

Appendix to Presentation by Rory Jaffe and Juliann Tenney

Research Compliance Conference

Health Care Compliance Association

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Federal Sentencing Guidelines

Document Samples:

Developing an Auditing and Monitoring Plan for Clinical Research

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Federal Sentencing Guidelines

§8B2.1. Effective Compliance and Ethics Program¹

(a) To have an effective compliance and ethics program ... an organization shall—

- (1) exercise due diligence to prevent and detect criminal conduct; and
- (2) otherwise promote an organizational culture that encourages ethical conduct and a commitment to compliance with the law. Such compliance and ethics program shall be reasonably designed, implemented, and enforced so that the program is generally effective in preventing and detecting criminal conduct. The failure to prevent or detect the instant offense does not necessarily mean that the program is not generally effective in preventing and detecting criminal conduct.

¹ Factors to Consider in Meeting Requirements of this Guideline.—

(A) In General.—Each of the requirements set forth in this guideline shall be met by an organization; however, in determining what specific actions are necessary to meet those requirements, factors that shall be considered include: (i) applicable industry practice or the standards called for by any applicable governmental regulation; (ii) the size of the organization; and (iii) similar misconduct.

(B) Applicable Governmental Regulation and Industry Practice.—An organization's failure to incorporate and follow applicable industry practice or the standards called for by any applicable governmental regulation weighs against a finding of an effective compliance and ethics program.

(C) The Size of the Organization.—

(i) In General.—The formality and scope of actions that an organization shall take to meet the requirements of this guideline, including the necessary features of the organization's standards and procedures, depend on the size of the organization.

(ii) Large Organizations.—A large organization generally shall devote more formal operations and greater resources in meeting the requirements of this guideline than shall a small organization. As appropriate, a large organization should encourage small organizations (especially those that have, or seek to have, a business relationship with the large organization) to implement effective compliance and ethics programs.

(iii) Small Organizations.—In meeting the requirements of this guideline, small organizations shall demonstrate the same degree of commitment to ethical conduct and compliance with the law as large organizations. However, a small organization may meet the requirements of this guideline with less formality and fewer resources than would be expected of large organizations. In appropriate circumstances, reliance on existing resources and simple systems can demonstrate a degree of commitment that, for a large organization, would only be demonstrated through more formally planned and implemented systems. Examples of the informality and use of fewer resources with which a small organization may meet the requirements of this guideline include the following:

- (I) the governing authority's discharge of its responsibility for oversight of the compliance and ethics program by directly managing the organization's compliance and ethics efforts;
- (II) training employees through informal staff meetings, and monitoring through regular "walk-arounds" or continuous observation while managing the organization;
- (III) using available personnel, rather than employing separate staff, to carry out the compliance and ethics program; and
- (IV) modeling its own compliance and ethics program on existing, well-regarded compliance and ethics programs and best practices of other similar organizations.

(D) Recurrence of Similar Misconduct.—Recurrence of similar misconduct creates doubt regarding whether the organization took reasonable steps to meet the requirements of this guideline....

(b) Due diligence and the promotion of an organizational culture that encourages ethical conduct and a commitment to compliance with the law within the meaning of subsection (a) minimally require the following:

(1) The organization shall establish standards and procedures to prevent and detect criminal conduct.

(2)²

(A) The organization's governing authority shall be knowledgeable about the content and operation of the compliance and ethics program and shall exercise reasonable oversight with respect to the implementation and effectiveness of the compliance and ethics program.

(B) High-level personnel of the organization shall ensure that the organization has an effective compliance and ethics program, as described in this guideline. Specific individual(s) within high-level personnel shall be assigned overall responsibility for the compliance and ethics program.

(C) Specific individual(s) within the organization shall be delegated day-to-day operational responsibility for the compliance and ethics program. Individual(s) with operational responsibility shall report periodically to high-level personnel and, as appropriate, to the governing authority, or an appropriate subgroup of the governing authority, on the effectiveness of the compliance and ethics program. To carry out such operational responsibility, such individual(s) shall be given adequate resources, appropriate authority, and direct access to the governing authority or an appropriate subgroup of the governing authority.

(3) The organization shall use reasonable efforts not to include within the substantial authority personnel of the organization any individual whom the organization knew, or should have known through the exercise of due diligence, has engaged in illegal activities or other conduct inconsistent with an effective compliance and ethics program.³

² Application of Subsection (b)(2).—High-level personnel and substantial authority personnel of the organization shall be knowledgeable about the content and operation of the compliance and ethics program, shall perform their assigned duties consistent with the exercise of due diligence, and shall promote an organizational culture that encourages ethical conduct and a commitment to compliance with the law. If the specific individual(s) assigned overall responsibility for the compliance and ethics program does not have day-to-day operational responsibility for the program, then the individual(s) with day-to-day operational responsibility for the program typically should, no less than annually, give the governing authority or an appropriate subgroup thereof information on the implementation and effectiveness of the compliance and ethics program.

³ Application of Subsection (b)(3).—

(A) Consistency with Other Law.—Nothing in subsection (b)(3) is intended to require conduct inconsistent with any Federal, State, or local law, including any law governing employment or hiring practices.

(B) Implementation.—In implementing subsection (b)(3), the organization shall hire and promote individuals so as to ensure that all individuals within the high-level personnel and substantial authority personnel of the organization will perform their assigned duties in a manner consistent with the exercise of due diligence and the promotion of an organizational culture that encourages ethical conduct and a commitment to compliance with the law...

(4)

(A) The organization shall take reasonable steps to communicate periodically and in a practical manner its standards and procedures, and other aspects of the compliance and ethics program, to the individuals referred to in subdivision (B) by conducting effective training programs and otherwise disseminating information appropriate to such individuals' respective roles and responsibilities.

(B) The individuals referred to in subdivision (A) are the members of the governing authority, high-level personnel, substantial authority personnel, the organization's employees, and, as appropriate, the organization's agents.

(5) The organization shall take reasonable steps—

(A) to ensure that the organization's compliance and ethics program is followed, including monitoring and auditing to detect criminal conduct;

(B) to evaluate periodically the effectiveness of the organization's compliance and ethics program; and

(C) to have and publicize a system, which may include mechanisms that allow for anonymity or confidentiality, whereby the organization's employees and agents may report or seek guidance regarding potential or actual criminal conduct without fear of retaliation.

(6) The organization's compliance and ethics program shall be promoted and enforced consistently throughout the organization through⁴

(A) appropriate incentives to perform in accordance with the compliance and ethics program; and

(B) appropriate disciplinary measures for engaging in criminal conduct and for failing to take reasonable steps to prevent or detect criminal conduct.

(7) After criminal conduct has been detected, the organization shall take reasonable steps to respond appropriately to the criminal conduct and to prevent further similar criminal conduct, including making any necessary modifications to the organization's compliance and ethics program.

(c) In implementing subsection (b), the organization shall periodically assess the risk of criminal conduct and shall take appropriate steps to design, implement, or modify each requirement set forth in subsection (b) to reduce the risk of criminal conduct identified through this process.⁵

Definitions.

“Compliance and ethics program” means a program designed to prevent and detect criminal conduct.

“Governing authority” means the (A) the Board of Directors; or (B) if the organization does not have a Board of Directors, the highest-level governing body of the organization.

“Standards and procedures” means standards of conduct and internal controls that are reasonably capable of reducing the likelihood of criminal conduct.

[“Substantial authority personnel” means individuals who within the scope of their authority exercise a substantial measure of discretion in acting on behalf of an organization. The term includes high-level personnel of the organization, individuals who exercise substantial supervisory authority (e.g., a plant manager, a sales manager), and any other individuals who, although not a part of an organization’s management, nevertheless exercise substantial discretion when acting within the scope of their authority (e.g., an individual with authority in an organization to negotiate or set price levels or an individual authorized to negotiate or approve significant contracts). Whether an individual falls within this category must be determined on a case-by-case basis.]

Background

This section sets forth the requirements for an effective compliance and ethics program. This section responds to section 805(a)(2)(5) of the Sarbanes-Oxley Act of 2002, Public Law 107–204, which directed the Commission to review and amend, as appropriate, the guidelines and related policy statements to ensure that the guidelines that apply to organizations in this chapter “are sufficient to deter and punish organizational criminal misconduct.” The requirements set forth in this guideline are intended to achieve reasonable prevention and detection of criminal conduct for which the organization would be vicariously liable. The prior diligence of an organization in seeking to prevent and detect criminal conduct has a direct bearing on the appropriate penalties and probation terms for the organization if it is convicted and sentenced for a criminal offense.

<http://www.uscc.gov/2004guid/RFMay04.pdf> reader-friendly version of amendments sent to Congress.

⁴ Application of Subsection (b)(6).—Adequate discipline of individuals responsible for an offense is a necessary component of enforcement; however, the form of discipline that will be appropriate will be case specific.

⁵ Application of Subsection (c).—To meet the requirements of subsection (c), an organization shall:

- (A) Assess periodically the risk that criminal conduct will occur, including assessing the following:
 - (i) The nature and seriousness of such criminal conduct.
 - (ii) The likelihood that certain criminal conduct may occur because of the nature of the organization’s business. If, because of the nature of an organization’s business, there is a substantial risk that certain types of criminal conduct may occur, the organization shall take reasonable steps to prevent and detect that type of criminal conduct....
 - (iii) The prior history of the organization. The prior history of an organization may indicate types of criminal conduct that it shall take actions to prevent and detect.
- (B) Prioritize periodically, as appropriate, the actions taken pursuant to any requirement set forth in subsection (b), in order to focus on preventing and detecting the criminal conduct identified under subdivision (A) of this note as most likely to occur.
- (C) Modify, as appropriate, the actions taken pursuant to any requirement set forth in subsection (b) to reduce the risk of criminal conduct identified under subdivision (A) of this note as most likely to occur.

CLINICAL TRIALS QUALITY ASSURANCE FAQ'S

What is the CTQA?

The Clinical Trials Quality Assurance (CTQA) Office is a section of the DUMC SOM Compliance Office. The purpose of CTQA is to verify that: 1) the rights and welfare of human subjects are met; 2) the conduct of the clinical trial is consistent with the approved protocol, including regulatory requirements, that reported study data are accurate, complete and verifiable from the source documents; and 3) to investigate complaints and/or allegations of noncompliance with research regulations or applicable laws. The staff will also help provide information to faculty and staff on regulatory compliance and Good Clinical Practice (GCP) Guidelines concerning human subjects, data collection and data management.

What CTQA can do?

- ***Conduct routine, proactive, on-site reviews***
- Conduct directed, reactive, “for-cause” reviews
- Assist in preparing sites for external audits
- Provide consultation to research personnel
- Assist principal investigator and study staff in conducting self assessments
- Monitor on-going research activities
- Collaborate with the IRB regarding regulatory issues raised by sponsors or other agencies
- Provide regulatory training and incidence resolution

What is the purpose of the CTQA review?

The purpose of the CTQA review is to:

- Assess compliance with applicable Federal regulations
- Assess compliance with the IRB and other institutional guidelines
- Determine that the rights and welfare of subjects enrolled in clinical trials have been/are properly protected
- Recommend and review action plans based on the review findings
- Provide education to research professionals
- Assist investigators perform self-assessments

How are protocols selected for review?

Protocols are selected for routine review by performing a query of the IRB database. Fields included in the query are:

- Absence of external monitoring or oversight
- Investigator initiated IND or IDE (includes both investigator and sponsor regulatory responsibilities for study conduct and reporting)
- Degree of risk – based on expected adverse events, type of study, or vulnerable population(s)
- Allegations of human subjects violations or noncompliance with Federal regulations
- Investigator experience
- Failure to submit IRB renewal, to answer modifications in a timely fashion, or to respond to IRB deferral issues

Who conducts the review?

QA reviewers will conduct the CTQA reviews. The CTQA team has direct clinical research experience and prior QA auditing experience. Adjunct reviewers will be available to assist with protocol specific situations.

Are CTQA personnel available to provide education and training?

Yes, CTQA personnel are available to provide both individual and group training sessions or to assist in identifying the appropriate educational needs. Training areas may include:

- Research Quality Improvement consultations – the nuts and bolts of conducting research according to Good Clinical Practice (GCP), providing self-assessment checklists, templates, and coordinating IRB educational session
- Voluntary Quality Assurance review of ongoing studies
- Obtaining consent and recruiting subjects
- Maintaining regulatory files

Do I (the PI and study coordinator) need to be present during the entire review procedure?

No, you do not need to be present during the entire review. However, you will meet with the CTQA team prior to the review for an opening meeting. You will also be asked to be available via pager or to check in periodically to answer any questions that may arise. Again, at the end of the review, a closing meeting will occur and you will be required to attend.

What information will be reviewed during the review?

- The approved research protocol and all IRB correspondence
- The consent document and process (if possible)
- The Regulatory Binder and affiliated study correspondence
- Adherence to the inclusion/exclusion criteria
- Adherence to study procedures
- Occurrence and reporting of adverse events
- Research article accountability (drugs, device, etc., if applicable)
- Selected Case Report Forms and the appropriate source documentation
- Data quality and management

What should I do if I identify problems when preparing for the review?

If you identify any errors or omissions while preparing for the review, please notify a CTQA reviewer for guidance. The most frequent advice that is given if an error or omission is identified is to document the occurrence of the event and place a signed dated memo regarding the event in the research file (known as a “note to file”). A report describing this event should also be submitted to the IRB along with a plan of corrective actions that will be taken to eliminate future occurrence of this problem.

What information should I have available for the review?

You will be asked to have the following information available for the review:

- Informed consent documents
- The research subject’s study binder/file (CRF)
- Source Documentation (for example, medical records, clinical and office charts, laboratory notes, memoranda, subject diaries, pharmacy dispensing records, recorded data from automated instruments, x-rays, laboratory reports)
- The regulatory file/binder
- Departmental SOPs

The better the condition and organization of these items prior to the review, the shorter the review time will be.

What problems may be identified during the review?

The most common deficiencies identified by the FDA are:

- Failure to follow the approved protocol
- Failure to keep adequate and accurate records

- Problems with the consent document
- Failure to report AE's
- Failure to report deviations and enrolling ineligible subjects
- Inappropriate delegation of authority

Who receives a report of the review findings?

Upon completion of the CTQ review, the staff will promptly draft a report of their findings. The report will include a deadline for any corrective actions as well as for a written response.

Depending on the type of review (directed or routine), copies of the report may be distributed to the following:

- Principal Investigator and Co-PI ^a
- Department Chair ^b
- IRB ^a
- Vice Dean of Research ^a
- Associate Dean of Compliance ^a
- Regulatory and/or Funding Agencies ^b

Note:

^a All reviews

^b Directed reviews and/or if major problems are identified requiring agency notification

Whom do I contact?

Lead Reviewer, Clinical Trials Quality Assurance
DUMC Box

Associate Reviewer, Clinical Trials Quality Assurance
DUMC Box

Letter of Intent to Review

Date

Name

Address

Address

RE: Protocol # and Title

Dear

This letter is to inform you that the protocol referenced above, for which you are the Principal Investigator, has been selected for a Quality Assurance Review. The Clinical Trials Quality Assurance (CTQA) Office would like to schedule the review to begin on one of the following dates:

- Date
- Date
- Date

Please contact the CTQA office either by e-mail (with a return receipt) or by telephone to schedule the actual date.

Please provide your selected dates within seven business days of the date of this communication. If a response is not received in that time, the CTQA office will make the selection of dates. Please prepare or reserve an appropriate space for the review to be conducted.

The CTQA office requires that a copy of the enrollment log be e-mailed or faxed to the CTQA reviewer within 48 hours of scheduling the review. Subject files to be reviewed will then be chosen and this selection will be relayed to you. You may then begin to gather all necessary source documentation (for example: medical records, "shadow" charts, and screening forms).

Please feel free to contact the CTQA office if there is a conflict in the scheduling or if you are no longer involved with this research protocol. Thank you in advance for your cooperation.

Sincerely yours,

Associate Reviewer, Clinical Trials Quality Assurance Office
Compliance Office, School of Medicine

Internal Review Preparatory Sheet

Protocol #

1. Letter/Scheduling Preparation

Action	Completed	By
Prepare "Letter of Intent to Review" (4 to 6 weeks prior)		
Check available dates		
Prepare e-mail version		
Add Intro to CTQA Attachment		
Add Subject Line: <i>"Notice of Intent To Review-IRB Protocol #:PROTOCOL TITLE"</i>		
Cc to: CTQA files		
Coordinators		
Co-PIs		
Mark e-mail: Return Receipt		
Confidential		
Prevent Copying		
High Delivery Priority		
Print copies for the office file		
Move to appropriate folders on S drive and CTQA Lotus Notes		
Mark CTQA calendar for 7 day check for response		
After response mark calendar for scheduled time and place (always allow for 2 days)		
Make Protocol Review Specific Folder		
Need Enrollment Log within 48 hours		
Choose subjects for review from enrollment log (3-5% or all if less than 10 subjects enrolled)		

E-mail PI/coordinator list of selected subjects		
Mark calendar to send out “Final Notice of Review” (2 weeks before scheduled date) and to send a 24 hour email		
Send Final Review Notice via E-mail		
Subject Line: “ Final Notice of Review- IRB Protocol #:PROTOCOL TITLE ”		
CC: Coordinator or scheduler		
Include review Assessment Tool Attachment		
Send an e-mail reminder 24 hours before review		

2. Opening Meeting Preparation

Action	Completed	By
Do Opening Meeting Agenda (use generic template plus addition of how long review will take)- put on letter head for PI distribution and make copy for office file		
Prepare the PI and coordinator interviews		
Put copies in office file		
Prepare Review Log copy		

3. File Preparation

Action	Completed	By
Protocol (and document previous version dates)		
Amendments		
IRB approval dates		
Consent Document (all previous version dates for subject being reviewed)		
Date subject contact began		
IRB minutes (if necessary)		
AE reports		
Outstanding Modification		

IRB credentialing		
HIPAA		

4. Worksheet Preparation

Action	Completed	By
Make eligibility checklist		
Modify review worksheets per protocol needs IRB Documentation Regulatory Binder Conduct of Study		
Prepare review cheat sheet		

5. Closing meeting Preparation

Action	Completed	By
Prepare closing meeting summary		
Prepare observation grid (2 copies)		

6. Items to take:

- Review File
- Copy of Letter of Intent
- Laptop
- Pens
- Paper
- Dictionary
- Post-its
- Paper clips

7. Post-Review

Action	Completed	By
Review Report Issued within 7-10 days (Mark calendar) [SEE FORM TEMPLATE]i		
Prepare Hard copy (send via campus mail) Send in Confidential Envelope		
Prepare Email (mark confidential, return receipt, and prevent copying)		

<p>Subject: <i>“Final Review Report RE: IRB Protocol# PROTOCOL TITLE Confidential and Privileged Under North Carolina Law”</i></p> <p>CC: CTQA File IRB PI/Coordinator Department Chair* (only if level 2+ observations)</p>		
<p>Mark calendar date for Corrective Actions Due</p>		
<p>Do follow-up as needed E-mail Follow-up Subject Line: <i>“Follow-up Reminder- RE: IRB Protocol# PROTOCOL TITLE Confidential and Privileged Under North Carolina Law”</i></p> <p>Create Written-Document Trail of any phone conversations</p>		
<p>Send reminders weekly (copy and document progress)</p>		
<p>Issue Recall Letter when all actions taken Send via E-mail Subject Line: <i>“Review Recall Letter RE: IRB Protocol # Protocol Title Confidential and Privileged Under North Carolina Law”</i></p> <p>CC: CTQA File IRB PI/Coordinator Department Chair* (only if level 2+ observations)</p> <p>Send hard copy via mail: CC: IRB</p>		
<p>Close Review</p>		

INTERNAL AUDIT CHECKLIST- FLOW SHEET

PROTOCOL # _____
PRINCIPAL INVESTIGATOR _____
AUDITOR ASSIGNED TO REVIEW _____

1. Letter of Intent To Audit:

	Date	By Whom	To Whom	Completed
Prepared				
Mailed				
Emailed				
7 day check				
Responded				
Filed				

2. Scheduled To Begin: _____ Estimated Length: _____

3. Should Receive Enrollment Log: _____ (within 48 hours)

Enrollment Log Received: _____

Must Fax By: _____ (within 48 hours)

Faxed Chosen Subjects: _____

Number of CRFs Chosen: _____

Subject's Chosen (add rows as necessary)

4. Prepared Audit Agenda: _____

5. Parties to be Available for Opening Meeting:

6. Final Notice to Audit(2 weeks Prior):

	Date	By Whom	To Whom	Completed
To Be Sent				
Filed				
Opening Meeting Scheduled				

7. IRB Information Reviewed/Copied:

Copied Current Protocol: _____

Prepared Amendment List: _____

Prepared Approval List: _____

Prepared Consent Form List: _____

Documented Date Subject Contact Began: _____

RPR/Waiver on File: _____

Minutes copied (if necessary): _____

Outstanding modifications checked: _____

AE report ran: _____

Credentialing: _____

Review Checklists Modified per Protocol? _____

Need to Do/Take:

8. Working Audit:

Audit Agenda being met? _____

Regulatory Binder(s) reviewed? _____

CRF's reviewed? _____

9. Closing Meeting Scheduled?

Date Scheduled?

10. Report of Observations:

	Date	By Whom	Comments
Prepared			
Presented			
Signed			
Copied/Filed			

11. Audit Report:

	Date	By Whom	To Whom	Completed	Comments
Prepared By					
Reviewed					
Sent					
			CC:		
Filed					

12. Receipt Received on: _____

By: _____

Filed: _____

13. Corrective Action Plan:

	Date	By Whom	To Whom	Completed	Comments
Received					
Sent					
Filed					

14. Follow-Up:

	Date Due	Date Received	Follow-up	Cleared
Report				
Action (add rows as needed)				

15. Audit Recall Letter:

	Date	By Whom	To Whom	Filed	Comments
Issued					
Sent					

16. Closed Date: _____

REVIEW CHECKLIST- IRB Documentation

PROTOCOL # _____

PRINCIPAL INVESTIGATOR _____

DATE REVIEWED _____

REVIEWER COMPLETING REVIEW _____

	Overall
Date of Initial IRB Approval	
Date of first subject contact	
Date of first protocol intervention	
AEs occurring	
AEs reported	
Approval of all amendments	
Date consent form signed and version date	
Annual renewal(s)	
Advertisement Approved	
Review Preparatory to Research Documented	
Subject Recruitment Methods	

Check For:

- Protocol never approved
- Approval Documentation Missing
- No Documentation of Initial ER
- ER not appropriate
- Subject enrolled prior to IRB approval
- Treatment prior to the signing of the consent form
- Re-approval delayed more than 30 days
- Subjects enrolled during delayed re-approval
- Missing renewal
- Expired Renewal
- Missing AE's
- Missing amendments (ER or Full board)

Consent Form Content:

	Present
All Federal Required Elements:	
DUHS Requirements	
HIPAA Requirements	
All pages Initialed	
Signed and Dated (real time) -if signed by representative-is it IRB approved for legal representation	
Process is Occurring	

**DUKE UNIVERSITY HEALTH SYSTEM (DUHS)
INVESTIGATOR REQUEST FOR PROTOCOL EXCEPTION**

A **protocol exception** is any temporary protocol deviation, e.g. enrollment of a subject who does not meet the eligibility criteria, and must be approved by the IRB prior to its initiation.

This form is to be used to request an exception to the protocol. It must be completed and submitted to the IRB Office before the exception to the protocol is performed. The IRB will contact the Principal Investigator regarding approval of the protocol exception.

Any permanent change to the protocol constitutes an **amendment** that must be submitted to the IRB for approval prior to initiation.

1. PROTOCOL INFORMATION

Protocol #:	
Principal Investigator:	
Title of Study:	

2. SUBJECT INFORMATION

Subject ID #:	
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3. PROTOCOL EXCEPTION

Briefly describe the protocol exception:
NOTE: Approval of the sponsor may be needed. Investigators must follow the sponsor's requirements for exceptions to the protocol.

4. RISKS AND POTENTIAL BENEFITS

What, if any, impact does the exception to the protocol have on the risks and potential benefits for subjects?

5. INFORMED CONSENT

Describe briefly, what subject(s) will be told about the exception to the protocol and the impact of the exception on risks and potential benefits to him/her.

6. SIGNATURE OF PRINCIPAL INVESTIGATOR (required)

Signature of Principal Investigator	Date

**DUKE UNIVERSITY HEALTH SYSTEM (DUHS)
MINOR PROTOCOL VIOLATIONS
TO BE REPORTED AT CONTINUING REVIEW**

Minor violations are to be reported to Clinical Trials Quality Assurance (CTQA) within three days, and to the IRB at continuing review. It is the responsibility of the Principal Investigator (PI) to determine whether a violation is a major or minor violation and to ensure proper reporting to the IRB. **Protocol violations** are deviations from the IRB-approved protocol that are not approved by the IRB prior to initiation or implementation. Reports of protocol violations should be submitted to the sponsor as outlined in the sponsor's protocol.

This form is to be used to report **minor** protocol violations at the time of continuing review. A minor protocol violation is one that does not affect subject safety, compromise the integrity of the study data, and/or affect the subject's willingness to participate in the study. Refer to CTQA guidelines document, Reporting Protocol Deviations, Exceptions and Violations for more information and for examples of major and minor violations.

Minor deviations related to study conduct should be noted in research files for individual subjects. Contact notes documenting communication with subjects that attempt to rectify violations, should be retained. For example, subjects who failed to attend a required study visit due to weather, failure to obtain sufficient blood volume to complete all research tests, or failure to return all questionnaires, should be noted with a plan for addressing the problem, if possible or relevant. These types of minor violations may be reported in a summary to the IRB on this form at continuing review. For example: Several subjects failed to return empty medication canisters, and were reminded to save these and bring them to subsequent study visits.

1. PROTOCOL INFORMATION

Protocol #:	
Principal Investigator:	
Title of Study:	

2. DESCRIPTION OF THE MINOR VIOLATIONS(S)

Summarize the protocol violations, corrective actions taken and preventive measures developed/implemented to prevent similar violations from occurring in the future.

3. SIGNATURE OF PRINCIPAL INVESTIGATOR (required)

Signature of Principal Investigator	Date

**DUKE UNIVERSITY HEALTH SYSTEM (DUHS)
INVESTIGATOR REPORT OF MAJOR PROTOCOL VIOLATION**

This form is to be used to report **major** protocol violations. It should be completed and submitted to the IRB and Clinical Trials Quality Assurance (CTQA) within X days after a major protocol violation occurs.

Protocol violations are deviations from the IRB-approved protocol that are not approved by the IRB prior to initiation or implementation. A major protocol violation is a violation that may affect subject safety, affect the integrity of the study data, and/or affect the willingness of the subject to participate in the study. Refer to CTQA document Reporting Protocol Violations, Deviations and Exceptions for more information and for examples of major and minor violations.

1. PROTOCOL INFORMATION

Protocol #:	
Principal Investigator:	
Title of Study:	

2. SUBJECT INFORMATION

Subject ID #	Date of Violation	Date of Discovery

3. DESCRIPTION OF THE VIOLATION

Briefly describe the protocol violation.

4. CORRECTIVE ACTION

For guidance on appropriate corrective action, refer to <i>Protocol Violations, Deviations and Exceptions</i> . For corrective actions listed below, please check all that apply.	
<input type="checkbox"/>	None to date
<input type="checkbox"/>	Note-to-file was prepared
<input type="checkbox"/>	Subject was consented/re-consented
<input type="checkbox"/>	Other, describe below
NOTE: Major violations should be reported to the sponsor in accordance with the reporting requirements in the sponsor's protocol.	

5. PREVENTIVE MEASURES

Describe below preventive measures developed/implemented to prevent similar violations from occurring in the future.

6. CHANGES TO THE PROTOCOL DOCUMENTS AND/OR CONSENT FORM

No	Yes	If Yes, submit amendment form and revised documents, as applicable.
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7. SIGNATURE OF PRINCIPAL INVESTIGATOR (required)

Signature of Principal Investigator	Date

Clinical Trials Quality Assurance
Quality Assurance/Peer Review Materials: Confidential and Privileged Under
North Carolina Law
Protocol Review Report

Review Number:
Assigned Reviewer(s):
Review Start Date: Review End Date:

Protocol Number:
Protocol Title:
Research Article (if any):

Principal Investigator:
Department/Division:
Primary Study Coordinator:
Additional Key Personnel:

Previous CTQA Reviews?:
 Yes (If Yes, continue) X No
Date(s): _____

Have there been FDA audits (if applicable) within the past 5 years?

Yes (If Yes, continue) X No
Date(s): (start with most recent) _____
 Yes No Yes No Warning Letter _____

Final Classification:
 No Actions Indicated
 Voluntary Actions Indicated
 Official Actions Indicated

Corrective Action Due Date:

Number of Subjects Reviewed:
Number of Informed Consents Reviewed:
Consent Process Reviewed: Yes X No

REVIEW SUMMARY

Scope

The purpose of this review was to assess the adherence to the Institutional Review Board approved study protocol, Good Clinical Practices (GCPs) guidelines, and State and Federal Regulations; to determine that the rights and welfare of human research subjects are being or have been adequately protected by the Investigator and her research staff; and to assess the integrity of the study data.

During this review, the study specific regulatory files, ___ subject files and appropriate source documentation were reviewed.

Introduction

This is a principal investigator initiated protocol to examine _____. The protocol has received no prior FDA or CTQA review. At the time of this review, the site had screened ___ subjects and had enrolled ___ subjects to the study drug. ___ subjects remain active on the study, ___ subject has completed the study, ___ subject discontinued from the study early, and ___ subjects withdrew consent. There have been ___ reported Serious Adverse Events (SAEs) related to this protocol.

This study is being conducted by _____. _____ has been in practice at Duke University Medical Center since _____. _____ is board certified in _____. Dr. _____ devotes approximately _____ of her time to private practice and _____ to research. Dr. _____ is involved with _____ clinical trials as the PI and has been involved in at least some aspect of clinical research for _____ years.

Dr. _____ has the responsibility of Principal Investigator for this trial. Dr. _____ is supported in this study by _____. Dr. _____ is responsible for all regulatory and procedural elements of the study.

The first study subject to screen for this clinical trial was screened on _____. A total of ___ subjects have been screened and _____ subjects have been enrolled into the trial. To date the subjects have been recruited from _____.

This was a routine Clinical Trials Quality Assurance review performed per the Clinical Trials Quality Assurance Review Standard Operating Procedures. The following is a summary of this methodology:

- Review of internal study files
- Opening meeting (initial introductions and interviews with PI and key staff)
- Facilities assessment
- Review of study/regulatory file and storage
- Source document verification
- Review of consent documents

- Review of research agent accountability records and storage

Executive Summary

Overall Review Assessment

Dr. _____ demonstrated knowledge of the protocol and study requirements. Dr. _____ was aware of the responsibilities as a Principal Investigator under the regulations and guidelines for the conduct of research trials and demonstrated that _____ was an integral part of the study and safety review process.

Study documents for all subjects reviewed were found to be present. Study specific regulatory files require organization, but appeared complete, and the facility appeared adequate for the study (i.e. physical environment, waiting area, etc.).

Overview of Review Observations (Please see the observations table below.)

The review concluded that voluntary corrective actions listed below are appropriate. There were ___ level ___ observations noted.

Observation Number	Observation/Corrective Action	Category (1-21/R or C)	Level of Significance (1,2,3)	Frequency (number of instances)
1	Observation: Corrective Action: Date to Complete:			
2	Observation: Corrective Action: Date to Complete:			
3	Observation: Corrective Action: Date to Complete:			
4	Observation: Corrective Action: Date to Complete:			
5	Observation: Corrective Action: Date to Complete:			
6	Observation: Corrective Action: Date to Complete:			
7	Observation:			

	Corrective Action:			
	Date to Complete:			

* Definition Levels by Significance:

1. Deficiencies that are correctable and do not have an impact on the quality and integrity of a study, reporting of a study, or investigator site.
2. Deficiency that may jeopardize the integrity and quality of a study, reporting of a study, investigator site, safety, protocols, federal regulations, ICH GCP, policies, and SOPs. These observations may or may not be corrected.
3. Deficiencies that have jeopardized the integrity and quality of a study, subject safety, reporting of the study and investigator site. An observation in this category may result in the repeat of a study or part of the study or the termination of the study. This observation may or may not be corrected.

** Findings Categories (Numbered 1-21)

R=Regulatory Issue

C= Clinical Issue

- | | |
|---|--|
| 1. Protocol Deviations | 12. Investigator Brochure |
| 2. FDA Form 1572 | 13. Sponsor/ Other Agency Correspondence |
| 3. CVs | 14. General Correspondence |
| 4. Medical License | 15. Memos to File |
| 5. G&C Documentation | 16. Training records |
| 6. IRB Correspondence and Documentation | 17. Consent Forms/ Consent Process |
| 7. IND Safety Reports | 18. Source Documentation |
| 8. SAE Reports | 19. Case Report Form Completion |
| 9. Laboratory Documentation | 20. Delegation of Authority |
| 10. Test Article Accountability | 21. SOPs |
| 11. Logs | |

Conclusions

Guidelines for Writing a “Memo to File”

The following are guidelines to help in writing a regulatory memorandum; a “Memo to File” or “Note to File.” If you have more specific needs, please contact the CTQA office.

Definition:

Clarifying documentation prepared in a memorandum format.

Purpose:

The purpose of a memo to file is to clarify missing or inaccurate data or procedures. The memo to file is not to be used as a “cure all.” However, under certain circumstances the memo to file can be used as an appropriate regulatory tool. These memos should be stored in the appropriate regulatory binder and with the source documentation. Depending on the event being documented, the IRB may require notification.

Examples: (this list is not intended to be all-inclusive)

When to use a memo to file:

- An assessment is missed or completed out of sequence
- Are unable to obtain a blood sample at a visit
- A subject failed to initial one page of a consent document
- If an original document is destroyed and only a copy remains
- A subject is lost to follow-up
- A subject is dropped from the study

Format:

- Preferably on letterhead or office stationary
- Include the date
- Protocol(s) memo is associated with
- RE: The specific subject(s) or events
- Cc: Any of the following that apply-Regulatory Binder, Source Documents, IRB, CTQA, Sponsor, etc.
- A detailed description of the event
- Signature (PI or Designee)