

Educational Platform for Clinical Research Associates

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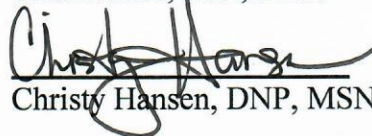
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Introduction

The National Institutes of Health (NIH) defined clinical trials as “research studies that explore whether a medical strategy, treatment, or device is safe and effective for humans. These studies also may show which medical approaches work best for certain illnesses or groups of people. Clinical trials produce the best data available for health care decision making” (Clinical Trials. (n.d.) NIH- National Heart, Lung, and Blood Institute. Retrieved from <https://www.nhlbi.nih.gov/studies/clinicaltrials>). Research is the primary purpose for a clinical trial. The Food and Drug Administration (FDA) mandates that clinical trials enforce strict scientific standards to ensure patient safety while produce reliable data and capturing complete study results (Code of Federal Regulations ICH Guidelines, 2004).

Clinical trials are important in the advancement of medical knowledge and subsequent patient care (Clinical Trials, n.d.). Should a clinical trial produce an effective treatment option, the medication or device that was studied could potentially have the ability to treat or eradicate a disease process. Results of any clinical trial include the possibility that what was studied may not be an effective potential treatment. Should the results not be proven effective, that research could be use the knowledge gained to develop another form of pharmaceutical or device which may indeed prove effective. The first priority when studying a medication or device is proving that the drug or device does no harm to an individual (Clinical Trials, n.d.)

Many people have a lack of understanding or are not educated about clinical trials. The study of pharmaceutical and devices is critical in the advancement of medicine and treatment processes. The medical community needs to be cognizant of new and potentially life-saving trials and pharmaceuticals that are currently in research or coming up to educate not only themselves

but their patients that they see and treat on a daily basis. Reviewing journal articles and participating in those trials can assist in the advancement of our understanding of diseases and how to effectively treat them. Many individuals are skeptical about participating in clinical trials due to a lack of understanding. Common myths regarding research include:

- Clinical trial volunteers are merely human guinea pigs.
- If I join a clinical trial, I might get a "sugar pill" or placebo instead of a real drug that doesn't effectively treat my condition.
- If I decide to participate in a clinical trial, I will not be able to change my mind and withdraw my participation (Ulrich, 2014)

These myths couldn't be further from the truth. Individuals who participate in clinical trials are not human guinea pigs. Scientists put all medications and devices through stringent screening and pre-clinical testing well before a human subject is ever entered into the study. The myth regarding "sugar pills" is not true either. While yes, a placebo is often times used, "the use of placebo pills solely depends on how serious the illness is, whether an existing treatment is available and other considerations that ensure a high standard of ethics (Ulrich, 2014). If there is a serious or life-threatening illness, the standard of care drug will be used instead of a placebo" (Ulrich, 2014). All individuals who enter in clinical trials are always free to leave the study at any time. However, it is always recommended that the patients inform the study team prior to stopping the study drug. The study team will advise the patients on how to safely and effectively discontinue the medication (Ulrich, 2014).

The FDA holds the sponsor accountable for ethical and safety aspects of the clinical trial. It is the clinical site's responsibility to provide oversight and ensure that the trial protocol is

being effectively managed and completed as per the individual protocol. A sponsor is “an individual, institution, company or organization (for example, a contract research organization) that takes the responsibility to initiate, manage or finance the clinical trial but does not actually conduct the investigation” (Clinical Trials: Sponsors and Sponsor-Investigators, 2012). The sponsor also provides or contracts the clinical research associates (CRA’s/monitors) to oversee the conduct of the trial at the clinical sites. Issues can arise even with monitoring a clinical trial even with the accountability checks that a clinical monitor completes.

Problem

The FDA does not have a specific training program for all of the levels of CRA’s. The sponsor’s and/or CRO’s (Clinical Research Organizations) have their own individual training, assessment tools and guidelines that their employees must complete. One of the struggles that CESCA Therapeutics INC has had is that the new incoming CRA’s have different backgrounds and experience in research. The entry skill level of being a CRA has been difficult to assess for management. Cesca Therapeutics INC. wants to ensure that they are sending out the highest quality of CRA’s as possible.

PURPOSE

There are two components to this project. The first component is to develop an assessment program for Clinical Research Associate’s (CRA’s) knowledge and skill level when entering into employment with Cesca Therapeutics Inc. The newly hired employees will have their clinical research knowledge as demonstrated by completing an entrance exam and demonstrated score with a minimum passing grade of 80%. The second component is to develop an educational session for those employees who do not successfully pass the entrance exam. It is

the goal of this project to create a quality training assessment while ensuring the competencies of the newly hired CRA's.

PUBLIC HEALTH SIGNIFICANCE/RATIONALE

The Association of Clinical Research Professionals (ACRP) defines the CRA, also commonly known as a clinical monitor role as one that “supervises, monitors, and supports the administration and progress of a clinical trial on behalf of a sponsor. The sponsor, whose intent is the research of pharmaceuticals, biologics, or devices, may employ these individuals either directly or indirectly via contract research organizations (CROs) or as independent consultants or contractors” (CRA Certification, 2017). Per the FDA regulations 21 CFR Part 312, 21 CFR Part 812 and other applicable regulatory requirements and guidelines require CRA's to ensure that the rights and well-being of human subjects are protected, to confirm that reported data is accurate, complete and verifiable source documents kept and to assure the clinical trial is conducted in compliance with the currently approved protocol and other applicable regulatory requirements and guidelines (Code of Federal Regulations ICH Guidelines, 2004).

The responsibility of the CRA is to ensure the accountability and accuracy of the data collected as well as the safety of the clinical population that is being studied. The CRA must also ensure that the clinical trial is being conducted in an ethical manner. All Clinical trials are conducted according to the FDA ICH (The International Council for Harmonization) GCP (Good Clinical Practice) guidelines. The CRA must have a high level of knowledge of FDA regulations and the protocol specific processes and testing for the clinical trial. The CRA's role is one where they act as the “go-to” personnel between the Clinical Trial sites and the Sponsors. The CRA's are also play a major role in collaboration and assisting the clinical sites as a resource for the assigned clinical trial. Qualities of an effective CRA include enthusiasm and an ability to exert a

positive attitude, while demonstrating excellent internal and external customer focus ability. The CRA must work in a multi team environment while developing and using appropriate planning and organizational tools to support one's self and their team. CRAs must leverage capabilities across company policies, while simultaneously ensuring effective data capture and patient safety have been completed. The CRA must work well in a team environment and also bring significant value to the group including experience, overall clinical trial knowledge and the ability work with diverse populations and individuals. CRA's must empower others while supporting the site staff in a way that the sites have appropriate oversight in their decisions pertaining to the trial and delegation of tasks. CRAs often have the ability to lead effective teams and also work as self-starters with minimal supervision.

With all of the responsibility the individual CRA's have, it is crucial that a company is aware of the level of knowledge that an individual has to effectively guide the clinical sites that are under their supervision. There are many instances where a CRA may have had many years of clinical trial experience, but it may not be disease specific to the indication that a sponsor is studying. This is the reason that Cesca Therapeutics Inc., has asked for an assessment program to be developed for new CRA's. Along with demonstrated work experience, this assessment program will aid in the educational expectation and knowledge to effectively perform their job requirements.

LITERATURE REVIEW

"The current mechanisms of research review and oversight have served the public well by protecting patients who participate (Finkelstein, Brickman, Capron, Ford, Gombos, Greene, Iafrate, Kolaczowski, Pallin, Pletcher, Staman, Vazquez & Sugarman, 2015). Clinical trials

“seek systems that systematically and efficiently assess and oversee quality improvement activities for their research projects (Finkelstein, et al., 2015). Clinical trials also work to higher the standard of care for patients. Finkelstein states that “quality improvement is designed to change local processes to reliably achieve accepted standards of care (Finkelstein, et al., 2015).

Another quality improvement strategy is “the development of educational resources to aid quality improvement project completion and mentoring support” (University of Glasgow, 2016). It is imperative to have a mentoring program within a company. CRA’s face many obstacles and barriers and need senior personnel to help guide them through challenges. Some barriers that CRA’s may face are:

- Knowledge with the trial indication
- Difficulties with study data due to lack of experience
- Subject enrollment and retention at study site
- The ability to effectively know how to deal with and respond accurately site questions,
- IP (investigational product) oversight
- Questions regarding serious events (Code of Federal Regulations ICH Guidelines, 2004).

Senior personnel who have experience on the job can mentor and educate new entry level CRA’s and train them appropriately and according to the FDA regulations

Degendorfer states that “quality assurance (QA), efficient timelines, improving risk management and cost effectiveness are critical to clinical trials and that ongoing assessment and tracking of metrics are essential to maintaining high quality, accountability and efficiency” (Degendorfer, Cole, Sellmann, Panzarella, Brown, & Tinker, 2015). CRA’s are held accountable to perform QA checks at every site monitoring visit. CRA’s must also

ensure that the data being entered is being entered in a timely fashion and according to the protocol. The CRA must be aware if the sites are maintaining a cost-effective budget as well. There are misconceptions that clinical trials have an abundance of money, this is not the case. Trial management must watch every dollar amount that is paid out to ensure that the trial will have enough funding to withstand the duration of the trial.

Quality improvement systems need to be implemented for all sites to maximize performance (Warden, Rush, Trivedi, Ritz, Stegman, & Wisniewski, 2004). When a study site faces an obstacle the first person they notify is the CRA. It is then the CRA's job to trouble shoot the problem. Subject retention of the appropriate patient is a major barrier often seen at study sites. The CRA is then responsible to help implement a plan to maintain the sites enrollment. The CRA has to guide (empower) the research coordinator to use "referral sources, add qualified clinicians to see study subjects, and increase activities to general referrals (e.g., lectures to promote awareness of the study and increase research coordinator time at the clinical sites)" (Warden, et al., 2004). The CRA will then track the progress of the subject retention design. When a quality improvement system is in place, the trial will run more effectively.

METHODS

Cesca Therapeutics Inc., has requested a CRA assessment tool (Appendix A) and an educational session supplement (Appendix C and D) to be created for their newly hired CRA's. Cesca would like to ensure that they are sending out both quality and knowledgeable CRA's to monitor their clinical trials. The CRA assessment tool is made up of 50 True/False questions that are worth two points apiece for a total of 100%.

Methods that were used to create the CRA assessment tool and the educational session were areas of clinical research that every CRA must be competent in. These topics were taken from the Federal Regulations handbook. The assessment tool questions were created from the Federal Regulation handbook topics and the clinical trials process from start to finish. The topics include:

- Phases of clinical trials
- Investigator Brochure's
- New Drug Application (NDA)
- Investigational New Drug Applications (IND)
- Toxicology
- Drug approval process
- Drug classifications
- Informed Consent Process
- Electronic trial data
- ICH/GCP requirements
- Serious Adverse Events (SAE's)/Adverse Events (AE's)
- Trial inspections and study close-out (Code of Federal Regulations ICH Guidelines, 2004).

IMPLEMENTATION/RESULTS

Cesca Therapeutics Inc., management team will administer the initial assessment tool to the new hires within the first week of onboarding. The individuals must pass with an 80% or higher in order to start working in the field. If the individual fails the initial assessment, a 4-hour educational session will be sponsored by the company and then the test will be administered again. This assessment must be passed in order for Cesca Therapeutics Inc., to endorse the new

employee. Once the initial assessment is completed, the management team can then determine which job title to give to the individual based upon past work experience (CRA I, CRA II or Senior CRA).

DISCUSSION

Warden stated “a clinical trial that runs efficiently and maximizes contributions to public health has a competitive advantage. The more efficiently a trial is run, the more likely it is to be successfully completed, and the lower the cost to complete the trial” (Warden, et al., 2004). This process must start from the top, the Sponsor. The sponsor must create a team environment that is sufficiently organized and operates as a cohesive unit. Within the cohesive unit, the CRA role plays a pivotal role. The CRA’s work, under the direction of the sponsor, is to oversee the daily functions of the clinical sites. CRA’s perform quality improvement assessments every time they perform a routine monitoring visit and at every clinical site. The CRA’s are continuously uniting the efforts of the PI’s and research coordinators to align their goals with the study requirements. During routine monitoring visits, the CRA’s must determine that all patients are educated and are receiving quality care to ensure the best outcome possible.

The CRAs monitoring visit report (MVR) is a key element in capturing the “site story.” The information gathered needs to be accurate, complete, and demonstrate the ability to gather data that captures all essential data points while ensuring subject safety. The quality of the content of this report is instrumental in demonstrating the safety and efficacy of the sponsor who is ultimately responsible for oversight of the clinical trial.

SPECIFIC COMPETENCIES DEMONSTRATED

I have obtained many competencies throughout my coursework at the University of Michigan-Flint. However, the competencies most valuable to this project were:

Competency 1) used a quantitative data collection method that incorporated basic clinical research standards of practice as well as current guidelines regarding the protection of human subjects who participate in clinical research. An entrance survey was developed to evaluate both new CRA's as well as seasoned CRA's. This tool can be utilized to assess current competency as well the educational needs of the CRA's who are employed by Cesca Therapeutics Inc. I used a survey because it was a generalized format that allowed for immediate assessment of current knowledge of both new and current employees. This tool will be an asset to the study management teams to ensure that all CRA's are competent in the field to monitor the clinical trials according to the ICH/GCP guidelines.

Currently there are no standardized surveys to assess clinical research competencies. The assessment tool that was created was based upon general principals and guidelines per the FDA best practices and standards and regulatory compliance. Therefore, the content of the survey was developed utilizing Federal Regulations set forth by the FDA that include ICH/GCP compliance (Code of Federal Regulations ICH Guidelines, 2004). Assessment tools were aligned with the Cesca Therapeutics Inc, mission that included the advancement of clinical research and improving technologies that support improving those with chronic and acute medical conditions. The assessment tool will assist in not only in establishing a standardized competency, but will allow management to development individualized educational platforms for those employees should they need additional training modules.

By developing this tool, Cesca Therapeutics Inc, will have a standardized assessment that covers not only basic clinical research knowledge but both pharmaceutical and medical device specific competencies. The assessment will also assist the management team to tailor learning activities that include specific educational areas of inadequacies of the individual learner should deficits be found upon completion of the initial assessment period.

Competency 2) Design a population-based policy, program, project or intervention. An educational session/intervention was designed for CRA's who did not meet the initial competencies. After the initial assessment is completed, an educational session was developed based on the additional learning needs to effectively participate in the CRA role. Additional educational needs were identified based on the individual learner's initial assessment score. The evaluation will provide guidance to the educators who can review the assessment and review the areas of improvement that are needed to perform the CRA job duties. For example, should the individual need additional guidance in regard to the informed consent process the educator can focus additional time and attention to that specific area. The role of the CRA is to provide oversight and guidance to the clinical sites who participate in the specified therapeutic clinical area. Before a CRA can be an effective resource for the clinical site he or she must first have the general knowledge and understanding of general ICH/GCP requirements. The CRA must also have the ability to understand the scope and roles of the sponsor, investigator and subjects who participate within clinical research.

Competency 3) Discuss multiple dimensions of the policy-making process, including the roles of ethics and evidence. The ability to standardize an assessment process for the CRA's will provide a companywide policy that demonstrates Cesca's ability to provide continuity of care

and oversight when developing clinical protocols and demonstrating the necessary data points that are captured throughout a clinical trial.

I learned through my coursework at the University of Michigan-Flint that the development of policies within a company can be used to standardize training, avoid errors and improve productivity for its employees. Written policies within any company is an on-going and ever-changing process. Cesca Therapeutic Inc has identified the problem that includes the fact that not all new hires possess the same educational background and on the job training/experience. The evidence provided with the assessment tool cannot only demonstrate additional educational needs, but provide an assessment that validates that the additional education was effective. Unlike other fields, clinical research exposes human subjects to potentially harmful or ineffective treatments. The sponsors who develop these treatments have an ethical responsibility to provide safe and effective care that does not put the subject at risk for unnecessary harm. The use of policies can be an effective tool to prevent harm to current and future patients who utilize the developing treatment.

Cesca can use this platform to develop additional policies that incorporate the lessons learned during the onboarding and continuing education of its employees. Pharmaceutical and medical device companies have an ethical responsibility to ensure that their CRA's are competent in all aspects of the job and that they have a full understanding of the Federal Regulations along with the ICH/GCP guidelines. It would be unethical to employ a CRA who does not have a documented understanding of the risks and responsibilities of clinical research.

Competency 4) Create or evaluate quality improvement principals. The assessment tool was also created for quality improvement as well. This tool will initially show the quality of the

CRA's that have just been hired and what improvements they may need in order to demonstrate quality work. The educational session serves as quality improvement also. After the CRA attends the educational session, they must re-take the assessment tool to ensure competency. Quality improvement will be measured by their assessment scores pre-and post-educational session. The post assessment score will demonstrate the improvement of the CRA.

Lastly, this project can play a vital role in the future of providing quality and knowledgeable CRA's for the company. Cesca Therapeutics Inc will have demonstrated effective onboarding process and maintaining and assessing clinical research knowledge through this platform. Cesca Therapeutics Inc will have demonstrated their dedication to the clinical research community by ensuring that they field the best and most competent CRA's possible. The ability to initiate a quality improvement system within a company can increase the likelihood that the current best practices and most appropriate care is provided to those they serve.

SYNTHESIS OF COMPETENCIES

Creating and evaluating quality improvement principals of the CRA role are crucial. Hughes states "Efforts to improve quality need to be measured to demonstrate "whether improvement efforts lead to change in the primary end point in the desired direction," (Hughes, 2008) meaning the primary endpoint for this project is the desired direction, fielding efficient and quality CRA's. The quality improvement project will measure the knowledge of the CRA's. Leadership ability will also be measured. Through the quality improvement process, the CRA's will be held accountable to help the clinical sites see the vision of the clinical trial and help them strive and produce the results that are needed from their site. CRA's may also be "required to

have additional efforts to bring a process back into acceptable ranges” (Hughes, 2008). Hence, CRA’s may face a situation where their clinical site is out of compliance with the protocol (acceptable range), it is then the CRA’s job to bring them back into compliance and to educate the study team how to remain in compliance (acceptable range). The CRA’s will do this by empowering the clinical sites through positive/constructive feedback to make the right decisions according the protocol. Cesca Therapeutics Inc has the belief that incorporating the quality improvement for CRA’s will ensure better performance and practice of the clinical sites.

Plan for Project DISSEMINATION

The results of this project will be tracked by Cesca Therapeutics Inc. The company will keep statistics on how many CRA’s pass the initial assessment, how many CRA’s pass after the educational session, and the quality of work the CRA’s possesses in the field. The management team will perform quality control visits to assess job performance and ongoing review of the CRA’s work. The quality control visits will demonstrate the effectiveness of the program and will allow for revisions if necessary.

Works Cited

- Clinical Trials*. (n.d.). Retrieved September 30, 2017, from NIH- National Heart, Lung, and Blood Institute: <https://www.nhlbi.nih.gov/studies/clinicaltrials>
- Clinical Trials: Sponsors and Sponsor-Investigators*. (2012, October 17). Retrieved October 3, 2017, from MaRS: <https://www.marsdd.com/mars-library/clinical-trials-sponsors-and-sponsor-investigators/>
- Code of Federal Regulations ICH Guidelines*. (2004). Philadelphia, PA: Clinical Research Resources.
- CRA Certification*. (2017). Retrieved 09 24, 2017, from The Association of Clinical Research Professionals: <https://www.acrpnet.org/professional-development/certifications/cra-certification/>
- Degendorfer, P., Cole, H., Sellmann, S., Panzarella, T., Brown, J., & Tinker, L. (2011). Development of clinical research process metrics and tracking improvement in quality assurance in clinical trials. *Journal of CLINICAL ONCOLOGY*, 29(15).
- Finkelstein, J. A., Brickman, A. L., Capron, A., Ford, D. E., Gombosev, A., Greene, S. M., . . . Sugarman, J. (2015). Oversight on the borderline: Quality improvement and pragmatic research. *Sage*, 12(5), 457-466.
- Hughes, R. (2008, April). Tools & Strategies for Quality Improvement and Patient Safety. *National Institute of Health*, Chapter 44.
- Martinez, D., Tsalatsanis, A., Yalcin, A., Zayas-Castro, J., & Djulbegovic, B. (2016). Activating clinical trials: a process improvement approach. *Trials*, 17, 106.
- Morreim, E. (2003). CLINICAL TRIAL LITIGATION: PRACTICAL REALITIES AS SEEN FROM THE TRENCHES. *Accountability in Research*, 12, 47-67.
- Research Data from University of Glasgow Update Understanding of Clinical Trials and Studies (Quality Improvement training for core medical and general practices trainees: a pilot study of project participation, completion and journal publication). (2016, Feb 5). *Health & Medicine Week*, 3369.
- Ulrich, J. (2014, December 11). *The Catalyst Debunking Common Myths about Clinical Trials*. Retrieved October 3, 2017, from PHRMA: <http://catalyst.phrma.org/debunking-common-myths-about-clinical-trials>
- Warden, D., Rush, J. A., Trivedi, M., Ritz., Stegman, D., & Wisniewski, S. (2004, November 23). Quality improvement methods as applied to a multicenter effectiveness trial-STAR*D. *Contemporary Clinical Trials*, 26, 95-112.



Appendix A

CRA Assessment Tool

- 1) IND (Investigational New Drug) Application is an application filed with the U.S. Food and Drug Administration (FDA) prior to human testing
 - A) True
 - B) False
- 2) New Drug Application (NDA) is an application to the FDA for approval to market new drug
 - A) True
 - B) False
- 3) Pre- Clinical studies should be done on animals, before the permit of clinical trial on human could be obtained
 - A) True
 - B) False
- 4) Phase I Clinical Evaluation involves controlled clinical trials of compound's potential usefulness and short-term risks
 - A True
 - B False
- 5) Toxicology and Safety testing tests to determine the potential risk a compound poses to man and the environment
 - A) True
 - B) False



- 6) Phase II studies are typically done in a small number of healthy volunteers (20-100), usually in a hospital setting where they can be closely watched and treated should there be any side effects
 - A) True
 - B) False
- 7) Phase III studies can involve several hundreds to several thousands of subjects
 - A) True
 - B) False
- 8) The drug approval process is very different in different parts of the world
 - A) True
 - B) False
- 9) Drugs may be classified in one of three ways: by chemical group, pharmacologically and according to their therapeutic uses?
 - A) True
 - B) False
- 10) The WHO (World Health Organization) defines a pharmaceutical specialty as “a simple or compound drug ready for use and place on the market under a special name or in a characteristics form”.
 - A) True
 - B) False
- 11) Transparency in the development of new drugs is NOT important when attracting investors?
 - A) True
 - B) False



- 12) The National Therapeutic Protocol (NTP) develops scientific information about potentially toxic chemicals which can be used for protection of public health and prevention of chemically-induced disease.
- A) True
 - B) False
- 13) CRA's (Clinical Research Associate) are always involved in filing of IND and NDA
- A) True
 - B) False
- 14) A Sponsor-Investigator is an individual who both initiates and conducts a clinical investigation and under whose immediate direction the investigational drug is being administered or dispensed?
- A) True
 - B) False
- 15) Studies shall not be initiated until 30 days after the date of receipt of the IND by FDA unless you receive earlier notification by FDA that studies may begin?
- A) True
 - B) False
- 16) If the pharmaceutical company will be supplying the drug, but will not itself be submitting the IND, the company is the sponsor
- A) True
 - B) False



- 17) The clinical testing (investigation) of experimental drugs (previously unproven in humans, therefore “experimental”) in humans is normally done in 5 phases (Phase I, II, III, IV, and V)
- A) True
 - B) False
- 18) The informed consent explains a patient’s rights as a participant in the trial
- A) True
 - B) False
- 19) In the United States, women of childbearing potential may be included in early studies prior to completion reproductive toxicology studies, providing that the studies are carefully monitored and all precautions are taken to minimize exposure *in utero*?
- A) True
 - B) False
- 20) There are no risks with any new treatment only benefits?
- A) True
 - B) False
- 21) Usually complete data are NOT available from the manufacturer for the safety of effectiveness of “natural” products
- A) True
 - B) False



- 22) A bias means the systemic tendency of any aspects of the design, conduct, analysis, and interpretation of the results of clinical trials to make the estimate of a treatment effect deviate from its true value?
- A) True
 - B) False
- 23) When using electronic trial data handling and/or remote electronic trial data systems, the sponsor should maintain adequate backup of the data and safeguard the blinding, if any (e.g., maintain the blinding during data entry and processing)?
- A) True
 - B) False
- 24) When trial subjects receive compensation, the method and manner of compensation should comply with the sponsor's requirement (s)
- A) True
 - B) False
- 25) A sponsor may transfer any or all of the sponsor's trial-related duties and functions to a CRO
- A) True
 - B) False
- 26) According to ICH Good Clinical practice (GCP) the investigator is responsible for implementing and maintaining quality assurance and quality control system?
- A) True
 - B) False



- 27) If the sponsor discontinues the clinical development of an investigational product, the sponsor should notify all the trial investigators/institutions and all the regulatory authorities?
- A) True
 - B) False
- 28) Subject withdrawal criteria (i.e., terminating investigational product treatment/trial treatment) and procedures specifying when and how to withdraw subjects from the trial/investigational product treatment but NOT the type and timing of the data to be collected for withdrawn subjects?
- A) True
 - B) False
- 29) Procedures for reporting any deviation (s) from the original statistical plan (any deviation (s) from the original statistical plan should be described and justified in the protocol and/or in the final report, as appropriate)?
- A) True
 - B) False
- 30) As the clinical investigator is a practicing physician guidance should NOT be provided in the IB on the recognition and treatment of possible overdose and adverse drug reactions that is based on previous human experience and on the pharmacology of the investigational product?
- A) True
 - B) False



- 31) Essential documents serve to demonstrate the compliance of the investigator, sponsor and monitor with the standards of Good Clinical Practice and with all applicable regulatory requirements?
- A) True
 - B) False
- 32) A final close-out of the trial can only be done when the monitor has reviewed both investigator/institution and sponsor files and confirmed that all necessary documents are in the appropriate files?
- A) True
 - B) False
- 33) After completion or treatment of the trial the documentation of investigational product destruction must be included in the Investigator but NOT the sponsor files?
- A) True
 - B) False
- 34) Trials may NOT use several doses of test drug and several doses of an active control, with or without placebo?
- A) True
 - B) False
- 35) Both inspections during clinical trials, and inspections after the completion of clinical trials are performed?
- A) True
 - B) False



- 36) The definition of “inspection” includes review of documents, facilities, records, and any other resources located at other establishments deemed appropriate by the regulatory authority (ies)?
- A) True
 - B) False
- 37) The definition of a Clinical Trial does NOT include ascertaining the safety or efficacy of the drug?
- A) True
 - B) False
- 38) The FDA has an obligation to determine compliance with the law even if a case is pending, and if on inspection further violations are found, to take additional steps as necessary to bring about correction?
- A) True
 - B) False
- 39) The Federal Food, Drug, and Cosmetic Act provides NO criminal penalties for refusal to permit a lawful inspection?
- A) True
 - B) False
- 40) Good Clinical Practices are defined as, “generally accepted clinical practices that are designed to ensure the protection of the rights, safety and well-being of clinical trial subjects and other persons?”
- A) True
 - B) False



- 41) Local SOPs for expedited reporting should be available for all countries in which clinical studies are performed by SPONSOR/CRO, otherwise the general regulations of this SOP should be applied?
- A) True
 - B) False
- 42) An AE (Adverse Event) is any untoward medical occurrence in a patient or in a clinical investigation subject administered an investigational product?
- A) True
 - B) False
- 43) An AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational agent?
- A) True
 - B) False
- 44) A serious injury is an injury that does NOT result in permanent impairment of a body function or permanent damage to body structure?
- A) True
 - B) False
- 45) SAE (Serious Adverse Events/ADRs (Adverse Drug Reaction) will be reported in writing by the Clinical Safety Officer, the Lead Clinical Research Associate or appropriate designee to the Sponsor's Medical Monitor, or his/her designee as per project-specific guidelines?
- A) True
 - B) False



- 46) A SAE/ADR is any untoward medical occurrence that occurs at any dose and is a medically important condition?
- A) True
 - B) False
- 47) The Sponsor/CRO may, upon request, provide expedited processing of selected clinical Trial non-serious adverse events to assist in drug evaluation?
- A) True
 - B) False
- 48) For the adverse event to be considered it must have a causal relationship with the investigational product?
- A) True
 - B) False
- 49) An AE must be reported to the IRB and sponsor within 24 hours of study team notification
- A) True
 - B) False
- 50) An SAE must be reported to the Sponsor within 24 hours of study team notification?
- A) True
 - B) False



Appendix B

Answers for CRA Assessment Tool

- 1) True
- 2) True
- 3) True
- 4) False
- 5) True
- 6) False
- 7) True
- 8) False
- 9) True
- 10) True
- 11) False
- 12) False
- 13) False
- 14) False
- 15) True
- 16) False
- 17) False
- 18) True
- 19) True
- 20) False
- 21) True
- 22) True
- 23) True



- 24) False
- 25) True
- 26) False
- 27) True
- 28) False
- 29) True
- 30) False
- 31) True
- 32) True
- 33) False
- 34) False
- 35) True
- 36) True
- 37) False
- 38) True
- 39) False
- 40) True
- 41) True
- 42) True
- 43) True
- 44) False
- 45) True
- 46) True
- 47) True
- 48) False
- 49) False
- 50) True



Appendix C
Clinical Monitoring Plan

Clinical Excellence in Stem Cell Applications

Clinical Monitoring Plan

This Monitoring Plan will be performed in conjunction with the Standard Operating Procedures (SOPs) for monitoring the study that are established by Cesca Therapeutics, Inc.

Monitoring will be performed by the sponsor's appointee.

Purpose

This plan facilitates compliance with ICH GCP, US FDA 21 CFR Part 312, 21 CFR Part 812 and other applicable regulatory requirements and guidelines which require Monitors or Clinical Research Associates (CRAs) to verify the following:

- The rights and well-being of human subjects are protected
- Reported data are accurate, complete and verifiable from source documents
- Trial is conducted in compliance with the currently approved protocol and other applicable regulatory requirements and guidelines.

Types of Monitoring Visits and Monitoring Activities

The Cesca Therapeutics CRAs are responsible for conducting the following types of monitoring visits for this study.

- Site qualification visits (Pre-Study Visit)
- Site Initiation Visits
- Routine Monitoring Visits
- Site Close-out Visits
- Co-Monitoring and Additional Monitoring Visits

Site Initiation Visit

- The Monitor will review the following information with the site investigator and also with the site staff.
- Latest version of the protocol for the study
- Informed Consent Forms (ICF) and processes
- AE and SAE definitions, reporting procedure and contact information
- Investigators Site File (ISF) maintenance
- Case Report Form (CRF) completion and maintenance
- Source documentation requirements
- Investigational medical device accountability requirements

SIV (continued)

During this visit, the Monitor will review the following with the Principal Investigator and with his/her staff as appropriate:

- Study goals and obligations
- Protocol procedures (with particular attention to inclusion/exclusion criteria, enrollment goals, adverse events, primary efficacy variables and GCP compliance)
- Informed consent procedure
- Randomization procedure
- AE/SAE reporting
- CRF completion and error correction requirements for adequate source documentation maintenance
- Maintenance of the investigator site file, study subject file and site visit log etc.
- Investigational status of test device/drug and requirements for accountability and traceability
- Communication guidelines with the IRB/EC and with other concerned authorities
- Delegation of responsibility
- Any other issue as deemed important to the conduct of the study

Routine Monitoring Visits

The first monitoring visit will be performed at each site within 10 working days after the randomization of the first subject into the study for that site.

The remaining routine monitoring visits will occur every 4-6 weeks apart or more depending upon subject enrollment status of each site, the more subjects a site has the more frequently the monitor will have to visit the site.

The interval for the monitoring visits may be longer or shorter than stated above depending on the subject enrollment rate, quality issues, trial site compliance or other trial site issues or concerns

Routine Visit (continued)

The following issues will be addressed at each routine monitoring visit as appropriate:

- Verify receipt of all documents and supplies needed to conduct the study
- Verify Informed consent obtained for each study subject
- Source document verification 100%
- Query resolution and CRF completion
- Investigational medical device accountability and or Drug accountability
- Check and review of the Investigator Site File (ISF) and all essential documents
- Clinical supply inventory
- AE/SAE reporting
- Enrollment issues and targets
- Laboratory specimen handling
- Protocol amendment and their approval by the IRB/EC
- Significant protocol deviations/violations
- Acceptability of facilities
- Personnel changes
- Safety Reports
- Updated essential documentation
- Any other issue as deemed important to the conduct of the study

Routine Visit (continued)

At the conclusion of the visit, or after review of the above information the CRA will meet with the site PI and site staff to review the observations of the conduct of the study at site, develop an action plan for identified issues and to answer the queries of PI and site staff (if any).

Frequency of Monitoring Visits

Subsequent monitoring visits will be conducted 4-6 weeks apart until the 6 months follow-up visit is complete for all the subjects of that site. After that the monitoring visit will be conducted 3 months apart until the last subject's last visit is complete

Investigational Medical Device

The CRA will ensure that the investigational medical devices and or drug shipment and receipt documentation are complete and in accordance with the handling requirements.

The CRA will check the expiry dates of the investigational medical device(s) and or drug on a regular basis and work with the site staff to ensure that there is sufficient quantity of valid investigational medical devices on site for the continuation of the study

Investigational Medical Device (continued)

Return and destruction of investigational medical device and or drug:

- The Monitor will verify accountability and reconciliation prior to return or destruction of any investigational medical device at the site.

CRF and Query Management

CRFs will be maintained electronically. The Monitor shall perform a 100% SDV. In addition, quality checks will be performed to ensure that the CRFs have been completed in accordance with the relevant guidelines. All CRFs monitored during a visit will be detailed in the Monitoring Visit Report. The Monitor assigned to a particular site will be responsible to ensure that the sites enter the data into the eCRF in compliance with the study requirements. The monitor will follow-up with the site staff for resolution of any outstanding queries.

Site Close-out Visit

A site close-out visit will be conducted to ensure appropriate documentation is present and complete. The visit will occur after the last subject's case report forms have been completed, and the study has been closed with the reviewing IRB/EC and all regulatory issues have been addressed.

A site close-out visit may be conducted earlier in the case of study termination by the Investigator, IRB/EC, Independent Data Monitoring Committee (IDMC) or Data Safety Monitoring Board (DSMB), Regulatory Authority or Sponsor.

Site Close-Out Visit (continued)

The following issues will be addressed at this visit:

- A complete review of the investigator site file to ensure that all essential documents, necessary CVs are present and current, all applicable versions of the protocol etc. are present, all applicable versions of the ICF are present, IRB/EC approval letters are present, all SAEs have been reported to the sponsor, IRB/EC and regulatory authority (if applicable) and documentation of submission of protocol deviations/violations to the IRB/EC and sponsor are present, notification and/or final report to the IRB/EC is present.
- A copy of the monitoring visit log is obtained
- A copy of the delegation of responsibility log is obtained
- All CRFs have been completed and appropriately filed
- All pending issues have been resolved
- Investigational medical device and or drug reconciliation records are completed and appropriately filed
- Investigational medical device and or drug shipment and return invoices are present and appropriately filed
- Maintenance and retention of study related documents are discussed
- Regulatory authority inspection process is discussed
- Notification of study close-out to IRB/EC is discussed

Site Close-Out Visit (continued)

The site close-out visit will be conducted within 30 days after the data base has been cleaned and locked. The site close-out visit will be conducted by the Monitor and he/she may be accompanied by an appropriate project team member. The duration of the site close-out visit will be 1-2 days.

Site Close-Out Visit

Following the Site close-out visit, the Monitor will complete the site close-out visit follow-up letter and the final site close-out visit report within 20 working days of the site close-out visit date and provide the site close-out visit follow-up letter to the site including the final site close-out visit report to the Clinical Project Manager.

Co-Monitoring and Additional Monitoring Visits

During the study it may be necessary for a Co-monitor to accompany the assigned Monitor to support on site monitoring activities.

Additional monitoring visits and/or co-monitoring visits will occur when triggered by:

- Site with high enrollment rates
- Sites with significant numbers of protocol deviations/violations
- Intensity of the protocol deviations/violations at site
- Unexpected safety issues
- Investigational medical device and or drug supply issues
- Necessary for site staff training
- Query resolution (issues that are unable to be resolved over the telephone)

Questions





Appendix D
Informed Consent Form

Clinical Excellence in Stem Cell Applications

Informed Consent-Introduction

No clinical investigator may involve a human being as a subject in research unless the investigator has obtained the legally effective informed consent from the subject.



Which Regulations Must be Followed

Code of Federal Regulations

- 21CFR Part 50
- 45CFR Part 46

CESCA SOP

ICH Good Clinical Practice Guidelines E6 4.6

Informed Consent Historical Background

The Nuremberg Code (1947)

–First modern ethical code requiring

- Voluntary consent
- Benefits outweigh risks
- Ability of the subject to terminate participation

Informed Consent Historical Background

Declaration of Helsinki (1964)

- Recommendations Guiding Medical Doctors in Biomedical Research Involving Human Subjects
- Adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964; revised in Tokyo, 1975; Venice, 1983; Hong Kong, 1989; South Africa, 1996; Edinburgh 2000; Note of clarification on paragraph 29; Washington 2002
- “Concern for the interests of the subject must always prevail over the interests of science and society”

Informed Consent Historical Background

Belmont Report (1979)

- Respect for Person
- Beneficence
- Justice

Informed Consent

The clinical site investigator (or other study designated staff who are conducting the informed consent interview) and the participant should exchange information and discuss the contents of the informed consent document. This process must occur under circumstances that minimize the possibility of coercion or undue influence. (21 CFR 50.20.)

The informed consent form must be signed by the subject or the subject's legally authorized representative. Each signed informed consent must be maintained by the clinical investigator and a copy of the document must be provided to the human subject.

Informed Consent: is an ongoing process not
just a document.

The ICF is an agreement not a contract



Why is Informed Consent Necessary?

Prospective subject will ...

- Understand nature of research
- Be informed of purpose, risks, benefits, and alternative therapies
- Make a voluntary decision about study participation

Informed Consent Form

Who develops the ICF document?

- Principal Investigator
- Sponsor

How is the ICF developed?

- Templates
- IRB provided checklist
- Level of risk determines type of ICF

Informed Consent Form

To be effective, the informed consent process must provide sufficient opportunity for the participant to consider whether to participate. ([21 CFR 50.20.](#))
FDA considers this to include allowing sufficient time for participants to consider the information and providing time and opportunity for the participant to ask questions and have those questions answered.

Elements of Informed Consent Form

Informed consent must contain eight required elements and, when applicable, six additional elements

It is the Principal Investigator/Sub-Investigator's responsibility to ensure the eight elements are provided to subject

Elements of Informed Consent Form 21CFR50.25

8 Basic Elements

1. Statement study involves research; purpose and expected duration of the subject's participation; and description of procedures
2. Description of any reasonable foreseeable risks or discomforts
3. Description of any benefits to the subject or to others
4. Disclosure of appropriate alternative procedures
5. Statement describing extent confidentiality of records will be maintained
6. For research involving more than minimal risk, an explanation whether any compensation and/or medical treatments are available if injury occurs
7. Explanation of whom to contact for answers pertinent to questions about research and research subjects' rights
8. Statement that participation is voluntary and that subject may discontinue participation at any time without penalty or loss of benefits

Elements of Informed Consent Form 21CFR50.25

6 Additional Elements (when appropriate)

1. Statement that particular treatment or procedure may involve risks to the subject (or to embryo or fetus if the subject may become pregnant)
2. Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent
3. Any additional costs to the subject that may result from participation in the research
4. The consequences of a subjects' decision to withdraw from the research and procedures for orderly termination of participation by the subject
5. A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject and
6. The approximate number of subjects involved in the study

Informed Consent Process

21 CFR Part 50.27

- The “informed consent shall be documented by the use of written consent form approved by the IRB and signed and dated by the subject...at the time of consent”

21 CFR 312.62 (b) & 812.140 add:

- “The case history for each individual shall document that informed consent was obtained prior to participation in the study.”

Informed Consent Process

- Those obtaining informed consent from subjects must be trained in the areas of human subject protection [Note: Ultimately it is the regulatory responsibility of the Investigator to ensure IC has been obtained and all regulations, laws, SOP's followed].
- Exchange of information between clinical investigators/study coordinators and subject
- Reading and signing the ICF
- Providing a copy to the subject

Informed Consent Process (cont).

- During the ICF discussion, the SC will measure the subject's comprehension and understanding by asking study specific questions
- Have Investigator review with subject any questions they may have in regards to the study
- If subject is willing to participate, ask subject to sign/date ICF; if requested on form, person obtaining ICF should sign/date form
- Have witness sign/date ICF (if applicable)
- Provide subject copy of the consent form

Informed Consent-Sponsor Verification

The clinical monitor shall:

- Check ICFs for proper execution
- Check all signatures and date are completed
- Check if ICF is IRB approved
- Check if legally authorized representative has signed, and verify that accompanying documentation for signature is correlated.
- Check that all versions of the ICF are on file
- Check that the implementation dates correlate with IRB approval dates

Monitor-Informed Consent Sample Checklist

	Subjects Screening and Enrollment and Visit Data
<input type="checkbox"/> Yes <input type="checkbox"/> No	All ICFs are signed and dated for all subjects and the process is fully documented in the source documents.
<input type="checkbox"/> Yes <input type="checkbox"/> No	All subjects have received a copy of the signed and dated ICF.
<input type="checkbox"/> Yes <input type="checkbox"/> No	Ensure that all ongoing patients have signed and dated the latest IRB approved version of ICF.
<input type="checkbox"/> Yes <input type="checkbox"/> No	Site personnel involved in the informed consent process have been delegated this responsibility by the PI on the Delegation and Signature Log.

Questions





References

- Government, F. (2004). *Code of Federal Regulations ICH Guidelines*. Philadelphia, PA: Clinical Research Resources.