**Principal Investigator Responsibilities in Clinical Trials**

**IT'S ELEMENTARY, MY DEAR WATSON...** The evidence is clear: the crime was committed **NOT** by the investigator, but by **MRS. PEACOCK**, the study coordinator, in the copy room, with a bottle of white-out!

**OH, BRAVO, HOLMES!**

[Cartoon image of Sherlock Holmes and Watson solving a crime]
Investigator Responsibilities per federal and international regulations:

- Properly qualified
- Protect rights, safety, and welfare of subjects
- Familiar with investigational product and its use
- Willing to comply with GCP and applicable regulations
- Maintain list of appropriately qualified persons delegated to work on study, and supervise them
- Have adequate resources and time to conduct the trial
- Ensure all persons are adequately informed/trained on the study
- Provide medical care to subjects and be responsible for all medical-related decisions
- Obtain appropriate IRB approvals
- Comply with protocol and document/report deviations
- Manage usage, storage, accountability of investigational product
- Follow randomization procedures
- Obtain informed consent per all regulations
- Ensure the accuracy, completeness, legibility, and timeliness of the data documented and reported
- Maintain all essential documents
- Report AEs and SAEs appropriately

**BOTTOM LINE...**

...PI has ultimate responsibility for ALL aspects of study conduct at the site
“PI is legally presumed to know, understand, and comply with all regulations and details of the specific study, regardless of educational opportunities or available administrative support.”

-Legal Issues in Clinical Research, What You Need to Know; Nosowsky and Meade, 2007

FDA Form 1572: informs the investigator of his/her obligations and obtains investigator’s commitment to comply.
Informed Consent

No investigator may involve a human as a subject in research until they have obtained legally authorized informed consent

Includes:
- fasting for screening blood draw
- changing medications to fulfill inclusion/exclusion criteria
- gathering prescreening health information from someone with whom you do not have a current research/treatment relationship

From our department’s ICF SOP:

“For interventional trials, Principal Investigator or sub- investigator must conduct and be present for the initial consent discussion and sign on the appropriate lines of the Informed Consent document (person conducting the consent discussion). The PRA cannot sign as the person conducting the consent discussion.”

** This also applies to re-consent discussions where the ICF revision is based on new, clinically important risks or benefits that may affect a patient’s willingness to continue participation!

Consent is more than a document, it’s a PROCESS

- Re-consent sometimes required for new information
  ➢ Communicated by regulatory coordinators
- “Informal” confirmation of ongoing consent throughout the study → document it
- Informed consent process note (usually completed by coordinator)
“If it's not documented, it didn't happen!”

Examples:
- Verbal discussions with subjects and any information/data obtained or direction given
- Medical observations and decisions
- Your awareness and assessment (if necessary) of any/all subject-related events
- Your training of study staff

Ways to document:
- Pre-made source documents
- EPIC note
- Summary of phone discussion
- Email

format is not important! As long as ALCOA is followed:

<table>
<thead>
<tr>
<th>A</th>
<th>Attributable</th>
<th>Who acquired the data or performed an action?</th>
</tr>
</thead>
<tbody>
<tr>
<td>L</td>
<td>Legible</td>
<td>Can you read and understand the data entries?</td>
</tr>
<tr>
<td>C</td>
<td>Contemporaneous</td>
<td>Were records documented at the time of the activity?</td>
</tr>
<tr>
<td>O</td>
<td>Original</td>
<td>Is it the first recorded observation (or a verified, true copy)?</td>
</tr>
<tr>
<td>A</td>
<td>Accurate</td>
<td>Is the result scientifically valid and error free?</td>
</tr>
</tbody>
</table>

COMPLETE
All data including any repeat or reanalysis performed

CONSISTENT
All elements of the analysis are date/time stamped and in the expected sequence

ENDURING
Recorded in a permanent, maintainable form throughout its lifecycle

AVAILABLE
For review, audit, or inspection over the lifetime of the record
CORRECTIONS (to any document):
1. SINGLE line through
2. Initial AND date (always TODAY’s date!)
3. Correct and explain if necessary

FOLLOW DICTATED DATE FORMAT!
Ex: DDMMMYYYY =01JAN2023

Every note, observation, assessment must be ATTRIBUTABLE to who made it, and made in REAL TIME initial and date!

NEVER: Back-date a signature
Use white-out
Attempt to erase/obscure mistakes
Use pencil
Delegation, Supervision, and Oversight

You are responsible for it all, but you can’t do it all!

- Delegation of Duties Log
  - Appropriate delegation – medical decisions/procedures/assessments only to medical professionals

- Training documentation
  - Regulatory team helps- watch for “RESPONSE REQUIRED” emails!

- Do you have adequate backup?

- Does the study documentation SHOW your involvement and oversight?

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**Study Personnel Signature and Delegation Form**

<table>
<thead>
<tr>
<th>Sponsor</th>
<th>F. Hoffmann-La Roche Ltd</th>
</tr>
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<tbody>
<tr>
<td>Principal Investigator</td>
<td>Dr. Enrique Alvarez</td>
</tr>
<tr>
<td>Protocol Number</td>
<td>MN43964</td>
</tr>
<tr>
<td>Site Number &amp; Country</td>
<td>353034</td>
</tr>
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<table>
<thead>
<tr>
<th>Staff Name</th>
<th>Staff Signature</th>
<th>Staff Initials</th>
<th>Study Role</th>
<th>Delegated Study Tasks</th>
<th>Date of Delegation</th>
<th>PI Initials</th>
<th>End of Tasks</th>
<th>PI Initials</th>
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</thead>
<tbody>
<tr>
<td>Timber Bourassa</td>
<td>TBB</td>
<td>SC</td>
<td>Regulatory</td>
<td>2, 4, 6, 7, 9, 10, 12, 13, 23</td>
<td>03 Nov 2022</td>
<td>110</td>
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<td>Nicole Gendelman</td>
<td>NFG</td>
<td>JF</td>
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<td>17, 18</td>
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<td>Joanna Panella</td>
<td>JPF</td>
<td>JF</td>
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<tr>
<td>Karen Snow</td>
<td>KSN</td>
<td>IM</td>
<td>Pharmacist</td>
<td>9, 11 a-b, 12 a-b, 13 a-b, 14 a-b</td>
<td>08 Nov 2022</td>
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<tr>
<td>Julie McLaughlin</td>
<td>JML</td>
<td>JK</td>
<td>Pharmacist</td>
<td>9, 11 a-b, 12 a-b, 13 a-b, 14 a-b</td>
<td>08 Nov 2022</td>
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<td>Nne Nwobodo</td>
<td>NNN</td>
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<td>Pharmacist</td>
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<tr>
<td>Diane Branham</td>
<td>DB</td>
<td>DB</td>
<td>Nurse Manager</td>
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<td>JJ</td>
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<td>MRI tech</td>
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<td>Cara Henriksen</td>
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</tbody>
</table>

**Key Study Tasks**

1. Obtain informed consent
2. Obtain medical/concomitant medication history
3. Perform physical exam
4. Take/Record vital signs (incl. weight, height)
5. Perform Neurological examination
7. Evaluate AE/SAE (medically qualified)
8. Make medical decisions (e.g., eligibility, evaluating test results (e.g., lab, MRI, others), etc.)
9. Use IXRS
10. a) Collect, b) Process, c) Ship lab samples
11. Manage a) IP receipt, b) IP storage
12. a) Prepare, b) Dispense, c) Administer IP
13. Perform a) IP accountability, b) IP compliance
14. Manage a) IP destruction, b) IP return
15. Make CRF entries, corrections & manage queries
16. Sign off on (e)CRF visit data (medically qualified)
17. Manage IRB/IEC communications & submissions
18. Maintain Investigator Site File
19. Perform EDSS
20. Perform 9HPT i and T25FWT
21. Perform MRI
22. Review safety reports
23. Other
Cannot (purposefully) deviate from the protocol without permission from sponsor

**UNLESS NECESSARY TO ELIMINATE IMMEDIATE HAZARD TO SUBJECT**

*Subject well-being/safety ALWAYS comes first*

All deviations from the IRB-approved protocol **must be documented**—no matter how minor/inconsequential

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**NOTE TO FILE**

**PROTOCOL DEVIATION**

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**Study:** 11-1111

**Study Title:** Study for Testing (DO NOT DELETE)

**Protocol Number:** Test Study-111

**Today’s date:** 5/12/2023

**Subject ID (if applicable):** 0001

**Date deviation was discovered:** *

**Brief description of deviation including background, relevant dates, action taken, outcome, follow-up:** *

**How is this a deviation from the IRB-approved protocol?** *

**What was the root cause of the deviation?** *

- Coordinator oversight
- Investigator oversight
- Research subject action
- Sponsor/CSR oversight (lack of direction)
- Oversight action by other research personnel (CTRC, pharmacy, etc)
- Other: *

**General Category:** *

- Out of Window Visit
- Missed Visit
- Missed Procedure or Assessment
- Incorrectly Done Procedure or Assessment
- Device-related to investigational drug device or investigational device
- Inclusion/Exclusion Criteria
- Other: *

**What is the corrective action plan (how will the study team prevent similar events in the future)?** *

The deviation must be reviewed by a study investigator.

**Option 1.** Prior to reviewing the form, use the “Send Form to Investigator” function to send this information to the investigator via email to get their assessment.

**IN OR SUB ASSESSMENT:**

- Did the deviation harm a subject?
- Did the deviation place a subject at increased risk of harm?
- Was the deviation made in order to eliminate apparent immediate hazard to a subject?

**IF ANY ABOVE QUESTIONS ARE ANSWERED “YES,” ALERT REGULATORY MANAGERS WITHIN 3 BUSINESS DAYS TO ASSESS FOR POSSIBLE FDA REPORTING**

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**Investigator Signature**

**Date**

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You will receive this information from coordinator as physical document or in an email.

*Assessment of potential harm to subjects*

Review and respond within 3 business days!
Adverse Events

(AE) = untoward medical experience in a subject in a study, regardless of relationship to study

Sources:
- Reported by subject
- Observations by clinical research staff
- Reports to research staff by family or medical care providers
- Documented in medical records, progress notes, etc.
- Lab results

Manage the adverse event to ensure that all appropriate resources are directed toward subject safety and well-being. Take action with investigational product per protocol instruction if necessary.

Investigator must assess WITHIN 5 BUSINESS DAYS
- Severity
- Expectedness per most recent Investigator’s brochure/product information, consent form
- Relatedness to study/study drug

Unexpected and possibly or definitely related? ➔ greater risk of harm to subjects then was previously known or recognized?
Serious Adverse Events (SAE)=

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolonging of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Other considered serious by Investigator (for example, events that would require medical or surgical intervention to prevent any of the above)

**MUST BE IMMEDIATELY REPORTED TO SPONSOR**

- Usually 24 hours
- Give whatever information available
- Provide follow-up/details and respond promptly to sponsor requests/questions

⚠ Your involvement, assessment, knowledge, and responsiveness when there is an SAE is **critical**
Medical-related duties and assessments cannot be delegated to a coordinator!

- **Lab results:**
  - PI/sub-I review:
    - 5 business days for non-critical/alert values
    - Next business day for critical/alert values
  - Out of range values: Clinically Significant (CS?) or Non Clinically Significant (NCS?)

- **ECGs**
  - PI/sub-I review:
    - 5 business days for normal results
    - Abnormal results: before subject leaves the visit
    - Abnormal results: CS/NCS?

- **AEs:** PI/sub-I review: 5 business days
- **SAEs:** PI/sub-I review: ASAP, 24 hours at the most

**DOCUMENTATION?**
Physical signature/date on a report, source document, log EPIC note
Email, text, phone conversation OK! But *document*

*You must be reachable and responsive!*
A Suspected Unexpected Serious Adverse Reaction in a study subject is identified by the sponsor.

Sponsor reports the event to the FDA and to all sites participating in the any study using that drug.

You must review to stay current on ongoing medical/risk information.

- Regulatory team will send each report to you via email.
- "RESPONSE REQUIRED"!
- Every time new info on the case is received, F/U report will be issued.
Consequences of Non-Compliance

- Potential compromise of:
  - subject safety
  - data validity
  - professional reputation/privileges of PI or institution
- Suspension or termination of study by IRB, sponsor, or institution
- Regulatory sanctions (OHRP, FDA, NIH, etc.)
  - Suspension or termination of protocols
  - Disqualification from research leadership or activities
  - Civil fines and penalties
  - Criminal enforcement (FDA, DOJ)
  - Fines
  - Imprisonment
PI or delegated clinician Sub-I must be available to coordinator at all times to discuss potential safety issues.

Make a plan with coordinator for how they can best get a hold of you.

Plan ahead for OOO time and inform your coordinator and backup sub-Is.

When discussing subject-related issues, email communication is preferable—attributable documentation of conversation = evidence that you are fulfilling your regulatory responsibility for sufficient oversight of the research and medical care of the subjects!