| UNC SCHOOL OF MEDICINE | Standard Operating Procedure | | |
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| **SOP 301, Version 1** | **Issued by:** SOM CRSO | **Issue Date:** 03.02.2023 | **Effective Date:** 04.03.2023 |

# 301.1: Performing the Responsibilities of the Principal Investigator

PURPOSE

This SOP describes the responsibilities and requirements of a University of North Carolina at Chapel Hill (UNC-Chapel Hill) School of Medicine (SOM) Principal Investigator (PI) conducting Human Subjects Research (HSR).

SCOPE

This procedure applies to all SOM PIs conducting human subjects research.

BACKGROUND

By agreeing to serve as the PI, the investigator assumes the overall responsibility for the conduct of research involving human subjects either for the study as a whole or as a participating study site. The PI may delegate study-related tasks to qualified individuals, but they cannot delegate the primary responsibility for oversight of the research or supervision of study-related tasks performed by study team members.

The responsibilities of PIs in the conduct of human subjects research are directly or indirectly described in:

- U.S. Department of Health and Human Services (HHS) Common Rule at 45 CFR Part 46[2]
- HHS Food and Drug Administration (FDA) at 21 CFR Part 11,[11] Part 50,[12] Part 54,[14] Part 56,[15] Part 312,[16, 17] Part 812[27, 28]
- FDA Investigator Agreement[30] or Statement[19, 37, 40]
- FDA and HHS OHRP (Office of Human Research Protections) guidance[9, 39]
- International Council for Harmonisation (ICH) E6 Guideline for Good Clinical Practice (GCP)[46]
- The applicable provisions of UNC-Chapel Hill Federalwide Assurance (FWA) and Institutional policies and standards.[64, 66, 70, 72, 73]

The PI is accountable for any regulatory violations that result from the failure to perform these responsibilities.

Note that this SOP describes the PI's responsibilities only. Additional responsibilities apply for a sponsor-investigator who initiate and conduct an FDA-regulated investigation.

PROCEDURE

1. **Obtain and/or develop the study protocol and associated documents**
   a. If creating the study protocol, ensure that it is ethically and scientifically sound.
   b. If a protocol has already been developed by an external sponsor, obtain a copy of the protocol upon any necessary execution of a Confidential Disclosure Agreement (CDA).

2. **Conduct an internal feasibility assessment**
   a. Prior to initiating a study, conduct an internal feasibility assessment to determine whether the project plan is practical, assessing accrual potential and required personnel, financial, and physical resources.[46(GCP 4.2)]

3. **Demonstrate and document qualifications and training**
   a. For the PI: [46(GCP 4.1)]
      i. Maintain an up-to-date curriculum vitae, licensure, and applicable certifications.
      ii. Develop and maintain a thorough understanding of the regulatory and study specific requirements.
      iii. Create and maintain a PI profile in the SOM Personnel Profile and Training System.
      iv. Complete and document[61] PI training as required by UNC-Chapel Hill,[71] SOM, the study sponsor, and all applicable regulatory authorities.
   b. For the study team:
      i. Verify and maintain documentation[61] that all study personnel (which may include personnel not employed by the SOM or UNC-Chapel Hill) complete training as required by UNC-Chapel Hill, SOM, the study sponsor, and all applicable regulatory authorities based on their delegated responsibilities.
   c. Routinely review qualifications and training documentation to ensure that it is current, complete, and aligns with delegated responsibilities.

4. **Delegate study-related tasks**
   a. Establish a plan for delegating responsibility.
   b. Delegate study-related tasks to study team members as appropriate based on protocol requirements and verified education/licensure, training, and experience.[39, 46(GCP 4.2.6)]
   c. Document delegation in writing (i.e., paper or approved electronic system) in the form of a delegation of authority (DOA) log[59, 68] that indicates the names of the qualified individuals to whom significant study-related duties have been delegated, describes those delegated duties, and documents the start and end dates of involvement in the study.[46(GCP 4.1.5)]

5. **Ensure initial and ongoing approval by an Institutional Review Board (IRB)**[3, 9, 25, 32 46(GCP 4.4), 62]
   a. Ensure that the IRB approval is obtained from the designated IRB for the study protocol and all applicable documents prior to initiation of any study procedures (including identification of potential participants).
   b. Update the IRB with any changes to the study protocol or applicable materials and documents prior to implementation.
   c. Ensure reportable information, deviations, or other safety events are communicated per the reviewing IRB's requirements.[65]
   d. Ensure that IRB renewal or administrative reviews are completed per the IRB's continuing review requirements.
   e. Notify the IRB of premature study termination or suspension and study completion.

6. **Ensure completion of any necessary ancillary reviews related to the human subjects research activities (**e.g. conflict of interest, scientific, radiation safety or biosafety, DSMB/DMC, UNCH collaboration survey, etc.)

7. **Ensure that any applicable agreements are prepared and executed by an authorized signatory official** (e.g. Clinical Trials Agreement (CTA), Data Use Agreement (DUA), Business Associate Agreement (BAA), Memorandum of Understanding (MOU), UNCH Facility Use Agreement (FUA), etc.)

8. **Exercise appropriate oversight of the overall finances of the project**
   a. Ensure compliance with UNC-Chapel Hill and sponsored award financial management practices.[70]
   b. Ensure that a Billing Coverage Analysis (BCA) is completed for all qualifying clinical trials.[53]

9. **Oversee and supervise the study**[37, 39, 46(GCP 4.2.5)]
   a. Develop and implement plans for oversight and supervision (e.g., routine meetings, review of study procedures, evaluation of delegated tasks, etc.).[39]
   b. Monitor study progress, protocol adherence, and study data integrity by periodically reviewing study records, including protocol deviations and adverse events as applicable. Supervise resolution of any findings as necessary.
   c. Ensure regular, timely, effective, and well-documented communication with relevant parties (e.g., participants, study team, IRB, sponsor, etc.).

10. **Ensure eligibility and informed consent of participants**
    a. Ensure adherence to the participant eligibility criteria; verify and document participant eligibility.
    b. Ensure that legally effective informed consent and HIPAA authorization[48] (as applicable) are obtained prospectively and documented unless a waiver has been approved by the reviewing IRB.[5, 7, 9, 13, 46(GCP 4.8), 63]
    c. Ensure that required (and any applicable additional) elements of informed consent[47] are included in the informed consent form unless a waiver has been approved by the reviewing IRB.
    d. Inform participants of significant new findings in a timely manner.
    e. Verify and document participants' willingness to continue participation in the study at reasonable intervals, dependent on the nature of the study.
    f. Make reasonable effort to document reasons for participant withdrawal.

11. **Ensure protocol compliance**[21, 28, 39, 46(GCP 4.5)]
    a. Conduct the study in accordance with the IRB-approved protocol.
    b. Obtain IRB and sponsor approval of any prospective changes to the protocol.
    c. If a change is necessary to eliminate an immediate hazard to participants, report the change, the reasons for the change, and the proposed protocol amendment (as applicable) to the reviewing IRB and sponsor as soon as possible.[65]
    d. Ensure that protocol deviations are identified, documented, reported, and remediated.[60, 65]

12. **Monitor for safety**[10, 18, 46(GCP 4.11), 65]
    a. Ensure that the investigator and members of the study team are aware of the safety monitoring and reporting requirements in the study protocol, Investigator's Brochure (IB), and Data and Safety Monitoring Plan (DSMP).
    b. Ensure that the evaluation of Adverse Events (AEs) or clinical decisions or care pertaining to the study is done by a qualified clinician.[46(GCP 4.3.1, 4.3.2)]
    c. Ensure that AEs are identified, treated, and followed until resolution or stabilization in accordance with the protocol.

d. Determine reportability of AEs to the applicable parties (e.g., IRB, sponsor, DSMB). [10, 18, 29, 38, 44]
e. Ensure that AEs are documented in a source document.[58]
f. Document review of and actions taken in response to safety letters.

13. **Maintain accurate and complete study documentation**[23, 33, 46(GCP 4.9)]
    a. Ensure that essential documents are filed as part of the study master file as they are generated or received.[46(GCP 1.23, 8)]
    b. Ensure that all source documents meet ALCOA (Attributable, Legible, Contemporaneous, Original, Accurate) standards, and that CRFs are consistent with source documents.
14. **Manage and protect study data**[4, 9, 23, 33, 45, 49, 50, 51, 52, 67, 68, 69, 74, 75]
    a. Store, transmit, retain, and dispose of data and records in accordance with the protocol, UNC-Chapel Hill policies, HIPAA, and other applicable regulations.
15. **Manage applicable test article**[46(GCP 4.6), 21, 22, 31, 32]
    a. Use UNC Health investigational drug services (IDS) for investigational drug studies.
    b. Maintain adequate records of delivery, inventory, use, and return/other disposition of the test article.
    c. Ensure that the test article is stored as specified by the sponsor and in accordance with applicable regulatory requirement(s).
    d. Ensure that the test article is used only in accordance with the approved protocol.
    e. Ensure that each participant understands the correct use of the test article and conduct appropriate accountability assessments as needed.
    f. Ensure that expired test articles are removed from stock in a timely manner and according to the sponsor's plan.
    g. Reconcile the test article.
16. **Facilitate monitoring activities, audits, and inspections**[20, 26, 34, 41, 42, 43, 46(GCP 1.6, 1.38, 5.18)]
    a. Ensure that relevant parties are notified of visits and are available, as applicable.
    b. For FDA, OHRP, or other external agency inspections or audits, the Office of Clinical Trials must be contacted in addition to all regular parties.
    c. If UNC Health network entities are engaged as collaborators, the Office of Research Support and Compliance (ORSC) must be notified to facilitate activities at the network site(s), as required.
    d. Ensure that any required documents (e.g., regulatory documents, participant records, investigational accountability records, as applicable) are complete, organized, and available for review.
    e. Ensure that adequate space is available to conduct the visit, audit, or inspection.
    f. Review applicable regulatory inspection procedures.[36, 43]
    g. Be available to answer questions and to meet with the monitor or inspector to review and discuss findings.
    h. Ensure that all findings are addressed and responded to in a timely manner.
17. **Prepare and submit reports**
    a. Ensure accurate, complete, and timely reports to the parties such as sponsors, funding agencies, and IRBs.[18, 24, 35, 46(GCP 4.10, 4.11, 4.12, 4.13)]
    b. If designated as the responsible party by the sponsor of an Applicable Clinical Trial (ACT), ensure proper registration and results reporting on ClinicalTrials.gov consistent with the requirements of the applicable authorities.[1, 54, 56, 57]

c. For clinical trials funded or supported by a federal department or agency, ensure that the IRB-approved consent form is posted on publicly available federal web site after recruitment closes and no later than 60 days after the last study visit.[6, 8, 55]

## DEFINITIONS, ABBREVIATIONS, ACRONYMS

Link to or scan the code to UNC-Chapel Hill SOM Clinical Research Glossary

## ASSOCIATED POLICIES, REGULATIONS, GUIDELINES

**The Department of Health and Human Services (HHS)**

1. HHS: 42 CFR 11, Clinical Trials Registration and Results Information Submission
2. HHS: 45 CFR 46 (Common Rule, 2018 Requirements)
3. HHS: 45 CFR 46.108, IRB Functions and Operations
4. HHS: 45 CFR 46.115, IRB Records (and Records Relating to the Research)
5. HHS: 45 CFR 46.116, General Requirements for Informed Consent
6. HHS: 45 CFR 46.116(h), Posting of Clinical Trial Consent Form
7. HHS: 45 CFR 46.117, Documentation of Informed Consent
8. OHRP: Informed Consent Posting
9. OHRP: Investigator Responsibilities FAQs
10. OHRP: Unanticipated Problems Involving Risks & Adverse Events Guidance

**HHS Food and Drug Administration (FDA)**

11. FDA: 21 CFR 11, Electronic Records, Electronic Signatures
12. FDA: 21 CFR 50, Protection of Human Subjects
13. FDA: 21 CFR 50, Subpart B – Informed Consent of Human Subjects
14. FDA: 21 CFR 54, Financial Disclosure by Clinical Investigators
15. FDA: 21 CFR 56, Institutional Review Boards
16. FDA: 21 CFR 312, Investigational New Drug Application
17. FDA: 21 CFR 312, Subpart D, Responsibilities of Sponsors and Investigators
18. FDA: 21 CFR 312.32, IND Safety Reporting
19. FDA: 21 CFR 312.53(c)(1), Investigator Statement
20. FDA: 21 CFR 312.56, Review of Ongoing Investigations
21. FDA: 21 CFR 312.60, General Responsibilities of the Investigator
22. FDA: 21 CFR 312.61. Control of the Investigational Drug
23. FDA: 21 CFR 312.62, Investigator Recordkeeping and Record Retention
24. FDA: 21 CFR 312.64, Investigator Reports
25. FDA: 21 CFR 312.66, Assurance of IRB Review

26. FDA: 21 CFR 312.68, Inspection of Investigator's Records and Reports
27. FDA: 21 CFR 812, Investigational Device Exemptions
28. FDA: 21 CFR 812, Subpart E – Responsibilities of Investigators
29. FDA: 21 CFR 812.3, Definitions
30. FDA: 21 CFR 812.43(c), Obtaining Agreements
31. FDA 21 CFR 812.100, General Responsibilities of Investigators
32. FDA 21 CFR 812.110, Specific Responsibilities
33. FDA: 21 CFR 812.140, Records
34. FDA: 21 CFR 812.145, Inspections
35. FDA: 21 CFR 812.150, Reports
36. FDA: Compliance Program Guidance Manual (CPGM)
37. FDA: Form FDA 1572
38. FDA: Guidance for Industry and Investigators, Safety Reporting Requirements for INDs and BA/BE Studies
39. FDA: Guidance for Industry, Investigator Responsibilities – Protecting the Rights, Safety, and Welfare of Study Subjects
40. FDA: Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors, Frequently Asked Questions – Statement of Investigator (Form FDA 1572)
41. FDA: Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors; Inspections of Clinical Investigators
42. FDA: Inspection Observations
43. FDA: Investigations Operations Manual
44. FDA: Investigator Responsibilities—Safety Reporting for Investigational Drugs and Devices, DRAFT Guidance for Industry

**Other Sources:**

45. HIPAA: Summary of the HIPAA Privacy Rule
46. ICH Harmonized Guideline: Integrated Addendum to ICH E6 (R1): Guideline for Good Clinical Practice E6 (R2)

**UNC-Chapel Hill:**

47. CRSO Guidance: Elements of the Informed Consent Form and HIPAA Authorization
48. IPO: HIPAA Research Policy
49. ITS: Information Classification Standard
50. ITS: Information Security Control Standard
51. ITS: Information Security Policy
52. ITS: Transmission of Sensitive Information Standard
53. OCT: Billing Coverage Analysis
54. OCT: Clinical Trial Registration Overview and UNC Policy Statement
55. OCT: Informed Consent Posting Requirements
56. OCT: Registering an Investigator-Initiated Clinical Trial Overview
57. OCT: Trial Registration Highlights
58. OCT CTQA: Adverse Event Log
59. OCT CTQA: Delegation of Responsibility Log
60. OCT CTQA: Deviations Log
61. OCT CTQA: Training Log
62. OHRE SOP 701: IRB Review Process
63. OHRE SOP 1101: Obtaining Informed Consent from Research Subjects

64. OHRE SOP 1301: FDA Regulated Research, Investigator Responsibilities
65. OHRE SOP 1401: Promptly Reportable Information
66. OHRE SOP 1501: Investigator Responsibilities, 2.2 Responsibilities
67. OHRE SOP 1501: Investigator Responsibilities, 2.2 Responsibilities, Data Security Plan
68. OHRE SOP 1501: Investigator Responsibilities, 2.3 Investigator Records
69. OHRE SOP 1901: Information Security
70. OSP SOP 200.04: Principal Investigator Responsibilities
71. OVCR: Principal Investigator Training
72. OVCR: Research Code of Conduct Policy
73. OVCR: Research Code of Conduct Standard
74. SOM: Information Security
75. UNC General Records Retention and Disposition Schedule

| **Revision History** | | |
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| **Version** | **Effective Date** | **Change Summary** |
| 301.1 | 04.03.2023 | New |
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