research does your academic biomedical institution perform? (Pharmaceutical, Medical Device, Biologics, Combination Product, etc.)

5) Does your academic biomedical institute require the PI to be the sponsor-Investigator with the reliance of the clinical research on the PI and not the institution for clinical trials? (due to the lack of direct academic institutional issued FDA warning letters in the last 5+ years)

6) During FDA inspection of your institution and clinical trial research, what patterns do you see in the FDA's GCP enforcement activities?

7) What FDA priorities and inspection red flags do you feel almost always lead to GCP violations?

8) How many regulatory staff members does your institution have?

9) Are regulatory consultants ever used for your institute's clinical trials?

10) Does your institution have a Quality Management System in place?

11) What areas of a Quality Management System would you suggest to concentrate on while establishing a QMS for an academic biomedical institution that performs clinical trial research?

12) Do your institution's Quality Management System incorporate a TMS or Six Sigma approach? If so, please explain.

13) What characteristics do you think that a successful Quality Management System consists of?

14) How do you promote the regulatory process to faculty and students, and related departments on campus? What efforts have you found to be most successful? What recommendations do you have for colleagues in academic biomedical institutions?

APPENDICE E

TOP 50 NIH FUNDED BIOMEDICAL ACADEMIC INSTITUTIONS

Organization	City	State	Country	Awards	Funding
JOHNS HOPKINS UNIVERSITY	BALTIMORE	MD	UNITED STATES	1,175	$552,916,420
UNIVERSITY OF CALIFORNIA, SAN FRANCISCO	SAN FRANCISCO	CA	UNITED STATES	1,172	$532,472,444
UNIVERSITY OF PENNSYLVANIA	PHILADELPHIA	PA	UNITED STATES	1,049	$437,142,838
UNIVERSITY OF MICHIGAN	ANN ARBOR	MI	UNITED STATES	1,019	$430,652,214
UNIVERSITY OF PITTSBURGH AT PITTSBURGH	PITTSBURGH	PA	UNITED STATES	913	$411,576,696
UNIVERSITY OF WASHINGTON	SEATTLE	WA	UNITED STATES	860	$404,235,156
STANFORD UNIVERSITY	STANFORD	CA	UNITED STATES	877	$397,312,142
WASHINGTON UNIVERSITY	SAINT LOUIS	MO	UNITED STATES	800	$368,176,402
UNIV OF NORTH CAROLINA CHAPEL HILL	CHAPEL HILL	NC	UNITED STATES	840	$367,090,820
UNIVERSITY OF CALIFORNIA SAN DIEGO	LA JOLLA	CA	UNITED STATES	807	$359,367,330
YALE UNIVERSITY	NEW HAVEN	CT	UNITED STATES	836	$344,992,419
UNIVERSITY OF CALIFORNIA LOS ANGELES	LOS ANGELES	CA	UNITED STATES	827	$341,760,043
DUKE UNIVERSITY	DURHAM	NC	UNITED STATES	694	$322,364,996
COLUMBIA UNIVERSITY HEALTH SCIENCES	NEW YORK	NY	UNITED STATES	753	$303,604,743
VANDERBILT UNIVERSITY	NASHVILLE	TN	UNITED STATES	715	$286,528,486
UNIVERSITY OF WISCONSIN-MADISON	MADISON	WI	UNITED STATES	598	$264,496,165
EMORY UNIVERSITY	ATLANTA	GA	UNITED STATES	632	$263,005,801
ICAHN SCHOOL OF MEDICINE AT MOUNT SINAI	NEW YORK	NY	UNITED STATES	487	$232,489,056
UNIVERSITY OF MINNESOTA	MINNEAPOLIS	MN	UNITED STATES	505	$224,829,480
FRED HUTCHINSON CANCER RESEARCH CENTER	SEATTLE	WA	UNITED STATES	254	$224,596,305

Organization	City	State	Country	Awards	Funding
UNIVERSITY OF ALABAMA AT BIRMINGHAM	BIRMINGHAM	AL	UNITED STATES	455	$213,766,679
NORTHWESTERN UNIVERSITY AT CHICAGO	CHICAGO	IL	UNITED STATES	488	$207,413,097
BAYLOR COLLEGE OF MEDICINE	HOUSTON	TX	UNITED STATES	430	$204,140,842
UNIVERSITY OF COLORADO DENVER	AURORA	CO	UNITED STATES	504	$191,934,593
OREGON HEALTH & SCIENCE UNIVERSITY	PORTLAND	OR	UNITED STATES	414	$189,364,591
UNIVERSITY OF CALIFORNIA AT DAVIS	DAVIS	CA	UNITED STATES	416	$182,574,944
HARVARD MEDICAL SCHOOL	BOSTON	MA	UNITED STATES	363	$176,414,178
NEW YORK UNIVERSITY SCHOOL OF MEDICINE	NEW YORK	NY	UNITED STATES	384	$173,131,698
UNIVERSITY OF SOUTHERN CALIFORNIA	LOS ANGELES	CA	UNITED STATES	354	$169,361,832
SCRIPPS RESEARCH INSTITUTE	LA JOLLA	CA	UNITED STATES	268	$165,580,680
UNIVERSITY OF CHICAGO	CHICAGO	IL	UNITED STATES	407	$162,395,009
UT SOUTHWESTERN MEDICAL CENTER	DALLAS	TX	UNITED STATES	424	$157,825,095
CASE WESTERN RESERVE UNIVERSITY	CLEVELAND	OH	UNITED STATES	347	$154,712,582
UNIVERSITY OF ROCHESTER	ROCHESTER	NY	UNITED STATES	348	$135,633,391
UNIVERSITY OF IOWA	IOWA CITY	IA	UNITED STATES	309	$134,384,449
OHIO STATE UNIVERSITY	COLUMBUS	OH	UNITED STATES	347	$127,460,836
UNIVERSITY OF FLORIDA	GAINESVILLE	FL	UNITED STATES	321	$126,013,557
UNIV OF MASSACHUSETTS MED SCH WORCESTER	WORCESTER	MA	UNITED STATES	311	$124,386,204
HARVARD SCHOOL OF PUBLIC HEALTH	BOSTON	MA	UNITED STATES	178	$120,160,210
UNIVERSITY OF UTAH	SALT LAKE CITY	UT	UNITED STATES	339	$119,510,249
UNIVERSITY OF MARYLAND BALTIMORE	BALTIMORE	MD	UNITED STATES	300	$118,117,470
SLOAN-KETTERING INST CAN RESEARCH	NEW YORK	NY	UNITED STATES	253	$117,195,796
INDIANA UNIV-PURDUE UNIV AT INDIANAPOLIS	INDIANAPOLIS	IN	UNITED STATES	317	$116,049,698
WEILL MEDICAL COLL OF CORNELL UNIV	NEW YORK	NY	UNITED STATES	263	$114,698,446
BOSTON UNIVERSITY MEDICAL CAMPUS	BOSTON	MA	UNITED STATES	224	$113,485,249

Organization	City	State	Country	Awards	Funding
UNIVERSITY OF CALIFORNIA BERKELEY	BERKELEY	CA	UNITED STATES	339	$111,411,913
UNIVERSITY OF VIRGINIA	CHARLOTTESVILLE	VA	UNITED STATES	300	$111,393,802
UNIVERSITY OF TX MD ANDERSON CAN CTR	HOUSTON	TX	UNITED STATES	254	$110,810,892
UNIVERSITY OF CALIFORNIA-IRVINE	IRVINE	CA	UNITED STATES	275	$101,011,205
UNIVERSITY OF ILLINOIS AT CHICAGO	CHICAGO	IL	UNITED STATES	265	$95,902,2

APPENDICE F

STUDY 00002646 UGA IRB APPROVAL

Phone 706-542-3199

APPROVAL OF PROTOCOL

September 24, 2015

Dear David Mullis:

On 9/24/2015, the IRB reviewed the following submission:

Type of Review: Initial Study
Title of Study: Establishing a Quality Management System for a Biomedical Academic Institution that Performs Clinical Research in Compliance with Good Clinical Practices

Investigator: David Mullis
IRB ID: STUDY00002646
Funding: None
Grant ID: None
The IRB approved the protocol from 9/24/2015.

In conducting this study, you are required to follow the requirements listed in the Investigator Manual (HRP-103).

Sincerely,
Adam Goodie, Ph.D.
University of Georgia
Institutional Review Board Chairperson
Office of the Vice President for Research
Institutional Review Board