

National Institutes of Health
NINDS Standard Operating Procedure
Title: Quality Assurance Protocol Monitoring

Version: 2.0
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1.0 PURPOSE

The purpose of this policy is to provide guidance regarding the independent monitoring of applicable clinical investigations conducted in the National Institute of Neurological Disorders and Stroke (NINDS). According to the International Conference on Harmonization Regulations (ICH E6), the intent of protocol monitoring is to provide objective appraisal of trials to verify that: 1) the rights and well-being of human subjects are protected; 2) the reported trial data are accurate, complete, and verifiable from source documents, and 3) the conduct of the trial is in compliance with the currently approved protocol, GCP and applicable regulatory requirements. Protocol monitoring is an important component in ensuring human subject protection and the quality of clinical trial data.

2.0 POLICY

Sponsors of clinical investigations are required to provide oversight of research to ensure adequate protection of the rights, welfare, and safety of human subjects and the quality and integrity of the resulting data submitted to the FDA, as per 21 CFR 312.50 (drugs) and 21 CFR 812.43(d) (devices).

21 CFR 312 – Investigational New Drug Application
Subpart D--Responsibilities of Sponsors and Investigators
Sec. 312.50 - General responsibilities of sponsors.

Sponsors are responsible for selecting qualified investigators, providing them with the information they need to conduct an investigation properly, ensuring proper monitoring of the investigation(s), ensuring that the investigation(s) is conducted in accordance with the general investigational plan and protocols contained in the IND, maintaining an effective IND with respect to the investigations, and ensuring that FDA and all participating investigators are promptly informed of significant new adverse effects or risks with respect to the drug.

21 CFR 812.43(d) – Investigational Device Exemptions
Subpart C—Responsibilities of Sponsors
Sec. 812.43 – Selecting investigators and monitors.

(d) Selecting monitors. A sponsor shall select monitors qualified by training and experience to monitor the investigations study in accordance with this part and other applicable FDA regulations.

Quality assurance monitoring is required for all types of clinical trials, including safety and toxicity studies (Phase I); efficacy studies (Phase II); efficacy, dose-ranging, and comparative trials (Phase III); and post-marketing studies (Phase IV). Applicable trials

also include non-intervention studies involving investigational drugs or devices to understand the mechanism of disease pathogenesis or the development of new technologies.

The NINDS Quality Assurance Office assists investigators in determining the protocol's independent quality assurance monitoring needs. The Office of the Clinical Director has developed a decision algorithm (see Appendix A) to determine the monitoring needs of all clinical research studies within NINDS, based on the identified sponsor and identified study risks.

NINDS utilizes two mechanisms for providing monitoring services: a Contract Research Organization (CRO) and the NINDS Quality Assurance Monitoring Committee (NINDS QAMC). A CRO provides external monitoring for new FDA-regulated clinical trials (Phase I, II, III, or IV) in which NINDS investigators are the sponsors of the trial. The NINDS QAMC provides monitoring of trials that utilize an investigational drug or device to study a disease mechanism (non-treatment) and/or small Phase I trials, which do not warrant external monitoring. For NIH-sponsored protocols in which NINDS investigators are not the sponsors of the IND/IDE, e.g., INDs for various PET ligands, the sponsor of the IND/IDE will be held responsible for monitoring the FDA documents, i.e., documents related to the IND/IDE (e.g., safety reports, annual report to FDA), and the NINDS QAMC will be responsible for monitoring protocol compliance and data management. Non-NIH sponsors are responsible for providing appropriate monitoring of those trials conducted at NINDS/NIH, in which the NINDS investigator is not the IND/IDE sponsor. Of note, a NINDS QA audit of a protocol may be conducted in addition to external monitoring of a trial.

The Monitor is responsible for organizing and conducting the monitoring visits, according to applicable standard operating procedures and regulatory requirements, reviewing preliminary observations with the Principal Investigator, documenting observations in a monitoring visit report, and submitting the report to the Principal Investigator.

The Principal Investigator and key research personnel (associate investigator(s), study coordinator) are responsible for fully cooperating with the development of the monitoring plan, monitoring procedures, and corrective action plans. The Principal Investigator is responsible for maintaining a record of all monitoring reports and corrective action plans, and for implementing corrective actions for any objectionable or otherwise non-compliant observations.

3.0 DEFINITIONS

Adverse Event: According to OHRP's guidance document, *Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events*, an adverse event is any untoward medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in research, whether or not considered related to the subject's participation in the research. In the context of FDA-required reporting, an AE means any untoward medical occurrence associated with the use of a drug or device in humans, whether or not considered drug or device related.

Audit: A systematic and independent examination of trial-related activities and documents to determine whether a particular human research activity was conducted and the data were recorded, analyzed, and accurately reported according to specified requirements, such as protocol requirements, NIH IRB standard operating procedures (SOPs), FDA GCP (when applicable) and applicable regulatory requirements (OHSRP SOP 23.3 A)

Case Report Form (CRF): A case report form is a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor on each trial subject.

Clinical Trial: The NIH definition of a clinical trial is “a research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes”.

Code of Federal Regulations (CFR): The Code of Federal Regulations is the codification of the general and permanent rules and regulations published in the Federal Register by the executive departments and agencies of the federal government of the United States. The CFR is divided into 50 titles that represent broad areas subject to federal regulation. Title 21 Chapter 1 is the portion of the Code of Federal Regulations that governs food and drugs within the US for the FDA.

Contract Research Organization (CRO): A contract research organization is a person or an organization (commercial, academic, or other) contracted by the sponsor to perform one or more of a sponsor's trial-related duties and functions.

Corrective Action Preventive Action (CAPA): A corrective action plan is a strategy for correcting or eliminating a problem that has already occurred or been identified. A preventive action plan defines the steps taken to eliminate the root cause of a problem to prevent it from recurring.

Data and Safety Monitoring Plan (DSMP): A written description of the procedures for reviewing accumulated data in an ongoing research protocol to ensure the safety of research participants and the continuing validity and scientific merit of the protocol (OHSRP SOP 17.3 A). The method and degree of monitoring should be commensurate with the degree of risk involved in participation and the size and complexity of the clinical trial. The DSMP should establish guidelines for the assessment and progress of a clinical trial, at established intervals, to review safety data and the critical efficacy endpoints, and to recommend whether to continue, modify, or stop a trial. The mechanism for data and safety monitoring ranges from monitoring by the PI to monitoring by an Independent Medical Monitor (IMM), Safety Monitoring Committee (SMC), or a Data and Safety Monitoring Board (DSMB).

Essential Documents: Documents that individually and collectively permit evaluation of the conduct of a study and the quality of the data produced (Refer to ICH E6, section 8. "Essential Documents for the Conduct of a Clinical Trial"). These 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.

Good Clinical Practice (GCP): A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected (OHSRP SOP 23.3 B).

ICH Guidelines: The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) is a project that brings together the regulatory authorities of Europe, Japan, and the United States and experts from the pharmaceutical industry in the three regions to discuss scientific and technical aspects of pharmaceutical product registration.

The purpose of ICH is to reduce or obviate the need to duplicate the testing carried out during the research and development of new medicines by recommending ways to achieve greater harmonization in the interpretation and application of technical guidelines and requirements for product registration. It is expected that harmonization will lead to a more economical use of human, animal and material resources, and the elimination of unnecessary delay in the global development and availability of new medicines while maintaining safeguards on quality, safety, and efficacy, and regulatory obligations to protect public health.

IDE: An Investigational Device Exemption (21 CFR 812)

IND: An Investigational New Drug Application (21 CFR 312)

Monitoring: The act of overseeing the progress of a specific research study and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, NIH HRPP policies, standard operating procedures (SOPs), FDA GCP (when applicable), and the applicable regulatory requirement(s). This is a continuous process throughout the life of a research protocol (OHSRP SOP 23.3 I). According to the International Conference on Harmonization Regulations (ICH E6), the intent of protocol monitoring is to provide objective appraisal of trials to verify that: 1) the rights and well-being of human subjects are protected; 2) the reported trial data are accurate, complete, and verifiable from source documents, and 3) the conduct of the trial is in compliance with the currently approved protocol, GCP and applicable regulatory requirements. Protocol monitoring is an important component in ensuring human subject protection and the quality of clinical trial data.

Monitoring Plan: A written document providing a description of how the study will be monitored, how often, and the specific activities to be performed at each visit. Factors that are considered include: complexity of the protocol (e.g., number of activities performed during each visit), disease being evaluated (rate of disease progression or response to treatment), experience of the study staff, number of study subjects enrolled, and rate of enrollment. The monitoring plan may change as the study progresses, depending on these factors.

Protocol Deviation: Any change, divergence, or departure from the IRB approved research protocol (OHSRP SOP 16.3 D and OHSRP 16 Appendix E).

Quality Assurance Office: The Quality Assurance (QA) Office is an office in the NINDS Clinical Trials Unit within the Office of the Clinical Director. The QA Office assists the Clinical Neuroscience Program by disseminating NIH and FDA policy and guidelines and by providing assistance to the research staff to ensure compliance with good clinical practice guidelines. The QA office provides oversight of protocol compliance by performing QA audits and QA monitoring of active protocols.

Serious Adverse Event (SAE) or Serious Adverse Drug Reaction (Serious ADR):

Any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect or
- Based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition (OHSRP SOP 16.3 B).

Source Document: The ICH E6 document, section 1.52, defines source documents as "Original documents, data and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries of evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments) involved in the clinical trial."

Sponsor: An individual who take responsibility for and initiates a clinical investigation. The sponsor may be an individual or pharmaceutical company, governmental agency, academic institution, private organization, or other organization. The sponsor does not actually conduct the investigation unless the sponsor is a sponsor-investigator (21 CFR 312.3 (b), 21 CFR 50.3(e), and 21 CFR 56.102(j)).

Sponsor-Investigator: An individual who both initiates and conducts an investigation, and under whose immediate direction the investigational drug, device or biologic is administered or dispensed. The term does not include any person other than an individual. The requirements applicable to a sponsor-investigator include both those applicable to an investigator and a sponsor (21 CFR 56.102 (k), 21 CFR 312.3, 21 CFR 50.3 (f)).

4.0 PROCEDURE

4.1 Protocol Selection

The Principal Investigator is responsible for identifying protocols, which require monitoring and notifying the NINDS Quality Assurance Office. The Quality Assurance Office reviews the protocol to determine the monitoring needs, i.e., CRO vs NINDS QAMC, based on the monitoring/auditing algorithm.

4.1.1 CRO as Monitor

If a CRO is required, the QA coordinator will contact the extramural project officer for the OCR Clinical Research Support Contract, to request the initiation of the visit. The request should include the following:

- Name of PI, study coordinator, and other key personnel involved in the study
- Protocol number and title
- Data management system description, e.g., CTDB, CiSTAR, Excel spreadsheets, File Maker
- Statistical plan
- Timeline of study visits, i.e., frequency of visits, interval between visits
- Available dates for Site Initiation Visit – should be approximately 4-6 weeks prior to the initiation of the study protocol

The CRO will initiate the development of a draft monitoring plan, budget, and determine availability for the Site Initiation Visit. The CRO and PI will set up an initial 1-2 hour meeting to discuss and agree upon the final monitoring plan including budget, visit frequency, number of visits, communications and timeline. The extramural project officer and the QA coordinator may participate in this meeting.

A final monitoring plan and budget will be sent to the project officer within 1 week of the meeting.

Once the monitoring begins, the CRO staff and the PI/Study coordinator will thereafter communicate directly with regards to the scheduled monitoring activities. The study coordinator should make arrangements with the medicolegal department approximately one month in advance of the visit, to reserve a room for the monitor to review medical records. Additionally, at least one week prior to the initial monitoring visit, the study coordinator should make arrangements to allow the Monitor access to protocol documents in PTMS.

Any issues or concerns regarding the CRO should be brought to the attention of OCR project officer via the QA coordinator. Specifically, the allocated budget will be limited to the monitoring tasks as outlined in the monitoring plan. Therefore, any additional contractor activities beyond the scheduled monitoring should be discussed with the project officer.

4.1.2 NINDS QAMC as Monitor

If the NINDS QAMC will provide monitoring of the trial, the NINDS QA coordinator will retrieve the protocol documents from PTMS and send electronic versions of the protocol documents to the monitoring committee members. The protocol documents will be reviewed for the development of a draft monitoring plan.. The monitoring plan will be finalized after the Site Initiation Visit. Following review of the documents, the Monitor will contact the Principal Investigator to schedule a Site Initiation Visit .

4.2 Scheduling a Monitoring Visit

Once the visit date is scheduled, a notice will be sent to the Principal Investigator

describing the purpose and agenda of the visit and the documents (if any) to be reviewed during the visit. Prior to the visit, the investigator should ensure that all necessary documentation is available for the visit and all key personnel are available on that date to participate in the visit. The Principal Investigator and/or appropriate study team members should be available to answer questions, retrieve documents, and facilitate the completion of the visit.

4.3 Monitoring Visits

4.3.1 Monitoring Plan

A monitoring plan will be developed by the Monitor prior to the Site Initiation Visit, which will outline the frequency of visits as well as the intent of interim visits. The determination of the extent and nature of monitoring may be based on considerations such as the objective, purpose, design, complexity, risk, disease, blinding, size, rate of enrollment, and/or endpoints of the trial. The monitoring plan will be finalized following the Site Initiation Visit.

4.3.2 Site Initiation Visit (SIV)

The agenda for the Site Initiation Visit will be determined by the Monitor and may include a detailed discussion and review of the protocol, drug accountability measures, adverse event reporting, case report forms, regulatory requirements, and the development of a monitoring plan. The Monitor may also tour laboratory facilities used during the protocol, as well as ancillary service areas, e.g., pharmacy, sample storage facilities (e.g. freezers), and phlebotomy.

Refer to Appendix B for a list of Essential Documents that may be reviewed during the SIV.

Following the Site Initiation Visit, the Monitor will provide the Principal Investigator with the final monitoring plan.

4.3.3 Site Interim Visits

Interim visits will be conducted by the Monitor according to the schedule outlined in the protocol monitoring plan. It is the responsibility of the investigator to notify the Monitor and schedule an interim visit, based on subject enrollment and participant endpoints. The purpose of the interim visit is to review regulatory documents, verify regulatory compliance as well as compliance with the protocol, and ensure coherence between CRFs and source documents.

According to ICH E6 5.18.4, the Monitor(s) should ensure that the trial is conducted and documented properly, by carrying out the following activities when relevant and necessary to the trial and the trial site:

4.3.3.1 Investigator qualifications and resources

Verify that the investigator has adequate qualifications and resources and these remain

adequate throughout the trial period, and that the staff and facilities, including laboratories and equipment, are adequate to safely and properly conduct the trial and these remain adequate throughout the trial period.

4.3.3.2 Investigational product

Verify for the investigational product(s):

- That storage times and conditions are acceptable, and that supplies are sufficient throughout the trial.
- That the investigational product(s) are supplied only to subjects who are eligible to receive it and at the protocol specified dose(s).
- That subjects are provided with necessary instruction on properly using, handling, storing, and returning the investigational product(s).
- That the receipt, use, and return of the investigational product(s) at the trial sites are controlled and documented adequately.
- That the disposition of unused investigational product(s) at the trial sites complies with applicable regulatory requirement(s) and is in accordance with the sponsor-investigator's authorized procedures.

4.3.3.3 IRB approved protocol and amendments

Verify that the investigator follows the approved protocol and all approved amendment(s), if any.

4.3.3.4 Informed consent

Verify that written informed consent was obtained before each subject's participation in the trial.

4.3.3.5 Investigator's brochure

Ensure that the investigator receives the current Investigator's Brochure, all documents, and all trial supplies needed to conduct the trial properly and to comply with the applicable regulatory requirement(s), as appropriate.

4.3.3.6 Investigator's knowledge about the trial

Ensure that the investigator and the investigator's trial staff are adequately informed about the trial.

4.3.3.7 Protocol compliance

Verify that the investigator and the investigator's trial staff are performing the specified trial functions, in accordance with the protocol and any other written agreement between the sponsor and the investigator/institution, and have not delegated these functions to unauthorized individuals.

4.3.3.8 Subject eligibility

Verify that the investigator is enrolling only eligible subjects.

4.3.3.9 Subject recruitment

Report the subject recruitment rate.

4.3.3.10 Source documents

Verify that source data/documents and other trial records are accurate, complete, kept up-to-date, and maintained.

4.3.3.11 Regulatory documents

Verify that the investigator provides all the required reports, notifications, applications, and submissions, and that these documents are accurate, complete, timely, legible, dated, and identify the trial.

4.3.3.12 CRF accuracy and completeness

Check the accuracy and completeness of the CRF entries, source data/documents, and other trial-related records against each other. The monitor specifically should verify that:

- The data required by the protocol are reported accurately on the CRFs and are consistent with the source data/documents.
- Any dose and/or therapy modifications are well documented for each of the trial subjects.
- Adverse events, concomitant medications, and intercurrent illnesses are reported in accordance with the protocol on the CRFs.
- Visits that the subjects fail to make, tests that are not conducted, and examinations that are not performed are clearly reported as such on the CRFs.
- All withdrawals and dropouts of enrolled subjects from the trial are reported and explained on the CRFs.

4.3.3.13 CRF corrections

Inform the investigator of any CRF entry error, omission, or illegibility. The monitor should ensure that appropriate corrections, additions, or deletions are made, dated, explained (if necessary), and initialed by the investigator or by a member of the investigator's trial staff who is authorized to initial CRF changes for the investigator. This authorization should be documented.

4.3.3.14 Adverse Event reporting

Determine whether all adverse events (AEs) are appropriately reported within the time periods required by GCP, the protocol, the IRB, the sponsor, and the applicable regulatory requirement(s).

4.3.3.15 Essential documents

Determine whether the investigator is maintaining the essential documents (see Appendix B).

4.3.3.16 Protocol deviation reporting

Communicate deviations from the protocol, SOPs, GCP, and the applicable regulatory requirements to the investigator and take appropriate action designed to prevent recurrence of the detected deviations.

4.3.4 Site Termination Visit

At the conclusion of the trial, the Monitor will perform a Site Termination Visit, to ensure that all study documents, including case report forms, collected study data, informed consent forms, drug accountability, and study regulatory documents are complete and filed at the end of the study. All study drug and other supplies must be accounted for and/or disposed of at the end of the study.

4.4 Monitor Findings

Findings will be classified according to Major or Minor deficiencies.

4.4.1 Major Deficiencies

- A major findings is a significant or recurring deviation of the protocol, such as:
- A deviation which significantly impacts the ability to record valid and accurate data on safety and/or efficacy
 - A deviation which violates the NIH or FDA regulations or policy
 - A deliberate deviation from the IRB approved protocol without prospective IRB approval or the participant's consent
 - A deviation which places the participant's safety at risk

4.4.2 Minor Deficiencies

- A minor finding is a deviation from the protocol, which does not place the subject at risk or does not affect the integrity of the data, such as:
- A minor deviation from the protocol, but there are no safety implications for study participants
 - A minor deviation from the protocol, but the data are usable and valid
 - A deviation from the protocol that is not deliberate or recurring and does not affect the participant's safety or the validity of the data

4.5 Monitor Report

4.5.1 Monitoring Report

Following the completion of each monitoring visit, the Monitor will review the findings and identify necessary corrective action. The Monitor will submit a draft monitoring report to the Principal Investigator within 2-4 weeks of completing the visit. The Principal Investigator should review the draft report for any inaccuracies or clarifications. If

discrepancy with the findings is noted, this should be discussed with the Monitor. A final signed report will then be submitted to the Principal Investigator. It is expected that all action items be implemented expeditiously.

Monitoring reports generated by the CRO will be submitted to the PI, the QA Office, and the extramural project officer for the OCR Clinical Research Support Contract, for review.

Monitoring reports generated by the NINDS QAMC will be reviewed with the Director of the Clinical Trials Unit and the NINDS Clinical Director. The Clinical Director will sign the final report.

The Principal Investigator should receive a final monitoring report from the Monitor as soon as possible after the report is finalized. The Investigator will maintain a copy of the monitoring report in the appropriate section of the regulatory files.

4.5.2 Significant Protocol Non-compliance

If significant protocol non-compliance is noted, the Clinical Director will require a special meeting with the QA Coordinator, the NINDS Clinical Director and the study team to discuss the plan for the implementation of corrective actions and process improvements arising from objectionable observations, as needed.

The Investigator will implement those corrective actions and improvements within a mutually agreed upon time period.

4.5.3 Corrective Action Preventative Action (CAPA)

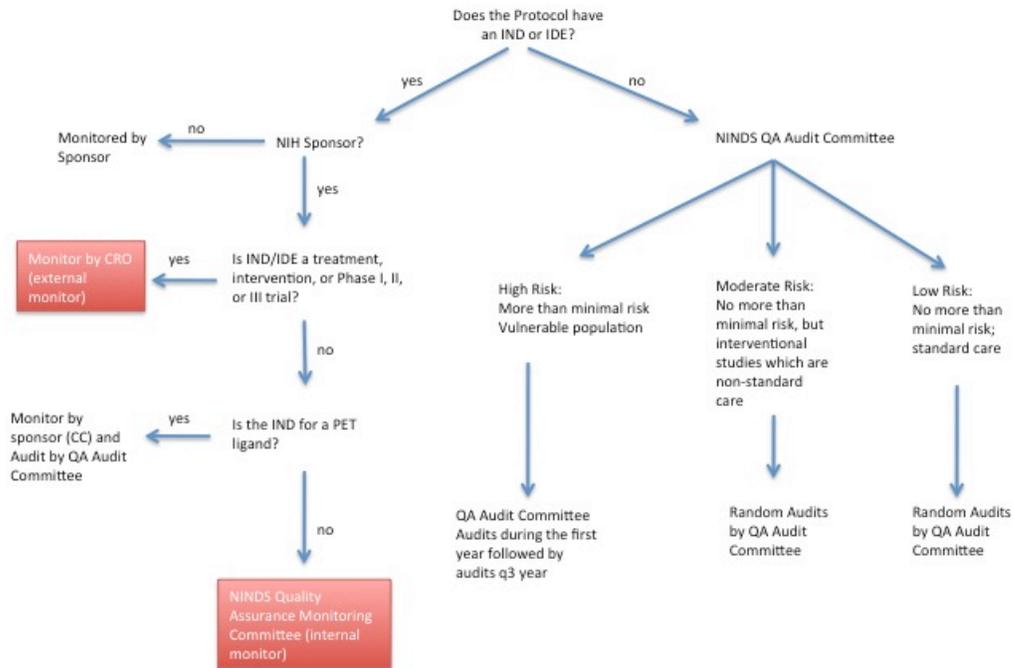
All major deficiencies must have a Corrective Action Preventive Action (CAPA) created, outlining how the deficiency will be corrected and prevented in the future.

5.0 LIST OF APPENDICES

Appendix A – QA Monitoring/Auditing Algorithm

Appendix B – Essential Documentation Checklist (ICH E6)

Appendix A – QA Monitoring/Auditing Algorithm



Updated: 12/2/14

Appendix B – Essential Documentation Checklist (ICH E6)

Regulatory Documents/IRB documented approval		Purpose	Before Trial	During Trial	After Trial
<input type="checkbox"/>	Original Protocol and IRB Approval ICH 8.2.7	To document that the trial has been subject to IRB/IEC review and given approval/favorable opinion. To identify the version number and date of the document(s).	<input type="checkbox"/>		
<input type="checkbox"/>	All Continuing Reviews with Approvals ICH 8.3.19	Interim or annual reports provided to IRB		<input type="checkbox"/>	
<input type="checkbox"/>	All Amendments with Approvals ICH 8.2.7 ICH 8.3.2	To document that the trial has been subject to IRB/IEC review and given approval/favorable opinion. To identify the version number and date of the document(s).	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/>	Informed Consent/Assent Forms with IRB Approval; including any revisions ICH 8.2.3 ICH 8.2.7 ICH 8.3.2	To document the informed consent To document that the trial has been subject to IRB/IEC review and given approval/favorable opinion. To identify the version number and date of the document(s).	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/>	Adverse Events Reporting; Notification by sponsor/investigator to FDA and IRB of unexpected serious adverse drug reactions and of other safety information ICH 8.3.17	Notification by sponsor/investigator to FDA and IRB of unexpected serious adverse drug reactions and of other safety information		<input type="checkbox"/>	
<input type="checkbox"/>	Other IRB correspondence, e.g., Radiation Safety, DSMB, Tech Transfer documents and Approvals ICH 8.2.9	To document appropriate authorization/approval/notification by the regulatory authority(ies) has been obtained prior to initiation of the trial in compliance with the applicable regulatory requirement(s)	<input type="checkbox"/>		
<input type="checkbox"/>	Advertisements for subject recruitment with IRB Approval; including any revisions ICH 8.2.3 ICH 8.2.7 ICH 8.3.2	To document that recruitment measures are appropriate and not coercive To document that the trial has been subject to IRB/IEC review and given approval/favorable opinion. To identify the version number and date of the document(s).	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/>	Any additional written material provided to patient with IRB Approval; including any revisions ICH 8.2.3 ICH 8.2.7 ICH 8.3.2	To document that subjects will be given appropriate written information (content and wording) to support their ability to give fully informed consent To document that the trial has been subject to IRB/IEC review and given approval/favorable opinion. To identify the version number and date of the document(s).	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/>	Investigator's Brochure (if multi-institutional study) and/or Safety Report ICH 8.2.1 ICH 8.3.1	To document that relevant and current scientific information about the investigational product has been provided to the investigator. Required only if not sponsor-investigator trial. The IB should be updated and reviewed during interim monitoring visits.	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/>	Institutional Review Board (IRB) composition ICH 8.2.8	To document that the IRB/IEC is constituted in agreement with GCP	<input type="checkbox"/>		
<input type="checkbox"/>	Notification by sponsor to investigators of updated safety information ICH 8.3.18	Notification by sponsor to investigators of updated safety information		<input type="checkbox"/>	

Regulatory Documents/FDA documented submissions/approvals		Purpose	Before Trial	During Trial	After Trial
<input type="checkbox"/>	IND/IDE application and FDA approval letter ICH 8.2.9	To document appropriate authorization/approval/notification by the regulatory authority(ies) has been obtained prior to initiation of the trial in compliance with the applicable regulatory requirement(s). Example: FDA "Safe to Proceed" letter or documentation of no response >30 days after receipt	<input type="checkbox"/>		
<input type="checkbox"/>	Amendments with Form 1571 and authorization/approval ICH 8.3.4	To document compliance with applicable regulatory requirements		<input type="checkbox"/>	
<input type="checkbox"/>	Annual Reports with Form 1571 ICH 8.3.19	Interim or annual reports provided to IRB and authority(ies)		<input type="checkbox"/>	

Investigator Information		Purpose	Before Trial	During Trial	After Trial
<input type="checkbox"/>	Investigator signature on protocol and amendments and/or email/memo from investigator acknowledging agreement to participate ICH 8.2.2 ICH 8.2.6	To document investigator and sponsor agreement to the protocol/amendment(s)	<input type="checkbox"/>		
<input type="checkbox"/>	Signed FDA form 1572/Investigator Agreement ICH 8.2.6	To document investigator and sponsor agreement to the protocol/amendment(s)	<input type="checkbox"/>		
<input type="checkbox"/>	Curriculum Vitae for all investigators and new investigators ICH 8.2.10 ICH 8.3.5	To document qualifications and eligibility to conduct trial and/or provide medical supervision of subjects	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/>	Financial disclosure (FDA form 3454) for all investigators listed on FDA form 1572 or documented DEC approval ICH 8.2.4	To document the financial agreement between the investigator/institution and the sponsor for the trial	<input type="checkbox"/>		
<input type="checkbox"/>	Signed agreement between Investigator and CRO (if applicable) ICH 8.2.6	To document agreements	<input type="checkbox"/>		
<input type="checkbox"/>	Site Initiation Monitoring Report ICH 8.2.20	To document that trial procedures were reviewed with the investigator and investigator's trial staff	<input type="checkbox"/>		
<input type="checkbox"/>	Site Interim Monitoring Report(s) ICH 8.3.10	To document site visits by, and findings of, the monitor		<input type="checkbox"/>	
<input type="checkbox"/>	Site Termination/Close-Out Monitoring Report ICH 8.4.5	To document that all activities required for trial close-out are completed, and copies of essential documents are held in the appropriate files			<input type="checkbox"/>
<input type="checkbox"/>	Relevant communication such as letters, emails, meeting notes, telephone calls ICH 8.3.11	To document any agreements or significant discussions regarding trial administration, protocol violations, trial conduct, adverse event reporting		<input type="checkbox"/>	

Protocol Management Documents		Purpose	Before Trial	During Trial	After Trial
<input type="checkbox"/>	Subject Screening Log ICH 8.3.20	To document identification of subjects who entered pretrial screening		<input type="checkbox"/>	

<input type="checkbox"/>	Subject Enrollment Log ICH 8.3.22	To document chronological enrollment of subjects by trial number		<input type="checkbox"/>	
<input type="checkbox"/>	Subject identification codes ICH 8.3.21 ICH 8.4.3	To document that investigator/institution keeps a confidential list of names of all subjects allocated to trial numbers on enrolling in the trial. Allows investigator/institution to reveal identity of any subject. To permit identification of all subjects enrolled in the trial in case follow-up is required. List should be kept in a confidential manner and for agreed upon time.		<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Signed informed consent forms ICH 8.3.12	To document that consent is obtained in accordance with GCP and protocol and dated prior to participation of each subject in trial.		<input type="checkbox"/>	
<input type="checkbox"/>	Case Report Forms – signed, dated, and completed; documented CRF corrections ICH 8.3.14 ICH 8.3.15	To document that the investigator or authorized member of the investigator’s staff confirms the observations recorded and all changes/additions or corrections were recorded and verified		<input type="checkbox"/>	
<input type="checkbox"/>	Source Documents/Data ICH 8.3.13	To document the existence of the subject and substantiate integrity of trial data collected. To include original documents related to the trial, to medical treatment, and history of subject		<input type="checkbox"/>	
<input type="checkbox"/>	Delegation of Authority Log – signature sheet ICH 8.3.24	To document signatures and initials of all persons authorized to make entries and/or corrections on CRFs and to perform research related protocol procedures		<input type="checkbox"/>	
<input type="checkbox"/>	Record of retained body fluid/tissue (if applicable) ICH 8.3.25	To document location and identification of retained samples if assays need to be repeated		<input type="checkbox"/>	

Drug/Device Management Documents		Purpose	Before Trial	During Trial	After Trial
<input type="checkbox"/>	Sample of Investigational Product (IP) label ICH 8.2.13	To document compliance with applicable labeling regulations and appropriateness of instructions provided to subjects	<input type="checkbox"/>		
<input type="checkbox"/>	Drug/Device accountability log ICH 8.3.23	To document that investigational product(s) have been used according to the protocol		<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Drug/Device shipment records (if applicable) ICH 8.2.15 ICH 8.3.8	To document shipment dates, batch numbers, and method of shipment of investigational product(s) and trial- related materials. Allows tracking of product batch, review of shipping conditions, and accountability.	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/>	Instructions for handling investigational products and trial related materials ICH 8.2.14	To document instructions needed to ensure proper storage, packaging, dispensing, and disposition of investigational products and trial-related materials	<input type="checkbox"/>		
<input type="checkbox"/>	Documentation of investigational product(s) destruction ICH 8.4.2	To document destruction of unused investigational product(s) by sponsor or at site			<input type="checkbox"/>
<input type="checkbox"/>	Medical/Laboratory/technical procedures and/or tests; and any updates or revisions during the trial <ul style="list-style-type: none"> • Certificate • Accreditation 	To document competence of facility to perform required test(s), and support reliability of results	<input type="checkbox"/>	<input type="checkbox"/>	

	<ul style="list-style-type: none"> • Quality Control documentation • Other validation ICH 8.2.12 ICH 8.3.7				
<input type="checkbox"/>	Laboratory normal values; and any updates or revisions during the trial ICH 8.2.11 ICH 8.3.6	To document normal values and/or ranges of the tests	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/>	Certificate of Analysis of IP shipped; COA for new batches shipped ICH 8.2.16 ICH 8.3.9	To document identity, purity, and strength of investigational products to be used in the trial.	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/>	Decoding procedures for blinded trials ICH 8.2.17	To document how, in case of an emergency, identity of blinded investigational product can be revealed without breaking the blind for the remaining subjects' treatment	<input type="checkbox"/>		
<input type="checkbox"/>	Randomization method/code ICH 8.2.18	To document method for randomization of trial population	<input type="checkbox"/>		