Converting from Paper-Based to Electronic Data Capture and Record Keeping in Clinical Trial Management: Benefits, Challenges and Practical Considerations

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Abstract

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Clinical research has lagged behind the technological advance of other healthcare fields. Most investigational sites depend on a paper-based data capture and record retention system. This practicum project examined the various benefits and challenges of electronic data capture and electronic record keeping systems. Electronic systems can improve data integrity, reduce trial cost and increase efficiency in the course of a clinical trial. However, electronic systems can also pose some challenges, including implementation and training cost, decreased productivity, and issues with data security and health record privacy. This project discussed some practical considerations for investigational sites transitioning to electronic systems. These aims were accomplished by review of the literature and consulting investigational sites through an email questionnaire.
CONVERTING FROM PAPER-BASED TO ELECTRONIC DATA CAPTURE AND RECORD KEEPING IN CLINICAL TRIAL MANAGEMENT: BENEFITS, CHALLENGES AND PRACTICAL CONSIDERATIONS

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CONVERTING FROM PAPER-BASED TO ELECTRONIC DATA CAPTURE AND RECORD KEEPING IN CLINICAL TRIAL MANAGEMENT: BENEFITS, CHALLENGES AND PRACTICAL CONSIDERATIONS

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CHAPTER 1

INTRODUCTION

As a field of healthcare science, clinical trial management focuses on determining the safety and efficacy of experimental medical interventions. This includes both investigational drugs and devices. Clinical research entails conducting clinical trials, investigations of prospective interventions on human subjects. Clinical research serves as a vital component of global healthcare. The field helps improve and advance medical care through discovery and vindication of novel treatments and interventions. Clinical research has emerged as perhaps the most innovative and fastest growing field of global healthcare. Since the execution of the first formal clinical study, a randomized control trial of streptomycin in pulmonary tuberculosis performed in the United Kingdom in 1946, clinical research has evolved and proliferated in profound ways. According to a market research report conducted by JZMed Inc., the value of the global clinical trial market surpassed $20 billion in 2010. The same report projects that this figure will top $38 billion in 2015 and likely reach more than $64 billion by the year 2020 (Figure 1).
Figure 1: Global CRO Revenue: Data compiled from The New Trends of Global Clinical Development Outsourcing Market, 2010-2020.  
*CRO – contract research organization

Drug development progresses in successive phases. In the United States, each new investigational product (IP) discovered in the process of research and development (R & D) must first undergo preclinical research during which experimental evidence in a laboratory setting attempts to support the underlying research hypothesis. The preclinical phase investigates an IP's chemistry, pharmacology and toxicology. The entire process of R & D and preclinical investigation usually lasts 3-6 years. After this, the sponsor can submit the drug to the Food and Drug Administration (FDA) for approval in the course of clinical trials through an Investigational New Drug Application (IND), also known as Form FDA 1571. The sponsor can begin conducting clinical research 30 days after the FDA has received their IND. The term “clinical trial” can imply Phase I, II, or III studies, each with different scopes and end goals. This process usually lasts 6-7 years, after
which an IP is eligible for approval by the FDA. Many IP’s also undergo Phase IV clinical trials.

Phase I trials enroll healthy subjects on a small scale and seek to demonstrate the safety of an IP in regard to dosing and side effects. A Phase I trial usually includes 20-80 subjects and addresses issues like pharmacokinetic testing, side effects and maximum tolerated dosing. If the IP demonstrates safe usage for human subjects, the drug can progress to Phase II. Phase II studies target individuals that could benefit from the intervention, and as a result, seek to establish the efficacy of an IP as well as its safety. Phase II trials involve several hundred subjects at multiple sites.

After a successful Phase II trial, an IP can continue to Phase III. Phase III trials hope to demonstrate that a prospective intervention, proved both safe and efficacious on a small scale, will exhibit similar results when tested on a large-scale target population. Phase III trials often include thousands or tens of thousands of subjects, depending on the goals of the sponsor, enrolled in hundreds of sites around the world. A Phase III trial involves an overall risk-benefit analysis, utilizing a vast body of data to determine if an IP’s benefits outweigh its risks for most patients. If an IP progresses through Phase III, it may be eligible for FDA approval. Even after a successful Phase III trial, it can take another six months to two years for a new drug to reach market, accounting for the FDA review process and manufacturing considerations. Cumulatively, it takes 10 – 15 years for an IP to reach market. Figure 2 depicts the approximate time apportionment for each phase from discovery to market for a new drug. Though not depicted in Figure 2, many
new drugs also undergo Phase IV research. Phase IV clinical trials seek to obtain additional information about an IP after it has been approved or marketed. Phase IV trials pursue supplementary data regarding the real-world effectiveness of an approved IP in terms of long term use, effect in various populations, etc. Phase IV trials enroll subjects in the target population, though the size of the trial varies.

![Approximate percentage of time required for each phase of drug development](image)

**Figure 2:** Approximate percentage of time required for each phase of drug development: Data compiled from “Faster evaluation of vital drugs” (1995) [58]. Does not include Phase IV (post market) research.

Two parties cooperate to conduct clinical trials: the investigational site and the sponsor. At the investigational site, a qualified medical professional serves as the study’s principal investigator (PI) and bears responsibility for study conduct as the leader of the clinical research team. The PI makes all decisions regarding patient treatment and medical interventions of any kind. On a practical level, the clinical research coordinator (CRC) acts as a liaison between the site and the sponsor, and
performs most trial-related tasks including patient visits, tests, procedures, source documentation and record keeping, oftentimes aided by sub-investigators. The sponsor funds and monitors the study, communicates with the FDA and enlists investigational sites to conduct their clinical trial. Sponsors often contract other companies, known as contract research organizations (CROs), to perform data management, statistical analysis, clinical operations, and other study-related tasks. A clinical research associate (CRA), commonly referred to as a “monitor”, represents the sponsor to verify source documentation and ensure site compliance with the study protocol, as well as federal regulations and good clinical practice (GCP).

Regulation serves as an essential aspect of maintaining the safety and general wellbeing of subjects enrolled in clinical trials. Initially formed in 1906, the FDA regulates all clinical research involving human subjects in the United States. The Center for Drug Evaluation and Research functions as the branch of the FDA that communicates with prospective trial sponsors and approves both new and ongoing trials. Moreover, each investigational site reports to an institutional review board (IRB), a designated group of people responsible for reviewing and approving every aspect of research involving human subjects at their assigned investigational site. The IRB primarily corresponds with the CRC to ensure subject safety at every stage of a clinical trial.

Conducting clinical trials requires copious amounts of data management and record keeping. Clinical trials require the maintenance and storage of the following regulatory documents: study protocol and amendments, training, monitoring and
authority delegation logs, an IP accountability log, adverse event and serious adverse event (AE/SAE) reporting, documentation for all correspondence between site and sponsor, and a multitude of other documents. Patient records consist of source documents for every visit, medical records, and a list of concomitant medications. All of this documentation continues to be stored after the study ends, oftentimes for decades afterwards. Traditionally, all clinical trial record keeping has been paper-based.

However, technological advances have spurred a shift toward electronic data capture (ED) and electronic record keeping in the medical field at large. Clinical research has shifted in the same direction, but many sites still employ paper-based systems. The University of North Texas Health Science Center’s (UNTHSC) Office of Clinical Trials (OCT) still depends primarily on a paper-based record keeping system. This practicum report demonstrated the benefits and challenges of converting to an electronic-based record keeping system, and described some practical considerations for implementing such a system relevant to OCT and investigational sites generally.

**SALIENT LITERATURE REVIEW**

Electronic health records, or EHR, have become an integral component of western medical care. EHRs store patient information regarding demographics, medical history, current medications and allergies, vital signs, prior treatment and procedure records, and an array of other medically relevant information. Storing these records electronically reduces cost, and increases productivity and efficiency.
EHR use has become virtually ubiquitous in the western medical paradigm, benefitting both patients and physicians.

Following the technological tide of the late 20th century, the push for electronic-based record systems began in the 1970s. Dr. Lawrence Reed developed the concept of problem-oriented medical records in the late 1960s, as well as the SOAP (subjective, objective, assessment, plan) method of documentation, to address the tension created between the multiplicity of problems faced by physicians and the necessity of a single-minded focus on each patient. Within the next decade, Dr. Reed’s system evolved to incorporate principles of electronic information retrieval, the most primitive form of the modern EHR. Concurrent to Dr. Reed’s innovations, the Regenstrief Institute developed the first electronic medical records system in 1972. In spite of these advances, Dr. Reed’s novel philosophies struggled to achieve popular recognition until the early 1990s. In 1991, the Institute of Medicine recommended that all physicians incorporate computers into their practice to improve patient care. Western medicine saw the widespread implementation of the EHR take root in the early 2000s.

In the same way that modern medicine relies upon an extensive record-keeping system, clinical research requires exhaustive documentation and employs complex data-capturing conventions. The benefits of EDC and electronic-based record keeping in clinical trials are well documented, exhibiting many of the same benefits as the integration of EHR in clinical practice. The three areas that can benefit the most from electronic record keeping and data capture systems are source documentation, regulatory documentation, and record storage and archiving.
Paper-based data capture involved with source documentation suffers from inaccuracy resulting from transcription mistakes, missed data points and miscellaneous human error. Regulatory documentation includes an extensive body of records that pose logistical challenges with organization and storage. This creates problems regarding document turnaround time and trial efficiency. Additionally, the FDA requires investigators to retain all records from a clinical trial, including both source and regulatory documentation, for a minimum of two years after the investigational product’s last marketing action. This may necessitate decades of record retention and significant financial obligation for paper-based documentation.

Though EHR systems function as the standard practice of modern healthcare, clinical trials have failed to keep pace with the technological advance of other healthcare fields. Clinical research did not even begin to incorporate electronic systems for record storage and data capture until the 1990s. These systems were often archaic and impractical, requiring specialized devices beyond the common personal computer to function. However, modern day EDC and electronic record storage systems offer numerous potential benefits to investigational sites, sponsors and contract research organizations (CROs), including cost, efficiency, data accuracy, potential for increased enrollment and ease of communication.

In spite of these possible gains, many research sites have faced difficulty implementing EDC and record storage systems. Some obstacles include the complexity of regulatory documentation, staff compliance, unclear role boundaries of site personnel, IRB considerations and the necessity of paper-based
documentation for some components of a clinical trial. However, sites that can overcome the initial hurdle of implementation stand to benefit significantly. Moreover, clinical research as a field may profit in equally significant ways, particularly in areas like enrollment and general trial efficiency.

DEFINING KEY TERMS

*Case report form (CRF):* a printed, optical, or electronic record of information that an investigational site reports to the sponsor for each trial subject, specified by the study protocol.

*Clinical research associate (CRA):* a person employed by a sponsor who oversees the progress of investigational sites participating in a clinical trial; their duties include source data verification, planning and initiation of a trial at each investigational site, and ensuring study protocol adherence, more commonly called a “monitor.”

*Clinical research coordinator (CRC):* a person employed by the investigational site to conduct administrative tasks on behalf of the principal investigator, acting as a liaison between the investigational site and the sponsor; their duties include data capture, administration of investigational product, and communication with both the sponsor and the Institutional Review Board.

*Data capture:* the process and method employed by investigators to record subject source data.

*Data element:* a single value observed for a subject in a clinical trial and recorded on a source document through paper-based or electronic data capture; examples include birth date, height, weight, blood pressure, and other relevant clinical
observations depending on the nature of the trial, also called a “data point” or “data value”.

*Electronic health record (EHR):* a digital repository of patient medical data that is stored, exchanged and accessed on a specified software platform in a secure manner by multiple authorized personnel, often referred to synonymously as an electronic medical record (EMR).

*Electronic record:* in the context of a clinical trial, any combination of text, graphics, data, audio, pictorial, or other information represented in digital form that is created, modified, maintained, archived, retrieved, or distributed by a computer system.

*Informed consent:* the ongoing process of exchanging information between the investigator and clinical trial participant, including all information about the study, potential risks and benefits of study participation, and alternative treatment options, so that the subject can make an informed decision to participate in, or continue participating in, the study.

*Institutional Review Board (IRB):* an FDA-mandated committee of persons responsible for approving, monitoring, and reviewing prospective and ongoing clinical trials with a focus on patient safety.

*Investigational product (IP):* a drug, device or biologic product undergoing research in a clinical trial to determine its safety and efficacy for human subjects in lieu of FDA approval.
**Investigational site:** a research team consisting of a principal investigator and various sub-investigators contracted by a sponsor company to conduct and manage a clinical trial in their patient population.

**Principal Investigator (PI):** a medically qualified professional, often a physician, who bears responsibility for the scientific and technical direction of a clinical trial conducted at an investigational site.

**Protocol:** the written description of all aspects and specifications of a clinical trial compiled by the sponsor and including the study’s objectives, design, methods, and any other information relevant to trial conduct; often amended by the sponsor throughout the course of the trial.

**Recruitment:** the context-dependent process by which investigational sites recruit subjects to participate in a clinical trial, also called “enrollment”.

**Source data verification (SDV):** the process by which a clinical research associate, or “monitor”, verifies the overall integrity of trial data recorded in source documents or case report forms.

**Source document:** the original record of information recorded concerning clinical findings, observations, or other activities in a clinical trial used for the reconstruction and evaluation of the trial; a case report form may serve as a source document in some instances.

**Sponsor:** the organization or person who oversees, and often funds, a clinical trial and bears responsibility for analyzing the study data.
CHAPTER 2

STATED OBJECTIVES

Clinical research has lagged behind the technological curve set by the rest of the healthcare industry, which has steadily transitioned to electronic record keeping systems. UNTHSC’s Office of Clinical Trials still depends primarily on a paper-based record keeping system. Electronic record keeping offers numerous pragmatic benefits. Effecting such a system can potentially save money, time and resources, increase productivity and efficiency both for CRCs and monitors, improve cooperation between CRCs working in the same professional setting, and decrease data point errors. The areas of clinical research that suffer the most from the current standard, and may therefore benefit the most from technological updating, are regulatory documentation, source documentation during a study, and record storage after completion of a trial. This practicum project demonstrated both the qualitative and quantitative benefits of utilizing an electronic record keeping and data capture system in clinical trials.

Despite the numerous potential benefits, many research sites cannot overcome the initial hurdles of implementing a new system. These obstacles include the high acquisition costs of electronic systems and the temporary loss of productivity due to the time and difficulty of learning a new system. This project described some of those challenges and discussed practical considerations for transitioning from paper-based to electronic systems for both OCT and clinical research sites generally. At OCT, this primarily entailed reorganizing the shared
drive accessible by all site staff, optimizing it to increase ease of use, and instituting initiatives to increase compliance site-wide.

MATERIALS AND METHODS

This practicum project reviewed salient literature to quantitatively assess the benefits of EDC and electronic record keeping in regard to data integrity, cost, productivity, and efficiency when compared to paper-based record keeping. This was accomplished by searching PubMed and Google Scholar with permutations of the keywords “clinical”, “research”, “trials”, “electronic”, “medical”, “health”, “records”, “record-keeping”, and “data capture”. Additionally, this project qualitatively assessed the benefits and challenges of EDC and electronic record keeping in regard to cost, productivity, efficiency, cooperation among coworker CRCs, and data security by reviewing relevant literature and interviewing CRCs and research professionals at OCT and other research sites through an email questionnaire (see Appendix B).

This project also discussed practical considerations for site transition from paper-based record keeping and data capture to electronic-based through the aforementioned interview process, giving particular focus to research sites that have successfully implemented some kind of electronic record keeping system. Finally, this project examined ways to improve the current OCT record keeping system in regard to the organization and use of the shared drive with particular emphasis on regulatory documentation and patient source materials for active trials.
SIGNIFICANCE

The healthcare industry is experiencing a “big data” revolution. In the minds of healthcare professionals, this means that the exorbitant amount of data management necessary for patient care has outstripped our current methods of analyzing and adapting that information in useful ways. Traditionally, a patient’s health record has included a detailed medical history, concomitant medications and dosing, family history, laboratory test results, etc. This body of information swelled significantly with the technological advance of medical imaging and promises to increase exponentially more as genomic sequencing becomes common practice in western medicine. As an example, between clinical text and imaging data Beth Israel Deaconess Medical Center in Boston, Massachusetts currently generates 20 terabytes of new health record data per year for a 250,000 active patient population. Following the current trend, the volume of data storage necessary for healthcare sites to maintain will continue to escalate considerably with the advent of new technologies.

Quality patient care now requires a complex and costly system of analytics to comprehensively process and interpret this vast body of information in meaningful ways. Information analytics on this scale has only been made possible through the rise of the EHR. In 2009, the Health Information Technology for Economic and Clinical Health (HITECH) Act authorized incentives to physicians willing to adopt EHR methods. According to a 2014 data brief from the Center for Disease Control (CDC), the percentage of office-based physicians who employed any kind of EHR methodology in their practice increased from 18.2% in 2001 to 48.3% in 2009 and
78.4% in 2013. From another viewpoint, office-based physician use of a holistic EHR system in their practice rose dramatically from 10.5% in 2006 to 48.1% in 2013. Figure 3 represents this data. The growing need for complex information analytics will soon necessitate systemic EHR use in every field of the healthcare industry.

![Percentage of Office-based Physicians with EHR Systems](image)

**Figure 3**: Percentage of office-based physicians with EHR systems: Compiled from Chun-Ju et al, 2001-2013. *EHR – electronic health record

The field of clinical trial management has experienced a similar groundswell of electronic-based system implementation in the past decade. In 2005, only 24% of trials incorporated EDC in their study management system. Prevalence of EDC system use rose dramatically in the following years. In 2012, 75% of clinical trials were likely to use EDC. This represents a yearly increase of 15% of clinical trials converting from traditional paper-based data capture to EDC. This trend will continue throughout the next decade of clinical research as EDC and electronic
record storage systems continue to improve in efficiency, ease of use, interoperability and cost-effectiveness.
CHAPTER 3

RESULTS AND DISCUSSION

Twelve investigational sites received the investigational site email questionnaire (Appendix B). Six sites responded: The Center for Cancer and Blood Disorders, University of Illinois, Texas Health Ben Hogan Sports Medicine, Baylor Scott & White Health Center for Clinical Effectiveness, ACRC Trials, and University of North Texas Health Science Center Office of Clinical Trials. With two exceptions, exactly one staff member responded to the questionnaire on behalf of their site (two staff members responded from Baylor Scott & White, and The Center for Cancer and Blood Disorders reported a conglomerate response from many staff members). Responses from the investigational sites were compared to salient research regarding data integrity, cost and workflow metrics related to the use of EDC and electronic record keeping.

Benefits

The clearest, most well documented and easily quantifiable benefit to incorporating electronic systems into clinical research is an improvement in “data integrity” \(^9\ 12\ 15\ 17\ 24\). Data collection and abstraction serves as the lifeblood of a successful clinical trial. In the course of conducting research, the CRC records original data points from subject testimony to create a source document. This data is then transcribed to a case report form (CRF) \(^7\). In some cases, the investigator records original data points directly to the CRF, in which case the CRF would
function as the source document. A high degree of data integrity is necessary for both the reliability of the trial in regard to IP viability and in reducing unnecessary cost associated with correcting data errors.

The idea of data integrity is multifaceted and speaks to the reduction of numerous types of data errors. Aspects of data integrity addressed by researchers can be separated into five discrete spheres: completeness, correctness, concordance, plausibility and currency. Completeness measures the degree to which all necessary data has been recorded and accounted for. Correctness requires that complete data is also true and accurate. Concordance speaks to consistency and agreement of data between two sources; in clinical research, these two sources are the CRF and source document. Plausibility ensures that the data makes logical sense when compared to source documents or other patient health records. Along the same line, currency addresses the timeliness and general relevance of plausible data.

EDC has been shown to reduce or eliminate multiple types of data errors in each of these spheres within the general idea of data integrity. The majority of data errors result from human fault in the course of data collection and transcription, with transcription errors occurring most commonly. Research investigating the various types of errors that result from poor data collection and transcription primarily addresses four varieties of error: lack of a source document, mismatched data between the source document and CRF, missing data points in the CRF, and data points that were redacted or modified on the source document with no date and initial to verify the change. Some less common errors mentioned
in the literature include multiple source documents for the same data point and illegible writing on either the source document or CRF 9 12 24.

EDC implementation has been shown to reduce most of these types of data error. In a retrospective data audit of 24 research sites, Nahm et al. (2008) compared data error rates for trials employing traditional paper-based data capture and those using EDC 12. In a large-scale analysis of 10,000 data points for each method, the researchers discovered 976 errors in trials using traditional data capture methods compared to only 14 in those using EDC. This equates to a 9.8% overall error rate for trial data using paper-based data capture and only 0.2% for EDC-capable trials 12. In a similar experiment, Pollard (2014) conducted a retrospective and prospective data audit at the Ben Hogan Sports Medicine Facility showing comparable results. In a retrospective analysis of 480 data points in trials using paper-based data capture and prospective analysis of 428 data points in trials using EDC, Pollard recorded 49 errors in paper-based trials and 6 errors in EDC-based trials. This resulted in an overall error rate of 10.2% and 1.4 %, respectively 9. Figure 4 depicts this data.
The two studies also showed continuity in examination of the most common types of data errors observed in clinical trials, as well as the types of data errors most positively affected by EDC. Nahm et al. identified the most common errors as those resulting from data transcription from the source document to the CRF, while Pollard’s data showed that the second and third most prevalent types of data error were, respectively, mismatched data points between the source document and CRF (18.4% of errors recognized), and missing CRF data (4.1%); the researcher theorized that both resulted from transcription error \(^9\ ^{12}\). Pollard’s study also demonstrated a significant portion of error resulting from missing source documents. However, the researcher noted that this problem stemmed from understaffing and insufficient responsibility delegation, and not primarily as a consequence of paper-based data capture. Additionally, both studies showed that the use of EDC essentially eliminated data error associated with missing CRF data.
Both researchers attributed this benefit to the safeguards inherent in EDC systems. EDC employs alarms, notifications, queries, automatic completions and reminders to ensure that healthcare professionals fill all necessary data fields\textsuperscript{9,12,24}.

Responses to the investigational site email questionnaire from CRCs regarding EDC and data integrity largely confirmed the quantitative research of Nahm et al. and Pollard. All six clinical sites interviewed indicated that their site employs some kind of EDC, and five of the sites addressed the effect of EDC on data integrity\textsuperscript{37,38,39,40,41,45}. Of those five clinical sites, three recognized some kind of benefit associated with EDC and data integrity\textsuperscript{37,39,41}. All three of those sites noted a reduction in incorrect/incoherent data\textsuperscript{37,39,41}. Two sites indicated that EDC had improved data accessibility among the research staff at their location\textsuperscript{37,41}. Conversely, two of those five research sites indicated either a neutral effect of EDC on data integrity or a negative effect resulting from user interface difficulty or implementation challenges\textsuperscript{38,40}.

The benefits of EDC in regard to data integrity are well documented. However, there has been debate concerning the most effective method of EDC. There are a variety of techniques currently in use, including pen-operated personal digital assistants (PDAs), netbooks, tablet PCs and scanning devices such as smart pens or optical character recognition devices\textsuperscript{15}. Walther et al. (2011) employed a double-data entry research design to compare three of these EDC methods: pen-operated PDA, netbook, and tablet PC. Data showed that after a three-week study period, the netbook and tablet showed the lowest overall error rates (5.0 % and 5.2% respectively), followed by the PDA at 7.9%. The researchers also broke down
their results by type of data. For free-text data errors, the tablet PC and netbook showed the lowest error rate. For date-entry errors, the tablet and PDA showed the lowest error rates (5.4% and 4.0%, respectively). For missing data points, the tablet and netbook again showed the lowest error rates (0.1% and 0.48%). Additionally, all EDC methods showed a marked reduction in overall error rate over the course of the three-week study timeline; the netbook error rate improved from 8.8% to 5.0%, the tablet from 6.3% to 5.2% and the PDA from 13.2% to 7.9%. This may indicate that data integrity associated with EDC use improves over time as a result of increased user proficiency.

The process of achieving IP approval is both costly and time-consuming, and as a result, reducing the monetary burden of clinical trials is vitally important to the efficiency of global healthcare innovation. R & D for a new chemical or biological entity can exceed $1 billion dollars and require 10-15 years from R & D to FDA approval. Only 333 new drugs and biologics achieved FDA approval in the United States from 2000 to 2010, and of those, just two out of ten produced enough revenue in marketing to compensate for R & D costs. Electronic-based systems in clinical trials have the potential to alleviate some of this burden. Whereas data integrity stands as the most statistically rigorous and easily quantifiable benefit associated with electronic-based systems, cost reduction is the most intuitive and widely recognized benefit. Cost reduction for electronic systems in clinical trials results from both EDC and electronic record keeping. However, due to the complex and inflated nature of clinical trial expenses, cost reduction is extremely difficult to quantify. However, the potential for monetary benefit of incorporating
EHR in a clinical setting is much better understood and similar benefits can be extrapolated to clinical trials. EHR systems have proven to increase operations efficiency in ways relevant to clinical research management, such as reduced staff resources necessary for data management, and decreased data storage and transcription costs. Implementing EHR systems has also posed some challenges in the clinical setting, including high costs and other difficulties associated with implementation, ongoing maintenance costs and loss of productivity due to user training. These obstacles will be discussed in the next section as they relate to electronic-based systems in the context of a clinical trial.

EDC use has been proven to reduce clinical trial costs by reducing the number of mistakes in data collection and management, shortening the average study duration, reducing the financial burden of trial queries, reducing data collection costs, and streamlining database processing. Green (2015) analyzed data from four different clinical trials, one each in Phase I, Phase II, Phase IIIa, and Phase IIIb, to perform a detailed cost comparison of EDC vs. traditional paper-based data capture (Phase IIIa trials are conducted before a new drug application is submitted to the FDA, and IIIb trials are conducted after). The research included 228 clinical study sites and 8,264 subjects over the course of 54 months. Green compared cost metrics in three areas: approved EDC budgets in each clinical trial, estimated costs for a paper model, and implementation and EDC costs applied under a Level 2 technology transfer and enterprise relationship pricing model (L2TTP projects cost savings associated with research sites internalizing EDC software use, and performing their own eCRF design and data management rather than
outsourcing these responsibilities to the software vendor). Green’s calculations project a significant and definitive cost reduction in each clinical trial phase associated with EDC implementation (Figure 5) \textsuperscript{21}.

![Cost Comparison of EDC vs. Traditional Trials](image)

**Figure 5**: Cost Comparison of EDC vs. Traditional Trials: Data compiled from Green (2015) \textsuperscript{21}. *EDC – electronic data capture, L2TTP – level 2 technology transfer pricing

In a separate study, Jeannic et al. (2014) retrospectively analyzed the study-related costs of 27 trials from 2001 to 2011 in which 16 utilized paper-based data capture and 11 employed EDC \textsuperscript{24}. Calculating total study expenditure as an estimate of labor-related and logistical costs, the researchers showed that the mean expense per patient was significantly less in the EDC trials ($497 compared to $1509 for the paper-based trials, a 67% reduction in cost per patient). Moreover, Jeannic et al. demonstrated that trials employing EDC resulted in a significantly shorter study duration when compared to their traditional counterparts. EDC trials required an average of 31.7 months from the opening of the first center to database lock.
compared to 39.8 months for paper-based trials, despite a longer median projected duration (27 months for EDC and 24 months for paper-based) \(^{24}\). Figure 6 represents this data.

**Figure 6:** Study Duration in EDC vs. Traditional Trials: Data compiled from Jeannic et al. (2014) \(^{24}\). *EDC – electronic data capture

EDC implementation has also been shown to reduce overall trial expense by decreasing the cost of successfully identifying and resolving data integrity issues \(^{26}\). In a three-year examination of ten Phase III studies involving a total of 6,700 subjects, Spink (2002) determined that the average cost associated with raising and resolving a query was $60 in paper-based trials compared to only $10 in EDC-based trials \(^{26}\). The researcher also showed that EDC usage decreased the number of queries per subject from an average of 5-20 for traditional studies to 0.25-1 for EDC-related studies \(^{26}\). This dynamic illustrates the interrelationship of EDC cost reduction with the previously discussed impact of EDC on data integrity. A similar
dynamic exists between EDC-associated cost reduction and productivity/efficiency, which will be addressed later.

Electronic record keeping and document storage may also potentially reduce study-related costs. The FDA requires both sponsors and investigational sites to maintain study-related documents in storage during the entire course of the trial, and for a minimum of two years after the IP’s last marketing action. As an illustration of the enormity and volume of data storage these regulations might entail, consider the document storage estimates for the Neurological Emergencies Treatment Trials (NETT) Network. In fall 2006, the National Institute of Neurological Disorders and Stroke funded the NETT Network to conduct large Phase III trials. The network includes a clinical coordinating center, a statistical and data management center, and 17 clinical hubs across the United States. Each clinical hub has an average of 12 potential spoke hospitals that act as patient recruitment centers; the network currently includes up to 226 spokes. As a part of its minimum regulatory requirements, the NETT network requires four documents for each clinical site (protocol IRB approval, informed consent IRB approval, clinical laboratory improvement amendments certification and College of American Pathologists certification), and six documents for each principal investigator (curriculum vitae, medical license, human subjects training certification, protocol training certification and two outcome measures certifications). Calculating ten investigators per site and an average of four document submissions during the course of the study, the overall number of regulatory documents in storage would total 57,856 per clinical trial. If the NETT network conducted five clinical trials,
the number of stored documents would increase to 289,280. Assuming that the average document consists of three sheets of paper and a normal banker box holds about 2,200 sheets of paper, the NETT network would need almost 400 banker boxes to store regulatory documents for just five clinical trials. This number does not account for additional documents stored by the investigational site, namely source documents and on-site regulatory paperwork, which would increase storage volume exponentially.

Though clinical trial budgets always allocate funds for record storage, minimal research has been done to quantify average costs associated with this expense or the positive effects that electronic systems may offer. However, all six investigational sites interviewed in the course of this project reported using some method of electronic record storage. Three sites evaluated the effect of these systems on overall study expense. One research site indicated a cost reduction associated with electronic record storage resulting from less necessary off-site storage. One site reported a net neutral effect of electronic storage on cost, and another site chose not to comment due to the complexity of such an evaluation. However, of the six investigational sites that indicated usage of some kind of electronic storage system, four noted a reduction in necessary storage space. This practicum project surmises some measure of cost reduction associated with that advantage.

Within the general realm of electronic record keeping, the field of clinical research is also moving towards utilizing systems that reuse patient EHR information to aid in patient identification and recruitment, and protocol feasibility
The viable repurposing of EHR data for use in clinical trials carries the potential for profound benefits in overall study expense. In a breakdown of the average total cost of achieving IP approval, 56.9% of funding supports research in Phases I, II and III, the research phases that depend on patient recruitment (including 35.7% funding for Phase III, the most recruitment-intensive phase) \(^{42}\). Though recruitment is a vital and costly component of clinical trials, only 7% of trials in the United States and 18% in Europe complete enrollment on time \(^{42}\). Depending on the nature and scope of the trial, trial postponement can cost the sponsor as much as $8 million each day that the IP is delayed from reaching market \(^{42}\). Electronic systems that can shorten a trial’s enrollment period can greatly reduce its overall costs.

Recognizing this tremendous potential, initiatives like the SHARP project in the United States and the EHR4CR project in Europe are attempting to build systems that can successfully mine and abstract patient EHR information for use in clinical trials \(^{14,36,42}\). The more developed of the two projects, EHR4CR began in 2011 as a five-year project geared towards finding solutions to these problems. The initiative received support from both public and private partners, including 10 pharmaceutical companies and 21 academic institutions \(^{14,36}\). The system consists of a four-step process: analysis of de-identified EHR information, return of patient demographic information, patient consent to share EHR with a clinical trial site, and patient re-identification by the physician that treats them \(^{42}\). In an effort to protect patient privacy, initial data analysis only informs investigational sites of patient
counts and never patient-level data until the patient gives consent. After the patient consents, only the physician who treats them can “unblind” their identity.\(^{14,42}\)

In these ways, electronic systems can shorten study length during both enrollment and execution. In addition to cost reduction, the effect of electronic systems on study duration falls within the broader category of productivity/efficiency. Productivity and efficiency are general terms often cited in the literature to describe the cumulative effect of numerous variables within clinical trials that affect time management and communication both for the sponsor and the site. As a result, this described benefit of incorporating electronic systems into clinical trials is also exceedingly complex, convoluted and difficult to quantify. Both EDC and electronic record keeping/storage increase productivity and efficiency in the clinical trial management from the angle of the investigational site and the sponsor.\(^{26,43,46}\)

Litchfield et al. (2005) conducted a multicenter, cluster-randomized clinical trial comparing the efficiency of EDC (Internet-based) versus conventional paper-based data capture. Their data demonstrates the benefits in efficiency experienced by sites that implement EDC.\(^{43}\) When comparing time taken for the database to be released after the last patient visit, the researchers calculated a mean duration of 33 days compared to 48 days for the paper-derived database. When analyzing the difference between the two methods in average time from a patient visit to a query resolution, they estimated 121.4 days for EDC and 182.1 days for paper. The researchers also calculated the difference in time from a patient visit to data entry, demonstrating an average duration of 10.2 days versus 95.4 days (Figure 7).
Additionally, Litchfield et al. conducted a survey among investigators at each type of site and determined that 71% of investigational sites preferred using EDC.43

![Efficiency of EDC vs. Traditional Trials](image)

**Figure 7:** Efficiency of EDC vs. Traditional Trials: Data compiled from Litchfield et al. (2005).43 *EDC – electronic data capture

EDC also offers tremendous benefits in efficiency to clinical trial sponsors by decreasing the time and cost necessary for monitoring. As previously mentioned, sponsors contract CRAs, more commonly known as monitors, to perform source data verification (SDV) and other examinations of investigational sites. The current paradigm requires CRAs to travel to sites and monitor each individual site in person.29 46 This process is both costly and time consuming. In order to decrease the time and cost burden, risk-based monitoring is now the standard of practice. Risk-based monitoring is a method of SDV that allows monitors to focus their energies on data points that represent the most important risks to data quality, subject safety and
sponsor investment (such as trial endpoints, IRB approvals, IP accountability, etc.)\textsuperscript{29,46}. However, this method prevents a CRA from performing 100\% SDV.

EDC presents the opportunity for remote monitoring. This process saves time and reduces cost for clinical trial sponsors by eliminating the need for on-site monitoring, and it increases overall data quality by allowing for timely, near-complete SDV\textsuperscript{46}. Mealer et al. (2013) compared analytics between remote monitoring and traditional on-site monitoring in two national clinical trial networks. Their analysis included five hospitals and 32 subjects, 16 per arm of the study. In comparison of time consumed per data value monitored, the researchers calculated a mean duration of 0.39 minutes for remotely monitored data points versus 0.5 minutes for conventional. In analyzing time consumed per CRF verified, Mealer et al. observed an average of 3.6 minutes compared to 4.6 minutes for data points monitored on-site (Figure 8). The researchers also cited 99\% SDV for remote monitoring trials\textsuperscript{46}. 

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EDC can also increase enrollment efficiency (the importance of streamlining trial recruiting has been previously described in the context of cost reduction). When patients are screened for a clinical trial, various demographics such as age, lifestyle choices, current medications, and medical history are verified against predefined criteria indicated in the trial protocol to determine if a subject qualifies for randomization. This process produces some quantity of invalidly enrolled subjects due to miscommunication, human error, etc. Through use of intelligent software that performs this verification, EDC improves data validation and increases recruitment efficiency by reducing the number of patients wrongly enrolled in a study. Spink et al. (trial design previously described) analyzed ten Phase III clinical trials and compared the percentage of enrolled subjects that were invalid in EDC trials vs. paper-based trials. The researchers demonstrated a 7.5% rate for EDC compared to 15% for paper-based trials.
Due to the tremendous complexity and context-dependent variability of the effect of electronic systems on clinical trial management, the investigational sites interviewed in the course of this practicum project expressed both satisfaction and reservation in evaluating productivity/efficiency. All six sites discussed the effects of electronic systems relevant to productivity/efficiency, and four sites assessed the cumulative effect of those systems. All four of those sites indicated that electronic systems have had a net positive effect on productivity/efficiency at their site, naming benefits of both EDC and electronic record keeping. Three investigational sites noted a reduction in regulatory document turn-around time. Four sites mentioned an improvement in inter-site communication dynamics. Two sites recognized an increase in the speed and efficiency of data capture due to EDC use. One site also mentioned remote monitoring as a benefit of EDC.

Challenges

The benefits of incorporating EDC and electronic record keeping systems into clinical trial management are numerous and well documented. As with technological advance in any field, electronic systems in the healthcare industry face a number of challenges to overcome before their use becomes ubiquitous. Clinical trial management is presently working through obstacles associated with incorporating electronic systems that have troubled the general healthcare field in its efforts to implement widespread use of EHR. The most notable of these challenges include high acquisition costs, ongoing maintenance costs and resources, temporary loss of productivity due to personnel training, persistent reduction of
productivity due to personnel compliance difficulties, and privacy/security concerns associated with sharing health record electronically.\textsuperscript{13}

Historically, the most prominent challenge faced by the healthcare field’s implementation of EHR has been the financial burden. Adoption of EHR software and hardware is the biggest concern. A 2002 study of a 280-bed acute care hospital estimated the 7-year cost of implementing EHR to be about $19 million USD.\textsuperscript{47} Research into the financial implications of EHR use in the outpatient setting shows similar results. Researchers estimate a cost of $50,000 - $70,000 to implement EHR in a three-physician clinical office.\textsuperscript{48} However, as EHR technology has improved and its use become more conventional, implementation costs have declined dramatically. A 2010 study of EHR expense in the clinical setting estimated implementation costs of $14,000 for a six-physician outpatient office and about $19,000 for offices of three physicians or fewer.\textsuperscript{55} Even after adoption and implementation of EHR systems, maintenance of those systems can still be extremely costly. Maintenance expenses include hardware replacement and upgrade, ongoing training for end-users, and technical support.\textsuperscript{13} A 2005 study examining 14 separate clinical practices estimated the ongoing costs of maintaining EHR systems to be about $8,412 per year.\textsuperscript{49} The study calculated that 91% of this cost resulted from hardware replacement, vendor software maintenance and support, and personnel compensation.

EHR incorporation can also cause a loss of productivity. Productivity loss encompasses any disruption in workflow caused by EHR implementation. These disruptions may present as a temporary loss of productivity in the implementation
phase, or a continuing loss of productivity due to lack of compliance with system use. These problems may result from software and hardware installation time consumption, necessary end-user training and technical support (both initial and ongoing), and the extensive time involved in converting existing paper records into an electronic format. Wang et al. (2003) performed a five-year cost-benefit analysis of overall productivity in clinical offices implementing EHR systems. The researchers observed a 20% loss of productivity during the first month of EHR use. However, this effect leveled out over time. The study noted a 10% loss of productivity in month two, 5% in month three, and virtually no loss of productivity by month four. Moreover, a 2011 study estimated that adopting EHR in 26 primary care practices required an average of 134.2 hours for training alone.

Patient privacy and health data security exchanged electronically also represents a significant concern. As EDC and electronic record systems became more common in clinical trial management throughout the late 1990s, the FDA began developing guidelines that centered mostly on health information security. The FDA released 21 CFR part 11 in March 1997 to establish criteria for clinical trial use of e-records and e-signatures. These requirements were reexamined in 2003 in response to investigator and sponsor concern. This proposal recommended additional rule making, exercised greater enforcement discretion and outlined practical guidelines to ensure patient protection with electronic system usage. The document outlines the FDA’s requirements for limited access to electronic systems with each user maintaining individual, password-protected access to the electronic database. The system must also establish an audit trail to track all changes made
to data, including when the change was made, by whom, and for what purpose. The FDA also requires external security safeguards to prevent altering, browsing, querying, or reporting of protected data by unauthorized users. Furthermore, both investigational sites and sponsors must backup electronic data and institute recovery protections to prevent data loss.

On a practical level, electronic system usage in clinical trials has faced similar complications as EHR usage in healthcare at large. EDC implementation has proved particularly challenging due to the vast diversity of clinical trial structures and the differing contexts and circumstances those trials are conducted in. The specific needs of each investigational site vary widely. In a 2013 study, Ravetija et al. examined both the benefits and challenges of EDC use in the context of a clinical trial. The researchers determined that the most significant disadvantages to EDC use were lengthy set-up time and general logistical difficulties related to implementation, excessive cost of system enactment, and data security associated with Internet information storage. In other words, EDC use in clinical trials faces the same obstacles of high cost, productivity disruption and data security difficulties that trouble EHR use in hospitals and clinics. These problems largely result from EDC design challenges and user interface difficulty. Issues associated with interface design include conduciveness to study protocol, standardization relevant to multiple variables, workflow usability, individual site preference, comprehensiveness for “low-tech” individuals, and cross-context relevance. Improved electronic system design will help combat these difficulties, and over
time, make EDC and electronic record system use more feasible in a variety of contexts.

In response to the email questionnaire, the investigational sites interviewed mentioned many of these challenges. Five of the investigational sites queried noted challenges associated with using or implementing electronic systems. Four sites indicated that universal compliance among all staff members at their site is a significant obstacle. Three sites noted that electronic systems often require some measure of training to implement. Two sites mentioned usability issues or general difficulties with the user interface. One site noted the time and cost of maintaining electronic systems as something of a challenge. In spite of the fact that data security and patient privacy represent the FDA’s biggest concerns with electronic system use, none of the sites interviewed cited these challenges.

Practical Considerations

In spite of the numerous benefits of implementing EDC and electronic record keeping systems, clinical trial management as a field has struggled to incorporate these systems effectively due to various practical challenges. Logistical obstacles often present the greatest deterrent for investigational sites attempting to adopt electronic systems. However, many sites have overcome these challenges and successfully installed and instituted these systems as their standard model of clinical trial management. Many other investigational sites are in the process of doing so. Any site that plans to replace their current paper-based data capture and
record keeping system with electronic methods must account for a number of practical considerations. The investigational sites interviewed in the course of this project responded to numerous questions regarding pragmatic strategies for converting to electronic systems.

Philosophies differ concerning the methodology a site should employ when adopting electronic systems. Timelines and methods contrast widely, and the most effective implementation strategy for a particular site depends primarily on individual context and circumstance. All six of the investigational sites interviewed noted that they had previously or soon planned to institute some kind of meaningful electronic system \(^{37,38,39,40,41,45}\), and four of those sites had already made significant strides in that effort \(^{37,38,40,41}\). Three sites detailed the strategy and timeline that their site utilized, or planned to utilize, to make those changes \(^{37,38,39}\). One site had been transitioning gradually over the course of the last 5-6 years and converted to electronic records one document at a time (in order: adverse events, informed consent form, patient visit form, regulatory signatures and training documentation) \(^{37}\). The second site had also been transitioning gradually in the past several years, but had been doing so study-by-study as their site began new trials \(^{38}\). The third site does not currently utilize electronic systems significantly but also plans to transition study-by-study \(^{39}\).

As previously discussed, electronic record keeping offers particular benefits related to document storage. Data security represents a necessary concern of electronic record keeping, both to ensure patient privacy and to prevent data loss. As such, storing records electronically in the course of a clinical trial necessitates
data backup in some kind of secure repository. Though the FDA does not require sites to backup electronically stored data, the agency has issued nonbinding recommendations on the subject. The FDA recommends that sites utilize "sufficient backup and recovery to prevent data loss" 23. They advise regular data backup and secure, preferably off-site storage of that data. The FDA also instructs investigational sites to maintain backup and recovery logs to measure the extent of data loss in the event of a system failure 23. All five of the investigational sites interviewed with useful electronic systems already in place utilize some kind of repository to backup data electronically 37 38 40 41 45. Four of those five sites also added that they backup their data daily 37 38 40 45. In addition, four of the investigational sites depend on a dedicated Information Technology Department to perform the task 37 38 41 45.

Also mentioned in this project as a benefit of utilizing electronic systems, investigational sites can expect an improvement in productivity concurrent to more effective inter-site communication. One practical way that sites can realize this benefit is to create a shared drive (or shared folder) that contains all relevant trial documentation, both present and past, for all studies conducted at the site. All six investigational sites interviewed described use of a shared drive to maintain trial documents. Five of the six sites mentioned an effort to maintain some kind of consistent naming conventions across all studies 37 38 39 40 41. However, one site also mentioned that they do not use the shared drive as their primary data storage location or method 37. Though the FDA has not issued any requirements or recommendations relevant to creating a shared drive, the National Institute of Health (NIH) has created some helpful guidelines 56. NIH recommends that that sites
limit access to the shared drive with password-protection. They also direct sites to design the drive with folder names that correspond to regulatory binder tabs and descriptive, consistent naming structures. Following these basic guidelines, investigational sites should design and organize their shared drive conducive to their unique needs and preferences. Accounting for NIH recommendations, examples given in the email questionnaire responses from other sites and OCT’s current system, this project proposes an improved shared drive organization for UNTHSC’s OCT (Figure 9). The schematic proposes that all trials past and present nest beneath the name of the CRC that coordinated the trial, along with a template folder designed for efficiency and ease of use when a CRC takes on a new study. Trial folders divide into three logical categories so that various site personnel can easily locate documentation relevant to their role: regulatory, accounting and trial subjects. The “Subjects” folder also contains a template folder for the efficient addition of new patients.
Figure 9: Schematic representation of UNTHSC's OCT improved shared drive organization. Commas separate discrete folders within a subfolder. *Abbreviations: CTA – clinical trial agreement, ICF – informed consent form, IB – investigator’s brochure, AE/SAE – adverse event/serious adverse event, CRF – case report form, Con Meds – concomitant medications

The investigational sites interviewed for this project described one other component of their respective electronic systems. Clinical sites may choose to transition from “wet ink” signatures to electronic signatures, particularly during the
informed consent process. Two of the sites interviewed mentioned the use of e-signatures at their site. Both of those sites employ e-signatures in their informed consent process. The FDA spells out its parameters for e-signature use in subpart C of CFR Title 21. These basic guidelines require the general exclusivity and authenticity of any type of e-signature applied to electronic records in the course of a clinical trial. However, the FDA does not currently maintain any specific requirements or guidelines for the use of e-signatures in the informed consent process.

Summary

As a professional field, clinical research has fallen behind the technological advance of other healthcare fields. While the vast majority of healthcare professionals employ some kind of electronic record keeping system, most investigational research sites, including UTHSC’s Office of Clinical Trials, depend primarily on a paper-based data capture and record retention system.

EDC and electronic record keeping systems offer a variety of potential benefits. Electronic systems improve data integrity, reduce trial cost and increase productivity/efficiency in the course of a clinical trial. However, electronic systems also present a number of challenges, including implementation and training cost, decreased productivity associated with end-user training and staff compliance difficulties, and issues with data security and health record privacy. This practicum project discussed some practical considerations for investigational sites transitioning to electronic systems, including transition strategies,
recommendations for backing up electronic records, creating a shared drive, and other potential systems for investigational sites to implement.

Limitations

The most prominent limitation to the widespread use of electronic systems in clinical trials is a lingering dependence on “wet ink” documents. Some records require physical signatures to authenticate, and many sites, even those that employ primarily electronic systems, tend to retain the paper copy of these documents alongside the electronic version. The subject’s original informed consent stands as the most important of these documents.

All five of the sites interviewed that utilize electronic systems on a meaningful scale indicated that they still preserve some kind of “wet ink” document. Three sites mentioned retaining the subjects’ original informed consent. Two sites indicated that they retain physical copies of all patient source documents. Three sites also identified regulatory documents as a record commonly kept in both paper and electronic form. One site specifically cited delegation of authority and training logs as a regulatory document retained in paper form.

In a more general sense, a discussion of the benefits and challenges of incorporating electronic systems faces the problem of extreme context dependence. Clinical trial management functions as a global enterprise, operating within the various societal norms and ethical considerations of a litany of cultures. Moreover, clinical trials investigate medical drugs and devices relevant to every conceivable
sub-specialty of healthcare. The sheer variability underneath the umbrella of the term “clinical trials” is staggering. Generalizations across all contexts of clinical research regarding cost effect, productivity/efficiency, data quality, and data security cannot be universally supported. Investigational sites must gauge the viability of these trends and generalities in their own context, and craft a unique implementation strategy for electronic systems.
CHAPTER 4

INTERNSHIP SITE

The Office of Clinical Trials functions on the campus of, and in cooperation with, the University of North Texas Health Science Center. The OCT is located within UNTHSC’s Patient Care Center and operates under the regulation of the university’s IRB. The OCT employs nine CRC’s as well as additional administrative staff and conducts over twenty clinical trials each year, usually Phase III, in a wide range of healthcare disciplines 59. While most trials are conducted in the Patient Care Center, some are coordinated at the Ben Hogan Sports Medicine Center and other locations in the Fort Worth, Texas area.

INTERNSHIP EXPERIENCE

Working under the mentorship of April Bell, I primarily conducted clinical trials involving cardiovascular research at the Patient Care Center and diabetic foot ulcer research at Ben Hogan Sports Medicine. I contributed to three cardiovascular studies, all investigating drug treatments for dyslipidemia, and two diabetic foot ulcer studies, one of which tested the efficacy of a drug to close persistent wounds and the other a drug for resolving infection. For the cardiovascular studies, I contributed to patient visits, obtaining informed consent, taking vital signs, handling and shipping blood samples, ordering trials supplies, data entry, patient enrollment and scheduling, and recording source data. For the diabetic foot ulcer studies, I participated in patient visits, obtaining informed consent, blood sample and wound
biopsy handling and shipping, data entry, taking vital signs, and ordering trial supplies.
Monday, June 1

Today was the first day of the internship. I spent most of the day reading informed consent documents for four of the studies that April is coordinating. Spire and Odyssey are both studies that deal with high cholesterol using the same medication that inhibits PCSK9, an enzyme that degrades the LDL receptor. Conversely, Strength is a new study that tests the efficacy of a drug called Epanova (a fish oil with high bioavailability) in treating hypertriglyceridemia and Santyl involves treating diabetic foot ulcers with an ointment called Clostridial Collagenase. While Spire, Odyssey and Santyl are all in progress, Strength is just about to begin enrolling. April also trained me to help out with Spire, and I sat in on a feasibility phone call regarding a study one of the other clinical coordinators is considering.

Tuesday, June 2

April and I spent most of the morning organizing various study materials that had been shipped to her by sponsor companies. Later in the morning, we went over to Ben Hogan to see a patient in the Santyl study. April taught me the process of preparing the room for a patient visit and some other specifics regarding the Santyl study. In the afternoon, April trained me for the Odyssey study and we began preparing binders for Strength in preparation for the site initiation visit tomorrow.
**Wednesday, June 3**

Today was occupied entirely by a Site Initiation Visit for the Strength trial. The monitor came in the morning and trained all of us in various aspects of the study including the data entry website, information on the drug itself and the protocol. The visit ended early in the afternoon. Afterwards, April and I began making binders for patient documents for those enrolled in Strength.

**Thursday, June 4**

April was not feeling well today, so she gave me the day off.

**Friday, June 5**

This morning was the first department staff meeting that I have been a part of. Every CRC talked a little bit about the progress of their various studies. After that, we saw a patient enrolled in the Spire study. He is a big fan of Ranger’s baseball, so we I talked about that with him while April conducted the visit. Next, April showed me how to prepare both frozen and ambient blood samples in the centrifuge and prepare them for shipment. Later in the morning, April and I went to my first advisory committee meeting. We decided that my research project will involve converting from paper to electronic recordkeeping. I spent most of the afternoon working through training modules for the Strength trial. Enrollment will begin next week.

**Monday, June 8**

April was out of the office today. I spent the day working on my research proposal and my medical school applications for the next cycle.
Tuesday, June 9

Today was another short day. April was out again. One of the other CRC’s, Srishti, covered her patient visit. I met Srishti in the morning at the Ben Hogan Center and assisted her with the visit for a subject in the Santyl trial.

Wednesday, June 10

I met April at the PCC this morning and spent most of the morning entering data regarding patient visits, drug accountability, etc. for our various studies. The sheer volume and scope of regulatory paperwork necessary to maintain is incredible. We saw a patient enrolled in the Odyssey trial just after lunch. After the visit, I prepared the blood samples to ship. April and I went to get dry ice, and she taught me how to ship frozen blood samples. I left for the day shortly after that.

Thursday, June 11

Today was a pretty slow day. There wasn’t much to do in the morning, so I met April at the PCC around noon. We spent the afternoon getting me set up and better acquainted with the various data entry sites for each trial.

Friday, June 12

I spent the morning finishing up the rest of the data entry that I had left undone yesterday. After that, I ordered lunch from Panera for a meeting with a representative from the Regeneron pharmaceutical company. They are the sponsor for the Odyssey trial. The mechanism for that study as well as Spire, PCSK9 inhibition, just achieved pre-approval by the FDA, so the sponsor wanted to check in with each site to see how things were going. They were concerned that perhaps the
FDA’s recent decision would deter patients from continuing in the study. I spent the afternoon calling prospective subjects for Strength.

Monday, June 15

April was out for the morning, so Srishti and I handled her patient visit. The subject was an older man enrolled in Odyssey. I prepared the blood samples for shipment, and April arrived shortly thereafter. After lunch we conducted our first screening visit for the Strength trial, which was considerably longer and more thorough than other visits I had been a part of due to the rigor and detail involved in the consent process.

Tuesday, June 16

I met April at the Ben Hogan Center late in the morning for the exit visit of our last patient enrolled in the Santyl trial. Afterwards, April showed me how to handle the blood samples from that particular study. This involved all the normal procedures and additionally, the preparation of a blood slide. We also had our monitoring visit today for the Santyl trial. The sponsor company is based in Fort Worth.

Wednesday, June 17

April and I saw two patients today. The first patient was an older woman enrolled in Spire, and the second was a subject in Odyssey. I handled all the blood samples and shipment necessities for both visits. I also took care of some data entry for Odyssey regarding concomitant medications and drug accountability for a few the patients in that trial.
Thursday, June 18

I spent the morning finishing up some of the data entry that I had left unfinished from yesterday. April also taught me how to order supplies for Odyssey. We were supposed to screen another patient for Strength, but he cancelled his appointment due to illness. I used the afternoon tying up loose ends for the weekend.

Monday, June 22

Today was extremely busy. We were scheduled to screen a patient for Strength as soon as the clinic opened this morning. Unfortunately, he slept through the appointment. We had more one more Strength screening miss her appointment as well, but we rescheduled her for tomorrow. The rest of the day included a successful Strength screening, a patient visit for Odyssey, and all the data entry, drug accountability, sample handling, etc. that each of those visits entails. We also had a close out visit for one of April’s other studies, Commander, which had closed without any enrollment due to the PI resigning from the university.

Tuesday, June 23

With Strength screening in full swing, today was another busy day. We screened two subjects for Strength and conducted two other patient visits for Spire. As per usual, I handled the data entry necessary for the visits as well as the preparation and shipping of the blood samples. Those four visits occupied the entire morning. In the afternoon, I finished up shipping the blood samples and requested medical history from various locations for two of our patients: one from Strength and one from Spire.
Wednesday, June 24

April was out of the office today, but I decided to come in anyway to catch up on some work. I spent the day shipping frozen blood samples, entering data we had gotten behind on due to the volume of patients we've been seeing, making binders to store and organize documents for new patients in Strength and finishing up some drug accountability for some Odyssey and Spire patients. At the end of the day we received a huge shipment of new IP for Spire, so Srishti and I logged and stored that as well.

Thursday, June 25

We had one patient for Spire this morning. Per usual, I prepared and shipped their blood samples. I spent the rest of the morning finishing work that I had not gotten to yesterday: labeling IP for Strength and completing more data entry. In the afternoon April and I went over to Ben Hogan and screened a new patient for Santyl.

Friday, June 26

I did not go to the office today because I wasn't feeling well.

Monday, June 29

Today was pretty uneventful. April and I didn't have any patients. I spent the day at PCC catching up on data entry, making new binders for Strength and other miscellaneous tasks.

Tuesday, June 30

I did not go to the office today because I wasn’t feeling well.
Wednesday, July 1

April and I had one patient for Spire this morning. He was actually one of the first few patients we had when my internship first began, so it was a good experience. April left right after the visit, but I stayed at the PCC working on other things the rest of the day. I made more binders for Strength, made new binders for Santyl updated some patients’ information and entered their data.

Thursday, July 2

I came into the office early today to finish some of my work from yesterday, which was calling Odyssey patients to inform them of a change in the payment method for the study. After that I went to Ben Hogan for the rest of the day. We had one patient screen for Dipexium and not qualify, one patient screen for Santyl and another patient no-show for their Santyl screening visit.

Friday, July 3

Holiday

Monday, July 6

I spent today working on my research proposal.

Tuesday, July 7

I spent today working on my research proposal.

Wednesday, July 8

I completed my research proposal today. April and I also attended an EHR training class for a program called NextGen.
Thursday, July 9

We saw two patients today at the Ben Hogan Center. The first was a patient just recently enrolled in Santyl (who happened to bring us lunch). The second was a Santyl screening. He had the worst diabetic foot ulcer that I have seen so far. Santyl requires blood work for the screening and exit visits, so I prepared and shipped the patient’s blood sample after the visit.

Friday, July 10

April attended an investigator’s meeting for our new trial, Pico, in Dallas, so I got the day off.

Monday, July 13

April and I had two patients this morning: a screening for Strength and a normal patient visit for Spire. I handled the blood samples for both patients, and then picked up dry ice for one of the other CRC’s. I spent the rest of the day working on data entry, calling patient’s to enroll in Strength and other miscellaneous tasks.

Tuesday, July 14

April and I had two patients today. We screened one patient for Strength in the morning and another in the afternoon. However, April decided to rescreen the second patient next month as a “washout period” for Lovaza, prescription fish oil that is excluded in the study. April also saw two other patients at the Ben Hogan Center, one for Santyl and a screening for Dipexium. I stayed at the PCC and did research for my thesis.
Wednesday, July 15

April and I only had one appointment today, for the Dipexium trial. Dipexium is also a diabetic foot ulcer study, but in comparison to Santyl, which lasts almost 5 months, Dipexium only lasts one month. Patients come into the clinic four times in the first week and then two more times in the next two weeks. Today’s patient was on Day 1, his second visit.

Thursday, July 16

April and I again spent all day at Ben Hogan. We had two patients. The first patient was the same person that we saw yesterday, on his third visit for Dipexium. The second was a screening visit for Santyl. We already screened him a few weeks before, but circumstance prevented him from coming back in the randomization window.

Friday, July 17

Today was a very busy day. April and I saw two patients at the PCC: a Spire subject for their week 11 visit and a Strength screening. We had one other patient not show up for his appointment. I handled and shipped the blood samples for both visits. After that, I spent the rest of the day doing a lot of data entry, putting binders together for some of next week's patients, helping one of the other CRC’s set up her printer, and other miscellaneous tasks.

Monday, July 20

April and I only had one patient today, a screening for Strength. However, April decided to screen fail him due to compliance issues, so we didn’t complete the entire visit and the patient won’t be continuing in the study. The rest of the day mostly
entailed a lot of data entry, particularly medical histories and concomitant medication lists. We also had a visit from our monitor for Strength today.

**Tuesday, July 21**

Today was a very busy day. April won't be here this Thursday and Friday, so we had to cram in all of our weekly Ben Hogan patients today. We had two Santyl screenings, two normal Santyl and visits and a day 7 visit for our only Dipexium patient. Srishti wasn’t there today, so I handled all of the data entry and blood sample handling. I also took care of some medical history and concomitant medication data for other patients in Santyl.

**Wednesday, July 22**

Today was very busy again. We had one patient for Odyssey, one for Spire and two screenings for Strength. The screening visits for all the studies are particularly lengthy due to the additional time involved for informed consent, medical history, medications, etc. I handled and shipped the blood samples for all the visits. After all that, April asked me to figure out a problem we had with one of our shipments for a Strength screening sample that never made it to the lab. Fed Ex apparently never picked up the package because it wasn’t there, so we have no idea where the package has gone. We will probably have to rescreen the patient in a few weeks.

**Thursday, July 23**

I had the day off today.

**Friday, July 24**

April was out of town today, so I helped one of the other CRC’s with our only patient for the day. The visit was for a Spire patient in week 12. I spent the rest of the day
handling his blood sample, catching up on data entry and drug accountability, and trying again to figure out what happened to that sample from last week. I shipped out two samples that day, and the other one reached its destination right on schedule. I am still not sure what happened to the other sample.

Monday, July 27

Today was a relatively low-stress day. April will be on vacation next week, so we don’t have any Strength screenings this week. As a result, our only patient visits are for Odyssey. However, our only patient today did not show up. I spent the day catching up on data entry, answering queries in our data tracking servers and taking care of other miscellaneous tasks.

Tuesday, July 28

April and I saw all of our patients for both Santyl and Dipexium today, so we were extremely busy. We spent the entire day at the Ben Hogan Center. In addition, April spent the day instructing the CRC who is going to see our patients while April is on vacation. We saw three patients for Santyl, one for Dipexium and our final Santyl patient did not keep his appointment due to an unforeseen hospitalization. Our monitor for the Santyl also came by today.

Wednesday, July 29

I spent today working on my thesis.

Thursday, July 30

April and I had another easy day today. We had one Odyssey patient in the morning and an Odyssey screening right after that. I took care of the data entry, drug accountability and blood samples for both patients. Additionally, I used the
afternoon to order additional supplies. I also finished putting together an email interview for my thesis. I discussed it with April, and she is going to put me in touch with a number of CRC’s that are willing to aid me in my research. April also reviewed our recent monitoring report for the Santyl study with me.

Friday, July 31

I spent today working on my thesis.

Monday, August 3

Day off

Tuesday, August 4

We saw all of our Santyl patients today at the Ben Hogan center. April is on vacation for the next two weeks. Another CRC, Isabel, is filling in for her. We saw two of our regular Santyl patients in the morning, and had another subject fail to attend his visit. All of this amounted to a short and fairly uneventful day.

Wednesday, August 5

Day off

Thursday, August 6

Day off

Friday, August 7

I spent the day shadowing Dr. Katarina Lindley D.O., a personal friend and family practitioner in Mineral Wells, Texas. I really appreciated her perspective regarding the difference in philosophies between osteopathic and allopathic medicine. She also had a lot to share about her experience attending an out-of-state D.O. school; she is an alumnus of Nova Southeastern College of Osteopathic Medicine.
Monday, August 10

I had today off again, but I received an email from Wilma, another one of the CRC’s at OCT, informing me that I package had been delivered for April that appeared to hold lab samples. As it turns out, the box contained the lost samples from our Strength screening patient a few weeks ago. It had been mailed back to us from Office Depot from UPS, though we had mailed it out with FedEx. I’ll ask April about that when she returns.

Tuesday, August 11

Today was very similar to last Tuesday. We saw all of our weekly Santyl patients this morning. I again worked alongside Isabel and Priyanka. In addition, we found out why one of our Santyl patients missed his visit last Tuesday: he had been hospitalized, constituting a SAE. Today was also the final visit for our only Dipexium patient; he came in today for his Day 28 follow-up visit. I may not have mentioned it previously, but Dipexium and Santyl are very different studies, though they both treat patients suffering from diabetic foot ulcers. Dipexium is a one-month study with the goal of resolving infection in patients with mildly infected wounds. However, Santyl is essentially a three-month study which attempts to achieve wound healing and ultimately closure.

Wednesday, August 12

Today was another day off, but Wilma emailed me again concerning boxes received for April. These turned out to be just screening kits and other study supplies April and I had ordered before she left.
Thursday, August 13

Day off

Friday, August 14

Day off

Monday, August 17

April and Srishti both returned from vacation today. Coincidentally, the FDA also began a month-long audit of the portion of OCT involved with tuberculosis studies. Fortunately, the audit does not affect our studies. I also found out today that Smith & Nephew has closed enrollment for Santyl, so we will not be screening any more new patients. As for the rest of the day’s events, we had two patients today and one more who did not show up. For the first visit, April and I rescreened the Strength patient whose lab samples got lost somewhere in transit by FedEx. The second was a standard visit for one of our Odyssey patients. We were supposed to have one more patient today as well. The patient called to confirm her appointment this morning but did not show up, and April cannot get in contact with her. I processed and shipped the lab samples for both patients. I also took inventory for lab kits and study supplies for each of our trials and ordered the things we will need in the upcoming weeks and months. Today being April’s first day back, there was not much else to do.

Tuesday, August 18

I met April at Ben Hogan today, and we saw two of our three weekly Santyl patients. Our third subject rescheduled his visit for Thursday. April and I also ordered additional supplies for both Santyl and Dipexium.
**Wednesday, August 19**

I was suffering from migraines today, so I did not meet April.

**Thursday, August 20**

April screened a patient for Strength this morning, and I met her at Ben Hogan after that to see our Santyl patient who rescheduled on Tuesday. We also screened a patient for Dipexium. Unfortunately, the subject did not qualify because his wound was slightly too small due to overly restrictive and nonsensical aspects of the protocol. By coincidence, the monitor for Dipexium was there today, so April expressed her critiques about the protocol. We are hoping to rescreen the patient next week if possible.

**Friday, August 21**

Today was a short and relatively uneventful day. The OCT had its monthly staff meeting this morning. This consisted mostly of each CRC updated the department on the status of their trials. After this, April and I saw one patient for Odyssey. I processed and shipped his blood samples, and that was it for the day.

**August 24-28**

We only had a few patients this week, so April allowed me to spend the entire week working on my thesis.

**Monday, August 31**

April and I saw two patients today. With enrollment closed for Santyl, we have been able to focus more on enrolling patients in Dipexium. April screened a patient for Dipexium last week who ended up qualifying for the study, so we saw the subject today for his third visit. After that, April and I returned to PCC to see a Strength
patient. April screened him last week, but his triglycerides fell just short of qualifying for the study. He came into today for a 1A visit, an additional screening allowed by the study protocol to see if his triglycerides had reached the appropriate level. Unfortunately, the patient had not been fasting, so we could not get the blood sample we needed. Besides all that, the FDA is still conducting their audit, which they will complete on Wednesday.

Tuesday, September 1

Today was a busy day at the Ben Hogan center. April, Srishti and I saw both of our regular Santyl patients. They will each continue in the study for another 4-6 weeks unless their wound heals entirely or they drop out of the study for another reason. We also screened a new patient for Dipexium, and they ended up qualifying. Dipexium screenings are extremely rigorous; they require a blood sample, wound culture, urine sample, photographs, wound dimension tracing, X-ray and a number of baseline quantities including INR, ESR and ABI. April also taught me how to use the ABI machine, which uses Doppler ultrasound and a sphygmomanometer to measure blood pressure in the legs to access the extent of peripheral artery disease.

Wednesday, September 2

April and I saw one patient today for a Strength follow-up screening visit. The study allows us to bring a patient back for up to 2 additional screenings if their triglycerides fall just under 200. I spent the rest of the day handling blood samples, filing patient records, making binders for prospective new patients in Dipexium, storing expired IP in Odyssey away for the monitor to destroy when they come again and organizing recently received trial kits for Odyssey.
Thursday, September 3

April, Srishti and I saw two patients today at Ben Hogan. The first was the 7th visit for one of our Dipexium visits and the second was a Dipexium screening. However, the patient did not qualify. His wound was not infected, and it was much too small.

Friday, September 4

We did not have any patients today, so I spent the day working on my thesis.

Monday, September 7

Holiday

Tuesday, September 8

We had a very busy day at Ben Hogan today. April and I arrived early in the morning to see our two returning Santyl patients. Both subjects are doing very well in the study and may only continue participating in the trial for a few more weeks if their respective wounds continue to heal well. Srishti joined us later in the morning to see one of our returning Dipexium subjects for their Day 7 visit. Per study protocol, this visit requires a wound culture, so I processed and shipped the patient’s biopsy after the visit. The rest of the day included two more Dipexium screenings. Unfortunately, neither subject qualified for the study. The first patient’s wound was neither infected nor large enough to qualify. The second subject, by unfortunate coincidence, had been prescribed a course of systemic antibiotics for a different problem. As a result, his wound was large enough but was not infected.

Wednesday, September 9

We did not have any patients, so I spent the day working on my thesis.
Thursday, September 10

April has asked me to spend the rest of the internship focusing on my thesis given our low number of patients currently enrolled in studies. Santyl is now closed for enrollment, and we only have a few screenings planned over the next few weeks. April also gave me some suggestions for improvement when I do come in to see patients. She wants me to focus on my body language and demeanor in an effort to project a more professional sensibility.

Friday, September 11

I spent the day working on my thesis.

Monday, September 14

I came into to PCC for just a few minutes this morning to have April review my daily logs and to discuss my thesis with her. She gave me some suggestions regarding the research portion of my report, particularly how to approach the shared drive.

Tuesday, September 15

April, Srishti, and I were at Ben Hogan today. We saw both of our returning Santyl patients, and both of them ended up exiting the study today with fully healed wounds. However, one of them is going to return each week for treatment of a different wound that developed during the course of the trial. We also saw one of our Dipexium patients for his Day 14 visit; this marks the end of his treatment. We will see him again in two weeks for a follow up visit. The Day 14 visit is essentially the same as the screening visit. I handled the blood sample, and shipped it to the lab along with his wound culture.
Wednesday, September 16

We do not have any more patients the rest of this week, so I am going to spend that time completing the first two chapters of my thesis. I am focusing on acquiring more email interviews for the research portion of my report.

Thursday, September 17

I spent the day working on my thesis. I completed the first two chapters and sent it to April, Dr. Gwirtz and Dr. Hodge for their improvement suggestions.

Friday, September 18

We did not have any patients, so I spent the day working on my thesis.

Monday, September 21

We did not have any patients, so I spent the day working on my thesis. I also picked up dry ice for Wilma, one of the other CRC’s at OCT.

Tuesday, September 22

I spent the day working on my thesis.

Wednesday, September 23

April and I were at both PCC and Ben Hogan today. First, we saw a prospective Strength patient for their 1A visit. His triglycerides were just barely too low to qualify for the study, however, the sponsor allows us to bring patients back for a 1A or even 1B visit if the subject is close to qualifying. Next we saw one of our Spire patients for his week 24 visit. I handled and shipped the blood samples for both visits. Later in the morning, April and I went to Ben Hogan for the Day 28 follow-up visit for one of our two Dipexium patients.
September 24-25

April and Srishti went to Las Vegas for a Santyl Investigator’s Meeting to reward the top enrolling sites for the study. April and Srishti enrolled more than 30 patients over the course of the trial.

Monday, September 28

April and I saw one patient today at PCC – a Month 3 visit for a Strength patient. We currently have only 3 subjects enrolled in the study due to the stringent triglyceride requirements of the protocol (we have screen failed 8 potential subjects). Fortunately, the sponsor just changed the protocol to make the triglyceride baseline a little more manageable. I handled and shipped the blood for the patient. We had another Strength patient cancel his appointment later this afternoon. I spent the rest of the morning doing data entry, drug accountability and entering patient data into Merge. In addition, enrollment for Odyssey closed today. This means that of our five studies, only two are open for enrollment (Strength and Dipexium). Spire closed earlier this year and Santyl a few months ago. However, April expects enrollment for Pico, another diabetic foot ulcer study, to begin before the end of the year.

Tuesday, September 29

We did not have any patients today, so I spent the day working on my thesis.

Wednesday, September 30

April and I had two patients at PCC this morning. Our first patient came for her Month 1 visit in Odyssey (she was the very last patient we randomized for Odyssey before enrollment closed). She had been having some problems self-administering her drug, so April walked her through that process again. Our next patient visit was
intended to be a screening for Strength. April had given the subject the consent to look over earlier in the week. However, after asking a few questions the patient chose to take a little bit more time to think it over. After our two patient visits, April and I sat down to discuss my thesis. April recommended that I take the rest of this week and all of next to focus solely on that.

**September 29 – October 11**

Per April's recommendation, I did not go to clinic or see patients during this time, but rather focused entirely on writing my thesis.

**Monday, October 12**

I checked in with April today to ask about the outlook for the coming week and offer my help. April instructed me to continue working on my thesis, and informed me that she would let me know if I am needed as the week progresses.
APPENDIX B

INVESTIGATIONAL SITE EMAIL QUESTIONNAIRE

To what degree has your site incorporated electronic record keeping and data capture methods? How have these methods affected your site in the following areas: source documentation, regulatory documentation and record storage after the completion of a trial?

How long have these systems been in place? What successive steps did your site take in order to transition to electronic data capture and record keeping? (For example, was the transition gradual? Did your site implement these changes study-by-study, one coordinator at a time, by a time line or all at once?)

What difficulties, challenges or obstacles did your site face in the course of implementing these new systems?

Are there any areas in which your site still depends on paper-based or "wet ink" documentation? Is this necessary/required?

What benefits has your site experienced as a result of implementing electronic data capture and record keeping methods? (cost, efficiency, reducing data entry errors, time management, cooperation among colleagues, care coordination)
In regard to your site’s electronic record keeping, what systems are in place to backup your site’s records? Is it on-site or off-site? How often is the data backed up? Is your site responsible for it or do you have an IT department that handles it?

If study data is maintained on a shared drive, does your site have standard naming conventions and folders for regulatory documents and/or patient files?


37.  Page R. "Interview with Dr. Ray Page of The Center for Cancer and Blood Disorders." E-mail interview. 12 Aug. 2015.
38.  Houseworth S. "Interview with Susan Houseworth of the University of Illinois." E-mail interview. 18 Aug. 2015.
39.  Pollard K. "Interview with Kalyssa Pollard of Texas Health Ben Hogan Sports Medicine." E-mail interview. 20 Aug. 2015.
40. Priest E, and Qiu. "Interview with Taoran Qui and Dr. Elisa Priest of the Baylor Scott & White Health Center for Clinical Effectiveness." E-mail interview. 11 Sept. 2015.

41. Marwah H. "Interview with Heema Marwah of ACRC Trials." E-mail interview. 30 Sept. 2015.


45. Bell A. “Interview April Bell of the University of North Texas Health Science Center Office of Clinical Trials.” Email interview. 5 Oct. 2015.


