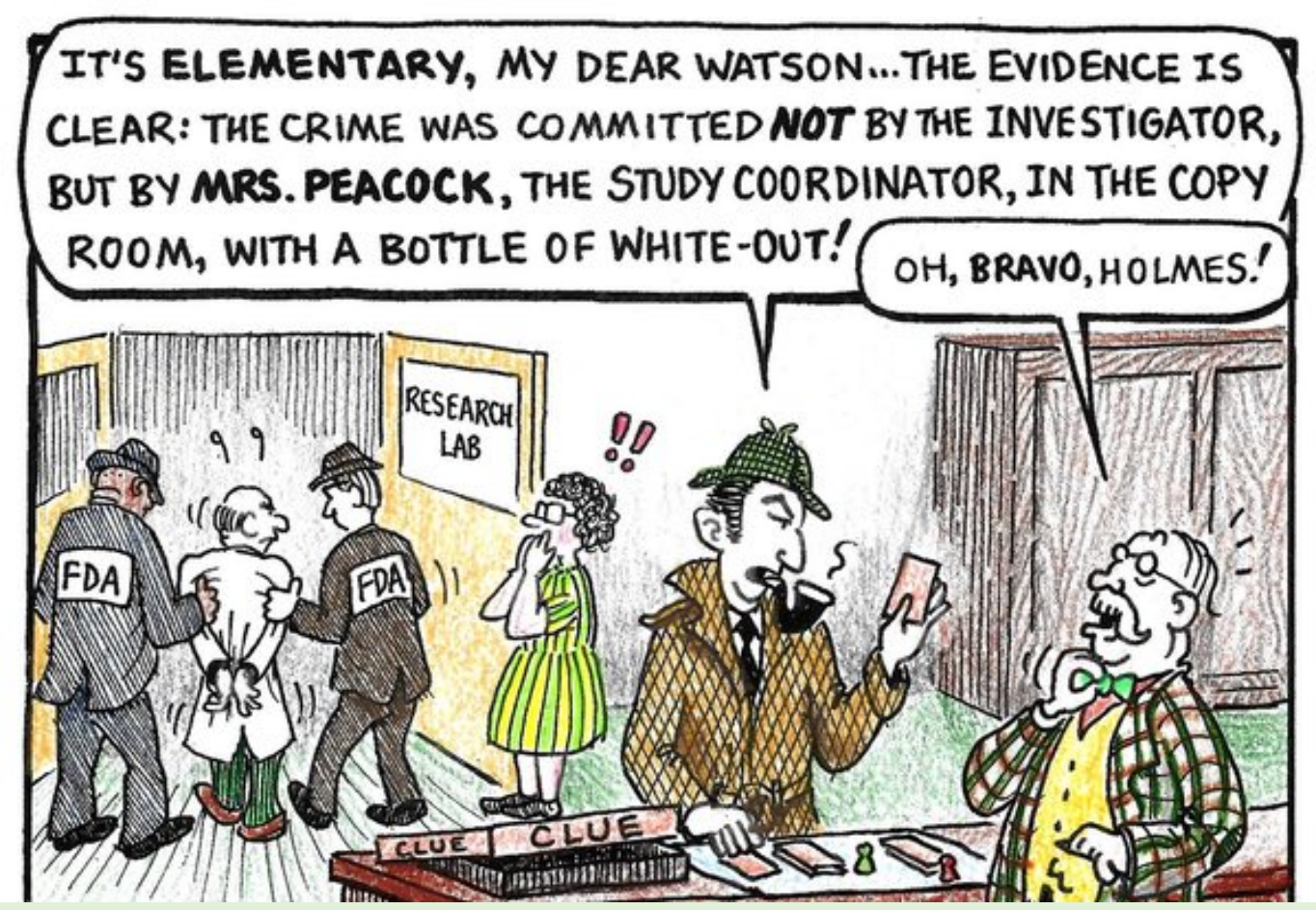
Principal Investigator Responsibilities in Clinical Trials



September 2023

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*

8. PROVIDE THE FOLLOWING CLINICAL PROTOCOL INFORMATION. *(Select **one** of the following.)*

☐ For Phase 1 investigations, a general outline of the planned investigation including the estimated duration of the study and the maximum number of subjects that will be involved.

☐ For Phase 2 or 3 investigations, an outline of the study protocol including an approximation of the number of subjects to be treated with the drug and the number to be employed as controls, if any; the clinical uses to be investigated; characteristics of subjects by age, sex, and condition; the kind of clinical observations and laboratory tests to be conducted; the estimated duration of the study; and copies or a description of case report forms to be used.

9. COMMITMENTS

I agree to conduct the study(ies) in accordance with the relevant, current protocol(s) and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of subjects.

I agree to personally conduct or supervise the described investigation(s).

I agree to inform any patients, or any persons used as controls, that the drugs are being used for investigational purposes and I will ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and institutional review board (IRB) review and approval in 21 CFR Part 56 are met.

I agree to report to the sponsor adverse experiences that occur in the course of the investigation(s) in accordance with 21 CFR 312.64. I have read and understand the information in the investigator's brochure, including the potential risks and side effects of the drug.

I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments.

I agree to maintain adequate and accurate records in accordance with 21 CFR 312.62 and to make those records available for inspection in accordance with 21 CFR 312.68.

I will ensure that an IRB that complies with the requirements of 21 CFR Part 56 will be responsible for the initial and continuing review and approval of the clinical investigation. I also agree to promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

I agree to comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 CFR Part 312.

INSTRUCTIONS FOR COMPLETING FORM FDA 1572
STATEMENT OF INVESTIGATOR

1. Complete all sections. Provide a separate page if additional space is needed.
2. Provide curriculum vitae or other statement of qualifications as described in Section 2.
3. Provide protocol outline as described in Section 8.
4. Sign and date below.
5. FORWARD THE COMPLETED FORM AND OTHER DOCUMENTS BEING PROVIDED TO THE SPONSOR. The sponsor will incorporate this information along with other technical data into an Investigational New Drug Application (IND). INVESTIGATORS SHOULD NOT SEND THIS FORM DIRECTLY TO THE FOOD AND DRUG ADMINISTRATION.

10. DATE *(mm/dd/yyyy)*	11. SIGNATURE OF INVESTIGATOR Sign

(**WARNING**: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)

The information below applies only to requirements of the Paperwork Reduction Act of 1995.

The burden time for this collection of information is estimated to average 100 hours per response, including the time to review instructions, search existing data sources, gather and maintain the data needed and complete and review the collection of information. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden to the address to the right:

Department of Health and Human Services
Food and Drug Administration
Office of Operations
Paperwork Reduction Act (PRA) Staff
PRAStaff@fda.hhs.gov

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB number."

DO NOT SEND YOUR COMPLETED FORM TO THIS PRA STAFF EMAIL ADDRESS.

FORM FDA 1572 (3/22) **PREVIOUS EDITION IS OBSOLETE.** **Page 2 of 2**

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)

Documentation

"If its not documented, it didn't happen!"

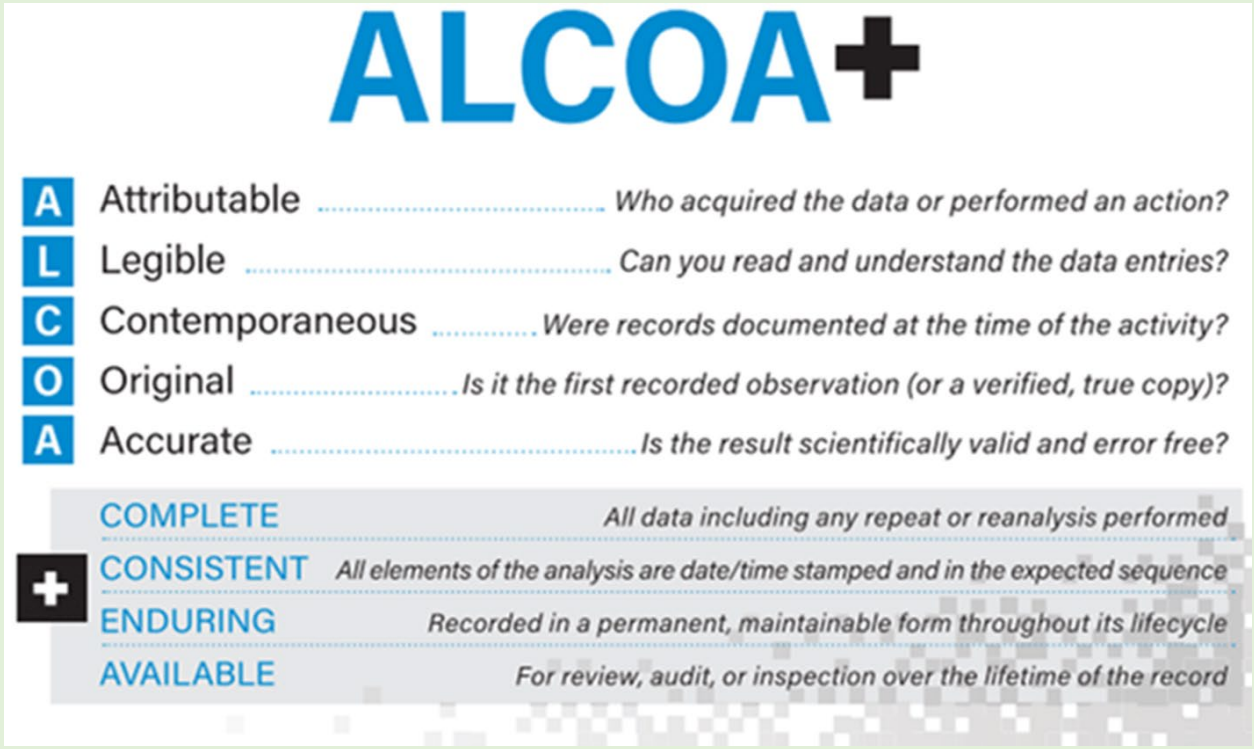
Examples:

- 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*:

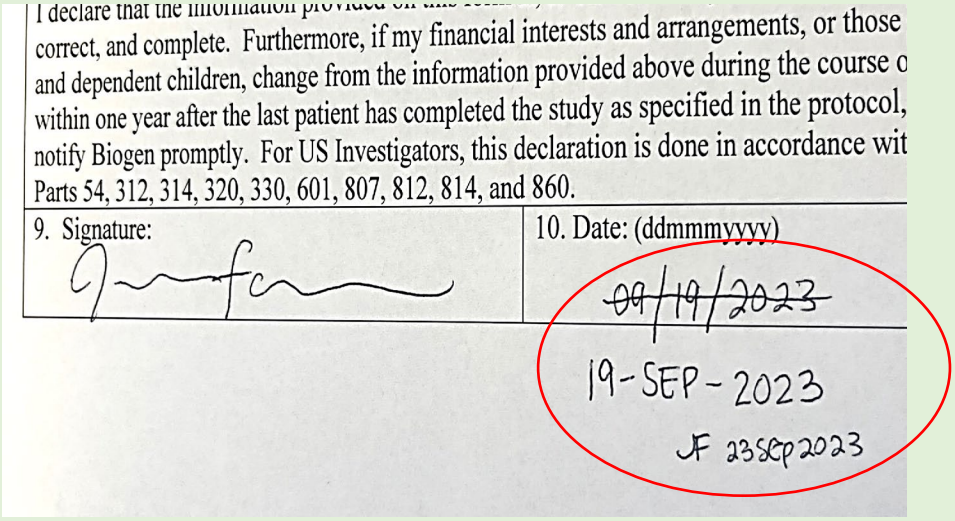


Documentation

- 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 =01**JAN**2023


I declare that the information provided on this [illegible]
correct, and complete. Furthermore, if my financial interests and arrangements, or those
and dependent children, change from the information provided above during the course o
within one year after the last patient has completed the study as specified in the protocol,
notify Biogen promptly. For US Investigators, this declaration is done in accordance wit
Parts 54, 312, 314, 320, 330, 601, 807, 812, 814, and 860.

9. Signature:	10. Date: (ddmmmyyyy)
	~~09/19/2023~~ 19-SEP-2023 JF 23SEP2023

- 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?***

IQVIA

Study Personnel Signature and Delegation Form

Sponsor	F. Hoffmann-La Roche Ltd	Protocol Number	MN43964
Principal Investigator	Dr. Enrique Alvarez	Site Number & Country	353034

Staff Name	Staff Signature[1]	Staff Initials	Study Role	Delegated Study Tasks	Date of Delegation[2] (DDMmmYYYY)	PI Initials	End of Tasks[3] (DDMmmYYYY)	PI Initials
Timber Bourassa		TRB	SC	2, 4, 6a-9, 10a-c, 15, 20, 23	03 NOV 2022			
Nicole Gendelman		NG	Regulatory	17, 18	03 NOV 2022			
Joanna Fanella		JF	Regulatory	17, 18	03 NOV 2022			
Karen Snow		KS	Pharmacist	9, 11 a-b, 12 a-b, 13a-b, 14a-b	08 NOV 2022			
Julie McLaughlin		JM	Pharmacist	9, 11 a-b, 12 a-b, 13 a-b, 14 a-b	03 NOV 2022			
Nne Nwobodo		NN	Pharmacist	9, 11 a-b, 12 a-b, 13 a-b, 14 a-b	04 NOV 2022			
Diane Branham		DB	Nurse Manager	12c	14 NOV 2022			
Justin Juvera		JJV	MRI tech	21	14 NOV 2022			
Cara Henriksen		CJH	MRI tech	21	10 Jan 2023			

Key Study Tasks		
1. Obtain informed consent	9. Use IXRS	17. Manage IRB/IEC communications & submissions
2. Obtain medical/concomitant medication history	10. a) Collect, b) Process, c) Ship lab samples	18. Maintain Investigator Site File
3. Perform physical exam	11. Manage a) IP receipt, b) IP storage	19. Perform EDSS
4. Take/Record vital signs (incl. weight, height)	12. a) Prepare, b) Dispense, c) Administer IP	20. Perform 9HPT i and T25FWT
5. Perform Neurological examination	13. Perform a) IP accountability, b) IP compliance	21. Perform MRI
6. AE/SAEs: a) Document, b) Report (administrative)	14. Manage a) IP destruction, b) IP return	22. Review safety reports
7. Evaluate AE/SAE (medically qualified)	15. Make CRF entries, corrections & manage queries	23. Other
8. Make medical decisions (e.g., eligibility, evaluating test results (e.g., lab, MRI, others), etc.)	16. Sign off on (e)CRF visit data (medically qualified)	24. Other

Protocol Deviations

Protocol Compliance = most commonly identified theme in FDA warning letters FY 2020

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

NOTE TO FILE
PROTOCOL DEVIATION

Study: 11-1111
Study Title: Study For Testing (DO NOT DELETE)
Protocol Number: Test-Study-111
Today's date: 5/16/2023
Subject ID (if applicable): 0001
Date deviation was discovered: *
Brief description of deviation including background, relevant dates, action taken, outcome, followup: *

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

What was the root cause of the deviation? *
Coordinator oversight/action
Investigator oversight/action
Research subject action
Sponsor/CRO oversight/action/direction
Oversight/action by other research personnel (CTRC, pharmacy, etc)
Other/NA

General Category *
Out of Window Visit
Missed Visit
Missed Procedure or Assessment
Incorrectly Done Procedure or Assessment
Deviation related to investigational drug dosing 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: Print this page, have investigator assess below criteria and sign form.
Option 2: After submitting this form, use the "Send Form To Investigator" function to send this information to an investigator via email to get their assessment.

PI OR SUB-I 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 IRB REPORTING

Investigator Signature _____ Date _____

→

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*

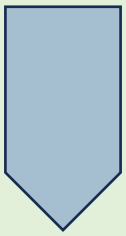
Safety Oversight

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*

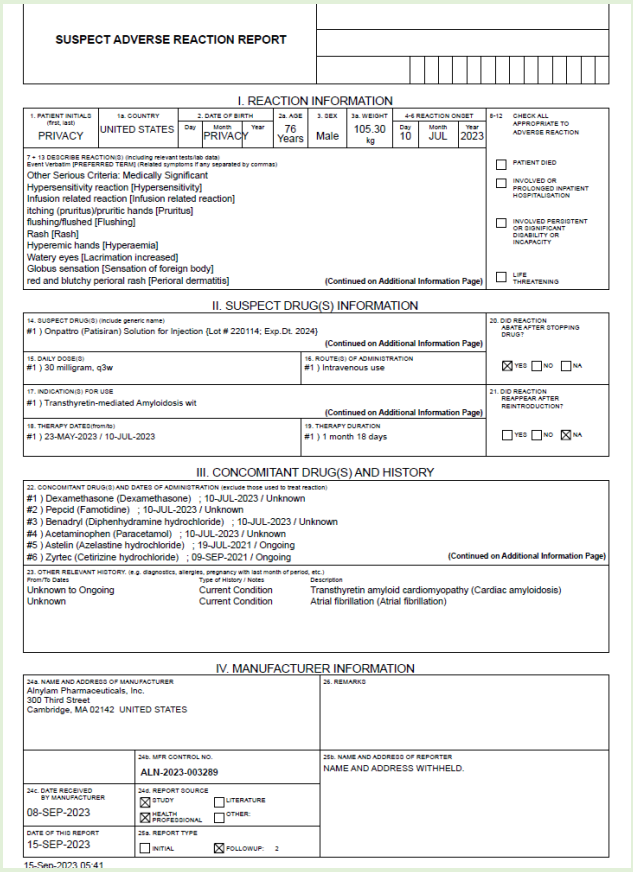
You must be reachable and responsive!

External safety events on drug studies- IND safety reports

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



SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year	8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
PRIVACY	UNITED STATES		PRIVACY		76 Years	Male	105.30 kg	10	JUL	2023	

7 + 13. DESCRIBE REACTION(S) (including relevant tests/lab data) Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

Other Serious Criteria: Medically Significant
Hypersensitivity reaction [Hypersensitivity]
Infusion related reaction [Infusion related reaction]
itching (pruritus)/pruritic hands [Pruritus]
flushing/flushed [Flushing]
Rash [Rash]
Hyperemic hands [Hyperaemia]
Watery eyes [Lacrimation increased]
Globus sensation [Sensation of foreign body]
red and blutchy perioral rash [Perioral dermatitis]

(Continued on Additional Information Page)

☐ PATIENT DIED
☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Onpattro (Patisiran) Solution for Injection {Lot # 220114; Exp.Dt. 2024}
(Continued on Additional Information Page)

20. DID REACTION ABATE AFTER STOPPING DRUG? ☒ YES ☐ NO ☐ NA

15. DAILY DOSE(S)
#1) 30 milligram, q3w

16. ROUTE(S) OF ADMINISTRATION
#1) Intravenous use

17. INDICATION(S) FOR USE
#1) Transthyretin-mediated Amyloidosis wit
(Continued on Additional Information Page)

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ NA

18. THERAPY DATES (from to)
#1) 23-MAY-2023 / 10-JUL-2023

19. THERAPY DURATION
#1) 1 month 18 days

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
#1) Dexamethasone (Dexamethasone) ; 10-JUL-2023 / Unknown
#2) Pepcid (Famotidine) ; 10-JUL-2023 / Unknown
#3) Benadryl (Diphenhydramine hydrochloride) ; 10-JUL-2023 / Unknown
#4) Acetaminophen (Paracetamol) ; 10-JUL-2023 / Unknown
#5) Astelin (Azelastine hydrochloride) ; 19-JUL-2021 / Ongoing
#6) Zyrtec (Cetirizine hydrochloride) ; 09-SEP-2021 / Ongoing
(Continued on Additional Information Page)

23. OTHER RELEVANT HISTORY, (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
Unknown to Ongoing	Current Condition	Transthyretin amyloid cardiomyopathy (Cardiac amyloidosis)
Unknown	Current Condition	Atrial fibrillation (Atrial fibrillation)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Alnylam Pharmaceuticals, Inc.
300 Third Street
Cambridge, MA 02142 UNITED STATES

26. REMARKS

24b. MFR CONTROL NO.
ALN-2023-003289

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
08-SEP-2023

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
15-SEP-2023

28a. REPORT TYPE
☐ INITIAL ☒ FOLLOWUP: 2

15-Sep-2023 05:41

- 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!