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Industry Perspective on Clinical Investigative Sites: Maximizing Sponsor Return on Investment

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INDUSTRY PERSPECTIVE ON CLINICAL INVESTIGATIVE SITES: MAXIMIZING SPONSOR RETURN ON INVESTMENT

INTERNSHIP PRACTICUM REPORT

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CHAPTER I

Introduction

The foundation of the Pharmaceutical, Medical Device, and Biologics industry is the constant development of novel drug and device therapies to combat disease and infirmity. In order to meet the goal of developing these novel therapies, pharmaceutical and device companies devote billions of dollars into a cycle of bench, laboratory, animal and finally human research, collectively called research and development (R&D), to produce new drugs and devices.[1] The focus of the human research aspect of this effort, clinical research, is driven by a series of pivotal studies involving humans to demonstrate the safety and efficacy of the therapeutic agent being tested. The patient data gathered through this process, performed by a network of clinical sites and study centers, is the backbone of drug and device development.

The cost of drug development has skyrocketed in the past few decades, in large part due to the higher costs associated with enrolling human subjects at clinical investigative sites across the globe.[2] Subjects are recruited into all phases of clinical studies primarily by physicians and their research study staff (collectively referred to as study sites). In order to meet patient enrollment recommendations stipulated by the Food and Drug Administration (FDA) and other regulatory authorities, and to conduct the research in a timely manner, a large number of physicians in geographically distinct regions of the United States (US), and the globe, are required. Each site constitutes an enormous investment in both money and time for the Sponsor. There are direct and indirect costs to ensure a site is well equipped to conduct a study. Some of the direct costs include training site personnel on protocol-specific requirements, Good Clinical

Practice (GCP) requirements, Institutional Review Board (IRB) reporting requirements, use of vendor supplies and equipment, and the manpower hours for travel, initiation, monitoring, close-out visits, and ongoing patient recruitment and retention costs. Indirect costs include, human costs in time, developing and implementing training, and site management. With so much time and money invested into each clinical site, it is of vital importance that sites perform up to the standards expected by the Sponsor.[3] According to the International Conference on Harmonization GCP (section 5.6)[4] it is the responsibility of the Sponsor Company to choose a site that is qualified to conduct the research, has proper training, and has adequate resources to conduct the trial. Sponsors will generally require far more than required by GCP including expected enrollment rates and expected screen failure rates (in accordance with their past experience in that therapeutic area, if any). Things to be considered in recruiting sites include: length of time conducting research, number of previous and ongoing studies (site work load), therapeutic specialty, previous research experience of the Principal Investigator (PI) and study coordinator, the industry influence of the PI (i.e. Key Opinion Leader in the field [KOL]), PI/site affiliation (either with a larger research consortium, Veteran's hospital, or an academic institution), and whether the site or investigator has had any FDA warning letters or violations.[5]

Although the Principal Investigator is accountable for the conduct of research at his/her site (ICH GCP section 4.1.1), it is widely accepted within the industry that the research study coordinator, or research nurse, has a significant impact on the outcome of a clinical trial at individual sites.[4] Coordinators generally conduct the bulk of the study-related procedures, paperwork, data entry, and patient recruitment and retention (cornerstones of efficient clinical research). They are often responsible for multiple studies at a single site, and the onus of quality research and data collection often appears to fall squarely on the shoulders of the coordinator.

With the increasing complexity of study protocols, and the increasing demands of Sponsor companies, it is important that when Sponsors conduct the site selection process, they do so with a focus on ensuring the site they choose employs trained and experienced coordinator(s) that understand the complexities and pitfalls of conducting clinical research. With so much influence, a coordinator can be a liability or an asset depending on the quality of work performed.[6] Previous experience and/or certification as a study/research coordinator are highly desirable. In addition, it is critical to understand the Investigator's staff availability to conduct the study and whether the sites current workload is manageable.

This Practicum Report was designed to identify those critical traits that are common to productive clinical investigative study sites. Those data metrics collected will be used in the development of a site evaluation tool, taking the shape of a questionnaire to be taken by the study coordinator, and may be used by the Sponsor Company in the recruitment of future sites for future clinical studies.

CHAPTER II

Internship Subject

This internship's main purpose, in broad terms, is to assist the internship company, in enhancing the current tools used in site selection and qualification for future potential sites and to develop additional tools for managing sites that, for whatever reason, have not met Sponsor standards. These goals were accomplished through a systematic review of desirable site attributes collected through an extensive literature review and interviews with internship site personnel, leading to the development of several methodologies to maximize the return on investment of the sponsor company.

Since clinical research is a site driven process, it is of critical importance that the sites selected by the Sponsor Company effectively perform to the standards expected of them. Recent data suggests that only twenty percent of sites enroll the agreed-upon number of subjects while the bottom quartile of sites enroll one or no subjects.[3] By estimating the Sponsor's investment in these sites, roughly $6 billion could be recouped by the industry as a whole if more effective methods for site selection and qualification can be implemented.[3] That represents a huge capital expenditure for Sponsor Companies that can drastically alter forecasting and planning of potential future studies. From the perspective of a small start-up, having the industry average of 20-25% of non- and under-performing sites consumes large amounts of precious capital and delays the clinical development of the entire portfolio of potential drug compounds. Such costs and delays illustrate the vital importance of effective site selection techniques since underperforming sites can delay potential FDA market approval.

Site selection is a long and arduous process that Sponsors and clinical research organizations (CROs) undertake months (and sometimes a year or more) in advance of initiating a clinical trial. Sites are pre-identified through various sources (referrals, web searches, past experience with the site, etc.); typically a questionnaire is sent out to explore in more depth a site's patient population, current workload, staff and infrastructure, clinical trial experience, and previous metrics regarding enrollment and screen failure rates (where available). Sponsors also take into account whether the site is part of a larger research cooperative or consortium, an academic or university site, or a Veteran's Affairs hospital setting; these kind of affiliations sometimes complicate payment and start-up processes and are thus sometimes less desirable than private practice research centers. Such questionnaires allow for Sponsors to further narrow down their list of potential investigators while doing so in a logical and consistent manner.

The next step in the selection process of site selection is to classify the list further based on the output generated by the questionnaire analysis and begin to schedule qualification visits for monitors, so that clinical research associates (CRAs) can evaluate the sites in person. This on-site visit is where a more thorough evaluation takes place, and where particular attention is paid to each of the following:

- The PI and study coordinator interaction
- Appropriate patient population
- Space for a monitor to work when visits occur
- Site processes for record and study material storage (well-organized, or haphazardly stored)
- Interviews with study personnel

A lot of these evaluations are based on subjective assessment that a seasoned monitor can bring to the table. If a site scores poorly on a number of these criteria, it will be unlikely that the Sponsor Company will select them.

Once these two tasks have been completed, sites are scored and ranked, usually through a committee process, based on the questionnaire and site qualification visit. The site selection committee will then proceed to determine which are worth pursuing as clinical sites. A sponsor often chooses a number of sites they would like to use as primary sites with additional sites as back-up sites (should enrollment lag behind the timeline significantly).

This process has been well-established industry wide; however, there is obviously room for improvement since so many sites successfully proceed through the site selection process yet will ultimately fail to perform as expected. Such underperformance is the target of this Internship Practicum Report as it will attempt to outline the problems, possible solutions, and suggest management guidelines that will seek to minimize site underperformance.

Significance

Clinical research is a highly regulated and site-driven process that relies on a coordinated effort between the site, the sponsor, and all vendors providing study-specific services. Sponsors contract the clinical sites to recruit subjects, perform research as outlined by study protocols, and to effectively and accurately record the data in an efficient and accurate method. The Food and Drug Administration (FDA) has strict guidelines about how clinical trials should be conducted, and retains final regulatory approval of any new chemical entity (drug) released in the US market. Since clinical development of novel compounds is such a resource- and time-intensive process, it is crucial that Sponsor Companies derive the greatest value from sites, while at the same time retaining the greatest degree of regulatory compliance and data integrity. Selecting sites that are more likely to perform in accordance with the most widely used standards of site performance (i.e. high recruitment and a low screen failure rate) is believed to be the most effective method for maximizing the return (the subject data that is collected) on the enormous investment in the site. The goal of this paper is to identify and quantify or rank other contributing high performance indicators, such as coordinator experience, research staff training, site infrastructure, Investigator involvement and prior research experience in order to provide Sponsors with further insight into site recruitment that can aid them in choosing sites that will meet enrollment and quality expectations.

Specific Aims

Specific Aim 1: To determine the ideal qualities of a clinical investigative site using metrics such as the ratio of screened to randomized subjects, subject retention rate, site response rate to Sponsor requests, study site personnel turnover rate, number of data queries, and the overall satisfaction with the clinical site by the Sponsor Company.

Data will be gathered from investigative clinical sites already in use by the Sponsor Company.

Specific Aim 2: Use data gathered in Specific Aim 1 to further enhance the Sponsor Company's site recruitment, evaluation, and management techniques in preparation for future studies.

Develop a skills inventory site evaluation questionnaire derived from metrics obtained from currently active clinical sites and integrate this inventory into existing site evaluation methods.

Specific Aim 3: Develop a classification system that categorically ranks sites based on previous performance and specific traits exhibited by the site.

Include non-quantifiable data from Sponsor personnel and anecdotal evidence.

Develop a method, or Working Practice Guideline, for managing sites for each categorical ranking in order to maximize site performance.

Materials and Methods

Through a systemic review of literature, anecdotal accounts from internship site colleagues and personal experiences, Specific Aim 1, was designed to identify those traits that are most important in an investigative clinical study site. Using metrics currently available at the internship site derived from clinical investigative sites already actively enrolling subjects in clinical studies, this Practicum Report correlated the available data of each site (site metrics and the monitor's subjective evaluation) and developed an assessment tool that captures and highlights those qualities that a currently ideal site would, and should, possess. Variables included the rate of subject recruitment, the ratio of screen failures to total number of randomized subjects, the number of data queries regarding subject information, number of protocol deviations, number of waivers requested/granted, and subject retention rates. Anecdotal accounts, obtained via an interview process, from current clinical study monitors and study managers at the internship site were compiled to obtain a better-rounded view of the current success of the site selection process.

For Specific Aim 2, the information obtained from Specific Aim 1 was used to develop a study coordinator questionnaire (or skills inventory assessment) to be administered to the site study coordinator in order to assist the internship site in identifying potential future sites for use in upcoming clinical studies that meet the requirements for the Sponsor. Particular attention was paid to the role of the clinical research coordinator, and how their previous experiences, certifications, training, and skill sets affect the data metrics mentioned above. The site questionnaire is a detailed set of questions, derived from the information gathered from Specific Aim 1, and will be used in conjunction with current site evaluation techniques and current Standard Operating Procedures (SOPs). Questions were crafted from information and anecdotal

accounts from current Sponsor and study site personnel along with information from a comprehensive literature search on the topic. Questions include situational scenarios, specific questions about patient population, questions about previous experience relevant to being a coordinator, the coordinators view of the PI/coordinator working dynamic, as well as their view of the clinical monitor/coordinator interaction process. The questionnaire is not an evaluation of personality in any way, but acts as a tool to identify specific skill sets and site attributes.

For Specific Aim 3, this practicum report developed a classification system that can be used to rank clinical sites according to site attributes, responses to the Site information questionnaire and the study coordinator questionnaire, the opinion of the clinical monitor, and other factors outlined later in this practicum report. Categories were developed with post-hoc data collection and evaluation, and are of a more general nature.

Literature Review: A comprehensive literature review was conducted to evaluate previous attempts to categorically rank clinical sites, as well as to discover any previously published material regarding the effective recruitment of new sites.

Data Collection: Internal internship site data from sites already in use and actively recruiting subjects in clinical studies was used to determine what qualities are most desirable for a potential site, and how these traits corresponded to performance. All data was site specific, with no identifiers of any subject information from any site and was used only to generalize regarding ideal site qualities. Data collected included:

- *Rate of subject recruitment*: The overall enrollment, as well as the rate of enrollment, is driven by the protocol and varies depending on the therapeutic area. Recruitment rates

can vary dramatically depending on the Sponsor, the indication of the investigational product, and the subject population being recruited. When those factors are taken into account, a Sponsor will stipulate their expectations regarding the number of subjects screened per week/month during the site evaluation and selection process. If a site failures to meet those expectations, then 'rescue' actions will likely be taken to boost the screening and randomization rate up to acceptable standards. It is important to note, however, that while recruitment and retention of subjects can be a major focal point of a Sponsor's efforts regarding site performance, it is the responsibility of the PI and the investigational site to ensure that they meet the expectations of the Sponsor Company.

- *The ratio of screen failures to total number of randomized subjects*: This metric is a very useful tool for determining how well site personnel can identify subjects that would be expected to qualify, and depending on the complexity of the protocol, can provide insight into how well the site personnel understand the enrollment criteria for that study. Since clinical studies are very controlled and have a large and very specific set of inclusion and exclusion criteria, it is important to recruit subjects that are the most likely to pass screening tests and qualify for the study. Although screen failures are an accepted part of clinical research (the cost of doing business), a high ratio of screen failures to randomized subjects could indicate any number of problems:
    - Insufficient subject chart review by the research staff
    - Screening by non qualified site personnel
    - Inadequate protocol training of site research personnel
    - Inclusion/Exclusion criteria that are too restrictive
    - Incomplete medical history from subjects referred from other physicians

- *Number of data queries per site regarding subject information*: Data queries, while variable, can provide a small part of the picture of overall site performance. A query, in broad terms, is a situation where the source data and the data entered into data capture systems don't match and a question to clarify has been issued. Normally the Sponsor will issue a query to a site and request clarification. In part this process depends on the quality clinical monitor(s) (some monitors just issue more queries than others), the quality of the sites' quality check (QC) process, the quality and experience of the coordinator, and on the quality of the data capture system (i.e., use of paper case report forms vs. an electronic data capture system that will auto query out of range values). Too many queries can signify a problem at the site with data entry, and too few queries can signify insufficient clinical monitoring at that site that would result inconsistent and contradictory data (although this is not always the case). It is important to acknowledge that while queries are troublesome and time-consuming from a site perspective, an appropriate number of queries can provide some reassurance to the Sponsor that proper due diligence is being done.
- *Number of protocol deviations*: Protocol deviations occur when study procedures and instructions have not been followed according to the protocol. Protocol deviations can be a very powerful, and misleading, indicator of site performance. While deviations from protocol are never a 'good' thing, strictly speaking, the type of deviations can vary from simple out-of-window deviations to major issues such as unauthorized drug holidays or missing lab draws. Depending on the type of deviation and its impact on the study, the total number of deviations is only a minor indicator of site performance. However, if

classified into major and minor categories, the number of 'major' or 'critical' deviations can be a very useful tool in site evaluation.

- *Subject retention rates*: Retention rates are critical in clinical studies, for obvious reasons. Not only do subjects represent an enormous investment in time and resources (both for the site and the Sponsor), but also a high dropout rate can adversely affect the study outcomes as a whole. Low subject retention rates can signify deeper problems within the study, depending on whether these discontinued subjects are the result of adverse events or not. Adverse events, while always a factor in at least some discontinued subjects, are not the only reason; prominent examples include subjects that fail to return for study visits, patients that withdraw consent (for various reasons), patients that begin to feel better and wish to stop study procedures, or subjects may simply want to stop for no reason at all. All such factors contribute to s study's retention rate, and much of the onus of subject retention falls on the site. In ideal situations, the site will take into account the likelihood of the subject completing all study procedures prior to enrolling the subject.

Interview: The interview process lasted approximately 30 minutes to 1 hour per subject interviewed, included only internship site personnel currently involved with ongoing clinical development that involved interaction with clinical sites. A standard questionnaire was developed as a basis for the interview.

Site Questionnaire: The site questionnaire was developed in order to aid the internship site in identifying sites that will more likely perform up to expectations. All questions were developed by the student investigator, and are intended to be taken by the site coordinator during the Site

Qualification Visit as part of the internship sites standard Working Guideline for the purpose of identifying certain site attributes as categorized in this research proposal. Questions are either multiple choice or fill-in-the-blank.

Categorical Ranking System: A categorical ranking was developed, based on measured site attributes and traits, answers to questionnaires, Sponsor personnel qualification assessment, and other factors that will assist them in the site selection process at the completion of the evaluation period. Assignment of rankings, or ratings, provides a more easily quantifiable metric (i.e., a grade) based on information gathered during the site evaluation process.

Results and Discussion:

Literature Review:

The issue of non-productive clinical sites is a well-documented and well-known problem in the industry; as such there is a wealth of information that describes the problems and complications involved. However, when searching for methods and strategies to minimize the impact, or to avoid and alleviate the issue, the literature available is only recently beginning to show methods that are being developed for more effective site selection. Opinions on how to deal with the problem range from selecting only those sites with a proven record of above average performance, using data metrics and equations (when available) to assess a site's performance, or outsourcing such qualification to third party companies that specialize in site recruitment. Other suggestions include the 'front loading' of studies - using site activation as the primary metric - or taking steps to encourage greater risk-taking by PIs when it comes to screening (resulting in higher screen fail rates) in order to generate faster enrollment of viable subjects.[7,8] With such a wide variety of opinions and ideas, a thorough literature review will illuminate any and all methods for improving site performance.

Neuer (2006) has suggested using established PI databases, instituting greater site accountability (via greater transparency), and incentivizing 'win/win' behavior as factors that lead to more effective clinical sites. She defines the desired elements as time to site readiness, how the site enrolls subjects relative to other sites, number of data queries, the time to resolution of queries, and screen failure rates.[3] When searching for new PIs and sites, the use of newly established PI databases can aid sponsors in identifying potential sites. Most databases that are being developed take into account data metrics derived from previous experience with that site in other clinical trials. If a site performs well on a previous trial, the odds are favorable that the site

will continue to perform up to par. Requiring increased site accountability can put more of the onus on the site to perform, thus leading to better performance. A new company called TrueTrials has developed an eBay style system that collects metrics from sites across geographic regions and then compiles this data and publishes the results via a rating system they developed. This sort of rating will encourage sites to maintain a high level of performance or risk damaging their rating, and thus, eliminated the possibility of future research being directed to their site. Such a system will, in theory, aid Sponsors in their search for productive sites, and sites that maintain a high performance rating will be solicited to participate in future trials. This presents the sort of "win/win" behavior that Neuer believes provides the greatest chance of an effective defense against recruiting sites that have a history of underperformance.

Davis (2007) has developed a study management tool for retrospective site evaluation based on an equation derived from metrics or site performance gathered from previous studies.[9] He posits that the two most important factors (enrollment rate [ER] and compliance rate [CR]) can be used to derive an objective measure of a site performance; thus, enrollment multiplied by compliance provides the performance score (PS). ER is the number of subjects enrolled at a site divided by the highest number of enrolled from any site. CR is the number of protocol deviations divided by total number of study visits monitored and subtracted from one.[9] ER is relatively easy to obtain (it relies on data points that are consistently measured across the industry); however, CR is dependent on the quality of the monitoring being done by the clinical monitor (CRA), and potentially dependent on the quality of the protocol (since deviations could be a result of a poorly written protocol). Since this can only be used as a management tool retrospectively, it has little value in forecasting site performance if no data metrics are available in advance of site qualification.

Marcarelli et al. (2007) conducted a review of medical device clinical investigators across the country to attempt to define exactly what qualities or actions had the greatest effect on site performance as derived from FDA clinical audit reports.[5] They postulated that the most productive sites would be located in densely populated regions, would have a large study staff available, and be would monitored on a regular basis; however, their findings were not always consistent with that view. During their review of the available data, Marcarelli concluded the following five points: 1) clinical site personnel were generally well trained, 2) site monitoring is important, 3) proper oversight by the lead PI is important regardless of the number of years of experience of any sub-investigators, 4) staff turnover is more important than size, and 5) high performing sites had very complete and accurate documentation procedures in place. However, their findings were not consistent with their hypotheses; roughly 62% of these researched sites were in regions with smaller populations (less than 500,000), and the size of the study staff was generally only 1 person, the study coordinator.[5] A well-trained and well-supervised research staff along with active and proper PI oversight were determined to be the most important factors when evaluating clinical sites, according to the authors.

The *Journal of Clinical Research Best Practices* published a series of articles regarding the topic of site performance, written by Dr. Hugo Stevenson from the multi-national CRO (clinical research organization) Quintiles, Inc.[10,11,12] The articles first postulate that the "product" of the research (i.e. the subject data) is generated as a byproduct of subject care, which is an extra workload for the site; as such the subject data acts as a hurdle that one must overcome through the combination of investigator motivation, external support from the sponsor, and an appropriate level of study site infrastructure.[10] If the Investigator has a high level of motivation, but a low level of support from the Sponsor and inadequate study infrastructure, the results of the

study will be less than satisfactory. Inversely, if the site has a very well-trained and established infrastructure and at least moderate support from the sponsor, the level of investigator motivation plays only a minor role on the quality of the data collected. It can be argued that while Sponsors will choose a PI based on any number of different criteria (key opinion leader, patient population, research experience, etc.) the most important factors are the sites research infrastructure and previous research experience that determine the quality and performance of a site. However, the problem is compounded in that sites with such extensive facilities (with the accompanying financial overhead to maintain research staffs) treat clinical research as a "business", and will focus their efforts on earlier Phase II and IIIa studies which tend to pay higher per-subject fees than late stage trials (phase IIIb and IV). This kind of 'refocusing' at some sites, presents a large problem for Sponsors. Even though a site may have performed admirably in a previous study protocol, if conducting a late-phase trial, the performance could potentially drop and, thus, puts the Sponsor Company in the position of having to 'rescue' the study with expensive techniques that attempt to compensate for disappointing enrollment.

Li, a leading pharmaceutical executive with a well-regarded assessment of this area, argues that recruitment is predictable in its unpredictability.[7,13] His opinion is that recruitment will always be a problem, and thus rather than 'expecting' sites to perform, you have to expect sites to *under*perform--thus his idea of 'front-loading' the study from the outset and improving site activation time to bring sites on faster (thus allowing them more time to recruit the required subjects). Front-loading is the concept of initiating more sites than a Sponsor would normally expect to need to meet enrollment guidelines while site activation is the time it takes to initiate a clinical site. If a clinical study is expected to require 100 sites for a phase III protocol, with 25 sites identified as potential back-up or 'rescue' sites, why not simply initiate the additional 25

rescue sites from the outset? In addition, improving site activation time will reduce the amount of time to first subject screened/randomized, which in turn will contribute to the prevention of timeline overruns and missed enrollment deadlines. According to Li, the goal of clinical site recruitment is finding the 'sweet spot' between the number of sites, and the resources available for site activation and recruitment.

By being able to predict under-recruitment and under-performance (recent literature and evidence suggests that up to 80% of studies are behind schedule due to recruitment and retention issues), Sponsors can account for this in your site-need calculations and will be able to compensate for the 'usual suspects' of slow recruitment and poor retention. By having the additional sites up and running from the very outset rather than having to initiate sites *post-facto* and incurring costs in the delay of clinical approval and development of the investigational drug or device.[7] Obviously additional upfront cost is a concern in this approach, especially for smaller start-up companies with limited capital to invest in additional site start-up fees, but it can be argued that the additional investment up front will pay dividends over the length of the trial.

Li also advocates the mantra of 'site activation' when discussing meeting enrollment timelines.[7] It takes a considerable amount of time and money to get a site from the selection stage to the enrollment stage, a period of time that can vary from site to site. The process involves obtaining IRB approval, contract and budget negotiations, study and vendor training, as well as scheduling site initiation visits by clinical monitors; all of these steps take time and money. Start-up costs tend to average $20,000/site in the pharmaceutical industry, not unsubstantial costs for sponsors considering a study with between 50 and 200 sites.[7] For example, if a Sponsor sets a 9-month timeframe on enrollment, it is most cost-effective and time

efficient to have as many sites as possible actively recruiting subjects for as much of that time as possible.

Goldfarb postulates that while site information questionnaires, sent out to sites by a Sponsor in an attempt to narrow potential sites for upcoming studies, are a widely used and very common tool; they are less than ideal at predicting future site performance.[14,15] Questions are posed primarily in true/false or multiple-choice fashion, which leaves little room for reading into the subtext of a site's ultimate ability to perform. Questions should be focused and specific, but at the same time, broad enough that the answer choices don't constrain the test taker to formulaic answers--it's a fine line to tread. The author makes note that it is often the more involved "war stories" that a site monitor, or qualifier, will hear while on site for qualification that will ultimately give the most significant insight into the site and its ability to deal with the complexities of a clinical study protocol. Therefore, the author gives some advice when designing and implementing site information questionnaires:

- Design questions that don't necessarily have a 'right' answer; understand a site's thinking process or standard operating procedures (SOPs) is more useful than right and wrong answer choices
- Be clear and unambiguous-- the more precise the questions, the more precise the answers will be
- Make sure that responses can be easily interpreted and collated
- Have predictive validity (but this can only be demonstrated over time)

Well-designed questionnaires should accurately pinpoint sites that should fit in well with the demands of the Sponsor. It is also very important to ensure that the site will be able to adjust

to working with a different Sponsor's new working methods and different demands and expectations. The site information questionnaire should be a tool used by both Sponsors and sites to ensure that both can agreeably work together to conduct the research. It's a two-way street; it's important to know (from a site's point of view) that a site can handle the demands of the Sponsor because some Sponsors do place extraordinary demands on sites.[14, 15] It serves no purpose if a site is unrealistic and answers the questions very optimistically; one of the most important aspects of the site information questionnaire is the two-way conversation between the sites and the Sponsor. Only with frank honesty can both sides' needs be properly served.

Table 1: Summary of Most Relevant Literature Regarding Site performance and Selection

Author	*Hypothesis*	Conclusion
Neuer	*Instituting greater site accountability will increase site performance by creating a win/win scenario*	Suggests that a rating system be instituted, possibly as a paid service, that will aggregate data metrics from sites in order to develop a rating system. This presents incentives for site to perform well, and provides Sponsors with important previous data metrics on performance
Stephenson	*Postulates that site selection is a result of three factors: site work-load, investigator motivation, and external support.*	Outlines a number of techniques that Sponsors can use to improve PI motivation, provide support for the investigative site, and minimize the required workload of the site in order to boost performance and build relationships with investigators.
Davis	*Developed an equation that combined with previous performance metrics can*	Enrollment rate multiplied by the compliance rate equals a performance score (as % grade). Can only be used

	qualitatively rank sites.	retrospectively by Sponsor to 'grade' sites.
Macarelli	*Attempted to define those traits that are most indicative of high or low performance.*	Well-trained and well-supervised research staff was determined to be the two most important factors when evaluating clinical sites. Interestingly, sites in less densely populated regions had higher measures of performance.
Gen Li	*Argues that the twin pillars of timely clinical research are front-loading site numbers and decreasing time to site activation.*	Suggests that Sponsors recruit more sites than anticipated, while at the same time improving site activation time. If sites are activated as early as possible during the enrollment window, that will allow for more time to recruit the required number of subjects into the study and thus reduce costly delays.
Goldfarb	*Believes that questionnaires can be very useful in evaluating potential sites, with the caveat that honestly and realism are important.*	An intelligently designed questionnaire, filled out realistically by the site personnel can serve both sides well. It is important to match sites and Sponsors together, since clinical research is a collaboration between the two. Without frank conversation, in-depth evaluation, and honest answers, both sides suffer.

Source: From multiple sources, see reference for full citations.

Ideal Site Attributes

Through a literature review, discussion with internship site personnel, and review of their database metrics, below are the most important attributes of a clinical site. Below are some of the metrics that had previously been collected by the internship site (as is general practice within the

industry), and a review of how each metric can be expected to correlate to overall site performance.

- *High rate of subject recruitment*: The total number of randomized and enrolled subjects is the paramount concern for Sponsors and CROs. Without subjects, clinical studies would never be able to generate efficacy and safety data from human subjects, and new therapies would never get approved. Subject randomization is the most frequently cited performance goal. Sites are expected to enroll a set number of subjects, which is outlined prior to site initiation. The enrollment goal varies from study to study and sites that do not meet enrollment goals and timelines will be subjected to more frequent communication from the sponsor.
    - Sites with larger more dedicated research facilities, and sites with more active PIs, trended toward being the highest enrolling sites in a recent internship site clinical study.[21] Thus is can be surmised that larger and better staffed sites are better equipped to enroll large numbers of patients, particularly those in areas with robust patient populations.
- *Trained and experienced research staff*: Things that get taken into account are the level of training and certification of the study coordinator. Certification through the Association of Clinical Research Professionals (ACRP) the Society of Clinical Research Associates (SoCRA) conveys some weight. Staff training in GCP is the gold standard and required by Sponsors as well as the FDA when conducting clinical trials. When selecting sites, it is worthwhile, from a Sponsor point of view, to inquire about previous training with lab vendors, electronic data capture (EDC) vendors, or any third party companies being used as part of the protocol study procedures. Previous training and familiarity with

these vendors could make the study start-up procedures more efficient and decrease the time to start up.

    - Sites with experienced research staff have usually fared significantly better when it comes to metrics like number of deviations and subject retention rates.[21] The greater experience of a site also manifests in time to first subject screening / randomized subjects. It can be surmised that more experienced coordinators are often more familiar with the processes that govern study and site start-up procedures.

- *Sufficient research infrastructure to support a clinical study and PI oversight*: With qualifying clinical sites, it is important to take inventory of the site's research infrastructure; i.e., does the site have access to a centrifuge for lab samples, an ECG machine, freezers for sample storage, dedicated research offices separate from standard subject care facilities?

    - Infrastructure also refers to staff (number of dedicated research professionals), standard operating procedures (SOPs), as well as processes in place to ensure proper oversight by the PI. Ideally, a research site would have at least one dedicated study coordinator working full-time along with several Sub-investigators and a research director/regulatory contact that takes care of the larger management aspects of the clinical research practice. SOPs are important for maintaining consistency across situations, and they provide further evidence to the sponsor that the site in question is likely to be more experienced with conducting research. It is also important that larger sites have processes in place to ensure that proper PI oversight if taking place and is well documented.

- *Excellent PI/study coordinator interaction*: While on site during the qualification visit, it is important that the sponsor representative gauge the interaction between the Principal Investigator and the study coordinator. Currently there is no scientific methodology for accurately and reliably measuring this subjective variable; it's an important indication of the level of involvement of the PI and provides insight into the working relationship between the two most important members of the clinical research team at the site. Since they are the most important site personnel, it is important that they have well defined roles and excellent lines of communication. Challenges often arise in the course of a protocol, and it's important (from the Sponsor's perspective) that the site continue to provide the sponsor with consistently clean data while always adhering to good clinical practice (GCP). A breakdown in PI-coordinator communication can present the sponsor with very complicated problems, ranging from slow subject recruitment, poor information flow regarding subject oversight, or more serious lapses in reporting of adverse events and a lack of proper PI oversight.
    - This metric is best quantified on a sliding scale (i.e. rated on a 1-10 scale) by a trained and experienced clinical monitor during the in-person site qualification report. One of the challenges with this approach is the ability to have one-on-one interaction with the actual study coordinator that will be assigned to the Sponsor's protocol. In smaller sites this sometimes does not become an issue, however with larger sites that have a larger study staff it can be difficult to forecast which coordinator will be assigned to your study.
- *An active and involved PI* is an extremely valuable commodity in clinical research. A PI with a very active scientific interest in the study drug or device is more likely to be

actively involved in recruiting subjects, more likely to see subjects rather than delegate to a sub-I or research nurse, and will be an advocate of the drug if and when the drug makes it to market down the road. Active PIs generally have higher enrollment rates, fewer discontinued subjects, and will generally have a quicker start-up time and time to first subject randomized. In an industry where time is money, this attribute is highly coveted.

    - Internal internship site clinical data supports the assertion that an active PI is key to maximizing the Sponsor's return on investment. Sites with active PI consistently had higher enrollments rates, fewer screen failures, and took less time to screen and randomize their first subjects.

- *Low screen fail ratio*: In the review of internal data, it was found that sites that had higher screen fail ratios were considered to be lower ranked in most every other category of evaluation. In the budget negotiation process, compensation for screen failures can vary dramatically, but most Sponsors will pay a per-procedure fee for such screen failures as a cost of doing business. Screen failures can result from inadequate chart review, poor inclusion/exclusion criteria review, labs that may have improved or regressed (thus eliminating that subject from the study), or any number of other complications. A common practice of capping the allowable number of paid screen failures can help to minimize costs somewhat, but also runs the risk of slowing recruitment if PIs feel screening borderline subjects is too risky without the guarantee of compensation from the Sponsor.
- *High subject retention rates*: High subject retention rates were consistent with the finding that 'better' sites had much higher rates of subject retention than 'below average.' Discontinued subjects cost the Sponsor, both in the lost investment in that subject as well

as the data that will not be captured for whatever portion of the study that was not completed.

    - Subject retention also trended well with active and engaged PIs.

- *Below average number of queries per case report form (CRF):* This is an important indicator of the site's ability to accurately enter data into the EDC and reflects on both the sites experience level and overall quality of the staff conducting research.
    - Sites that were rated as 'better' consistently had average, or below average, number of queries per CRF.[21] This leads to the conclusion that better sites have methods and working practices in place to ensure the accurate transcription of data from source documents into the EDC systems, which reduces the number of queries from the Sponsor.
- *Number of deviations*: With such a wide range of possible protocol deviations, a classification system for deviations should be developed in order to more easily determine if there is a problem at the site level, or if they are minor deviations (such as out-of-windows visits).
    - Deviations do correlate to positively to poor performance; however, it is important to note that this applies only to deviations that are classified as major deviations.[21] More minor deviations such of out-of-window study visits do not correlate to site performance.[21]
- *Number of waivers granted*: The number of waivers that are granted to a site by the Sponsor is sometimes related to the number of protocol deviations. Waivers are generally undesirable from the Sponsor perspective, as they are indicative of protocol deviations or less than desirable situations. For instance, a subject could present with lab values that are

slightly out of range. The medical monitor could be contacted and, in conjunction with discussions with the PI, it could be decided to provide a waiver to the subject.

- While waivers do happen, there is a trend in the industry towards doing away with waivers altogether. Some Sponsors no longer allow waivers to be issued to sites, for any reason, and instead prefer strict adherence to the protocol.

Evaluation of Clinical Sites Already in Use by Sponsor

Using the site evaluation tool developed by Jason Davis[9], Table 1 shows an example of 10 hypothetical well performing sites were they to be ranked. The tool is an equation based on enrollment rate multiplied by compliance rate to give a total performance score (expressed as a percent grade). Enrollment rate (ER) is the total number of randomized subjects divided by the highest number of subjects randomized. Compliance is calculated by taking the total number of deviations per site divided by the number of monitored study visits subtracted from one.

Randomized subjects ÷ highest randomized total	**= Enrollment Rate**
1 – (deviations ÷ monitored study visits)	**= Compliance Rate**
enrollment rate X compliance rate	**=Performance score**

Table 2: Top 10 Clinical Sites as Evaluated by the Performance Score Tool[2]

Site	Randomized	# of Deviations	Enrollment Rate (ER)	ER2	Compliance Rate (CR)	Performance Score (PS)	PS2
1	21	29	1.00	2.10	0.93	93%	195%
2	15	12	0.71	1.50	0.96	68%	144%
3	13	2	0.62	1.30	0.99	61%	129%
4	10	5	0.48	1.00	0.97	46%	97%
5	9	6	0.43	0.90	0.96	41%	87%
6	9	6	0.43	0.90	0.96	41%	87%
7	10	30	0.48	1.00	0.84	40%	84%

8	8	3	0.38	0.80	0.98	37%	78%
9	9	22	0.43	0.90	0.87	37%	78%
10	8	18	0.38	0.80	0.88	34%	71%

Table 2 illustrates that site performance can be easily quantified, with this example being only one of many methods used to rank and quantify site performance. In this hypothetical example, it lists the top ten highest ranked sites (according to this ranking tool) and the variables that it takes into account. This particular tool places considerable emphasis on two things; enrollment and deviations. In this case, there were 3 sites that enrolled more subjects than were initially expected, and since the denominator of the ER is the highest total of randomized subjects it puts sites that enrolled a lower (but still more than acceptable) total number of subjects in a rather harsh light.

Randomized subjects ÷ enrollment goal	**= Enrollment Rate 2**
1 – (deviations ÷ monitored study visits)	**= Compliance Rate**
enrollment rate 2 X compliance rate	**=Performance score 2**

This explains the ER2 and PS2 columns in Table 2, as the ER2 is an enrollment rate where the denominator is the expected number of subjects (rather than the highest enrolled total of ER1) that sites were anticipated to enroll, as such the top three sites then have exaggerated PS2 scores due to the inflated ER2 values with this new calculation. This sort of data manipulation is an example of the kind of care that Sponsors should take when using this kind of tool to evaluate site performance; the context and situation should always be taken into account prior to making conclusions about the data.

Outside of the top 10 sites (45 total in this study) the remainder of sites fell into the industry average of non- or under- performance; between 20-30 % enrolled less than half the

number of subjects of the enrollment goal set out prior to study initiation. While not unexpected, this underperformance can be a problem for a small start-up company with limited resources and time. With enrollment shortfalls being the primary cause of failure to obtain FDA approval across the industry, it is important to realize that delays this problem represents roughly $1 million of potential lost revenue per day of delay (depending on the indication for which the study drug is targeted).[16] With such heavy costs associated with these delays, it is important that Sponsors consider alternative methods to improve site performance in order to beat the well-established industry averages and develop long-term relationships with sites that have a track record of high performance while building an internal database of investigators in order to facilitate more efficient selection of Investigators for future clinical programs. This kind of site evaluation can aid Sponsors in the site selection process for future studies, and it can be expected that sites that fail to score well on measures such as this one will be less likely to be used by the Sponsor Company moving forward with other clinical studies.

Methods to boost site performance

Since it is difficult to beat such industry averages of a 20-25% non-productive rate, as outlined previously in this practicum report, it is important to have a solid strategy in place in the event of underperformance. The first step in this process is to set certain markers for poor performance; these markers (see Table 3: Lagging Performance Indicators) should be considered signals for immediate and strong intervention on the part of the Sponsor--'rescue actions.'

Table 3: Lagging Performance Indicators

Red Flags that Suggest Lagging Performance
Sloppy data (excessive queries or source inconsistencies)
High number of major protocol deviations
Slow subject recruitment
High discontinuation rate

Above average screen failure rate

Since site performance is such a fluid and variable concept, it is important that the methods to boost performance be just as fluid and variable. As part of Specific Aim 3 of this Practicum Report, listed below are a number of management techniques that can be used to boost site performance.

1. Additional site training

Providing additional training to a site is just one of the gold standard practices of improving site performance with the curriculum being either protocol, GCP, or study specific. New site personnel may have started since the Investigator meeting, and a clinical monitor could provide the additional protocol-specific and GCP-related training to aid the site in more effective research methods. With the more difficult protocols that involve more frequent and more complicated laboratory draws, daily diaries, or glucose logs, it is important that all research staff be well-trained in all aspects of the protocol and the intricacies of the study procedures. Sponsors are placing increasing demands on study staff in this regard and are often disappointed at the results, which is why on-going site training is key to maximizing performance.

Vendor-specific training can also dramatically improve the quality of data being gathered from clinical sites. Electronic data capture (EDC) has quickly become the standard of data capture in large multi-center clinical trials.[6] It is important that study staff be trained to use EDC vendor being used for that specific study, with these vendors usually providing training alongside Sponsor training at Investigator meetings. If the study is using an outside laboratory for sample analysis, be sure that all study staff have been properly trained on all aspects of the sample collection, shipping, and labeling processes to reduce the number of ruined or mislabeled samples. These kinds of issues tend to crop up consistently in larger studies and they cost both

the Sponsor and the site when problems arise. Prevention is the preferred method of problem solving; however, if problems such as those listed in Table 3 begin to surface, then one-on-one training by the CRAs or other Sponsor personnel should be arranged to ensure protocol compliance and good clinical practice.

2. Recruitment encouragement

One of the easiest (but costliest) performance-boosting actions that can be taken is to incentivize the site to enroll additional subjects. This can be done in any number of ways: increase the per-subject fees, add milestone incentives that encourage sites to hit certain enrollment goals within a pre-defined timeline, up-front payments in lump sums to help with start-up processes, or increase the amount of compensation for screen failures (thus encouraging the site to screen more aggressively).

These methods have only so much merit, however, and monetary incentives do not always work. Sites with smaller, or less than ideal, patient populations likely will not be able to boost enrollment regardless of the payment incentives (but could possibly be encouraged to boost performance in ways other than enrollment). Increasing payments to sites also assumes that clinical research sites are heavily influenced by monetary compensation when this is not always the case. Extraneous factors complicate the ability of sites to enroll and randomize subjects, and Sponsors should use monetary incentives only in certain circumstances where there is a clear problem (i.e. where the PI feels that excessive demands have been placed on sites than was originally expected, thus requesting additional compensation). Another factor to consider when monetizing enrollment is the recent PhRMA Guidelines, which places considerable restrictions on what Sponsors can and cannot provide as motivation to sites.[17] These recent guidelines have

also placed considerable emphasis on eliminating Conflict of Interest of the PI, and such incentivizing payments are increasingly being seen as undue influence on the PI for the outcome of the research. Sponsors should be very wary of such incentivizing payments, as they are increasingly being scrutinized by the FDA.

Therefore, rather than incentivizing subject recruitment, it could be beneficial to incentivize site activation time as advocated by Li. Time to IRB approval and time to first subject screened/randomized are both interesting targets for 'milestone payments.'

3. Introduce competitive recruitment environment

There is some evidence to suggest that introducing a competitive recruitment environment could assist Sponsors in meeting enrollment timelines. Publishing enrollment numbers, either in company newsletters or during PI/coordinator conference calls, can 'shame' some underperforming sites into refocusing their efforts. Sometimes, just the competition raises the bar, when sites feel like they are competing for a prize or bragging rights; either way, this is yet another tool that Sponsors can use to re-energize a site to perform up to expected standards.

4. Hire part time CRC for data entry (last resort): send CRA to 'babysit' a site

Inconsistent data, as indicated by a high number of outstanding queries and above average queries per form, are the trademarks of poorly executed research at clinical sites and often the most visible indicator of looming problems. One method to resolve these issues is to increase CRA monitoring visits both in number and duration. Although this method is less than ideal, since it is a 'rescue' action rather than a preventative measure, it does have a well-established place in the arsenal of any Sponsor Company. The first step is to identify the issues that are causing the sloppy data (i.e. an inexperienced coordinator, poor EDC training, inadequate

resources), and then have the CRA onsite to assist the coordinator/PI with solving the problem, or to provide more one-on-one training for the coordinator.

Another solution that can be utilized by the site is to provide funds to hire a part-time contract study coordinator for a given period of time or by having the Sponsor locate and provide the needed personnel through a contract firm. The additional trained coordinator could provide the extra push to have data cleaned and entered, while freeing up the primary coordinator to refocus their efforts on subject recruitment, retention, and study-related procedures. This kind of approach does have a relatively positive track record of success, but much depends on the quality and experience of the part-time coordinator(s) being provided to the site. It is important that the Sponsor Company thoroughly review the candidate's curriculum vitae and ensure that their qualifications meet or exceed Sponsor expectations. Providing a less than ideal 'hired gun' will provide less than ideal results (at best) or compound the problem and alienate the clinical site staff (at worst). Again, this is a method of last resort; it is an expensive solution to a preventable, and all too common, problem that is far more reactive that is normally desired. More preventative action is always preferred to reactive solutions like those outlined above.

Subject Retention

Subject retention is a factor that can make or break a clinical study. If the retention plan is poorly planned, either in conception or execution, the number of discontinued subjects will begin to surpass acceptable values, and the clinical development program may be halted in its tracks before gaining momentum. There is a wealth of literature on the topic of subject retention, with as many opinions as there are people in the field, but that does not mean that there are not any number of methods that Sponsor Companies should be able to easily implement that will bolster subject retention rates.

Table 4: Boost recruitment and retention

How to increase subject retention
Encourage subject/site relationship building Provide informational pamphlets and materials to the subject Develop relationships with high enrollers and active PIs Educate subjects and PIs about common AEs

One common and relatively successful method of retaining subjects is to provide subjects with retention materials. PhRMA guidelines allows for Sponsors to provide limited retention materials that relate to the study drug or the disease/condition being studied. Providing study-related supplies and materials to subjects can go a long way in showing patients the value (for them) of remaining an active subject in the clinical trial. For example, in the case of a diabetes trial, a Sponsor could provide Sharps containers, educational materials to educate subjects about their disease and coping methods, glucose monitoring strips, and diabetic socks free of charge to all subjects as they complete certain time-dependent milestones within the treatment phase of a study. Prescription cards, which patients can use to purchase their required concomitant medication are also very useful methods of recruitment and retention; it also benefits the Sponsors by ensuring the subjects will be able to continue on any required concomitant medications (preventing protocol deviations) required by the protocol. These things may seem small to an outsider, but small gifts can go a long way in keeping subjects focused on the benefits of the study drug and their contribution to science.

Education can also go a long way in keeping students committed to the study and compliant with their medications or treatments. It can be useful to provide subjects with a pamphlet or newsletter outlining some of the aspects of the investigational product as learned during the clinical trial. Keeping the pharmacology at a lay person level with plenty of illustrations and a clear outline regarding the risks and benefits of the study drug can really help

subjects understand what kind of medication they are actively taking (if not on placebo, obviously). The educational material could also include more information regarding some of the more common adverse events that have been observed in previous studies with other subjects. By outlining the risks very clearly, the educational pamphlet can also provide strategies for minimizing the impact of these side effects on a subject's daily life.

Study Coordinator Questionnaire and the Impact of the Study Coordinator

Table 5: Coordinator Traits

Ideal Coordinator Traits
Attention to detail GCP knowledge and experience Excellent line of communication with PI Understands/respects role of clinical monitors Grasps the importance of PI oversight

The most consistent and unequivocal conclusion from the literature review, internship site personnel interviews, and personal experience (from both this internship and previous industry experience) is that having an experienced and well-trained study coordinator is the most significant factor that determines site performance. Thus this questionnaire's main goal is to identify those traits that the internship site deems to be the most desirable in a trained and experienced coordinator, as outlined in Table 5. The questionnaire was designed to be taken by the site coordinator to be assigned to a study, or by the site manager, and should aid in streamlining and improving the site selection process.

Classification and Ranking Tool for Site Selection

As part of this practicum report, a classification and ranking tool was developed in order to aid the Internship Site in the final stage of site selection at the conclusion of data collection regarding sites. Throughout the process of site selection and evaluation, large amounts of data are collected regarding the site from various sources. With such varied sources, it can become difficult to cull through all the available data in an efficient and effective method. Using the data collected, a final ranking can be calculated. Using the categories listed below, each site can be ranked from 1 to 5 (1 being the low least favorable and 5 the more favorable) in each of the categories, with the final score being the sum of all the others. Site with a higher final score could potentially be considered potentially better.

- Experience in Therapeutic area: choosing a site that has experience (and the proper subject population) in a particular therapeutic area will increase the odds of obtaining an adequate subject population and reduce screen failure rates. If a site has to work too hard to find subjects, performance suffers.
- Competing Studies: the number of competing studies being conducted at a site brings up the concern that each site would cannibalize the others subject population, making recruitment difficult for both studies. 'Good' sites realize this and attempt to avoid this situation by ensuring that competing studies do not have overlapping enrollment periods.
- Location: geographic location can sometimes factor into the decision to use a site. From the Sponsor perspective, a site in a remote location would be more expensive to travel to and require longer travel times to reach. This in turn raises the cost of business at the site,

in terms of monitor travel and expenses. Being able to have several site in smaller geographic ‘pockets’ maximizes usage of available resources and reduces the strain on the monitoring workforce.

- Administrative Considerations (IRB/Regulatory concerns): Sites that are able to use a central IRB (that is a third party IRB not affiliated with any one particular institution), reduce the cost and time commitment of Sponsors considerably. Sites that have a local IRB, primarily VA, hospital, and academic sites, require far more regulatory paperwork than those having a central IRB. From a Sponsor perspective, it is often much preferred for a site to be able to use a central IRB. This cuts down on IRB fees and reduces the time to site initiation.
- Personnel: The information gathered during the questionnaire and site qualification visit process should be used here to assign a score based on a site’s quality and quantity of trained and available research personnel. This category takes into account more than just the number of study staff; the average level of research experience, GCP training, and any certifications from accredited organizations should also factor into the equation.
- Access to Proper Subject Population: Based on the available data from this site, does the site have access to an appropriate and large enough subject population in order to recruit an acceptable number of subjects? Other factors include their expected number of screened subjects per week and the number of subjects in their database.
- Interdepartmental Relationship: this category should be used to score a site on its expected ability to cooperate between departments (if an academic site) or between practices to obtain subject referrals from other sites. Since recruitment is the driving force behind clinical research, it is important that a site make every effort to obtain as many

qualified subjects as possible, and referral networks can be an effective method to do just that.

- Overall Monitor Impression: This category is designed to provide a ‘gut feeling’ of the clinical monitor, or other Sponsor personnel, that conducted the site qualification visit. This should take into account all the intangibles regarding a site. Things to take into account includes: body language of the PI and coordinator interaction, rapport between study personnel, gut feelings of the monitor regarding how prepared this site would be to take on a particular study protocol. This is a subjective measure, but one that depends on having a qualified and trained evaluator on hand to perform the task of site qualification.

The categories listed above represent only an outline of what can be adapted by a Sponsor for use in their working guidelines. The overall goal of the category ranking tool is to input all information gathered during the selection process and output a single final score that can be used by a Sponsor to quantify the overall value or expected performance of a site, thus aiding the overall site selection process

CHAPTER III

Internship Experience

My internship experience has been an exciting opportunity and an extremely productive learning experience for me. As a member of the clinical team, I was exposed to mid-to-late stage clinical trials with an exciting new drug compound XXX, in a fast paced and exciting team-oriented work environment.

Primary duties included any number of tasks that were asked of me by either of my internship mentors including, but not limited to, data trending and analysis, study start-up procedures, in-house monitoring, database lock assistance with ongoing trials, and study-maintenance tasks. Being exposed to the fast paced environment of a small start-up pharmaceutical firm has given me the opportunity to experience clinical development of novel compounds from a wide lens perspective with exposure to multiple aspects of clinical research. See appendix 3 for the daily journal log, briefly outlining my daily tasks during my internship practicum.

Internship Site

My internship site is a start-up biopharmaceutical company, currently developing drugs for cancer, inflammation, and neurodegenerative diseases. It offers antioxidant inflammation modulating drugs, as well as drugs that correct protein mis-folding. The company also develops drugs for the treatment of renal/cardiovascular and autoimmune diseases. It is based in Irving, Texas and employs approximately 50 full-time employees in multiple departments.

Acknowledgments

I would like to take the opportunity to express my gratitude to the entire clinical team for contributing to my research and for all the lessons I've learned in my short time at the internship site; in particular I would like to acknowledge: Liisa Tingue and Barbara Richardson for their steadfast support, mentorship, and guidance throughout my internship practicum.

I would also like to acknowledge Dr. Patricia Gwirtz, Ph.D. for her unwavering support throughout my time at UNT Health Science Center. Without her, this thesis would not be possible.

APPENDIX 1: Site Information Questionnaire

<table>
<tr><th colspan="4">Site Information:</th></tr>
<tr><td colspan="2" rowspan="2">Principal Investigator's Name:</td><td colspan="2">Specialty(s):
1.
2.</td></tr>
<tr><td colspan="2">Board Certified?
1. ☐ Yes ☐ No
2. ☐ Yes ☐ No</td></tr>
<tr><td colspan="2">Site Name and Address:</td><td colspan="2">Institution Name and Address (if different):</td></tr>
<tr><td>Site Phone Number:</td><td>Site Fax Number:</td><td>Contact Phone Number:</td><td>Contact Fax Number:</td></tr>
<tr><td>Contact Person:</td><td colspan="3"></td></tr>
<tr><td colspan="2">Contact Person's email address:</td><td colspan="2"></td></tr>
<tr><td colspan="2">PI's email address:</td><td colspan="2"></td></tr>
<tr><td colspan="4">Our Institution is (check all that apply):
☐ Private Practice ☐ Research Group ☐ SMO/TMO ☐ Academic ☐ VA Hospital ☐ Other:_____</td></tr>
<tr><th colspan="4">Administrative & Institutional Review</th></tr>
<tr><td colspan="4">Can you use a Central Institutional Review Board? ☐ Yes ☐ No</td></tr>
<tr><td colspan="4">Contact information for individual responsible for regulatory document completion: ☐ (check if same as contact person)</td></tr>
<tr><td>Name:</td><td>Phone:</td><td>Fax:</td><td>Email:</td></tr>
<tr><td colspan="3">Estimated days required for start-up process (i.e. regulatory documents and contract completion):</td><td></td></tr>
<tr><td colspan="2">If local IRB approval is required, please complete the following:</td><td colspan="2"></td></tr>
<tr><td>IRB Name:</td><td colspan="3"></td></tr>
<tr><td>Frequency of IRB Meetings:</td><td colspan="3"></td></tr>
<tr><td colspan="2">What is the lead time required for IRB submissions?</td><td colspan="2"></td></tr>
<tr><td colspan="4">Is other board review required (i.e. Scientific Review, Ethics, Privacy, etc)? ☐ Yes ☐ No</td></tr>
</table>

If yes, provide name(s):			
What is the lead time required for other board submissions?			
How many weeks from IRB approval to receipt of approval letter of other board?			
Who has authority to negotiate the Clinical Trial Agreement? *(i.e. contract and budget)*		Name:	
Telephone Number:	Fax Number:	Email:	
Who will execute the Clinical Trial Agreement? ☐ Institution ☐ Investigator ☐ Both			
Name of Institution:			
Average number of weeks from Clinical Trial Agreement receipt to execution?			

Staff & Facilities

What days are research patients seen at your site?		
How many hours per day are you open to see research patients?		
Please answer the following questions for ALL coordinators (part and full time)	**Full-Time**	**Part-time**
How many coordinators do you have on staff?		
What percentage of time do the coordinators allocate to clinical research?		
What is the average number of years of study coordinator experience?		
Please describe your processes for handling studies when a coordinator is unavailable or on vacation for more than a day or two?		
How many days per week is the PI on site where the study is being conducted?		
Number of years experience as a PI?		
Number of physicians in your practice?	Number of physicians experienced as investigators or sub-investigators?	
Where will study drug be stored? ☐ Pharmacy ☐ Other (please give address) ☐ Site address listed above		
If study drug will be stored in a pharmacy, please note the pharmacy hours:		
Has the FDA or other regulatory agency ever audited your site? ☐ Yes ☐ No ***If yes, please attach all report(s)***		
Please check all equipment available at your site: ☐ ECG ☐ Weight Scale ☐ Centrifuge ☐ ECHO		

☐ X-Ray

☐ Internet access Freezer: ☐ -20C ☐ -70C ☐ Secure drug storage

Recruitment & Patient Population

In your most recent study with a similar patient population, how ere subjects recruited? ***(Please check all that apply):***

☐ Patient Database ☐ Advertising ☐ Referrals ☐ Health fairs
☐ Other

Please describe:

What are the ***two*** most common ethnicities in your patient population ***(please select the largest two groups):***

☐ Hispanic ☐ African American ☐ Asian American ☐ Native American
☐ Caucasian ☐ Other: _____

Total number of patients in database/practice:	
What percentage of your patient population is seasonal?	

(Please indicate which studies your site participated in, and how many in each phase of research)

	Phase I	**Phase II**	**Phase III**	**Phase IV**
☐ Diabetes				
☐ Diabetes-induced CKD (aka Diabetic Nephropathy)				
☐ Hypertension				
☐ Hypertension-induced CKD				
☐ Other _____				

Who will be responsible for conducting the majority of the study procedures?

☐ Principal Investigator ☐ Sub-Investigator ☐ Research Nurse ☐ Other:_____

Please complete for the **LAST 4 CKD or HTN/diabetes-induced CKD STUDIES COMPLETED**:

Indication	Enrollment Goal	Number of Subjects Screened	Number of Subjects Randomized	Number of Subjects Completed	Length of Enrollment Period	Time to first patient randomized after site initiation	Date Study Closed

Based on an eGFR of **XX-XX**mL/min/1.73m2 as a primary entry requirement, how many patients will your site be able to screen per week?	
Based on an eGFR of **XX-XX**mL/min/1.73m2 as a primary entry requirement, how many patients will your site be able screen per week?	

Study Specific Information

How many patients do you treat each month for the following:
☐Diabetes-induced CKD _____ ☐HTN induced CKD_____

Has your site had experience with endpoint studies? ☐Yes Type: _____ ☐No

How many CKD/Diabetes studies are currently ongoing at your site, or are expected to be ongoing within the next 6-12 months?	
If studies are ongoing, how many will be actively recruiting patients during the same time frame?	

Additional Comments:

Name: (please print)	Title:	Date:

Thank you for your attention and response.

If you have any questions, please call:

Are there other physicians you would recommend who may also be interested in participating in clinical research studies of this type?

Name:	Phone:	Fax:

APPENDIX 2: The Study Coordinator Questionnaire

This was developed with input from internship site personnel, based on traits that are most desired in a study coordinator. The questionnaire is meant to be an addendum to a site qualification visit, and to be taken by the study coordinator that will be assigned to the clinical study in question (if possible), or taken by the site manager.

1. Identify and rank from first to last how you would approach the situation of a patient that the PI called you to enroll that was perhaps questionable to enroll? *(Please explain your reasoning process and any actions you would take to determine the subjects eligibility to enroll, please check only those that apply)*

___ ☐ Call sponsor (or Medical Monitor) to discuss

___ ☐ Discuss further with investigator

___ ☐ Randomize and exit patient later

___ ☐ Suggest more tests to confirm the inclusion and exclusion criteria

___ ☐ Other (explain your answer, and the reasoning behind it):_____

_____

2. At the completion of a clinical study, how much do you believe the quality or cleanliness of the data collected at your site reflects upon you?

☐ It reflects **very much** upon me

☐ It reflects **moderately** upon me

☐ It reflects **minimally** on me

3. What steps do you take, as a coordinator, when a randomized patient presents themselves and requests to discontinue the investigational drug? *(Please rank in order, which steps you would take when faced with a similar situation, from 1st to last. Only rank those actions that you would take, and leave blank the actions you would not take.)*

___ ☐ Discuss the situation with the patient to determine the reason for their desire to discontinue

___ ☐ Confer with the PI (or sub-I) to discuss options with the patient

___ ☐ Contact the Medical Monitor at the Sponsor Company

___ ☐ Discontinue patient immediately and encourage them to come back for a final follow-up visit

4. From a study coordinator's perspective, how do you view your interaction with the clinical monitor (CRA) who is assigned to your site--what adjectives could be used to describe this interaction? *(Please give at least 3 adjectives)*

   i. _____

   ii. _____

   iii. _____

5. Which of the following statements would best classify your routine while a monitor is on site?

   ☐ I tend to remain with the monitor while they are on site, in case they have questions

   ☐ I make myself available at several times throughout the day as needed

   ☐ I allow the monitor time to complete the work at their own pace without my interference

   ☐ I see to my other responsibilities, and let the monitor take care of themselves

6. How important, is it for you to ensure that clinical tasks (eCRF data entry, study procedures, etc.) are done as soon as the study visit is completed or within 5 days?

☐ **Very** important

☐ **Moderately** Important

☐ **Not** important

Please explain your reasoning for the selection above: _____

_____

7. How often is the PI present and available in the *day-to-day activities* (study visits and informed consent) of your site?

☐ Very present and available (at the research site everyday)

☐ Moderately available, can be consulted as required (on-site at least 3 times per week)

☐ Minimally available (on-site only once per week, or if problems arise)

☐ Only available as required by the protocol

Please describe the processes in place at your site to ensure adequate PI oversight of all patients enrolled in clinical studies *(please give as much detail as possible)*:

_____

_____

_____

_____

8. Who at your clinical site has the responsibility of reviewing and classifying adverse events when patients present them?

☐ Principal Investigator

☐ Study Coordinator

☐ Other: _____

9. How much experience do you have with Electronic Data Capture (EDC)?

    a. How many studies have you worked on that utilized EDC? (please provide a number)_____

    b. What EDC systems, if any have you used in the past? *(Please list all that apply)* _____

    _____

    _____

    c. Do you prefer EDC or paper and why?

    _____

    _____

10. What are your most and least preferred functionalities of Electronic Data Capture? *(Please explain **WHY** they are your least/most favorite)*

    a. Least favorite functionality: _____

    _____

    b. Favorite functionality: _____

    _____

11. As a study coordinator, how do you provide input into your sites Standard Operating Procedures for the conduct of clinical research at your site? *(Please select the answer choice that best matches your situation)*

- ☐ I am intimately involved in the creation of SOPs at my site
- ☐ My input is used by others in the creation and revision of SOPs at my site
- ☐ I review and am ultimately responsible for adhering to SOPs
- ☐ I am not involved in the SOP writing or revising processes at my site
- ☐ N/A- my site does not have SOPs

APPENDIX 3: Daily Log of Internship Activities

Week of November 30, 2009

M – Introduction to Reata

T – Briefed on upcoming and current internship site studies

W – Review of current drug information and previous studies

Th – Meet with study managers to discuss new study

F – Prepared start-up documents for regulatory review for upcoming study

Week of December 7, 2009

M – IRB submission for new study

T – Prepared start-up documents for new study

W – Compile new contacts and site contacts for new study

Th – Review vendor proposals for new study

F – Protocol synopsis review and editing

Week of December 14, 2009

M – Protocol review and prep for new study

T - Protocol review and prep for new study

W – Waiver/protocol deviation review for 0804 study

Th – Reviewed revised vendor proposals for new study

F – Sent out and prepared regulatory packets for each site for 0902 study

Week of December 21, 2009

Holiday week—no work all week

Week of December 28, 2009

M – Review incoming regulatory packets

T - Budget review on per-procedure basis

W – Prepared per-patient budgets for each site for 0902 study

Th - HOLIDAY

F – HOLIDAY

Week of January 4, 2010

M – Deviation/trending analysis for 0804 study

T - Deviation/trending analysis for 0804 study

W – Review with new study manager current 0902 study status

Th – Regulatory Documents and IRB for 0902

F – Contacting sites for reg documents and IRB submissions

Week of January 11, 2010

M – Deviation analysis for 0804 study and regulatory document tracking for 0902 study

T – Prepare Diary and Glucose tracker

W – Source Documents

Th – Training slide prep

F – Training slide prep

Week of January 18, 2010

M – Prepare for Protocol training

T – PI Training

W – PI Training

Th – SC Training

F – SC Training

Week of January 25, 2010

M – Regulatory document review

T - Regulatory document review

W – Reg binders for screening sites

Th – 902 study IVRS

F – Project for Barb/safety files

Week of February 1, 2010

M - Regulatory document review

T - Regulatory document review

W – 902 amendment

Th – Worked with 804 patient database

F - Worked with 804 patient database

Week of February 8, 2010

M – 902 regulatory documents

T – 804 data cleaning

W – 804 data cleaning

Th – N/A

F – N/A

Week of March 1, 2010

M – 902 enrollment tracking

T – 804 data lock

W – Protocol amendment

Th – Data lock/interview personnel

F – Interview personnel

Week of February 15, 2010

M – UAT for 902

T – UAT for 902

W – 804 PK sample breakdown

Th – 804 data lock analysis

F – 804 data lock analysis

Week of March 8, 2010

M – 804 data lock

T – Interview personnel

W – PI database

Th – 804 data lock/PI database

F – Site Questionnaire Question

Week of February 22, 2010

M – 902 enrollment tracking

T – UAT for 902

W – New IB training

Th – 804 data lock analysis

F – 804 data lock analysis

Week of March 15, 2010

M – Site selection project

T – PI database

W – PI database

Th – 804 data lock

F – N/A

Week of March 22, 2010

M – Site selection project

T – Site selection project

W – Site selection project

Th – data listing review

F – Drug holiday log

Week of March 29, 2010

M – Site selection project

T – Locked status review

W – 804 data listings

Th – Locked status review

F – Data listings

Week of April 5, 2010

M – Locked status review

T – Site selection duties

W – 804 data listings

Th – Locked status review

F – Data listings

Week of April 12, 2010

M – Site selection project

T – Locked status review

W – 804 data listings

Th – Locked status review

F – Data listings

Week of April 19, 2010

M – Site selection duties

T – Site selection duties

W – Site selection duties

Th – Site selection duties

F – Site selection duties

Week of April 26, 2010

M – Site selection duties

T – Site qualification visit tag-along

W – Site selection duties

Th – Site selection duties

F – Site selection

Week of May 3, 2010

M – Site selection duties

T – data lock

W – Site selection duties

Th – Site selection duties

F – data lock duties

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