FDA Bioresearch Monitoring (BIMO) Checklist

Regulation	Documents Needed (one copy for FDA auditor and one copy for logging)	Actions or Questions Which May Be Asked	Complete?	Initials
Upon notification of FDA audit, immediate steps must be taken in a variety of areas. Please see the attached "Immediate Action Checklist" and institute as soon as a date of audit is determined. A letter may be sent to the PI requesting certain documents be copied and ready for the inspection. Make sure there are two copies of every document (one for the investigator/one for the CTO records).				
Introduction				
Regulations establish specific responsibilities of sponsors for ensuring (1) the proper conduct of clinical studies for submission to FDA and (2) the protection of the rights and welfare of subjects involved in clinical studies. Individual responsibilities include: 1) Obtain agency approval, where necessary, before studies begin. 2) Manufacture and label investigational products appropriately. 3) Initiate, withhold, or discontinue clinical trials as required. 4) Refrain from commercialization of investigational products. 5) Control the distribution and return of investigational products. 6) Select qualified investigators to conduct studies. 7) Disseminate appropriate information to investigators. 8) Select qualified persons to monitor the conduct of studies. 9) Adequately monitor clinical investigations.	1-Name, address, and contact information of Sponsor 2-Name, address, and contact information of CRO. 3-Name, address, credentials, and contact information of all monitors who were on the trial. 4-Copies of all monitoring reports with list of dates, monitor visiting, and outcome report (letter may need to be obtained from PI). 5-Complete Adverse Event and SAE listing from Pharmaceutical Company; must be cross referenced with Protocol Deviation list of OSU CTO.	When will the PI be available for the site visit? *There must be central notification as soon as possible as CTO QA/CRM act as hosts/monitors.* Please explain the role of each of the people named and be familiar with the dates they were involved with the study. *Ensure DOA (if present), is complete with all spaces/columns filled i.* Each SAE will be checked against the corresponding research subject record. Preparation in advance will assist in having "no surprises".		

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10) Evaluate and report adverse experiences. 11) Maintain adequate records of studies. 12) Submit progress reports and the final results of studies.				
The auditor will meet at a prescribed place and be escorted to the Principal Investigator of the study. There he/she will present the 482: Notice of Inspection.	The 482 will be reviewed by the auditor with the PI and signed by the PI. Copy will be given to PI. A copy of the 482 should be made and kept with the study records.	The auditor will present their credentials: give the PI a copy of their business card with their badge number and show the PI their badge. *They cannot allow you to photocopy or touch the badge.* They will then verify the information on the 482 (notice of inspection).		
Determine the overall organization of the clinical research activities and monitoring of the selected studies.	1-Principal Investigator contact name, mailing address, contact number and email address. 2-List of all sub-I's on the study with same information as above. ***Combine 1 & 2 into one document.*** 3-Dates of the study: IRB approval, opening to enrollment, 1st enrollment, last enrollment (closed to enrollment). 4-List of all trials the PI is on divided by their role as: • PI • Sub-I 5-These lists will require you to have the following headings: • Name of IRB of record, address, contact number • Local ID number (FWA) • Trial specific title and ID #	These questions are asked of the Principal Investigator at the time of initial interview. The PI should be able to describe the conduct of the trial and how the organization supports this: • Discuss your role as well as that of your sub-I's. • What is your preparation to be a PI (Length of Service at this University, Credentials, CV review) • What was the process for opening this study here at OSU: CSRC, OSU IRB/WIRB, SIV, PIV, trial opening? • How does the consent process go? Who consents the patient? • Who monitors the study and the patient's safety? • How are AEs assessed? • How do you communicate with the research team and the study		

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	• Status (open & enrolling, closed to in follow-up, permanently closed) • IND # for the drugs on the trial • Who holds the IND: sponsor, investigator & which investigator 5-For all PI and Sub-I's: • 1572's and /or investigator agreements for throughout the entire study • CVs • Signed Financial Disclosures 6-List of dates for all Investigator meetings, site initiation visit date, who attended, sign-in sheets and copy of information covered (slide deck, etc.).	sponsor? • How is (the specific trial endpoint) determined; in collaboration with the sponsor? By the PI alone? • Specific questions about values from outside labs and verification.		
Obtain relevant organizational charts that document structure and responsibilities for all activities involving investigational products. a. **Identify** all departments, functions, and key individuals responsible for areas of sponsor activities such as protocol development, selection of investigators, statistical analysis, clinical supplies, monitoring, and quality assurance. b. **Determine** who has the authority to review and approve study reports and data listings. c. **Determine** who is responsible for final evaluations and decisions in the review of adverse events and safety	1-Have an up to date copy of the department's organizational chart 2-Have complete copies of all position descriptions (job descriptions) for all personnel working in the department. Salary information should be redacted. 3-Document with IRB name and address & name of IRB Chairman. 4-Have a copy of all protocol version(s) printed and ready in the audit room along with all IRB approval letters. Include a copy of the Investigator signature pages. 5- Have a copy of all master ICF version(s) printed and ready in the audit room along with the IRB approval letters.	In general these documents show reporting relationships, define roles, and show preparedness. The documents may be taken with the investigator for review later. Ensure Org Chart is as up to date as possible. Copy of all versions of the protocol calendar		

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information.	6-Copy of the first investigator brochure approved for the study by IRB. 7-Have a delegation log completely filled out (including title and responsibilities, all blank spots or role assignments completed *completely*) for each person involved in the trial. This includes NPs, PAs, research staff, and clinical staff as appropriate. This should be available from the Regulatory binder and all signatures present. 8-Have a complete copy of the sponsors AE and SAE log; this should be compared with the site's Protocol Deviations and match or be corrected.	Be prepared to answer questions regarding the specific AEs. This is when the clinician content expert may be called upon.		
Obtain a list of outside services and contractors (CROs, monitors, laboratories, IRBs) and **document** the services they provide and who is responsible for their selection and oversight. Also **document** the accurate location/address of these contracted parties.	1-List/address of CRO 2-List/contact #/address of monitors 3-All Monitor logs 4-List/address of laboratories 5-IRB/address/contact # used for this trial			
Verify trial is listed correctly on clinicaltrials.gov	1-Screen print of clinicaltrials.gov webpage for trial. 2-Registration date for the trial. 3-Date first patient enrolled. 4-Verify consent form has this statement: "A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most the Web site will include a	Was the trial registered within 21 days of enrollment of the first subject? Are the primary and secondary outcomes measures listed correctly?		

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	summary of the results. You can search this Website at any time."			
SELECTION AND MONITORING OF CLINICAL INVESTIGATORS				
Obtain a list of all investigators and **determine** if there is a Form FDA 1572 (21 CFR 312.53(c)(l) or a signed investigator agreement (21 CFR 812.43(c)) for each clinical investigator identified. Regulations require that the sponsor/CRO select clinical investigators qualified by training and experience (21 CFR 312.53(a), 511.1(b)(7)(i), and 812.43(a)). **Determine** the sponsor's/CRO's criteria for selecting clinical investigators. **Determine** if the sponsor/CRO provided the investigators with all necessary information prior to initiation of the clinical trial. This may include clinical protocols or investigational plans, labeling, investigator brochures, and previous study experience.	1-Have a copy of each investigator's: • 1572, • CV, and • Financial Disclosure of all Investigator(s) on the Key Personnel Log. 2-Be able to produce documents that verify all of the above were completed before the study opening, or in the case when investigators were added, they completed these requirements before they consented/enrolled a patient. 3-Provide evidence (sign in sheet, certification, verification email, etc. and copy of educational materials) that the PI and Sub-I's completed the training/education compliantly. 4-Sponsor provides a complete list of the monitors and their contact information.	Most of these questions are covered during the time of the initial 482 presentation in our experience. The investigator can come back to these in a different manner; they can ask you question about the PI/Sub-I's preparedness or involvement. "How do you ensure the personnel working on the study are adequately prepared?" or "How does the PI communicate with you and maintain oversight of the study?" (i.e. SIV, PIV, inservices in staff meetings, weekly team/census meetings, amendment updates, in-person conversations, email, phone calls).		
Determine if the sponsor/CRO/monitor identified any clinical investigators who did not comply with the investigational plan or FDA regulations. If so, did the sponsor/CRO secure prompt compliance? (When there is a CRO, **determine** who has the responsibility to follow up on noncompliance and	Have copies of documents demonstrating any investigators who did not comply with the investigational plan or FDA regulations and the actions that resulted.	Were there any clinical investigators who were removed from the trial at this site? Are there any PIs/Sub-Is who have caused non-compliance with the trial? If there are we should be aware of it and monitoring that they are not		

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secure investigator compliance, the sponsor or the CRO.) When instances of continued clinical investigator noncompliance are identified, **obtain** evidence of prompt correction or termination of the investigator's participation in the study.		participating in the trial.		
Identify any clinical investigator sites where studies were terminated and the circumstances involved. **Review** monitoring reports for those clinical investigators and **determine** if those instances were promptly reported to FDA as required by 21 CFR 312.56(b). [Since termination of an investigator's participation in a device study would require return or disposal of the investigational device(s), a report is likewise required under 812.150(b)(6).]	Sponsor will provide this information. If there is knowledge (such as in the case of our having sub-sites, this information would be assembled and reported.	Were there any clinical investigators who were removed from the trial at this site?		
Identify any non-compliant clinical investigators who were neither brought into compliance nor removed from the study (participation in the study terminated) by the sponsor as required by 21 CFR 312.56(b) and 812.46(a). **Determine** the reason their participation in the study was not terminated.	Have copies of documents demonstrating any investigators who did not comply with the investigational plan or FDA regulations and the actions that resulted.	Were there any clinical investigators who were removed from the trial at this site? Are there any PIs/Sub-Is who have caused non-compliance with the trial?		
SELECTION OF MONITORS				
Review the criteria for selecting monitors and determine if monitors meet those criteria. **Determine** how the sponsor/CRO	There is a separate investigator sent to the Commercial Sponsor/Pharmaceutical Company. This audit can be concurrent or at a proximate time period. This	You may be asked if there were issues/problems with monitors. This has previously occurred and should be answered honestly but with limited		

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allocates responsibilities when more than one individual is responsible for monitoring functions, e.g., a medical monitor may have the responsibility for medical aspects of the study (and may be a physician) while other monitors may assess regulatory compliance.	information is held by the sponsor; they are responsible for this.	information. For example: "There were many different monitors for this trial." "There was inconsistent instruction offered by monitors." If possible clarify the question and work towards a yes/no answer. Be sure you're being asked a question.		
MONITORING PROCEDURES AND ACTIVITIES				
The FDA inspector has the responsibility to review and obtain a copy of the monitor's SOPs, determine how monitoring was done, and ensure the frequency and scope of the monitoring was consistent with the investigational plan. In the absence of written procedures, conduct interviews of the monitors as feasible and/or otherwise **determine** how monitoring was conducted. **The auditor is required to review** pre-trial and periodic site-visit (monitoring) reports to **determine** when they were reviewed by the sponsor/CRO and, where clinical investigator noncompliance with the investigational plan or regulations was indicated, what follow-up was initiated and how quickly action was taken by the sponsor/CRO. We should be aware of these reports and have at minimum knowledge of their content; a copy is preferred.	1-Have a copy of all monitor reports (letters, etc.). 2-Have the Monitor Visit Log available and completed. Cross check that the monitor log corresponds to the monitor letters. 3-Review all letters for response to the items requiring remediation in the letter; have an explanation for those items that have not been resolved.	With the prevalence of multisite clinical trials, traditional monitoring techniques – early and frequent on-site visits at all clinical sites – have become resource intensive. **Regulations do not prescribe a specific monitoring technique, simply stating that sponsors are required to select monitors qualified by training and experience to monitor the investigational study (21 CFR 312.53(d), 511.1(b)(8)(ii), and 812.43(d)).** Reference the sponsor's/CRO's/monitor's procedures (written SOPs or procedures or stated practices) for the following. ***Please be aware that our asking questions about monitoring practices and requesting different monitors who meet our needs is within the rights of this regulation.*** How often did the monitor visit? They will review the record and may make declarative statements; await a direct question.		
Determine if the	1- Monitor notes, post-visit letters, and	***The DOA Log, list of study personnel,***		

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sponsor/CRO/monitor assured, through documentation, that the clinical investigation was conducted in accordance with the investigational plan submitted to FDA. **Determine** if there is documentation that the responsibilities of the clinical investigators were carried out according to the FDA regulatory requirements (21 CFR 312.60. 312.61, 312.62, 312.64, 312.66, 312.68, (312.69 if the investigational product is a controlled substance), 812.100, 812.110, 812.140(a), (d), and (e), and 812.150(a)).	communications. Have copies made to give to the investigator of all of the following: 1- Training certificates 2- SIV training sign-in sheet 3- SIV slide deck, handouts, content 4- Emails that support completion of training requirements for all personnel who participated in the study.	***and personnel who actually participated in the trial should all match, be complete, and everyone should appear on the DOA Log with assigned responsibilities and be able to demonstrate training with a certificate, email, or sign-in sheet. The investigator will note anyone who is not and ask you to produce that documentation.*** ***The investigator may also ask how personnel were trained as amendments occurred in the study. Everyone needs to answer the same way and you must be able to produce this documentation.***		
REVIEW OF SITE RECORDS				
a. **Determine** if monitoring visits included a comparison of individual subject records and other source documents with case report forms (CRFs) submitted to the sponsor. b. **Determine** if, when, and by whom CRFs are verified against supporting documents (hospital records, office charts, laboratory reports, etc.) at the study site. c. **Determine** if all CRFs are verified during monitoring visits. If a representative sample was selected, determine how the size and composition of the sample were selected. d. **Determine** if a form is used for data	The inspector may ask for some charts or all charts at once. If they don't ask, don't volunteer. Wait for them to ask and only bring what they ask for; the charts are not brought to the room in advance "in preparation" like we do with other audits. What enters the audit room is what is asked for and only what is asked for. In this way, if a problem is found the team immediately fans out to review the rest of the records for that problem and remediates as fast as possible. As a rule of thumb, if there are less than 10 records they will review all records. If more than 10 you await them asking for the records and note any pattern or similarity. As time goes on you can ask how they choose the records but they may or may not tell you.	Much of this section is the initial review of the research subject records and is often done in comparison of the CRO's findings. If there is poor or inconsistent follow-up, problems are not responded to in a timely manner, or there are a significant number of queries/CRF corrections be prepared to answer questions targeted in this area. In addition the monitor looks for trends; if they find 1-2 problems they will drill down and look for this problem in all charts so note the "trends" and convey this to the team so they can begin focusing on this in the remaining research records. Make sure all source documents are signed and dated!		

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verification and **obtain** a copy. **Obtain** a copy of any written procedures (SOPs and guidelines) for data verification. e. **Determine** if the sponsor/CRO/monitor, or a data management company contracted by the sponsor/CRO, makes corrections to CRFs and if confirmation or verification from the clinical investigator is obtained when such changes are made. f. **Determine** how the sponsor/CRO assures that IRB approval is obtained prior to the enrollment of subjects in the study. g. **Determine** how the sponsor/CRO assures that informed consent is obtained from all subjects in the study. h. If sponsor-generated, site-specific data tabulations are provided by the assigning Center, **compare** the tabulations with CRFs submitted by the clinical investigator	Source documents within research records will be reviewed for completeness, signature/date. This is somewhat standard QA, reading the story of the research subject record. Need to have and be able to demonstrate the IRB of record and the approvals. Investigator will ask two important Focus areas of questions of the Host and Regulatory person: 1. "What is the process for opening a new study?" and How do you handle study amendments (what is your step by step process, especially when the amendment results in ICF changes?" 2. The host or person speaking for the study will be asked how they verify and enrollment with the sponsor, transmit information, receive verification by sponsor, confirming	This is where the inspector may need a driver for IHIS so they can follow all of the records. The more the record is printed, the less this will be needed. There must be a policy on source document correction and CRF correction which you can produce. Often CRF correction is dependent on the sponsor's policy. Ensure that there is one and you can produce it or articulate it. Have the following documents ready: • All IRB approvals printed out with copies. • All ICF verifications from sponsor/CRO printed and filed in the regulatory binder. The site is responsible for study enrollment; ensure you know the procedure for consenting. You will likely be asked to recite this out loud and answer questions. ***This may be asked as two questions or as one but this is important because it is about Human Subject (research participant) safety. This should be rehearsed and perfected into as few concise a statement as possible.*** Ensure the host is able to articulate the process for consenting and enrolling a patient step-by-step.		

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	randomization, and receive notification of test article shipment.			
QUALITY ASSURANCE (QA)				
Determine if there was an independent audit/data verification to determine the sponsor's compliance with clinical trials SOPs and FDA regulations. The sponsor will need to answer this question as the audit is not generally subject to FDA inspection.	Sponsor is expected to generate results of data and provide to site at pre-audit. In this way the site verifies that all data is current and ready to go. ***Any discrepancies must be known and corrected at this time.*** Any results from this visit will generally not be put in writing; they are conferred verbally because anything in writing is discoverable and they do not want to "lay out a roadmap" for the inspector. ***Attending these daily de-briefings and being aware of the results is the responsibility of the QA and leadership team.***	Clinical trial quality assurance units (QAUs) are not required by regulation. However, many sponsors obtain independent audits/data verifications to determine the sponsor's compliance with clinical trial SOPs and FDA regulations. These audits/data verifications may be conducted with or without the existence of an actual QAU. All QAUs and/or auditing personnel should be independent of, and separate from, routine monitoring or quality control functions. Findings that are the product of a written QA program will not be inspected without prior concurrence of the assigning FDA headquarters unit. ***This is the advance team that prepares you for the audit. In the event the sponsor does not offer to send this group it should be requested.***		
SAFETY/ADVERSE EVENT REPORTING				

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1. A sponsor must notify FDA and participating investigators (in addition to reviewing IRBs for device studies) of the following types of information associated with the use of investigational articles. a. Drugs/biologics 312.32(c) – IND safety reports of potential serious risks within 15 calendar days after the sponsor determines that the information qualifies for reporting; no later than 7 calendar days if unexpected fatal or life-threatening suspected adverse reaction; 312.32(d) follow-up reports as applicable. b. Drugs in bioavailability and bioequivalence studies that are exempt from the IND requirements 320.31(d)(3) – Report any serious adverse event within 15 calendar days; if fatal or life-threatening, within 7 calendar days; follow-up reports as soon as information is available. d. Devices 812.150(b)(1) – Written report within 10 working days after the sponsor first receives notice of the unanticipated adverse device effect. **Determine** if safety information/unanticipated adverse device effects were reported to FDA as required by regulations.	A complete list of all SAEs should be obtained from the sponsor. Investigator will look over the report they have already been given and look for the same information at the site. Investigator will also ask specifically about the site's handling of reports and how the PI reviews them, how often, and in what manner (appointment, team meeting, etc.). Be aware and notify the PI of any event reports which did not adhere to the timeline. Again notify the PI in advance of any not reported in a timely manner.	The sponsor SAE list must: 1. Be cross-referenced with the Oncore list of SAEs for accuracy and completeness. 2. The SAE list must be checked for complete information with date of discovery, date of submission, and detail. 3. Be aware of all of the details surrounding each SAE. If there was a dis-connect and the staff wasn't notified in a timely manner by the PI (even though he knew about the SAE) be prepared. 4. Identify any instances where we are late in reporting. 5. Know if Event Reports are reviewed in a timely manner by the PI; ensure all are signed off. ***Have the policy for handling SAEs, AEs, and reporting present and know what it says; you may need to articulate it.***	AKL (6/24/13): have Jerri generate script for IND SR review and signature	

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3. **Determine** if safety information/unanticipated adverse device effects were reported to participating investigators (and to reviewing IRBs for device studies) as required by the regulations. 4. **Review** the procedures (e.g., frequency, scope) the sponsor/CRO uses for the receipt, evaluation, and monitoring of safety information/unanticipated adverse device effects, as well as the process for updating the investigator brochure. If applicable, review the composition and function of the safety team/committee (for drugs and biologics). **Obtain** copies of any notification to investigators relating to safety information/unanticipated adverse device effects.	Host and staff involved in clinical care may be asked: • "How did you notify the PI of an SAE? • "How was the sponsor notified of an SAE?" • "How were issues of safety or SAEs shared with Sub-Is and the rest of the team." How was this documented?" • "How were IB updates communicated to the key personnel?" • "What mechanism does OSU have in place to ensure the safety of the research participants is maintained?"	***This section focuses on how the team communicates with each other and how the PI leads the team in human subject safety. Answers that emphasize good communication are very important and "reassuring" to the investigator. These include:*** • ***We have weekly meetings where we go over events that have happened and key information which are attended by all clinical and investigator staff.*** • ***Emails will go out to the participating team when there is new information which is important to the safety of our participants.*** • ***We communicate directly with the PI and the Sub-Is involved and they share this information with other Sub-Is.***		
DATA COLLECTION AND HANDLING				
Review all signed 1572s/agreements associated with the study(ies) specified in the assignment. I**dentify** any clinical investigators with	Two copies of the 1572 with all PIs and Sub-Is listed will be made and ready to give to the inspector.	Double check complete list against Oncore personnel and the team's recollection of personnel involved.		

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signed 1572s/agreements not included in the marketing application/submission and **document** the reason they were not included.	CVs, COIs also with two copies ready to hand over to the inspector. Clear documentation of changes in the 1572 if Sub-Is are added after study opening.	Have SOP related to these activities ready for examination. Host must be able to respond why additional investigators were added and that they were trained appropriately.		
Determine if the number of subjects in the studies performed under an IND/IDE is the same as the number reported in the sponsor's documents (NDA/PMA). **Determine** the number of subjects listed in each of the clinical trials and compare the number of subjects in the tabulations to the corresponding CRFs submitted to the sponsor. **Document** any subjects not included in the NDA/PMA and the reason they were not included.	Sponsor documentation will be compared with the site study documentation for accuracy. Patient listing from Oncore and sponsor list of patients.	Host must know the number of patients enrolled and the number of screen fails. Host must have a complete listing of above. Talk with CTO medical directors and ensure COI training is covered in PI/Sub-I training.		
Review the sponsor's written procedures (SOPs and guidelines) to assure the integrity of safety and efficacy data collected from clinical investigators (domestic and international).	The inspector does this on their own. We currently do not have a way of checking on this.			
RECORD RETENTION				
Determine if the sponsor obtained financial disclosure information from each investigator before his/her participation in the clinical trial, as required by 21 CFR Part 54 and 21 CFR 312.53(c)(4) and 812.2(b)(5) and 812.43(c)(5). **Determine** if the sponsor received	Inspector may ask about the record retention policy: • "What is your record retention policy?" • "When there is a change in the COI of an investigator, what is the procedure?"	We have a brand new SOP which: 1. Copy will be made available for the audit. 2. Host will understand and be able to articulate the policy matches the FDA guidance on record retention specified in Title 21, Subpart D, Section		

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prompt updates regarding relevant changes in financial disclosure information from investigators during the study and for one year after study completion. **Determine** if the sponsor reported to FDA (on Form FDA 3454 and 3455, respectively), all pertinent investigator disclosures and certifications of financial information as required by 21 CFR 54.6. **Determine** if the sponsor retained the documentation to support the certifications and disclosures of investigators' financial information that was reported to FDA.		312.47: "A sponsor shall retain the records and reports required by this part for 2 years after a marketing application is approved for the drug; or, if an application is not approved for the drug, until 2 years after shipment and delivery of the drug for investigational use is discontinued and FDA has been so notified.		
ELECTRONIC RECORDS AND ELECTRONIC SIGNATURES (Guided by: http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126953.pdf)				
Computerized systems are commonly used in clinical investigations to create, modify, maintain, archive, retrieve, and/or transmit clinical data. Regardless of the type of system used by the clinical site, an important principle to understand when evaluating clinical research data is that the regulatory requirements for the clinical data do not change whether clinical data are captured on paper, electronically, or using a hybrid approach. Data must be reliable and usable for evaluating the safety and/or effectiveness of FDA-regulated products. Another important point is that the agency has stated in its guidance entitled, "Guidance for Industry Part 11, Electronic Records; Electronic Signatures – Scope and Application" (Part 11 Guidance) that only certain electronic records will be subject to 21 CFR Part 11 (Part 11), and that the agency intends to exercise enforcement discretion with regard to specific Part 11 requirements. Part 11 describes the technical and procedural requirements that must be met if a firm chooses to maintain records electronically and/or use electronic signatures. Part 11 is a companion regulation to other FDA regulations and laws. It is in these other regulations and laws, called "predicate rules," where specific requirements for issues such as recordkeeping, record content, signatures, and record retention are addressed. Records that are required to be maintained under the predicate rules and that are maintained in electronic format *in place of paper format*. Records that are required to be maintained under the predicate rules, that are maintained in electronic format *in addition to paper format*, and *are relied on to perform regulated activities.* Records that are submitted to FDA, under predicate rules, and that are in electronic format. Electronic signatures that are intended to be the equivalent of handwritten signatures, initials or other general signings that are required by the predicate rules.				
The FDA will explore all aspects of the	The inspector may ask specific questions	Title 21 CFR Part 11 of the Code of	-	

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electronic medical record system including validation of computerized systems; use of computer-generated, time-stamped audit trails; use of legacy systems; generation of copies of records; protection of records (i.e., record retention and availability). **Determine** whether electronic records and/or electronic signatures are required by predicate rules, and/or are used in place of paper records (or relied upon to perform regulated activities) and handwritten signatures. If this is the case, requirements of Part 11, as interpreted by the Part 11 Guidance, apply. If this is not the case, Part 11 requirements do not apply, and the paper records should be evaluated for compliance with the applicable regulations. **Determine** whether electronic data and data collection methods are defined in the study protocol. **Describe** any computerized system(s) used at the study site(s) to generate, collect, or analyze data (e.g., stand alone personal computer, web-based system, hand-held computers). **Determine** how the sponsor/CRO has ensured that sites have access to their original electronic records and how this access is maintained for the required data retention period at a minimum. (e.g., if there is an SOP and	such as the following: • "What is your policy on electronic records." • "When did you move/transfer from paper records to electronic records?" • "What is the date you moved from paper to EPIC/IHIS?" • "What type of training did you receive on EPIC/IHIS?" • "Can you show me the training materials?" • "What Is you electronic signature policy?" • "How do you maintain the security of the paper records?" • "How do you maintain the security of the electronic records?" • "How do you know what has happened in the past with this patient?" • "How do you know if the record has been changed?" • "How were you trained on the EDC system used by this sponsor?"	Federal Regulations deals with the United States Food and Drug Administration (FDA) guidelines on electronic records and electronic signatures. Part 11, as it is commonly called, defines the criteria under which electronic records and electronic signatures are considered to be trustworthy, reliable and equivalent to paper records (Title 21 CFR Part 11 Section 11.1 (a)). These are known as "predicate rules" (referenced above). Have the following documents copied and be prepared to hand over the copies to the inspector: • IHIS go live date • IHIS training deck • Electronic record policy • Electronic signature policy • Study specific EDC training materials • Documentation SOP with EDC and IHIS information included. • Position descriptions of CRCs, CRSs, and CRDCs demonstrating initial ability to manage data successfully. In addition know: • There is a policy and an audit trail that tracks all changes to the EMR • EMR is kept secure by use of password protection which is changed every XX days		

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if it is followed).		• Paper records are stored in a secure locked area which is not accessible by non-CTO personnel. • Know what data capture system was used for this trial and what the security features were. • Know there is an audit trail mechanism (by federal law) on the E-DC system used. Have IHIS and EDC driver available at all times.		
Determine if the sponsor/CRO has established procedures to create, modify, maintain, or transmit electronic records, e.g., user manuals, operating instructions, access policies and procedures, training policies, or management controls. **Determine** if the sponsor/CRO has procedures to demonstrate that the computerized system was tested for its intended use (e.g., documentation of user acceptance testing). **Determine** how the sponsor/CRO documents that there are sufficient personnel with the necessary education, background, training, and experience to ensure that all protocol requirements that employ electronic systems are correctly performed. **Determine** if the sponsor/CRO has procedures for identifying training needs to ensure that all pertinent	While much of this section is related to the sponsor, we will receive questions on how the sponsor communicated initial training and changes to us.	The following documents are important to this section. Have copies available: • SIV initial training for CRDCs (slides, training paperwork) • Sign-in sheet of above • Training records of all CRDCs (certificates or emails) • CRDC position descriptions • Amendments and update additional trainings • User manuals provided by the sponsor • CRC, CRS, CRDC job descriptions • Screen shots should be able to be easily made and sent to print. CRDC should be able to: • Articulate where you find answers to questions on the EDC. If there is a "?" on the data base and this is where questions		

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personnel (e.g., individuals who develop, maintain, and/or utilize computerized systems, including staff at the clinical sites) are trained to adequately perform their assigned responsibilities. **Determine** how the sponsor/CRO ensures that only authorized personnel have access to study data – e.g., if there is a log of authorized users for each clinical site; if all users – at the sites, sponsor, CRO, data processing center – have appropriate user IDs, passwords, and access privileges.		are answered be prepared to point it out and demonstrate. • Articulate how data was extracted from the patient specific records and input into the data base (EDC)		
Describe procedures for collection, retention, and transmission of data at each clinical site. That is, **determine** if there are file transfer protocols for electronic clinical data transmitted to and from the clinical site/sponsor/CRO/data processing center. **Determine** whether original data entries and changes can be made by anyone other than the clinical investigators. **Determine** how the electronic data were reviewed during monitoring visits. If any data monitoring was accomplished remotely, **determine** what was covered and **obtain** copies of any SOPs and/or documentation of such reviews.	Inspector may ask: • "What is the process for data entry?" • "What do you do if the data needs correction?" • "Who can make data corrections?" • "How is the PI kept abreast of changes or needs with data?" • "How did the monitors review the data?"	CRDC should be able to state the process by which data is collected, extracted, and input into the EDC. CRDC then should be able to verbalize the process for transmission to the sponsor. CRDC should be able to verbalize how the documents and information remain secure (password protected, etc.). CRDC must be able to verbalize the process for correcting inaccurate data or updating with new data. CRDC must be able to state the process for the CRO/Monitor reviewing and remediating data.		
Determine who is authorized to access	Be able to identify who has authorized access to the EDC, IHIS, and other data	CRDC should be able to state the process by which data is collected,		

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the system. **Describe** how the computerized systems are accessed (e.g., password protected, access privileges, user identification). **Determine** how information is captured related to the creation, modification, or deletion of electronic records (e.g., audit trails, date/time stamps). **Describe** whether there is backup, disaster recovery, and/or contingency plans to protect against data loss. Were there any software upgrades, security or performance patches, or new instrumentation during the clinical trial? Could the data have been affected? D**escribe** how error messages or system failures were reported to the sponsor, CRO, or study site and the corrective actions, if any, which were taken. **Determine** how the system and data were handled during site closure.	bases (Oncore). The points to the left can all be asked as direct questions. Sponsor should make available to site the "disaster recovery plan" for data backup.	extracted, and input into the EDC. CRDC then should be able to verbalize the process for transmission to the sponsor. CRDC should be able to verbalize how the documents and information remain secure (password protected, etc.). CRDC must be able to verbalize the process for correcting inaccurate data or updating with new data. CRDC must be able to state the process for the CRO/Monitor reviewing and remediating data. Site must be aware if there were any data software updates, system failures, error messages, performance patches, security problems, etc.		
TEST ARTICLE				
Integrity: Describe the sponsor's procedures to ensure the integrity of the test article from manufacturing to receipt by the clinical investigator: **Determine** if the test article met required release specifications. For drugs, review the Certificate of Analysis, if available. For biologics,	This section, dealing with the investigational drugs, records (DARFs), and pharmacy is very important. The investigator may ask: • "How was investigational drug sent to this site?" • "How was investigational drug received by this site?"	***By FDA definition, investigational drug is ILLEGAL drug and this is taken very seriously by the FDA inspector.*** ***The answers to the questions at left should be prepared in advance.*** ***The IDS visit will be scheduled at the inspector's discretion; the IDS***		

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review the Certificate of Analysis, where appropriate and available, and/or the lot release documentation. **Determine** if the test article is not in its final form and requires preparation, manipulation, or processing by the clinical protocol and/or manufacturer's instructions (e.g., mixing plasma with bone chips immediately before use or manipulation of a study subject's cell or tissue specimen) prior to receipt by the subject. **Determine** where the test article was stored and if the conditions of storage were appropriate. **Determine** how the sponsor verified test article integrity during shipment to the clinical study sites. **Determine** if the test article was properly labeled (See 21 CFR 312.6, 511.1(b)(1), and 812.5). **Determine** if the test article was recalled, withdrawn, or returned.	• "What records are kept for investigational drug at this site?" • "How was the investigational drug prepared? Packaged? Dispensed?" • What was your role in the preparation and dispensing of the investigational agent?" • "What SOPs do you use in your department?" • "How was the test article stored?" • "Where was the investigational drug prepared and dispensed?" • "When can I schedule a tour of the IDS?" • "Can you please show me your records on the storage and shipment of the investigational drug?" • "How did you know the agent was treated appropriately during shipment?" • "How is the investigational agent labeled? Who does that?"	***pharmacist is expected to make themselves available.***		
Accountability: **Determine** whether the sponsor maintains accounting records for use of the test article including: Names and addresses of clinical investigators receiving test articles. See 21 CFR 312.57, 511.1(b)(3), and 812.140(b)(2). Shipment date(s), quantity, batch or code mark, or other identification	The main intent of this section is directed at the sponsor. Our responsibility is to ensure that the receiving agent for investigational agent at OSU is the IDS and no other place. Our records for receipt must match the sponsors; on either pre-audit preparation or by request of the sponsor we need to ensure our times and dates are accurate	Check shipment records with IDS. Verify all DARFs have drug logged in, the count is correct, and there are no "blank spots". IDS must be able to articulate drug destruction and show an SOP for this. Do the counts reconcile?		

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number of test article shipped. See regulations above. Final disposition of the test article. See 21 CFR 312.59, 511.1(b)(7)(ii), and 812.140(b)(2). (**A detailed audit should be performed when serious violations are suspected.) **Determine** whether the sponsor's records are sufficient to reconcile test article usage (compare the amount shipped to the investigators to the amount used and returned or disposed of). c. **Determine** whether the clinical investigator appropriately documented any manipulation or processing of the test article and, if the investigator did manipulate or process the test article, **verify** that all relevant requirements set forth in the protocol were met and fully documented. d. **Determine** whether all unused or reusable supplies of the test article were returned to the sponsor when either the investigator(s) discontinued or completed participation in the clinical investigation, or the investigation was terminated. e. If the test article was not returned to the sponsor, **describe** the method of disposition and **determine** if	with shipment records.	Were there any problems or issues in this trial with the investigational agent (i.e. inadequate supply, drug shortages, shipment problems, etc.)? What was the policy of the study for drug return/destruction? Can you show me in the pharmacy manual for this trial where that is? Review the protocol drug manual/investigational agent section and ensure all covenants were met. Be able to articulate whether the investigational agent was supplied, charged for, and show that part of the ICF.		

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adequate records were maintained. f. For device studies, **determine** how the sponsor controls and monitors the use of devices that are not single-use products, such as lithotripters or excimer lasers. g. **Determine** if the sponsor is charging for the test article and **document** the fees charged.				

DEVICES **N/A**

Requests for inspections from the Center for Devices and Radiological Health (CDRH) generally involve Significant Risk (SR) device studies that require full compliance with the Investigational Device Exemption (IDE) regulations at 21 CFR 812. In addition to covering the identified SR device study, the investigator should **determine** whether the sponsor/CRO/monitor is involved in Non-significant Risk (NSR) device studies which require compliance with the abbreviated IDE requirements at 21 CFR 812.2(b). The abbreviated requirements address labeling, IRB approval, informed consent, monitoring, records, reports, and prohibition against promotion, including compliance with 21 CFR 812.5, 812.7, 812.46. 812.140(a)(3)(i), and (b)(4) and (5), 812.150(b)(1) through (3) and (5) through (10). NSR device studies do not have to have an IDE application approved by FDA. When appropriate, the investigator should choose at least one (1), but no more than three (3), NSR device investigations to **determine** the level of compliance with the abbreviated requirements.

Humanitarian Use Devices (HUDs) and Humanitarian Device Exemptions (HDEs) (see also the guidance document on the Humanitarian Device Exemption (HDE) Regulation: Questions and Answers, available at (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm110194.htm) Please see above regulations and FDA 7348.810, Section O. for additional guidance as needed.

See Title III – Pediatric Medical Device Safety and Improvement Act of 2007 – in the medical device provisions of the Food and Drug Administration Amendments Act (FDAAA) of 2007 available at http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/Overview/MedicalDeviceUserFeeandModernizationActMDUFMA/UCM109100.pdf.

EMERGENCY RESEARCH

See 21 CFR 50.24 and the departmental SOP for guidance in this area of research.

INTERNATIONAL DATA – HUMAN DRUGS AND BIOLOGICS

Sponsors are not required to conduct non-U.S. clinical trials under an IND, but often submit data from international study sites to FDA in support of marketing or research applications. In 2008, FDA revised its criteria for accepting non-IND, non-U.S. clinical studies as support for an IND or a new drug application (NDA). See 21 CFR 312.120 (accessible from http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm155713.htm). This revised section of the regulation became effective October 27, 2008. See Section Q. of FDA 7348.810 for further information.

DEVICES

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Background: Requests for inspections from the Center for Devices and Radiological Health (CDRH) generally involve Significant Risk (SR) device studies that require full compliance with the Investigational Device Exemption (IDE) regulations at 21 CFR 812. In addition to covering the identified SR device study, the investigator should **determine** whether the sponsor/CRO/monitor is involved in Non-significant Risk (NSR) device studies which require compliance with the abbreviated IDE requirements at 21 CFR 812.2(b). The abbreviated requirements address labeling, IRB approval, informed consent, monitoring, records, reports, and prohibition against promotion, including compliance with 21 CFR 812.5, 812.7, 812.46. 812.140(a)(3)(i), and (b)(4) and (5), 812.150(b)(1) through (3) and (5) through (10). NSR device studies do not have to have an IDE application approved by FDA. When appropriate, the investigator should choose at least one (1), but no more than three (3), NSR device investigations to **determine** the level of compliance with the abbreviated requirements. Humanitarian Use Devices (HUDs) and Humanitarian Device Exemptions (HDEs) (see also the guidance document on the Humanitarian Device Exemption (HDE) Regulation: Questions and Answers, available at (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm110194.htm) For additional information on IDE regulations see FDA 7348.810, Section O, for adult and pediatric specific regulations.				
EMERGENCY RESEARCH				
Emergency research regulations are covered in FDA 7348.810, Section P, and 21 CFR 50.24. Please see these sections for specific guidance.				
INTERNATIONAL DATA – HUMAN DRUGS AND BIOLOGICS				
Sponsors are not required to conduct non-U.S. clinical trials under an IND, but often submit data from international study sites to FDA in support of marketing or research applications. In 2008, FDA revised its criteria for accepting non-IND, non-U.S. clinical studies as support for an IND or a new drug application (NDA). See 21 CFR 312.120 (accessible from http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm155713.htm). This revised section of the regulation became effective October 27, 2008.				
NONCLINICAL LABORATORY STUDIES				
Determine if the sponsor conducted or contracted for nonclinical studies related to the product that is the subject of the clinical study(ies) specified in the assignment – i.e., studies subject to 21 CFR Part 58, Good Laboratory Practice for Nonclinical Laboratory Studies. If so, **collect** copies of information documenting where and when the nonclinical studies were conducted. For contracted studies, **collect** copies of the agreement with the contracted party.	We must be able to produce the CLIA certificate for our lab and demonstrate (a.) there were no other labs used or. (b.) the other labs were on the 1572 and we had their CLIA certification certificate.			
Sponsors are required to provide a statement in applications/submissions	Speak with the sponsor and ensure this covenant has been met.			

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to FDA that nonclinical studies were conducted in compliance with 21 CFR Part 58 or, if the study was not conducted in compliance with those regulations, a brief statement of the reason for noncompliance. This statement must appear in the Notice of Claimed Investigational Exemption for New Animal Drug studies, IND and IDE applications, and marketing applications/submissions (for devices this statement must appear in a PMA) (21 CFR 312.23(a)(8)(iii), 314.50(d)(2)(v), 314.125(b)(15), 511.1(b)(4)(ii), 514.1(b)(12)(iii), 601.2(a), 812.27(b)(3), 814.20(b)(6)(i)). **Collect** copies of documentation used to support a sponsor's statement that the studies were GLP compliant or the rationale as to why the studies were not conducted in compliance with the regulation.				
Determine if the sponsor approved the nonclinical study protocol(s). **Collect** any available documentation.	Sponsor responsibility.			
The regulation requires that specific information pertinent to test and control article characterization is available either before study initiation or concomitantly (21 CFR 58.105). This includes: stability testing; documentation for each batch of the identity, strength, purity, and composition or other characterization that defines the article; and documentation of methods of synthesis, fabrication, or derivation.	Sponsor responsibility.			

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Determine whether the sponsor or the test facility was responsible for meeting these requirements. **Collect** documentation regarding where and when the testing was conducted as well as copies of any resulting reports.				
Determine where nonclinical studies data and records are retained and **collect** the name and address of that location. The test facility is required to retain, with a few specified exceptions, all raw data, protocols, final reports and specimens as specified in 21 CFR 58.195(b). If the test facility goes out of business during the required records retention period, the regulation requires that all data and records required to be retained be transferred to the sponsor's archives and that FDA be informed of this transfer (21 CFR 58.195(h)). If such a transfer occurred, **determine** the location of the sponsor's archives and **collect** documentation that FDA has been notified of the transfer.	Sponsor responsibility.			
SAMPLE COLLECTION				
Samples may be obtained at the direction of the assigning Center.	CTPL process may be reviewed by inspector; be prepared to • Show records • Show timelines for study samples • Show shipping weigh-bills • Explain variances • Show email correspondence accounting for discrepancies	Review all to the left with CTPL and ensure staff is able to answer these questions.		
During the inspection, if collection appears warranted, contact the	At any time in the visit, the inspector may confer with the branch that assigned the			

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assigning Center for further instructions.	inspector or the district or federal office. Please be aware that the district office is in Columbus (German Village) and the area expert in BIMO inspections is housed there.			

ESTABLISHMENT INSPECTION REPORTS (EIRs)

If the inspection assignment resulted from FDA's receipt of a marketing application/submission, information contained in the EIR may be used in support of marketing approval or denial. If the inspection was assigned "for cause" or as part of general surveillance, information contained in the EIR may be used to determine if the ongoing study should be allowed to continue, either in its entirety or at specific sites. Therefore, the EIR must **document** all findings that could significantly impact the decision-making process.

RESOURCES

Key Links:
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?cfrpart=312

http://www.fda.gov/ICECI/EnforcementActions/BioresearchMonitoring/ucm133777.htm

http://www.fda.gov/ICECI/EnforcementActions/BioresearchMonitoring/ucm133562.htm

http://www.hhs.gov/ohrp/policy/ohrpregulations.pdf

http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?cfrpart=11

v. 2; April 2013.

Internal meeting notes:

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