Everything You Need to Know About Being a Clinical Trial Sponsor

J. Kaitlin Morrison, PhD

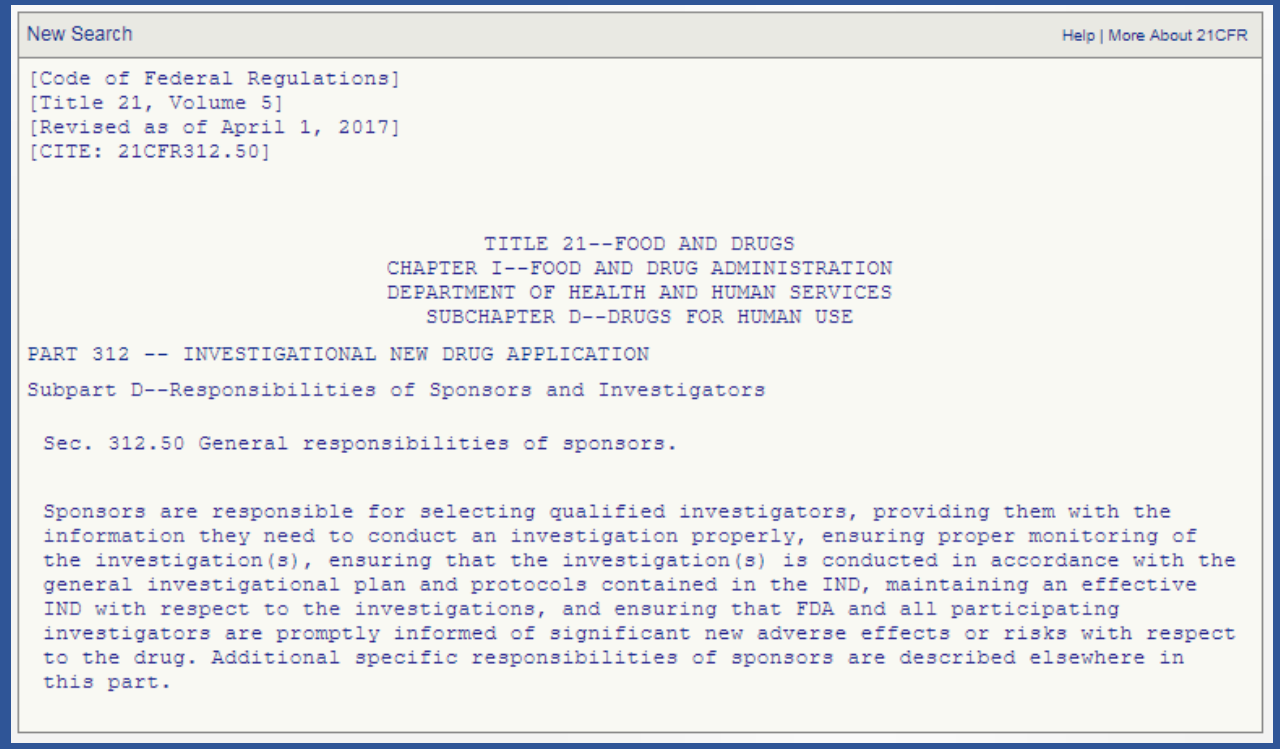
Kaitlin_Morrison@med.unc.edu

Definition of a Sponsor

Sponsor: An individual or entity who takes responsibility for and initiates a clinical investigation.

- an individual
- a pharmaceutical company
- government agency
- academic institution
- other organization

Clinical Investigator: An individual who conducts a clinical investigation under whose immediate supervision the investigational drug/device is administered.



New Search | Help | More About 21CFR

[Code of Federal Regulations]
[Title 21, Volume 5]
[Revised as of April 1, 2017]
[CITE: 21CFR312.50]

TITLE 21--FOOD AND DRUGS
CHAPTER I--FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES
SUBCHAPTER D--DRUGS FOR HUMAN USE

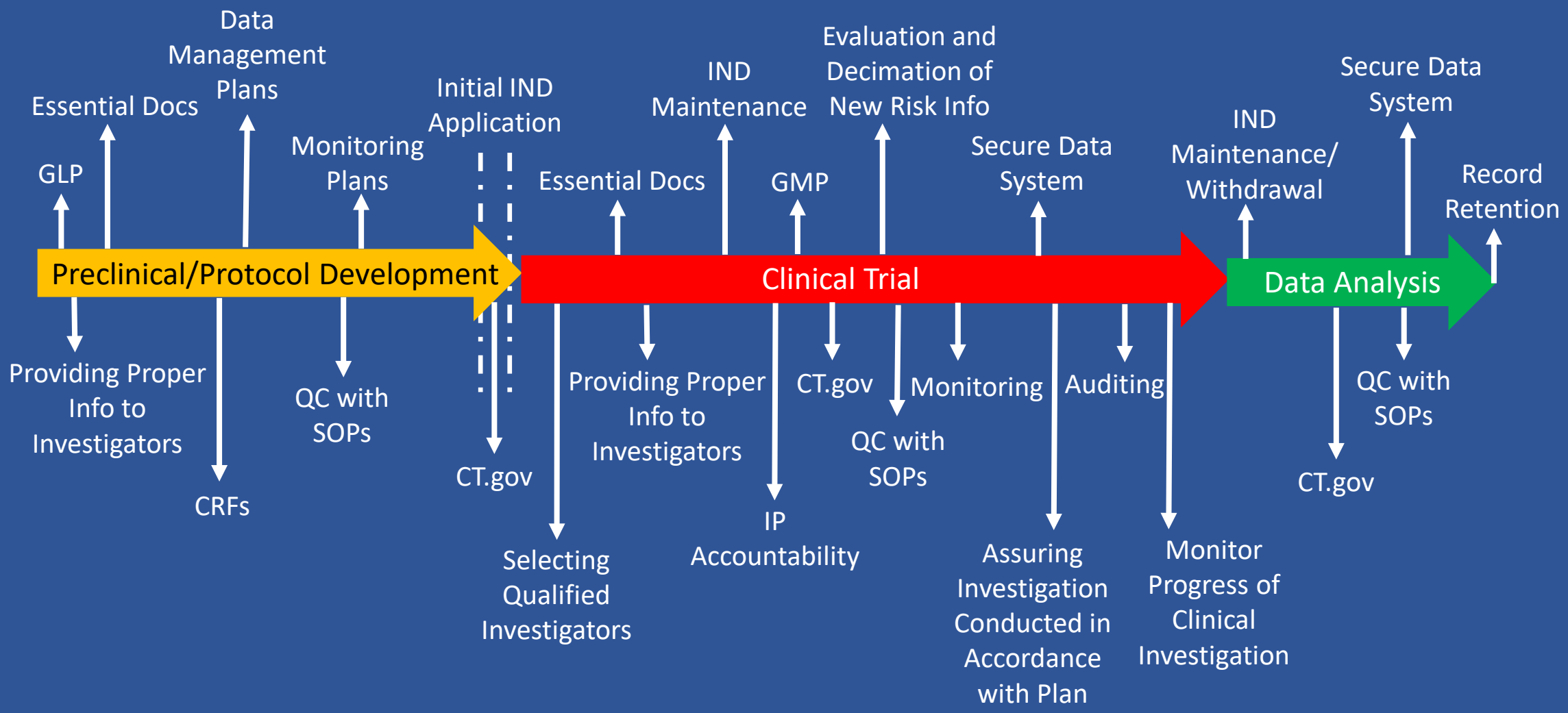
PART 312 -- INVESTIGATIONAL NEW DRUG APPLICATION

Subpart D--Responsibilities of Sponsors and Investigators

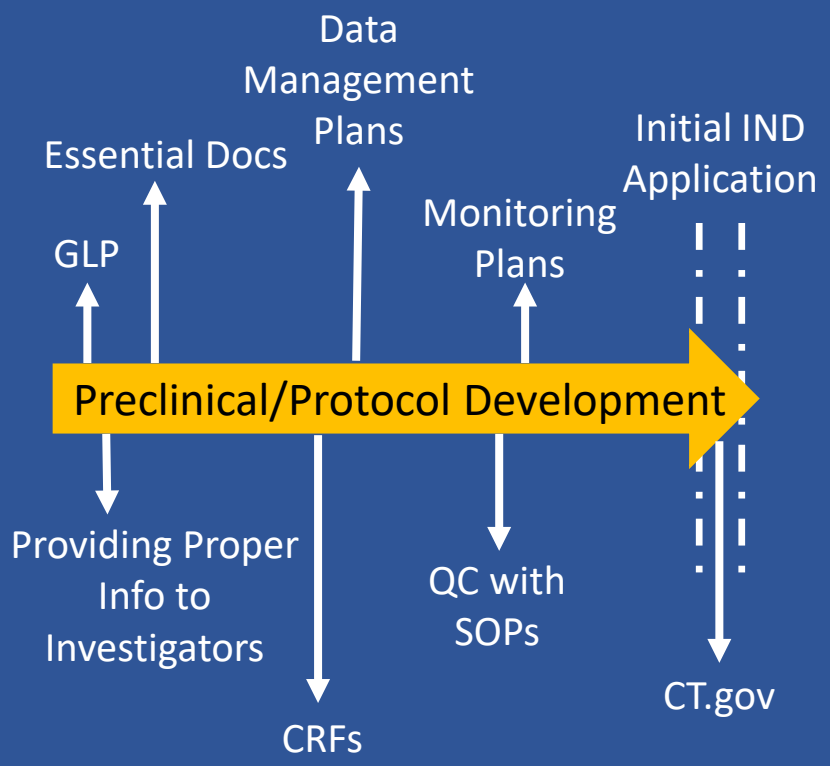
Sec. 312.50 General responsibilities of sponsors.

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

Clinical Trial Life Cycle- Sponsor Obligations



Preclinical/Protocol Development



Providing investigators with the information needed to conduct an investigation properly

- Starts with protocol design
  - Protocol Development

RECALL PROCEDURES

The study protocol contained procedures for reporting adverse events to the sponsor and the IRB.

*Notes from an FDA inspection

Approximately half (45%) of all substantial amendments were deemed “somewhat” to “completely” avoidable.

- Protocol design flaws
- Inconsistencies in the protocol narrative
- Infeasible eligibility criteria

Getz, K.A., et. al. The impact of protocol amendments on clinical trial performance and cost. Ther. In. Reg. Sci. 2016. 50(4) 436-441.

Providing investigators with the information needed to conduct an investigation properly

- Starts with protocol design
  - Protocol Development

UNC has protocol template resources to help you:

https://research.unc.edu/clinical-trials/scientific-review-committee/

Below are several templates for developing protocols. The most complete is the "Clinical Trials Protocol Template" for which there are two links — an educational one, including examples, and the shell, which is prepared for adding study-specific text as directed by the educational guidance.

- Clinical Trials Protocol Template – draft guidance from NIH & FDA
- Clinical Trials Protocol Template – shell

Here are alternative templates which are not as complete, but targeted to particular types of study.

- Protocol Template: Interventional Study
- Protocol Template: Registry Repository Study
- Protocol Template: Observational Study
- Protocol Template: Retrospective Descriptive Study

Lineberger Comprehensive Cancer Center Has Additional Cancer Centric Resources:

https://unclineberger.org/iit/forms-templates/

LCCC Protocol Templates

Instructions on use of Templates

Cellular Therapy Template

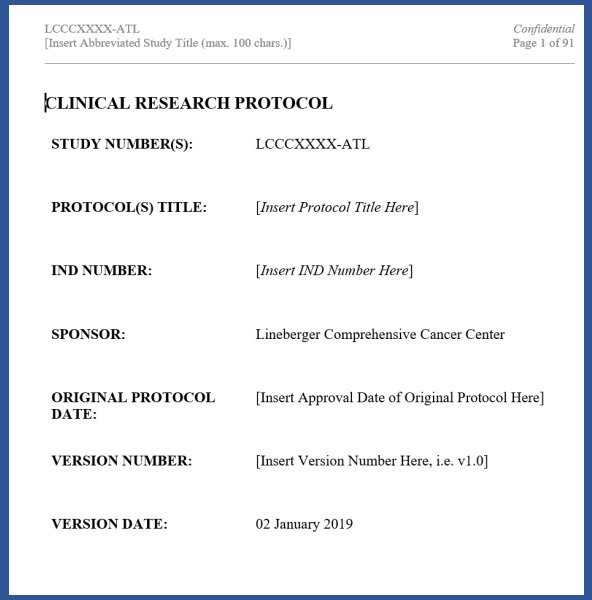
Chemotherapy Treatment protocol template

Radiation Treatment protocol template

Health Services Research protocol template

Specimen-based Research protocol template

Imaging Study Protocol Template



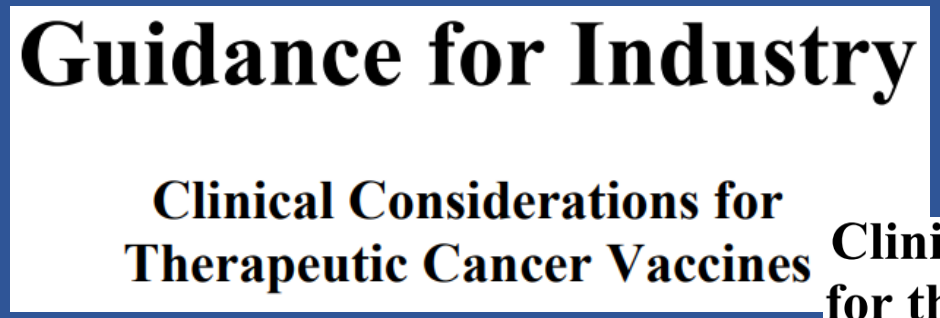
LCCCXXXX-ATL
[Insert Abbreviated Study Title (max. 100 chars.)]
Confidential
Page 1 of 91

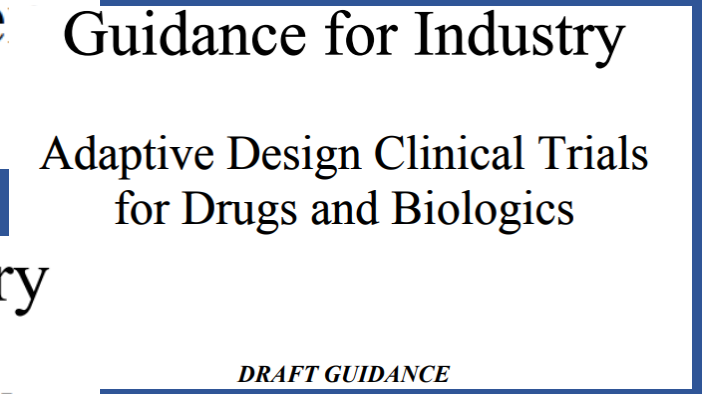
CLINICAL RESEARCH PROTOCOL

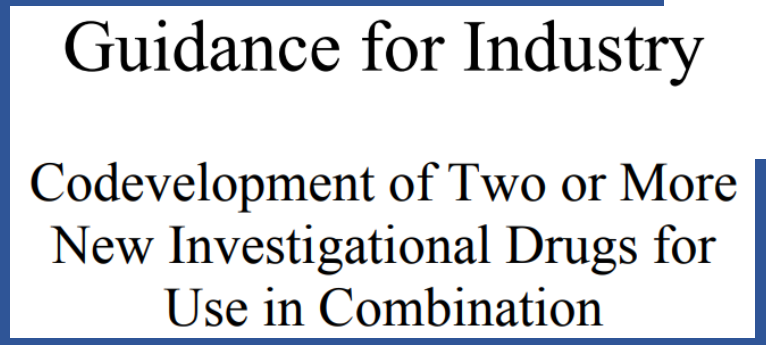
STUDY NUMBER(S):	LCCCXXXX-ATL
PROTOCOL(S) TITLE:	[*Insert Protocol Title Here*]
IND NUMBER:	[*Insert IND Number Here*]
SPONSOR:	Lineberger Comprehensive Cancer Center
ORIGINAL PROTOCOL DATE:	[Insert Approval Date of Original Protocol Here]
VERSION NUMBER:	[Insert Version Number Here, i.e. v1.0]
VERSION DATE:	02 January 2019

Providing investigators with the information needed to conduct an investigation properly

- Starts with protocol design
  - Protocol Development
  - Regulatory Strategy







Providing investigators with the information needed to conduct an investigation properly

- Starts with protocol design
  - Protocol Development
  - Regulatory Strategy
  - Protocol Review Meetings

Get everyone in the room to read and discuss the protocol:

- PI
- Study Coordinator
- Data Coordinator
- Regulatory Coordinator
- Lab
- Anyone else who touches the protocol…

"Should utilize **qualified individuals** (e.g. biostatisticians, clinical pharmacologists, and physicians) as appropriate **throughout all stages of the trial process** from designing the protocol and CRFs and planning the analysis to analyzing and preparing interim and final clinical trial results"

Providing investigators with the information needed to conduct an investigation properly

- Starts with protocol design
  - Protocol Development
  - Regulatory Strategy
  - Protocol Review Meetings
  - Protocol Review Committee (PRC) or Scientific Review Committee (SRC)

PRC's Primary Function:

- Enhance the quality of clinical research by providing constructive criticism

Judge the Acceptability based on:

1. Background justification
2. Scientific design/merit
3. Risk/benefit ratio
4. Biostatistics
5. Feasibility
6. Resource utilization

Please address all submissions to:

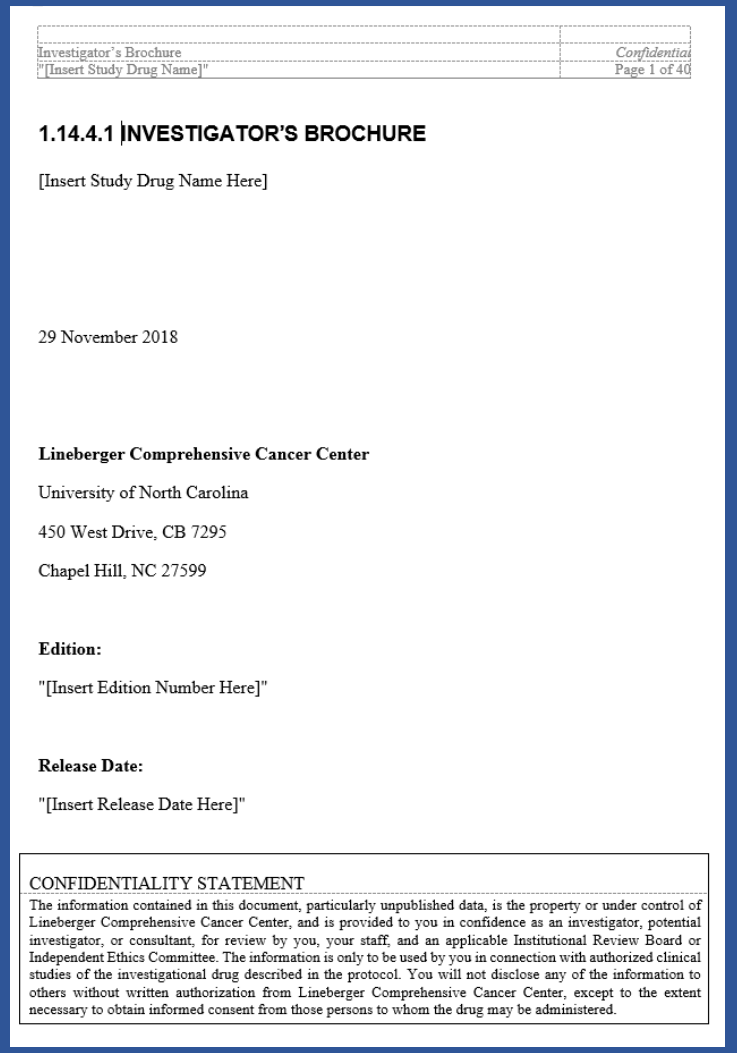
Stacy Maxwell
Protocol Review Committee Coordinator
UNC Lineberger Comprehensive Cancer Center
3rd Floor CB #7295
Telephone: 919.962.8566
Email

To submit your study for Scientific Review, please complete the SRC Review Request form found here. Send the completed form along with your full protocol (not grant proposal) to SRC@unc.edu.

Providing investigators with the information needed to conduct an investigation properly

- Starts with protocol design
  - Protocol Development
  - Regulatory Strategy
  - Protocol Review Meetings
  - Protocol Review Committee (PRC)

- May involve writing an Investigator's Brochure (IB)



Investigator's Brochure | *Confidential*
"[Insert Study Drug Name]" | Page 1 of 40

1.14.4.1 INVESTIGATOR'S BROCHURE

[Insert Study Drug Name Here]

29 November 2018

Lineberger Comprehensive Cancer Center

University of North Carolina

450 West Drive, CB 7295

Chapel Hill, NC 27599

Edition:

"[Insert Edition Number Here]"

Release Date:

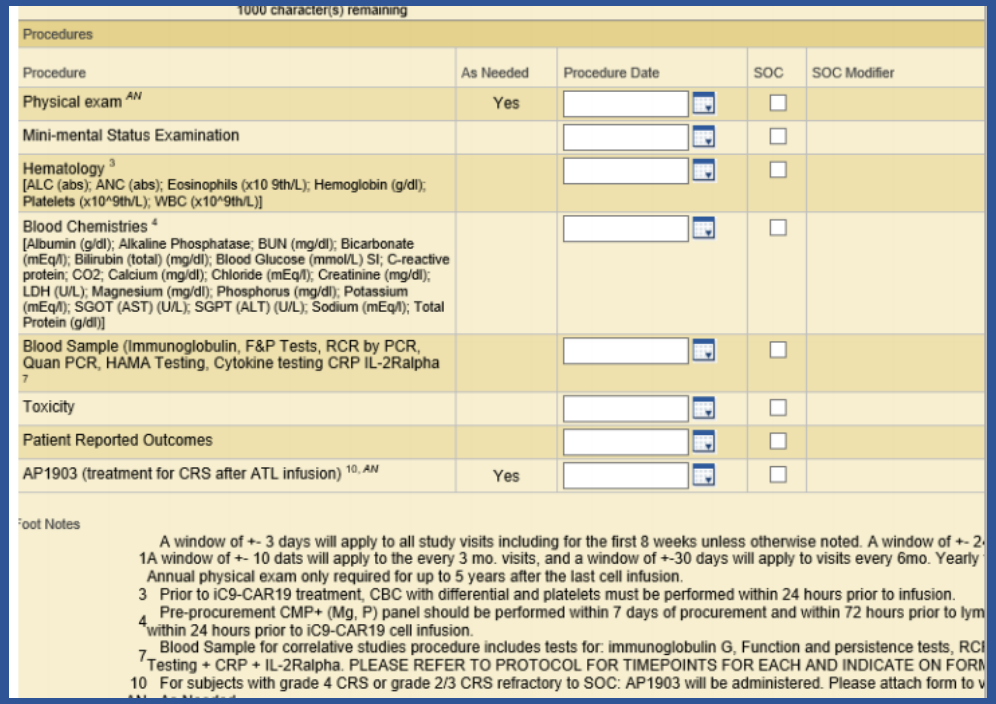
"[Insert Release Date Here]"

CONFIDENTIALITY STATEMENT

The information contained in this document, particularly unpublished data, is the property or under control of Lineberger Comprehensive Cancer Center, and is provided to you in confidence as an investigator, potential investigator, or consultant, for review by you, your staff, and an applicable Institutional Review Board or Independent Ethics Committee. The information is only to be used by you in connection with authorized clinical studies of the investigational drug described in the protocol. You will not disclose any of the information to others without written authorization from Lineberger Comprehensive Cancer Center, except to the extent necessary to obtain informed consent from those persons to whom the drug may be administered.

Providing investigators with the information needed to conduct an investigation properly

- Starts with protocol design
  - Protocol Development
  - Regulatory Strategy
  - Protocol Review Committee (PRC)
  - Protocol Review Meetings
- May involve writing an Investigator's Brochure
- Data Collection Design and Development
  - Definition of Critical Data Values
  - Creation of eCRFs (and completion guidelines)
  - Study Specific Data Management Plans



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Procedures

Procedure	As Needed	Procedure Date	SOC	SOC Modifier
Physical exam [AN]	Yes			
Mini-mental Status Examination				
Hematology [3] [ALC (abs); ANC (abs); Eosinophils (x10 9th/L); Hemoglobin (g/dl); Platelets (x10^9th/L); WBC (x10^9th/L)]				
Blood Chemistries [4] [Albumin (g/dl); Alkaline Phosphatase; BUN (mg/dl); Bicarbonate (mEq/l); Bilirubin (total) (mg/dl); Blood Glucose (mmol/L) SI; C-reactive protein; CO2; Calcium (mg/dl); Chloride (mEq/l); Creatinine (mg/dl); LDH (U/L); Magnesium (mg/dl); Phosphorus (mg/dl); Potassium (mEq/l); SGOT (AST) (U/L); SGPT (ALT) (U/L); Sodium (mEq/l); Total Protein (g/dl)]				
Blood Sample (Immunoglobulin, F&P Tests, RCR by PCR, Quan PCR, HAMA Testing, Cytokine testing CRP IL-2Ralpha [7]				
Toxicity				
Patient Reported Outcomes				
AP1903 (treatment for CRS after ATL infusion) [10, AN]	Yes			

Foot Notes

A window of +- 3 days will apply to all study visits including for the first 8 weeks unless otherwise noted. A window of +- 2
1A window of +- 10 dats will apply to the every 3 mo. visits, and a window of +-30 days will apply to visits every 6mo. Yearly
Annual physical exam only required for up to 5 years after the last cell infusion.
3 Prior to iC9-CAR19 treatment, CBC with differential and platelets must be performed within 24 hours prior to infusion.
4 Pre-procurement CMP+ (Mg, P) panel should be performed within 7 days of procurement and within 72 hours prior to lym
within 24 hours prior to iC9-CAR19 cell infusion.
7 Blood Sample for correlative studies procedure includes tests for: immunoglobulin G, Function and persistence tests, RCI
Testing + CRP + IL-2Ralpha. PLEASE REFER TO PROTOCOL FOR TIMEPOINTS FOR EACH AND INDICATE ON FORM
10 For subjects with grade 4 CRS or grade 2/3 CRS refractory to SOC: AP1903 will be administered. Please attach form to v

Maintaining an effective IND

What goes into an initial IND Application?

1. **Form FDA 1571**
2. Table of Contents
3. Introductory Statement
   a. Name of Drug and active ingredients
   b. Pharmacological Class
   c. Structural formula
   d. Formation
   e. Route of administration
   f. Objectives and Duration
   g. Status of drug in other countries
4. General Investigational Plan
   a. Rationale
   b. Indication
   c. Approach to evaluate treatment
   d. Drug Related Risks
5. **Investigator Brochure**
6. **Protocol**
   a. **Study Protocol**
   b. Informed Consent Form
   c. **Investigator and Facility Data (Form FDA 1572)**
7. **Chemistry, Manufacturing and Control**
8. Pharmacology and Toxicology
9. Previous Human Experience
10. Additional Information
    a. Drug Dependence and Abuse Potential
    b. Radioactive Drugs
    c. Pediatric Studies
11. Biosimiliar User Fee Cover Sheet
12. **Clinical Trials Certification of Compliance**

UNC has IND resources to help you:

Contact: Amanda Wood

https://tracs.unc.edu/index.php/services/regulatory/ind-and-ide-application-support

LCCC has Comprehensive IND Management Services that Support all LCCC INDs:

Contact: J. Kaitlin Morrison, PhD

LCCC_IND@unc.edu

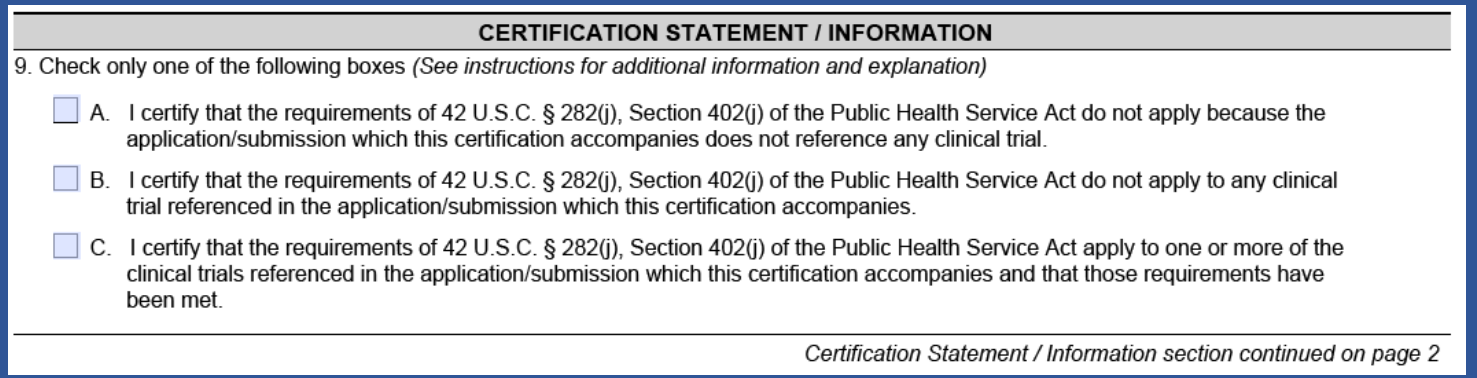
Compliance with ClinicalTrials.gov

- What is the purpose/why does FDA require this?
  - Help patients find trials
  - Enhance design of trials
  - Prevent duplication of unsuccessful or unsafe trials
  - Build public trust

- FDA requires Responsible party (**sponsor**) to **register** with and submit results information of applicable trials to clinicaltrials.gov
  - Descriptive information
  - Recruitment information
  - Location and contact information
  - Administrative data

Form FDA 3674

- Certification of compliance with clinicaltrials.gov
- Determination of whether your study requires results reporting on clinicaltrials.gov



CERTIFICATION STATEMENT / INFORMATION

9. Check only one of the following boxes *(See instructions for additional information and explanation)*

- ☐ A. I certify that the requirements of 42 U.S.C. § 282(j), Section 402(j) of the Public Health Service Act do not apply because the application/submission which this certification accompanies does not reference any clinical trial.
- ☐ B. I certify that the requirements of 42 U.S.C. § 282(j), Section 402(j) of the Public Health Service Act do not apply to any clinical trial referenced in the application/submission which this certification accompanies.
- ☐ C. I certify that the requirements of 42 U.S.C. § 282(j), Section 402(j) of the Public Health Service Act apply to one or more of the clinical trials referenced in the application/submission which this certification accompanies and that those requirements have been met.

Certification Statement / Information section continued on page 2

UNC has resources to help you:

Contact: Monica Coudurier

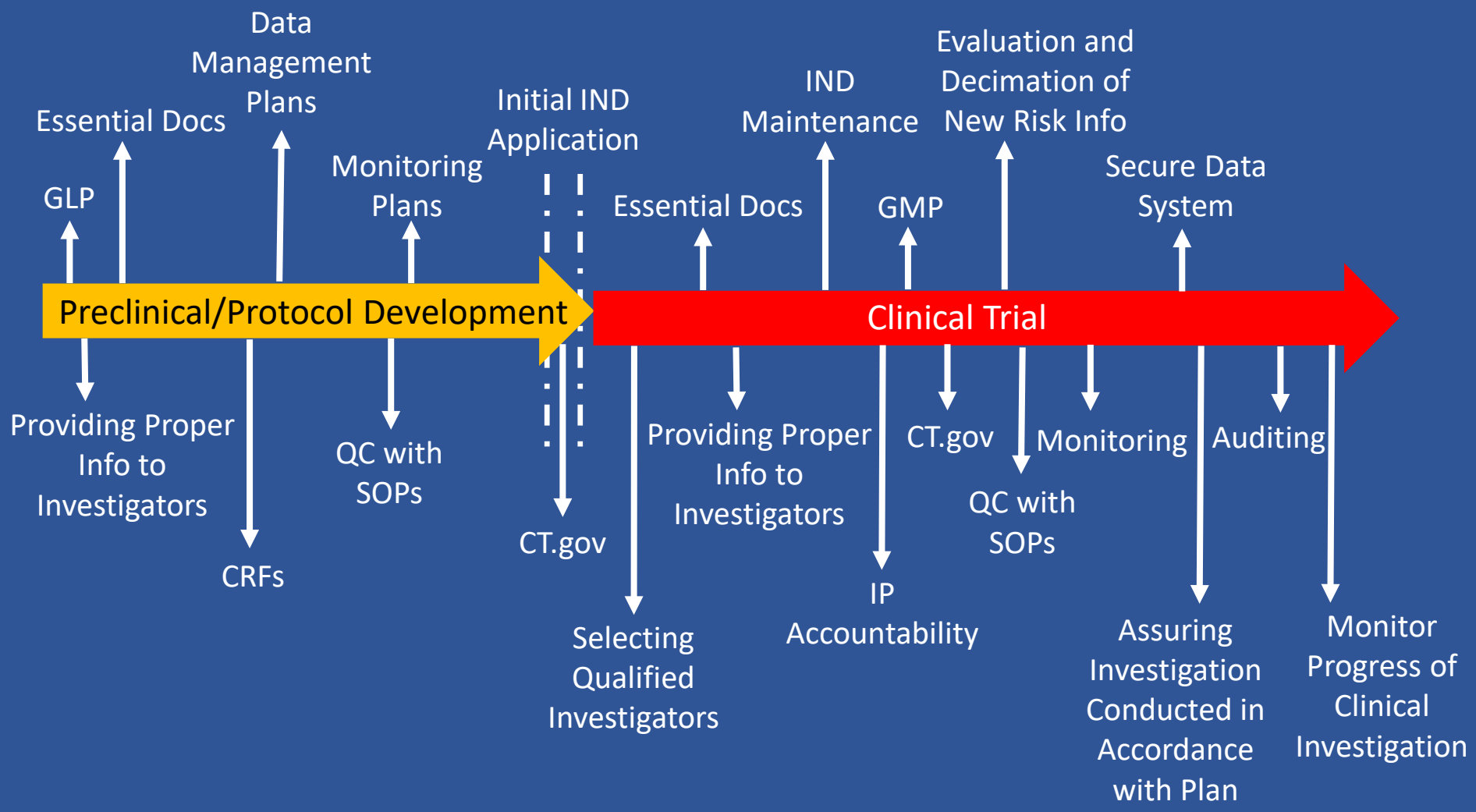
https://research.unc.edu/clinical-trials/clinical-trials-gov/

LCCC has specific cancer resources to help you:

Contact: Mary O'Dwyer

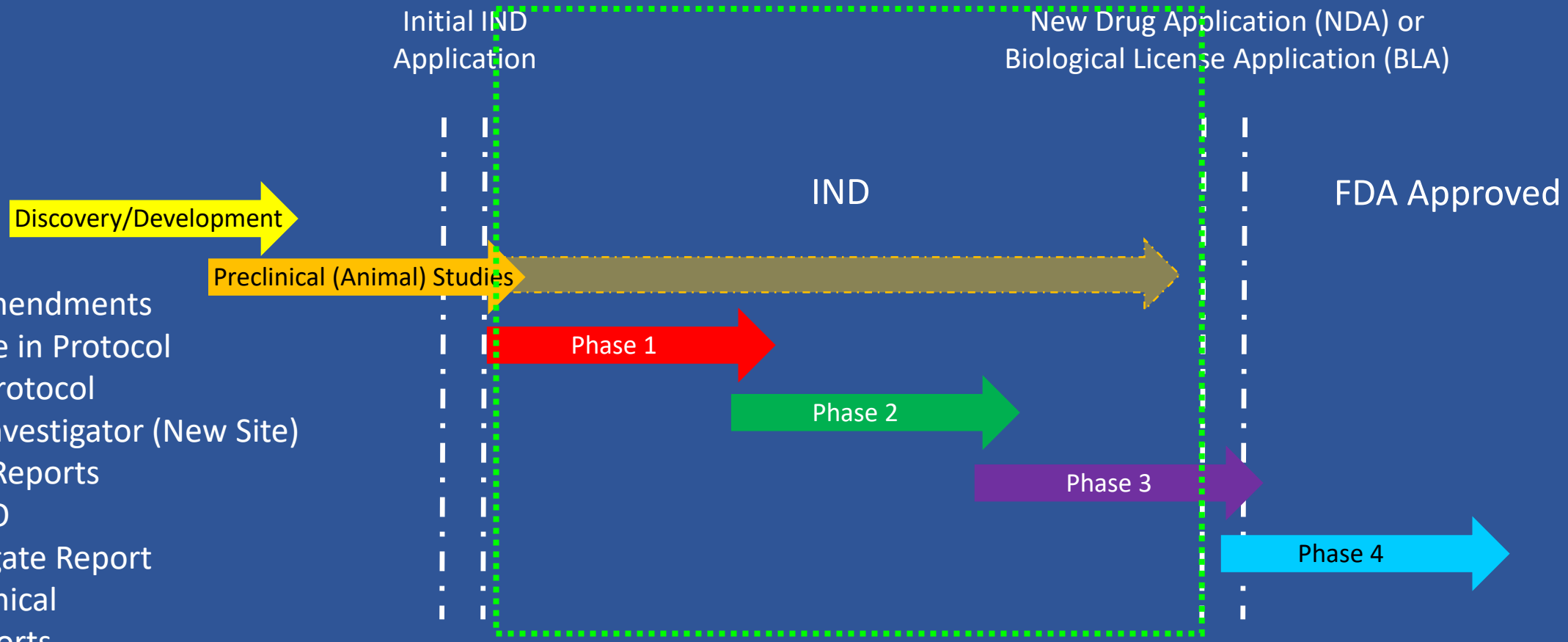
https://research.unc.edu/clinical-trials/clinical-trials-gov/

Clinical Trial



Maintaining an effective IND

What needs to be done to maintain an IND?



- Protocol Amendments
  - Change in Protocol
  - New Protocol
  - New Investigator (New Site)
- IND Safety Reports
  - UPIRSO
  - Aggregate Report
  - Pre-clinical
- Annual Reports
- Continued Communication with FDA
- Withdrawal
- Change in Sponsors/PIs

Preparation → Drafting IND → FDA Review → **Safe to Proceed**

Maintaining an effective IND

What are your resources?

UNC has IND resources to help you:

Contact: Amanda Wood

https://tracs.unc.edu/index.php/services/regulatory/ind-and-ide-application-support

LCCC has Comprehensive IND Management Services that Support all LCCC INDs:

Contact: J. Kaitlin Morrison, PhD

LCCC_IND@unc.edu

- LCCC SOPs (complete with working instructions and templates)
  - **Protocol Amendments:**
    - SOP-2 Amendment CPO IIT (updated)
    - SOP-4 Administrative Letters (updated)
    - SOP-54 LCCC IND Protocol Amendment Change in Protocol
  - **New Sites:**
    - SOP-55 LCCC IND Protocol Amendment New Investigator
  - **Communication from FDA:**
    - SOP-53 LCCC IND Distribution of FDA Emails
  - **Annual Reports**
    - SOP-45 LCCC IND Annual Reports
  - **Determining if your study requires an IND**
    - SOP-3 Determining IND Status (updated)
  - **Changes in PI, Sponsor or Medical Monitor**
    - SOP-43 Change in Principal Investigator (updated)
    - SOP-57 LCCC IND Change in Sponsor, MM or PI
    - SOP-56 Change in Multi-Center PI
    - SOP-16 LCCC IND Submission of Updated Form FDA 1572 to FDA
  - **Safety**
    - SOP-5 Action Letters
    - SOP-13A and B LCCC IND Safety Reporting
  - **IND Withdrawal**
    - SOP-58 LCCC IND Withdrawal

ClinicalTrials.gov

- What is the purpose?
  - Help patients find trials
  - Enhance design of trials
  - Prevent duplication of unsuccessful or unsafe trials
  - Build public trust

- FDA requires Responsible party (**sponsor**) to **register** with and submit results information of applicable trials to clinicaltrials.gov
  - Descriptive information
  - Recruitment information
  - Location and contact information
  - Administrative data

Data Element	Deadline for Updating
Study Start Date	30 calendar days after the first subject is enrolled (if the first human subject was not enrolled at the time of registration).
Intervention Name(s)	30 calendar days after a nonproprietary name is established.
Availability of Expanded Access	30 calendar days after expanded access becomes available (if available after registration); and 30 calendar days after an NCT number is assigned to a newly created expanded access record.
Expanded Access Status	30 calendar days after a change in the availability of expanded access.
Expanded Access Type	30 calendar days after a change in the type(s) of available expanded access.
Overall Recruitment Status	30 calendar days after a change in overall recruitment status.
Individual Site Status	30 calendar days after a change in status of any individual site.
Human Subjects Protection Review Board Status	30 calendar days after a change in status.
Primary Completion Date	30 calendar days after the clinical trial reaches its actual primary completion date.
Enrollment	At the time the primary completion date is changed to “actual,” the actual number of participants enrolled must be submitted.
Study Completion Date	30 calendar days after the clinical trial reaches its actual study completion date.
Responsible Party, by Official Title	30 calendar days after a change in the responsible party or the official title of the responsible party.
Responsible Party Contact Information	30 calendar days after a change in the responsible party or the contact information for the responsible party.
Device Product Not Approved or Cleared by U.S. FDA	15 calendar days after a change in approval or clearance status has occurred.
Record Verification Date	Any time the responsible party reviews the complete set of submitted clinical trial information for accuracy and not less than every 12 months, even if no other updated information is submitted at that time.

UNC has resources to help you:

Contact: Monica Coudurier

https://research.unc.edu/clinical-trials/clinical-trials-gov/

LCCC has specific cancer resources to help you:

Contact: Mary O’Dwyer

https://research.unc.edu/clinical-trials/clinical-trials-gov/

Selecting Qualified Investigators

- Do they have the right credentials?
- Do they have clinical trial experience?
- Do they have appropriate resources and staff?
- Feasibility Questionnaires

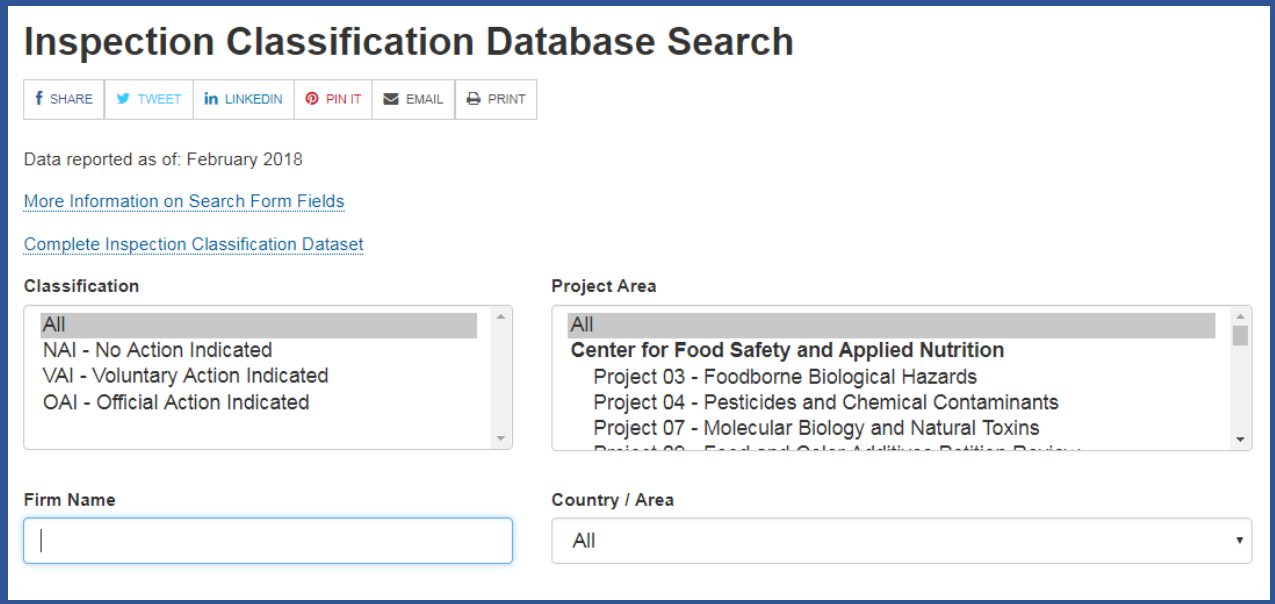
The final responsibility for the trial's conduct lies with the sponsor, so FDA wants to make sure that you have selected appropriate individuals to conduct the study.

Warning Letters:
https://www.fda.gov/ICECI/EnforcementActions/WarningLetters/

Inspections:
https://www.fda.gov/ICECI/Inspections/ucm222557.htm

Inspection Citations:
https://www.fda.gov/ICECI/Inspections/ucm346077.htm

Search FDA Databases



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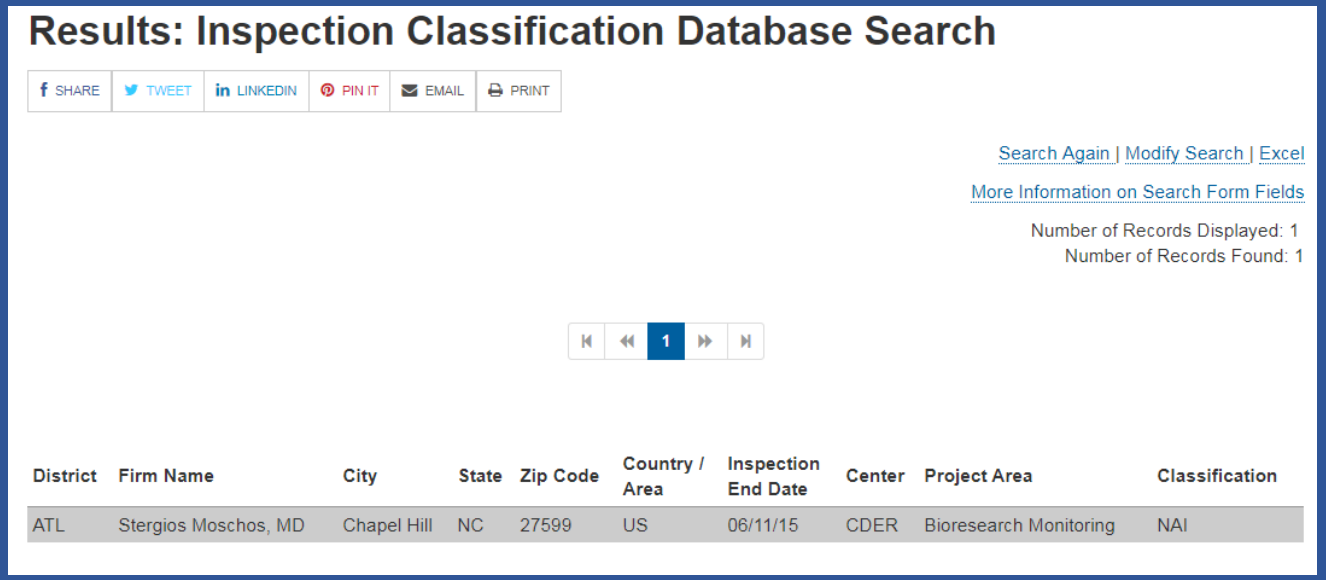
Multicenter Regulatory Associate Searches these databases.



Results: Inspection Classification Database Search

SHARE | TWEET | LINKEDIN | PIN IT | EMAIL | PRINT

Search Again | Modify Search | Excel

More Information on Search Form Fields

Number of Records Displayed: 1
Number of Records Found: 1

1

District	Firm Name	City	State	Zip Code	Country / Area	Inspection End Date	Center	Project Area	Classification
ATL	Stergios Moschos, MD	Chapel Hill	NC	27599	US	06/11/15	CDER	Bioresearch Monitoring	NAI

Collection of Essential Documents

Why are Essential Documents Important?

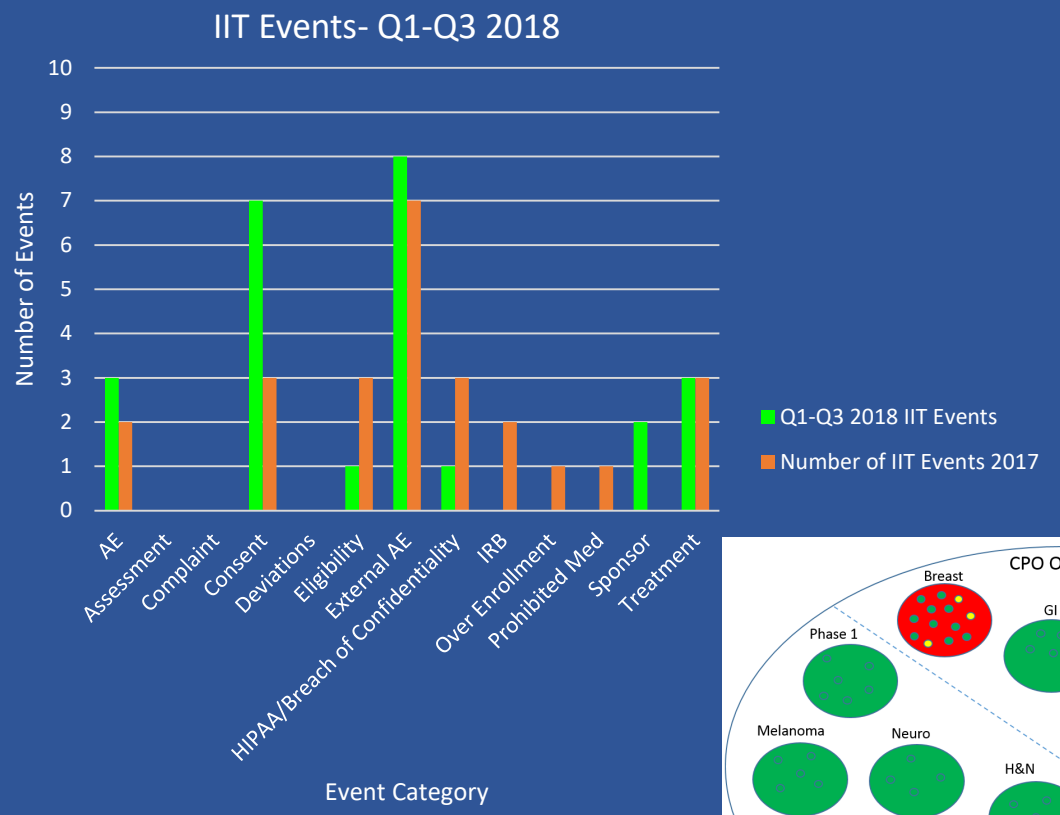
- Form FDA 1572
  - The Investigator's Contract with the Sponsor
- CVs
  - Investigator's qualifications
- Financial Disclosures
  - Are there other vested interests?
- Training
  - Do the colleagues/employees have the information they need to conduct the research properly?
- Delegation of Authority
  - Has the investigator given permission for tasks to be performed by others?

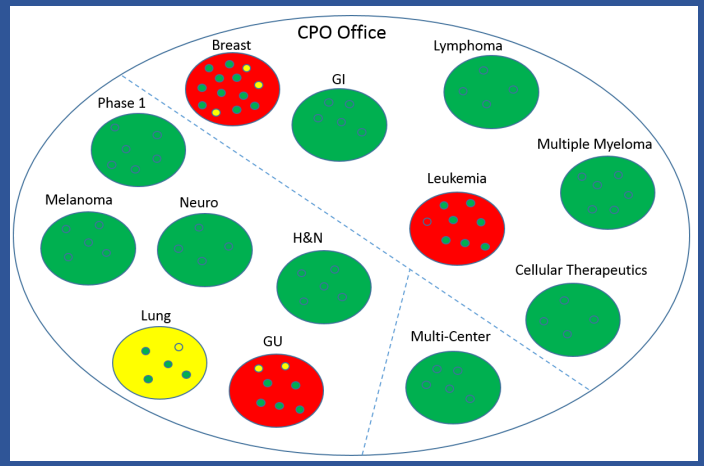
You are making sure that your affiliate site investigators are qualified and that understand their FDA obligations.

Providing investigators with the information needed to conduct an investigation properly

How do we do this?

- Protocol Amendments
  - LCCC SOP-2 Amending CPO IIT Trials
- Action Letters (Letter dictating that immediate action must be taken)
  - LCCC SOP-5 Action Letters
- Administrative Letters
  - LCCC SOP-4 Administrative Letters
- Investigator Brochure Updates
- Clinical Research Form (CRF) Updates
- PRC/SRC
  - Amendment Reviews
- Analysis of deviations or questions in regards to the protocol





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- Clinical Research Form (CRF) Updates
- PRC/SRC
  - Amendment Reviews
- Analysis of deviations or questions in regards to the protocol
- Start Up Meetings
  - LCCC SOP-12 Start Up Meetings
- Protocol Amendment/IB Update Training

Get everyone in the room to work through how the protocol will be operationalized and to train the study team:

- PI
- Study Coordinator
- Data Coordinator
- Regulatory Coordinator
- Lab
- Anyone else who touches the protocol…

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  - LCCC SOP-12 Start Up Meetings
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MULTICENTER SITES

- Multicenter Site Initiation Meetings
- Team Calls
- IND Safety Report Distribution
  - SOP-13 Part B LCCC IND Safety Reporting Multicenter
  - SOP-5 Action Letters
- Ensure responsibilities of coordinating investigators and other participating investigators are documented prior to the start of the trial.
- Ensure facilitated communication

Ultimate responsibility: Keeping participating investigators informed of new info, particularly with respect to AEs and safe use of the IP.

May be distributed by means of:

- periodically revised IB
- reprints of published studies or reports
- letters to clinical investigators

Providing investigators with the information needed to conduct an investigation properly

How do we do this?

Training for Study Personnel was provided by the Sponsor Monitor at the site initiation visit as seen in the [redacted] Initiation Visit Checklist and [redacted] Monitoring Visit Log stored in the regulatory box **(Refer to Exhibits 6 and 7)**. Copies of PowerPoint presentations used to train study personnel on the protocol, responsibilities, Good Clinical Practices (GCP), device accountability, regulatory binder contents, eCRFs and data collection processes were contained in the Training file of the regulatory box.

MULTICENTER SITES

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- Team Calls
- IND Safety Report Distribution
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  - SOP-5 Action Letters
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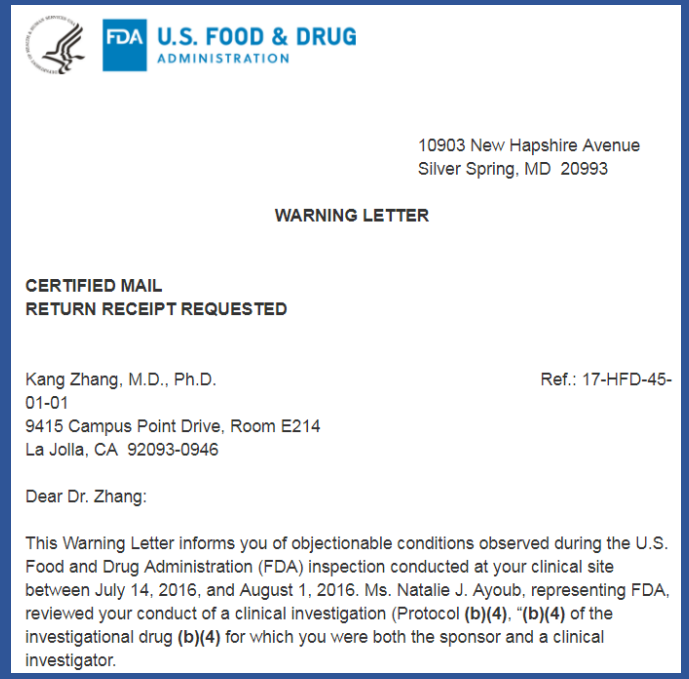
IP Accountability

Why can the federal government (FDA) regulate investigational product?

Give permission for interstate shipment of an IP

- Must have acceptable:
  - Temperature
  - Storage conditions
  - Storage time
  - Reconstitution and procedure and devices for product infusion
- Must inform all involved parties of these determinations

As a sponsor we must have IP accountability to protect subject safety and data validity.



FDA U.S. FOOD & DRUG ADMINISTRATION

10903 New Hapshire Avenue
Silver Spring, MD 20993

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Kang Zhang, M.D., Ph.D. Ref.: 17-HFD-45-01-01
9415 Campus Point Drive, Room E214
La Jolla, CA 92093-0946

Dear Dr. Zhang:

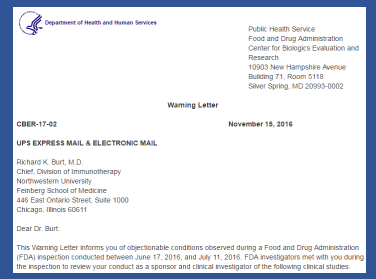
This Warning Letter informs you of objectionable conditions observed during the U.S. Food and Drug Administration (FDA) inspection conducted at your clinical site between July 14, 2016, and August 1, 2016. Ms. Natalie J. Ayoub, representing FDA, reviewed your conduct of a clinical investigation (Protocol **(b)(4)**, "**(b)(4)** of the investigational drug **(b)(4)** for which you were both the sponsor and a clinical investigator.

Your inability to account for the disposition of 25 units of unused supplies of study drug raises significant concerns regarding the adequacy of your oversight and control of investigational drug. In addition, your failure to maintain adequate and accurate drug accountability records raises concerns about the validity and integrity of the data collected at your site.

IP Accountability

Why can the federal government (FDA) regulate investigational product?

Give permission for interstate shipment of an IP



Department of Health and Human Services

Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research
10903 New Hampshire Avenue
Building 71, Room 5118
Silver Spring, MD 20993-0002

Warning Letter

CBER-17-02 November 15, 2016

UPS EXPRESS MAIL & ELECTRONIC MAIL

Richard K. Burt, M.D.
Chief, Division of Immunotherapy
Northwestern University
Feinberg School of Medicine
446 East Ontario Street, Suite 1000
Chicago, Illinois 60611

Dear Dr. Burt:

This Warning Letter informs you of objectionable conditions observed during a Food and Drug Administration (FDA) inspection conducted between June 17, 2016, and July 11, 2016. FDA investigators met with you during the inspection to review your conduct as a sponsor and clinical investigator of the following clinical studies:

- Ship IP only to investigators participating in the investigation.

Once an investigator is added to the study, the IP may be shipped and the investigator may begin participating in the study. The sponsor must notify FDA of the new investigator within 30 days

2. You failed to submit a protocol amendment to FDA when there was a significant change in protocol design. [21 CFR § 312.30(b)(1)(ii) and 312.30(b)(2)(i)(*a*).] Further, you failed to submit a protocol amendment to FDA when new investigators were added to carry out a previously submitted protocol within 30 days of the investigators being added. [21 CFR § 312.30(c).]

A. You failed to submit a protocol amendment within 30 days of adding the following five clinical investigators at four investigational sites to the **(b)(4)** Protocol:

- Dr. J.S. (Canada Site 102) who enrolled 2 subjects between 2009 and 2010.
- Dr. J.V. and Dr. C.O. (Brazil Site 103) who enrolled 3 subjects between 2009 and 2014.
- Dr. J.B. (Sweden Site 104) who enrolled 14 subjects between 2011 and 2016.
- Dr. B.S. (United Kingdom Site 105) who enrolled 11 subjects between 2014 and 2016.

During the inspection, we found that you prepared new protocol versions when you added new investigators; however you failed to submit these protocol amendments to FDA.

Version Number	Version Date	Investigator Addition
7	6/25/07	Added clinical investigators from two new sites, Brazil and Canada
15	12/11/13	Added clinical investigator from two new sites, Sweden and the United Kingdom
17	9/25/14	New clinical investigator in Brazil

Your response letter states that you submitted a Form FDA 1572 and curriculum vitae for the investigators at the current enrolling sites to FDA on July 12, 2016. Your response is not acceptable because you did not indicate that you have put a corrective action plan in place to prevent similar violations in the future.

As a sponsor we must have IP accountability to protect patient safety.

IP- Good Manufacturing Practices (GMP)

Ensure IP is manufactured in accordance with GMP.

The IP must be coded and labelled in a manner that complies with the applicable regulatory requirements

As a sponsor we have to ensure subject safety and data quality by ensure potency, purity and identity of our IP.

IP- Good Manufacturing Practices (GMP)

Ensure IP is manufactured in accordance with GMP.

The IP must be coded and labelled in a manner that complies with the applicable regulatory requirements

As a sponsor we have to ensure subject safety and data quality by ensure potency, purity and identity of our IP.

Warning Letter

WL: 320-15-11

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

June 22, 2015

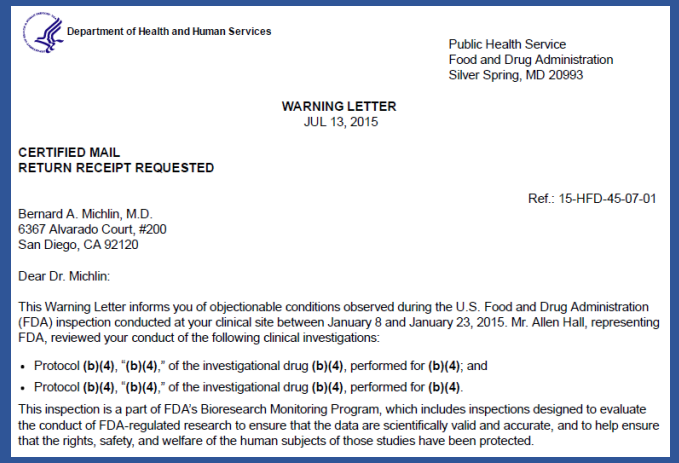
Mr. Syveon D. Liu
CEO & Owner
Attix Pharmaceuticals
184 Front St. East, Unit 801
Toronto, ON, M5A 4N3
Canada

Dear Mr. Liu:

We inspected your pharmaceutical manufacturing (repackaging) facility, Attix Pharmaceuticals, 184 Front St. East, Unit 801, Toronto, Ontario, Canada, from November 10, 2014, through November 14, 2014. Our investigator from the U.S. Food and Drug Administration (FDA) identified significant deviations from current good manufacturing practice (CGMP) for the manufacture of active pharmaceutical ingredients (APIs).

These deviations cause your APIs to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. 351(a)(2)(B), in that the methods used in, or the facilities or controls used for, their manufacture, processing, packing, or holding do not conform to, or are not operated or

Ensuring that the investigation is conducted in accordance with the general investigational plan/protocol



Department of Health and Human Services

Public Health Service
Food and Drug Administration
Silver Spring, MD 20993

WARNING LETTER
JUL 13, 2015

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Ref.: 15-HFD-45-07-01

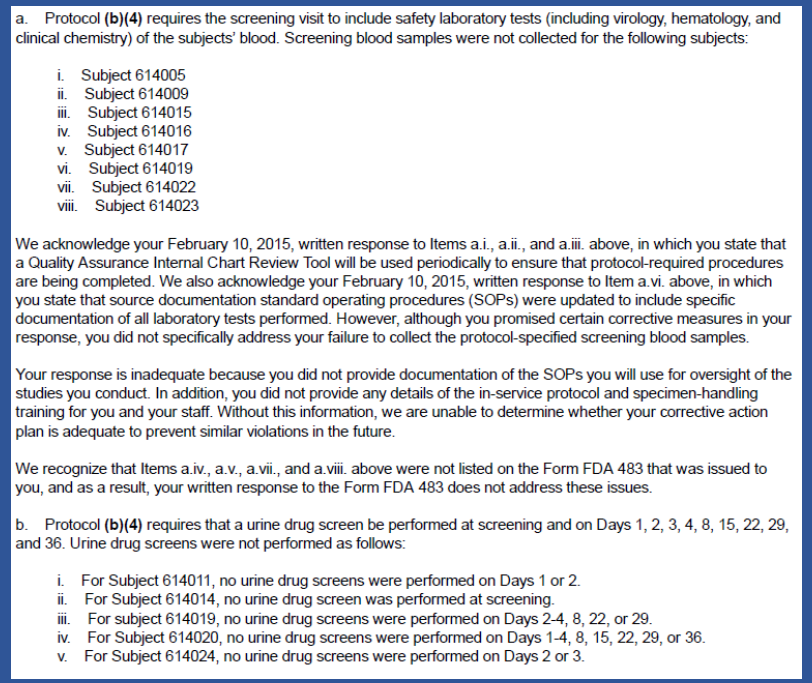
Bernard A. Michlin, M.D.
6367 Alvarado Court, #200
San Diego, CA 92120

Dear Dr. Michlin:

This Warning Letter informs you of objectionable conditions observed during the U.S. Food and Drug Administration (FDA) inspection conducted at your clinical site between January 8 and January 23, 2015. Mr. Allen Hall, representing FDA, reviewed your conduct of the following clinical investigations:

- Protocol **(b)(4)**, "**(b)(4)**," of the investigational drug **(b)(4)**, performed for **(b)(4)**; and
- Protocol **(b)(4)**, "**(b)(4)**," of the investigational drug **(b)(4)**, performed for **(b)(4)**.

This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of FDA-regulated research to ensure that the data are scientifically valid and accurate, and to help ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.



a. Protocol **(b)(4)** requires the screening visit to include safety laboratory tests (including virology, hematology, and clinical chemistry) of the subjects' blood. Screening blood samples were not collected for the following subjects:

i. Subject 614005
ii. Subject 614009
iii. Subject 614015
iv. Subject 614016
v. Subject 614017
vi. Subject 614019
vii. Subject 614022
viii. Subject 614023

We acknowledge your February 10, 2015, written response to Items a.i., a.ii., and a.iii. above, in which you state that a Quality Assurance Internal Chart Review Tool will be used periodically to ensure that protocol-required procedures are being completed. We also acknowledge your February 10, 2015, written response to Item a.vi. above, in which you state that source documentation standard operating procedures (SOPs) were updated to include specific documentation of all laboratory tests performed. However, although you promised certain corrective measures in your response, you did not specifically address your failure to collect the protocol-specified screening blood samples.

Your response is inadequate because you did not provide documentation of the SOPs you will use for oversight of the studies you conduct. In addition, you did not provide any details of the in-service protocol and specimen-handling training for you and your staff. Without this information, we are unable to determine whether your corrective action plan is adequate to prevent similar violations in the future.

We recognize that Items a.iv., a.v., a.vii., and a.viii. above were not listed on the Form FDA 483 that was issued to you, and as a result, your written response to the Form FDA 483 does not address these issues.

b. Protocol **(b)(4)** requires that a urine drug screen be performed at screening and on Days 1, 2, 3, 4, 8, 15, 22, 29, and 36. Urine drug screens were not performed as follows:

i. For Subject 614011, no urine drug screens were performed on Days 1 or 2.
ii. For Subject 614014, no urine drug screen was performed at screening.
iii. For subject 614019, no urine drug screens were performed on Days 2-4, 8, 22, or 29.
iv. For Subject 614020, no urine drug screens were performed on Days 1-4, 8, 15, 22, 29, or 36.
v. For Subject 614024, no urine drug screens were performed on Days 2 or 3.

One of the most common reasons for a clinical investigator to get a warning letter is not following the investigational plan.

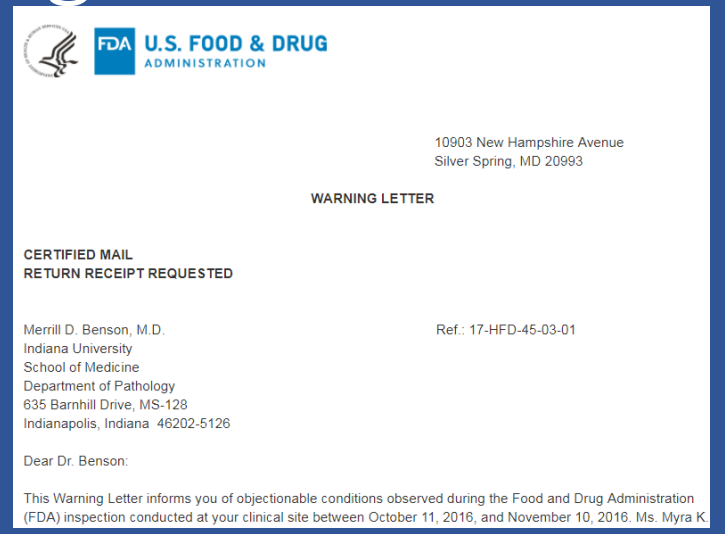
Ultimately, the sponsor is responsible for ensure an investigator is following the plan and bringing the investigator into compliance if they are not.

Ensuring that the investigation is conducted in accordance with the general investigational plan/protocol

Single Subject Exceptions are Not Following the Investigational Plan…

- **Eligibility criteria maintain safety of our patients and integrity of our data**

- **FDA does not embrace eligibility exceptions.**
  - Example Guidance from FDA:
    - **Protocol Read:** "Adequate pulmonary function with FEV1, FVC and DLCO >50% of expected corrected for hemoglobin. Exceptions may be allowed for patients with pulmonary involvement after discussing with the PI."
    - **FDA Response:** "Section 4.3.10 describes **intent to violate the protocol by enrolling ineligible patients.** This language should not appear in the protocol as it is not compliant with Good Clinical Practice."



U.S. FOOD & DRUG ADMINISTRATION

10903 New Hampshire Avenue
Silver Spring, MD 20993

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Merrill D. Benson, M.D.
Indiana University
School of Medicine
Department of Pathology
635 Barnhill Drive, MS-128
Indianapolis, Indiana 46202-5126

Ref.: 17-HFD-45-03-01

Dear Dr. Benson:

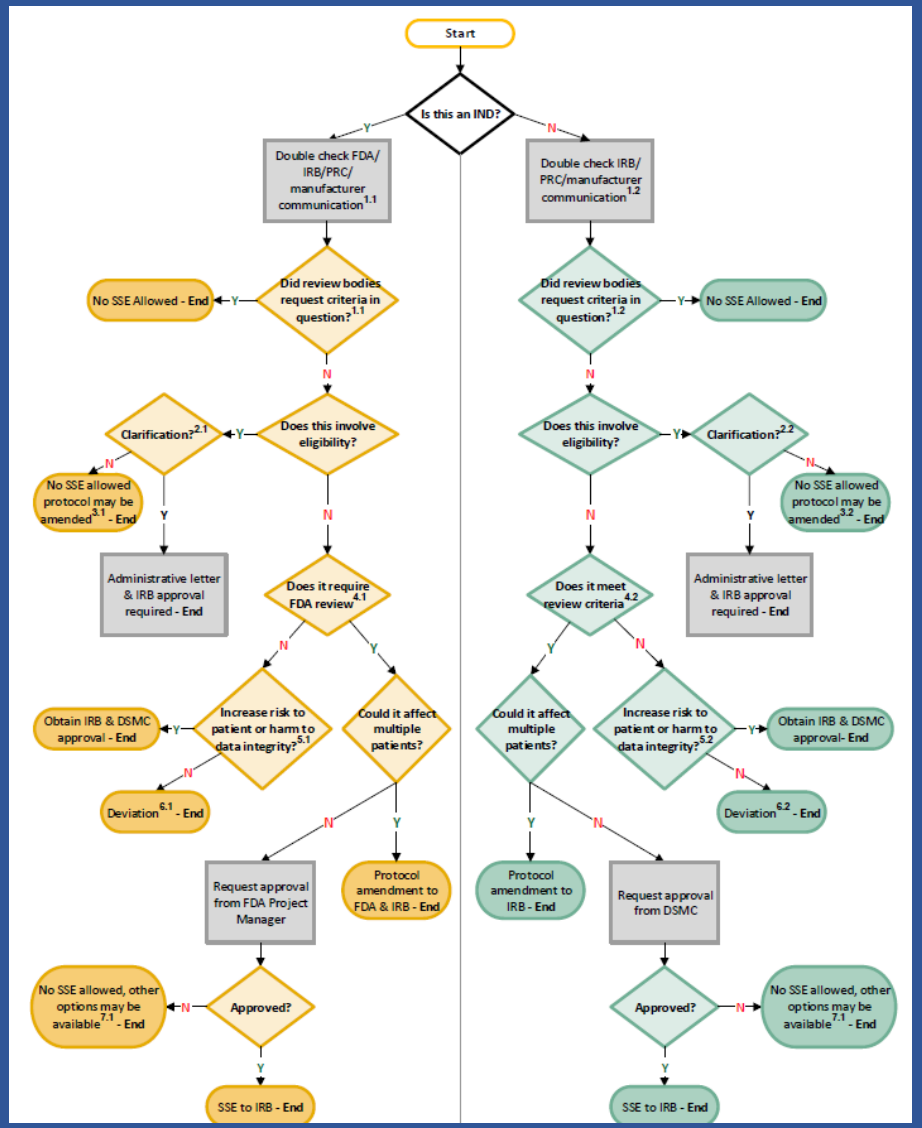
This Warning Letter informs you of objectionable conditions observed during the Food and Drug Administration (FDA) inspection conducted at your clinical site between October 11, 2016, and November 10, 2016. Ms. Myra K

"You failed to ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60].

…the investigational plan for Protocol (b)(4) requires you not to enroll subjects who meet the exclusion criteria. You failed to adhere to these requirements.

The investigational plan required you to exclude subjects with renal insufficiency…You enrolled subject CM 04 into Protocol (b)(4) on December 19, 2014, even though this subject had a history of renal insufficiently…In your…written response…you acknowledge that this subject…did not meet eligibility requirements…You also indicate that you made an exception to this exclusion criterion and enrolled this subject because…you were aware that the subject was followed by a nephrologist for renal insufficiency…and that laboratory tests indicated that the subject's renal function had been stable for more than 1 year before the subject entered the study…We emphasize that the eligibility criteria for each clinical investigation are designed both to optimize interpretability of collected data, and to minimize foreseeable harm to enrolled subjects. Enrollment of subjects who do not meet the eligibility criteria jeopardizes subject safety and welfare, and raises concerns about the validity and integrity of the data collected at your site."

Ensuring that the investigation is conducted in accordance with the general investigational plan/protocol



LCCC Single Subject Exception Policy

- IITs
  - No Eligibility SSEs allowed
  - Others may be allowed if you follow proper regulatory review→ use the decision tree
  - Suggestions to place SSEs:
    - Compassionate Use IND
    - Protocol Amendment
    - Administrative Letter

Ensuring proper monitoring of investigation(s)

What is monitoring?

- The act of **overseeing the progress of** a clinical trial, and of ensuring that it is conducted, recorded and reported in accordance with the protocol, SOPs, GCP and applicable regulatory requirements.
- **Continuous**
- **Risk-Based**
- Includes:
  - Precise tracking of patient accrual
  - Ongoing assessment of patient eligibility and evaluability
  - Adequate measures to ensure timely submission of study data
  - Adequate measures to ensure timely medical review and assessment of individual patient data
  - Timely reporting of adverse events

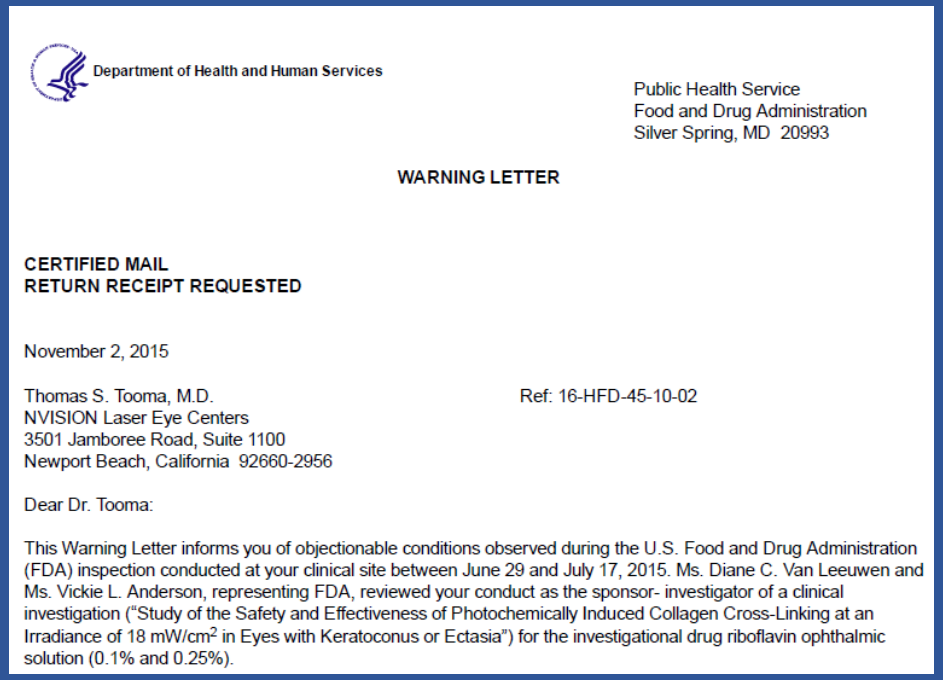
*"Monitoring is **not optional**. Required by 21 CFR 312.50.*

- *Responsibilities of sponsors*
- *Selecting monitors qualified by training and experience (21 CFR 312.53(d))*
- *Monitor the ongoing investigations (21 CFR 312.56)*
- *Ensure proper monitoring (21 CFR 812.40)"*

Ensuring proper monitoring of investigation(s)

Why do you need to monitor?

- How can you tell if you are guaranteeing subject safety if you don't double check?
- How can you tell if the data are reliable if you don't double check that it is accurate?
  - If data coming out of the study are not reliable is it worth the risk to give the IP to additional subject?
- Are their trends across multiple sites?
- How can you improve the process?
  - Re-education?
  - Protocol Amendment?
  - Administrative Letter?
- To FDA data not collected (no matter what the reason) are missing data.
- Monitoring Plans help identify critical values upfront.



Department of Health and Human Services

Public Health Service
Food and Drug Administration
Silver Spring, MD 20993

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

November 2, 2015

Thomas S. Tooma, M.D.
NVISION Laser Eye Centers
3501 Jamboree Road, Suite 1100
Newport Beach, California 92660-2956

Ref: 16-HFD-45-10-02

Dear Dr. Tooma:

This Warning Letter informs you of objectionable conditions observed during the U.S. Food and Drug Administration (FDA) inspection conducted at your clinical site between June 29 and July 17, 2015. Ms. Diane C. Van Leeuwen and Ms. Vickie L. Anderson, representing FDA, reviewed your conduct as the sponsor- investigator of a clinical investigation ("Study of the Safety and Effectiveness of Photochemically Induced Collagen Cross-Linking at an Irradiance of 18 mW/cm^2 in Eyes with Keratoconus or Ectasia") for the investigational drug riboflavin ophthalmic solution (0.1% and 0.25%).

2. You failed to ensure proper monitoring of the clinical investigations [21 CFR 312.50 and 312.56(a)].

FDA regulations require that sponsors ensure proper monitoring of clinical investigations, and ensure that their clinical investigators conduct the investigations in accordance with the general investigational plan and protocols contained in the IND. Our investigation found that you failed to ensure proper monitoring of the inspected study. The records associated with the inspected study do not indicate that proper monitoring was performed.

In your August 4, 2015, written response to the Form FDA 483, you acknowledged that you depended on the surgeons to conduct the trial according to protocol, and that you did not have a monitor for this study. In addition, you acknowledged that you were not aware of all that was required of you as a sponsor.

Ensuring proper monitoring of investigation(s)

Why do you need to monitor?

- How can you tell if you are guaranteeing subject safety if you don't double check?
- How can you tell if the data are reliable if you don't double check that it is accurate?
  - If data coming out of the study are not reliable is it worth the risk to give the IP to additional subject?
- Are their trends across multiple sites?
- How can you improve the process?
  - Re-education?
  - Protocol Amendment?
  - Administrative Letter?
- To FDA data not collected (no matter what the reason) are missing data.
- Monitoring Plans help identify critical values upfront.

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Ref: 15-HFD-45-06-01

Alain Moussy
Chief Executive Officer
AB Science
3 Avenue George V
Paris, France

Dear Mr. Moussy:

Failure to ensure proper monitoring of the investigations and failure to ensure that the investigations are conducted in accordance with the general investigational plan and protocols contained in the IND [21 CFR 312.50 and 312.56(a)].

a. Your monitoring failed to identify and correct clinical investigators' failure to report SAEs within protocol-specified timeframes.

The following SAEs were not reported within 24 hours of the occurrence or the investigator's knowledge of the event in accordance with the protocol, and were not identified by the monitor in monitoring visit reports:

i. Subject 03102 in Protocol **(b)(4)** experienced thrombocytopenia on May 4, 2009, but the site did not report the thrombocytopenia to the sponsor on an SAE form until April 30, 2013.

ii. Subject 03111 in Protocol **(b)(4)** experienced leukopenia and neutropenia on June 8, 2010, but the site did not report the leukopenia and neutropenia to the sponsor on an SAE form until May 2, 2013.

b. Your monitoring failed to identify and correct a clinical investigator's failure to perform protocol-required laboratory tests.

The following protocol-required hematologic laboratory tests were not performed and were not identified by the monitor during monitoring visits:

1) Week 1 for Subjects 033-008-01 and 033-008-02
2) Week 5 for Subject 033-008-05
3) Week 6 for Subject 033-008-05
4) Week 7 for Subject 033-008-05

Ensuring proper monitoring of investigation(s)

Why do you need to monitor?

- How can you tell if you are guaranteeing subject safety if you don't double check?
- How can you tell if the data are reliable if you don't double check that it is accurate?
  - If data coming out of the study are not reliable is it worth the risk to give the IP to additional subject?
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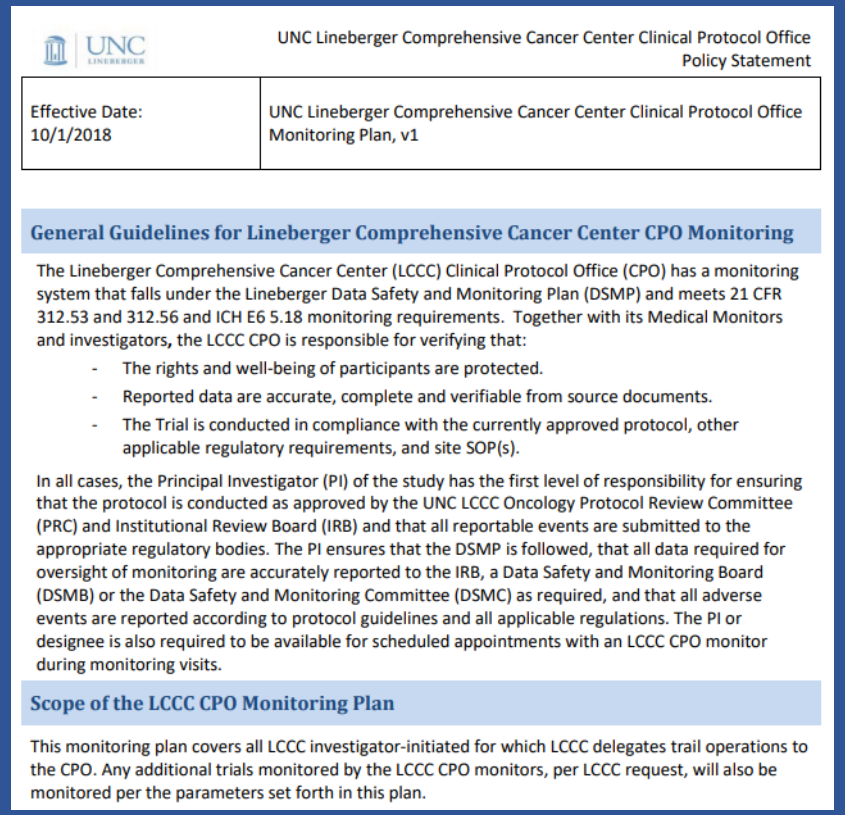


UNC Lineberger Comprehensive Cancer Center Clinical Protocol Office
Policy Statement

Effective Date: 10/1/2018	UNC Lineberger Comprehensive Cancer Center Clinical Protocol Office Monitoring Plan, v1

General Guidelines for Lineberger Comprehensive Cancer Center CPO Monitoring

The Lineberger Comprehensive Cancer Center (LCCC) Clinical Protocol Office (CPO) has a monitoring system that falls under the Lineberger Data Safety and Monitoring Plan (DSMP) and meets 21 CFR 312.53 and 312.56 and ICH E6 5.18 monitoring requirements. Together with its Medical Monitors and investigators, the LCCC CPO is responsible for verifying that:

- The rights and well-being of participants are protected.
- Reported data are accurate, complete and verifiable from source documents.
- The Trial is conducted in compliance with the currently approved protocol, other applicable regulatory requirements, and site SOP(s).

In all cases, the Principal Investigator (PI) of the study has the first level of responsibility for ensuring that the protocol is conducted as approved by the UNC LCCC Oncology Protocol Review Committee (PRC) and Institutional Review Board (IRB) and that all reportable events are submitted to the appropriate regulatory bodies. The PI ensures that the DSMP is followed, that all data required for oversight of monitoring are accurately reported to the IRB, a Data Safety and Monitoring Board (DSMB) or the Data Safety and Monitoring Committee (DSMC) as required, and that all adverse events are reported according to protocol guidelines and all applicable regulations. The PI or designee is also required to be available for scheduled appointments with an LCCC CPO monitor during monitoring visits.

Scope of the LCCC CPO Monitoring Plan

This monitoring plan covers all LCCC investigator-initiated for which LCCC delegates trail operations to the CPO. Any additional trials monitored by the LCCC CPO monitors, per LCCC request, will also be monitored per the parameters set forth in this plan.

Monitoring protects patient safety and data quality.

Remember as a sponsor we are responsible for the trial as a whole across all sites.

Data Quality Monitoring

- Review clinical data programmatically and manually
- AE data review according to DSMC and FDA report/review schedules
- Queries issued and monitored for resolution

Data resources, June 2016

	OnCore Demographic				ss_001v21 form		
SeqNum	Hospital	Status	FU Death Date	Off Study Date	Survival Status	Death Date	Cause of Death
101	UNC-CH	EXPIRED	3/27/2013	2/17/2013		.	
102	UNC-CH	EXPIRED	7/17/2015	7/17/2015		.	

Data resources: AdverseEvent2V21 form

SeqNum	Hospital	Toxicity	Cycle of Onset	Grade	Onset Date	Attribution	Serious
101	UNC-CH	Back Pain	.	1	12/12/2015	Unrelated	No
104	UNC-CH	Dyspnea	.	1	7/1/2013	Probable	No
104	UNC-CH	Lymphocyte Count Decreased	20	1	5/17/2014	Possible	
107	UNC-CH	White Blood Cell Decreased	2	1	.	Probable	No
109	UNC-CH	Hypocalcemia	.	1	6/22/2013	Unrelated	No

Auditing

Why to we audit/what is the difference between auditing and monitoring?

- **Defined as:** A **systematic** and **independent** examination of trial-related activities and documents to determine whether the evaluated trial-related activities are conducted, and the data were recorded, analyzed, and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), GCP, and the applicable regulatory requirement(s).
- **More comprehensive-** monitoring is a snap shot of data (for example: first or second patient where audit at random)
- Typically monitors are employed by the sponsor where auditors get to **look from the outside**
- Auditors **look at the sponsor**
- No personal relationships, **unbiased approach**, identify holes
- Monitor maintenance, audit **deep dive**
- Part of the auditing is to make sure the monitoring is working
- Required per Good Clinical Practices (GCP)

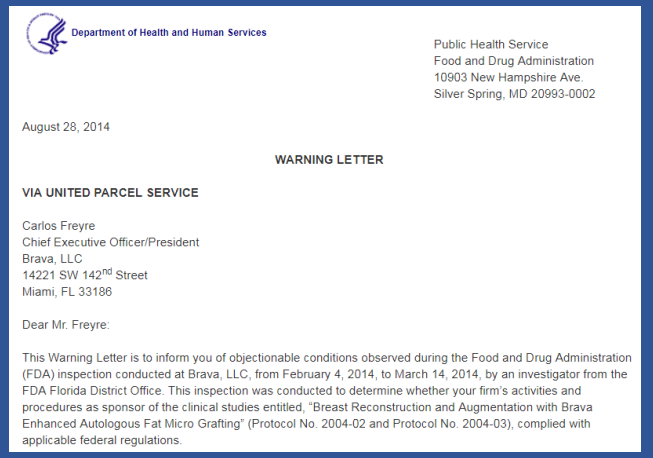
UNC has resources to help you:

https://research.unc.edu/clinical-trials/ctqa/

Discontinue shipment of IP to Noncompliant Sites

- Deviation at any site is a deviation on the clinical trial
- Deviations are cumulative
- Sponsor responsible for oversight of all sites
- Need to monitor they compliance and whether the sponsor need to re-educate the site
- If a site can not be brought into compliance it is the sponsor's responsibility to **stop** the site's participation—**Otherwise the sites continued noncompliance is also the sponsor's**

"A sponsor who discovers that an investigator is not complying with the signed agreement (Form FDA-1572), the general investigational plan, or the requirements of this part or other applicable parts shall promptly either secure compliance or discontinue shipments of the investigational new drug to the investigator and end the investigator's participation in the investigation. If the investigator's participation in the investigation is ended, the sponsor shall require that the investigator dispose of or return the investigational drug in accordance with the requirements of 312.59 and shall notify FDA."



Department of Health and Human Services

Public Health Service
Food and Drug Administration
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002

August 28, 2014

WARNING LETTER

VIA UNITED PARCEL SERVICE

Carlos Freyre
Chief Executive Officer/President
Brava, LLC
14221 SW 142nd Street
Miami, FL 33186

Dear Mr. Freyre:

This Warning Letter is to inform you of objectionable conditions observed during the Food and Drug Administration (FDA) inspection conducted at Brava, LLC, from February 4, 2014, to March 14, 2014, by an investigator from the FDA Florida District Office. This inspection was conducted to determine whether your firm's activities and procedures as sponsor of the clinical studies entitled, "Breast Reconstruction and Augmentation with Brava Enhanced Autologous Fat Micro Grafting" (Protocol No. 2004-02 and Protocol No. 2004-03), complied with applicable federal regulations.

1. Failure to ensure proper monitoring of the investigation and to promptly inform the IRB and FDA of significant new information about an investigation. [21 CFR 812.40 and 21 CFR 812.46(a)]

A sponsor is responsible for ensuring proper monitoring of the investigation, and that all clinical investigators participating in the investigation adhere to the signed agreement, the investigational plan, applicable FDA regulations, and any other conditions of approval imposed by the reviewing Institutional Review Board (IRB) or FDA. Our review of the inspection report revealed that your firm failed to take appropriate steps to ensure proper monitoring of the above-listed study. Your firm's lack of monitoring resulted in failure to detect the following:

a. Several clinical investigators, including Dr. **(b)(4)** and Dr. **(b)(4)**, did not obtain informed consent from study participants prior to enrollment in the clinical study or failed to obtain informed consent altogether.

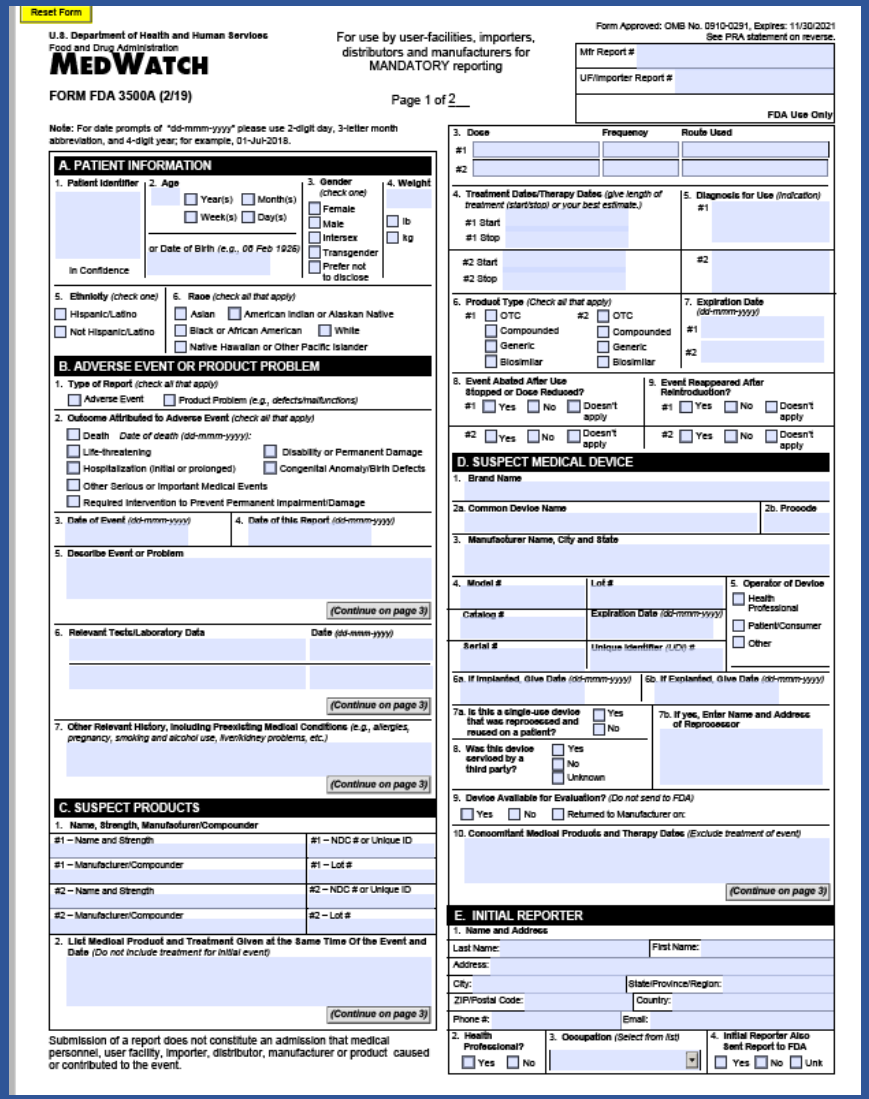
b. Active study participants were not re-consented with the latest IRB-approved informed consent form, dated June 13, 2013. This revised version included information to inform study participants that FDA regulates the Brava system when it is used in conjunction with fat grafting.

A sponsor who discovers that an investigator is not complying with federal regulations shall promptly either secure compliance or discontinue shipments of the device to the investigator and terminate the investigator's participation in the investigation.

Review and evaluate drug safety and effectiveness data

What Kind of Data?

1. Clinical Data



Reset Form

U.S. Department of Health and Human Services
Food and Drug Administration

MEDWATCH

FORM FDA 3500A (2/19)

For use by user-facilities, importers, distributors and manufacturers for MANDATORY reporting

Page 1 of 2

Form Approved: OMB No. 0910-0291, Expires: 11/30/2021
See PRA statement on reverse.

Mfr Report #
UF/Importer Report #
FDA Use Only

Note: For date prompts of "dd-mmm-yyyy" please use 2-digit day, 3-letter month abbreviation, and 4-digit year; for example, 01-Jul-2018.

A. PATIENT INFORMATION

1. Patient Identifier — In Confidence
2. Age — Year(s) Month(s) Week(s) Day(s) or Date of Birth (e.g., 06 Feb 1926)
3. Gender (check one) — Female, Male, Intersex, Transgender, Prefer not to disclose
4. Weight — lb, kg
5. Ethnicity (check one) — Hispanic/Latino, Not Hispanic/Latino
6. Race (check all that apply) — Asian, American Indian or Alaskan Native, Black or African American, White, Native Hawaiian or Other Pacific Islander

B. ADVERSE EVENT OR PRODUCT PROBLEM

1. Type of Report (check all that apply) — Adverse Event, Product Problem (e.g., defects/malfunctions)
2. Outcome Attributed to Adverse Event (check all that apply) — Death Date of death (dd-mmm-yyyy): Life-threatening, Hospitalization (initial or prolonged), Other Serious or Important Medical Events, Required Intervention to Prevent Permanent Impairment/Damage, Disability or Permanent Damage, Congenital Anomaly/Birth Defects
3. Date of Event (dd-mmm-yyyy)
4. Date of this Report (dd-mmm-yyyy)
5. Describe Event or Problem — (Continue on page 3)
6. Relevant Tests/Laboratory Data — Date (dd-mmm-yyyy) — (Continue on page 3)
7. Other Relevant History, Including Preexisting Medical Conditions (e.g., allergies, pregnancy, smoking and alcohol use, liver/kidney problems, etc.) — (Continue on page 3)

C. SUSPECT PRODUCTS

1. Name, Strength, Manufacturer/Compounder
   - #1 – Name and Strength
   - #1 – NDC # or Unique ID
   - #1 – Manufacturer/Compounder
   - #1 – Lot #
   - #2 – Name and Strength
   - #2 – NDC # or Unique ID
   - #2 – Manufacturer/Compounder
   - #2 – Lot #
2. List Medical Product and Treatment Given at the Same Time Of the Event and Date (Do not include treatment for initial event) — (Continue on page 3)

Submission of a report does not constitute an admission that medical personnel, user facility, importer, distributor, manufacturer or product caused or contributed to the event.

3. Dose — Frequency — Route Used — #1, #2
4. Treatment Dates/Therapy Dates (give length of treatment (start/stop) or your best estimate.) — #1 Start, #1 Stop, #2 Start, #2 Stop
5. Diagnosis for Use (Indication) — #1, #2
6. Product Type (Check all that apply) — #1 OTC, Compounded, Generic, Biosimilar; #2 OTC, Compounded, Generic, Biosimilar
7. Expiration Date (dd-mmm-yyyy) — #1, #2
8. Event Abated After Use Stopped or Dose Reduced? — #1 Yes No Doesn't apply; #2 Yes No Doesn't apply
9. Event Reappeared After Reintroduction? — #1 Yes No Doesn't apply; #2 Yes No Doesn't apply

D. SUSPECT MEDICAL DEVICE

1. Brand Name
2a. Common Device Name — 2b. Procode
3. Manufacturer Name, City and State
4. Model # — Lot # — Catalog # — Expiration Date (dd-mmm-yyyy) — Serial # — Unique Identifier (UDI) #
5. Operator of Device — Health Professional, Patient/Consumer, Other
6a. If Implanted, Give Date (dd-mmm-yyyy) — 6b. If Explanted, Give Date (dd-mmm-yyyy)
7a. Is this a single-use device that was reprocessed and reused on a patient? — Yes No
7b. If yes, Enter Name and Address of Reprocessor
8. Was this device serviced by a third party? — Yes No Unknown
9. Device Available for Evaluation? (Do not send to FDA) — Yes No Returned to Manufacturer on:
10. Concomitant Medical Products and Therapy Dates (Exclude treatment of event) — (Continue on page 3)

E. INITIAL REPORTER

1. Name and Address — Last Name: First Name: Address: City: State/Province/Region: ZIP/Postal Code: Country: Phone #: Email:
2. Health Professional? — Yes No
3. Occupation (Select from list)
4. Initial Reporter Also Sent Report to FDA — Yes No Unk

Review and evaluate drug safety and effectiveness data

What Kind of Data?

1. Clinical Data
2. Reporting from Other Studies

Juno Therapeutics Reports Clinical Hold on the JCAR015 Phase II ROCKET Trial

July 07, 2016 04:05 PM Eastern Daylight Time

SEATTLE--(BUSINESS WIRE)--Juno Therapeutics, Inc. (NASDAQ:JUNO), a biopharmaceutical company focused on re-engaging the body's immune system to revolutionize the treatment of cancer, today announced that it has received notice from the U.S. Food and Drug Administration (FDA) that a clinical hold has been placed on the Phase II clinical trial of JCAR015 in adult patients with relapsed or refractory B cell acute lymphoblastic leukemia (r/r ALL), known as the "ROCKET" trial. The clinical hold was initiated after two patient deaths last week, which followed the recent addition of fludarabine to the pre-conditioning regimen.

Juno has proposed to the FDA to continue the ROCKET trial using JCAR015 with cyclophosphamide pre-conditioning alone. In response, the FDA has requested that Juno submit, as a Complete Response to the Clinical Hold: a revised patient informed consent form, a revised investigator brochure, a revised trial protocol, and a copy of the presentation made to the agency yesterday. Juno will submit the requested information to the FDA this week.

Juno's trials and plans for its other CD19-directed CAR-T cell product candidates, including JCAR017, are not affected.

Re: Cases of Acute Kidney Injury and Myelosuppression reported for NAME given in combination with NAME and NAME

This report describes the results of an aggregate analysis of serious suspected adverse reactions occurring in patients enrolled on clinical trial *LCCC XXXX*.These serious suspected adverse reactions include:

- Acute Kidney Injury (AKI)
- Myelosuppression

A review of the Investigators' Brochure for NAME (Edition 13) revealed that neutropenia, leukopenia, thrombocytopenia, lymphopenia and eosinophilia are uncommon adverse events. Additionally, increased serum creatinine is a common investigational finding.

The Prescribing Information (2017) for NAME lists myelosuppression including neutropenia, thrombocytopenia, and anemia as common adverse events. The Prescribing Information for NAME lists cumulative renal toxicity and dose related myelosuppression as warnings for use of NAME.

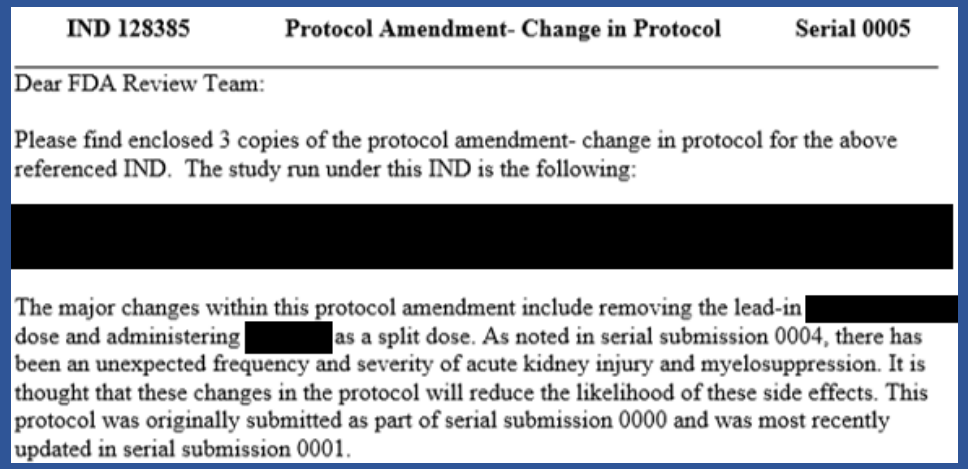
Recently (starting April 10, 2017), three patients discontinued/had delayed study treatment per the LCCC XXXX protocol due to AKI and/or myelosuppression. These events led to an aggregate analysis of the adverse reactions experienced by all subjects enrolled on the study. This review indicated that AKI was occurring at a greater than expected frequency in the enrolled subjects. Additionally, the review indicated that myelosuppression occurred at both a greater frequency and a greater severity than expected.

The analysis lead to the discovery that AKI and myelosuppression played a part in the discontinuation of treatment in 4 of 6 enrolled patients. 5 out of a total of 6 patients (83%) enrolled experienced AKI. 4 out of a total of 6 patients (67%) enrolled were hospitalized during protocol treatment (plus 1 additional patient was hospitalized due to complications after cystectomy). 4 out of the 6 patients (67%) experienced grade 3 or 4 myelosuppression. In summary, although AKI and myelosuppression are common and expected adverse events associated with combination therapy with NAME and NAME, the frequency of these toxicities in the first 6 patients enrolled on this study is higher than expected.

Review and evaluate drug safety and effectiveness data

What Kind of Data?

1. Clinical Data
2. Reporting from Other Studies
3. Aggregate Reporting
   - Sponsors should have a **systematic approach for safety surveillance**:
     - Process for reviewing, evaluating, and managing accumulating safety data
     - From the entire clinical trial database— **at the level of the IP** (meaning across studies)
     - At appropriate intervals



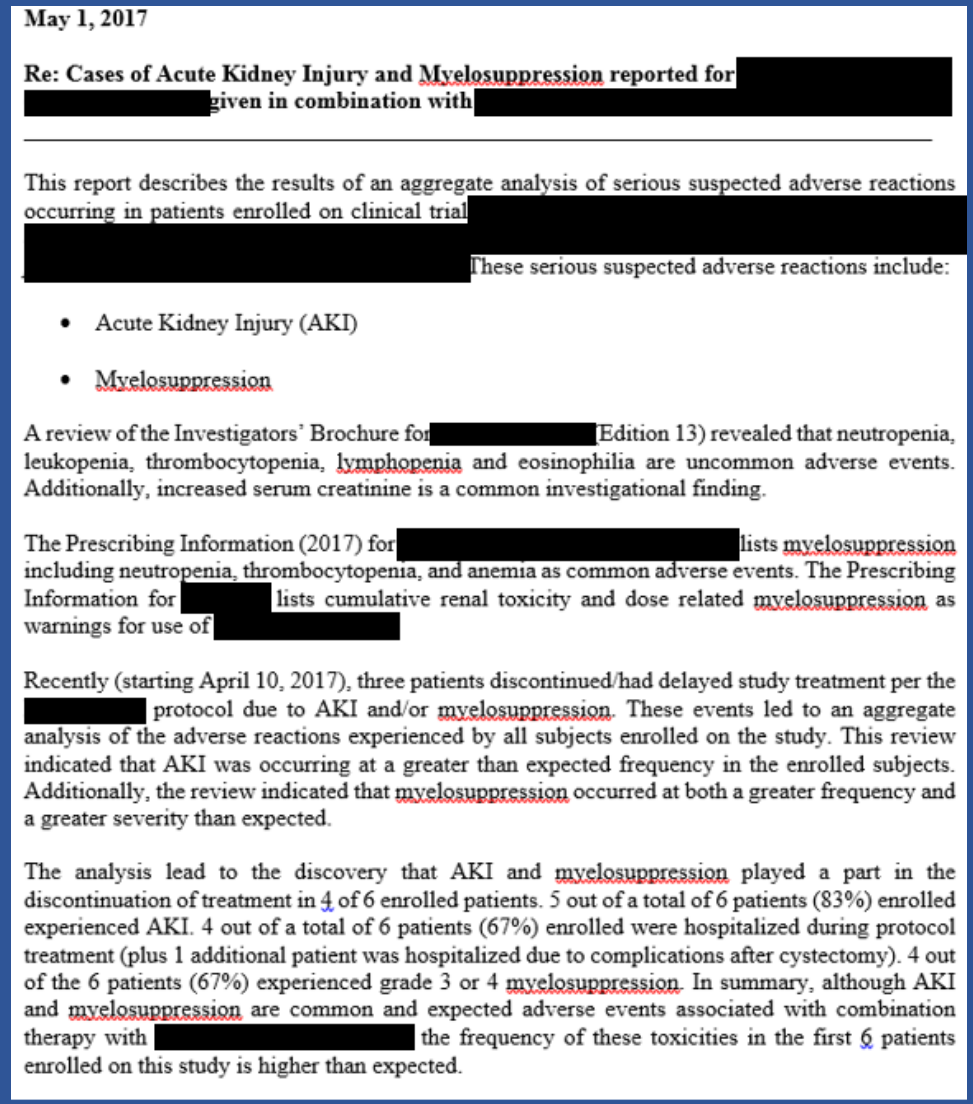
IND 128385 **Protocol Amendment- Change in Protocol** **Serial 0005**

Dear FDA Review Team:

Please find enclosed 3 copies of the protocol amendment- change in protocol for the above referenced IND. The study run under this IND is the following:

[redacted]

The major changes within this protocol amendment include removing the lead-in [redacted] dose and administering [redacted] as a split dose. As noted in serial submission 0004, there has been an unexpected frequency and severity of acute kidney injury and myelosuppression. It is thought that these changes in the protocol will reduce the likelihood of these side effects. This protocol was originally submitted as part of serial submission 0000 and was most recently updated in serial submission 0001.



May 1, 2017

Re: Cases of Acute Kidney Injury and Myelosuppression reported for [redacted] given in combination with [redacted]

This report describes the results of an aggregate analysis of serious suspected adverse reactions occurring in patients enrolled on clinical trial [redacted] These serious suspected adverse reactions include:

- Acute Kidney Injury (AKI)
- Myelosuppression

A review of the Investigators' Brochure for [redacted] Edition 13) revealed that neutropenia, leukopenia, thrombocytopenia, lymphopenia and eosinophilia are uncommon adverse events. Additionally, increased serum creatinine is a common investigational finding.

The Prescribing Information (2017) for [redacted] lists myelosuppression including neutropenia, thrombocytopenia, and anemia as common adverse events. The Prescribing Information for [redacted] lists cumulative renal toxicity and dose related myelosuppression as warnings for use of [redacted]

Recently (starting April 10, 2017), three patients discontinued/had delayed study treatment per the [redacted] protocol due to AKI and/or myelosuppression. These events led to an aggregate analysis of the adverse reactions experienced by all subjects enrolled on the study. This review indicated that AKI was occurring at a greater than expected frequency in the enrolled subjects. Additionally, the review indicated that myelosuppression occurred at both a greater frequency and a greater severity than expected.

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Review and evaluate drug safety and effectiveness data

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Overall Treatment-Related Toxicity
Frequency Table
By Toxicity

Toxicity	Count (%) N=21	Toxicity Grade 1	2	3	4
Abdominal Pain	1 (4.76%)	.	1	.	.
Agitation	1 (4.76%)	1	.	.	.
Alanine Aminotransferase Increased	1 (4.76%)	1	.	.	.
Alkaline Phosphatase Increased	2 (9.52%)	2	.	.	.

[redacted]

Incidence of Adverse Events with ALL ATTRIBUTIONS included
Incidence Defined as (# of Patients with Adverse Events) / (Total # of Patients at the Risk in Given Time)
Numerator = AE occurred from study began to 04/11/2016; Denominator = patients were treated from study began to 04/11/2016

Toxicity Category	Toxicity	Combined Count (%) N= 21	LCCC[redacted] Count (%) N= 6	LCCC[redacted] Count (%) N= 15
Gastrointestinal Disorders	Abdominal Pain	1 (4.76%)	1 (16.67%)	0(0)
	Anal Pain	1 (4.76%)	0(0)	1 (6.67%)
	Constipation	7 (33.33%)	1 (16.67%)	6 (40.00%)
	Diarrhea	4 (19.05%)	2 (33.33%)	2 (13.33%)
	Dry Mouth	1 (4.76%)	0(0)	1 (6.67%)
	Dyspepsia	1 (4.76%)	1 (16.67%)	0(0)
	Dysphagia	1 (4.76%)	0(0)	1 (6.67%)

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4. Pre-Clinical Findings
   - Findings in animal or *in vitro* testing that suggest significant risk in humans exposed to the drug
     - Mutagenicity
     - Teratogenicity
     - Carcinogenicity
     - Reports of significant organ toxicity at or near the expected human exposure
   - **Even if conducted by a different sponsor**

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Who is responsible for determining if the events are Related, Serious, Life-Threatening…etc.?

The Sponsor!!

The sponsor determines if the event is reportable to FDA for all sites.

Review and evaluate drug safety and effectiveness data

Who helps the sponsor with this review and the determinations?

1. Medical Monitor
2. Data Safety Monitoring Committee (DSMC)

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Review and evaluate drug safety and effectiveness data

Who helps the sponsor with this review and the determinations?

1. Medical Monitor
2. Data Safety Monitoring Committee (DSMC)

What then must the sponsor do?

1. Report to FDA
2. Notify all participating investigators
3. Confer with FDA to determine if an investigation should be discontinued
4. Determine if IP presents unreasonable risk, then notify FDA, IRBs and all investigators.

Who is responsible for determining if the events are Related, Serious, Life-Threatening…etc.?

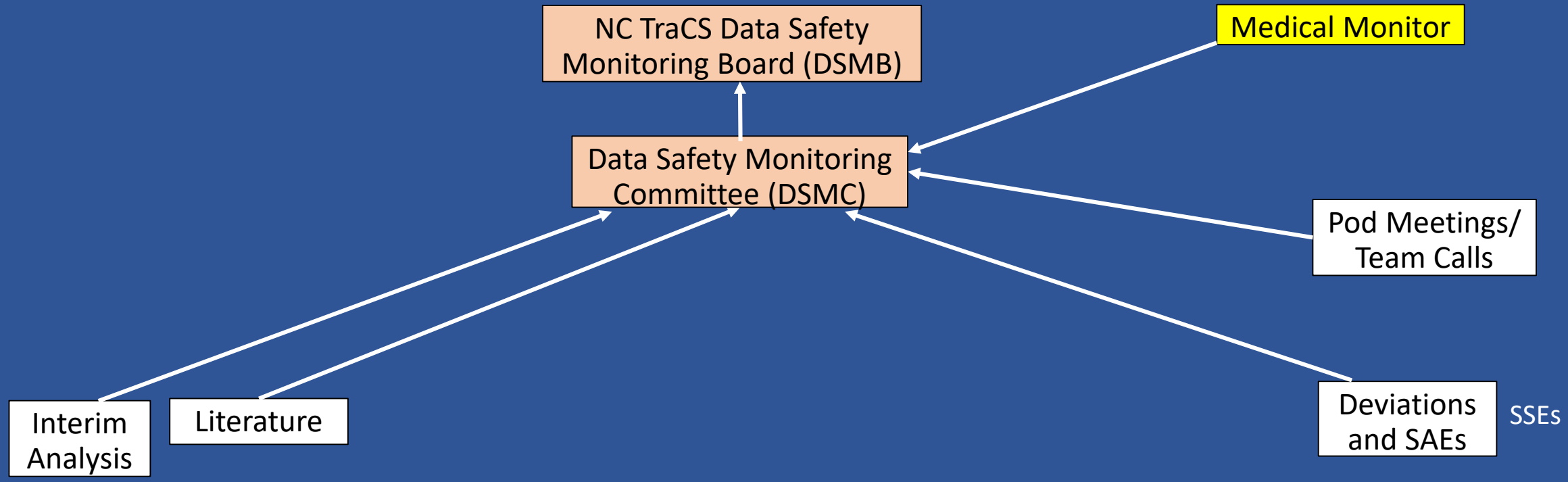
The Sponsor!!

The sponsor determines if the event is reportable to FDA for all sites.

Safety

- LCCC SOP-5 Action Letters
- LCCC SOP-13A and B LCCC IND Safety Reporting

Monitor the progress of all clinical investigations being conducted under its IND

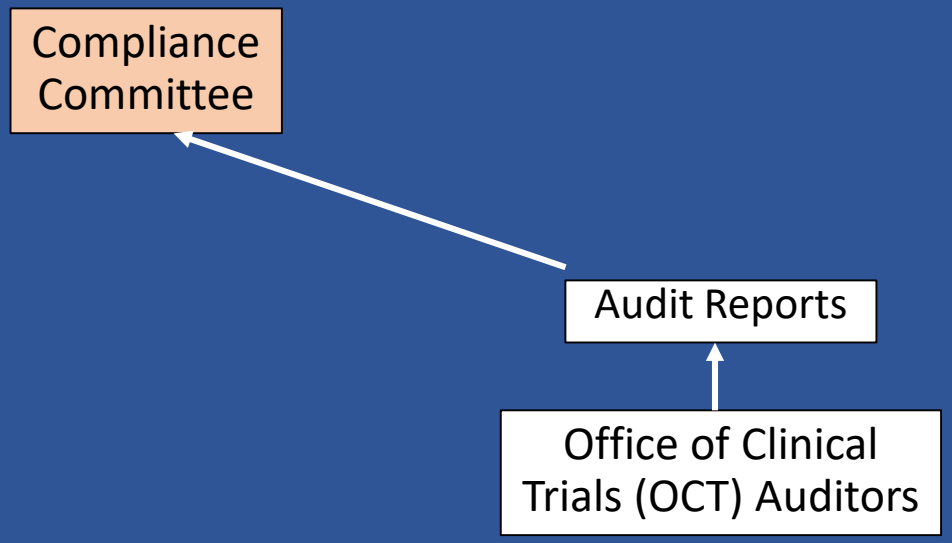


DSMC is the primary agent for assuring data and safety monitoring. Responsible for review of these trials.

- Has the authority to suspend research activities or to refer trials to the PRC or IRB for such actions.
- DSMC meets monthly, with ad hoc review and additional meetings called when necessary.

Duties defined in the LCCC DSMC Charter- Undergoing final formatting for finalization in Q1 2019

Monitor the progress of all clinical investigations being conducted under its IND



Compliance Committee

Audit IIT trials to:

- Authenticate compliance
- Capture accurate data

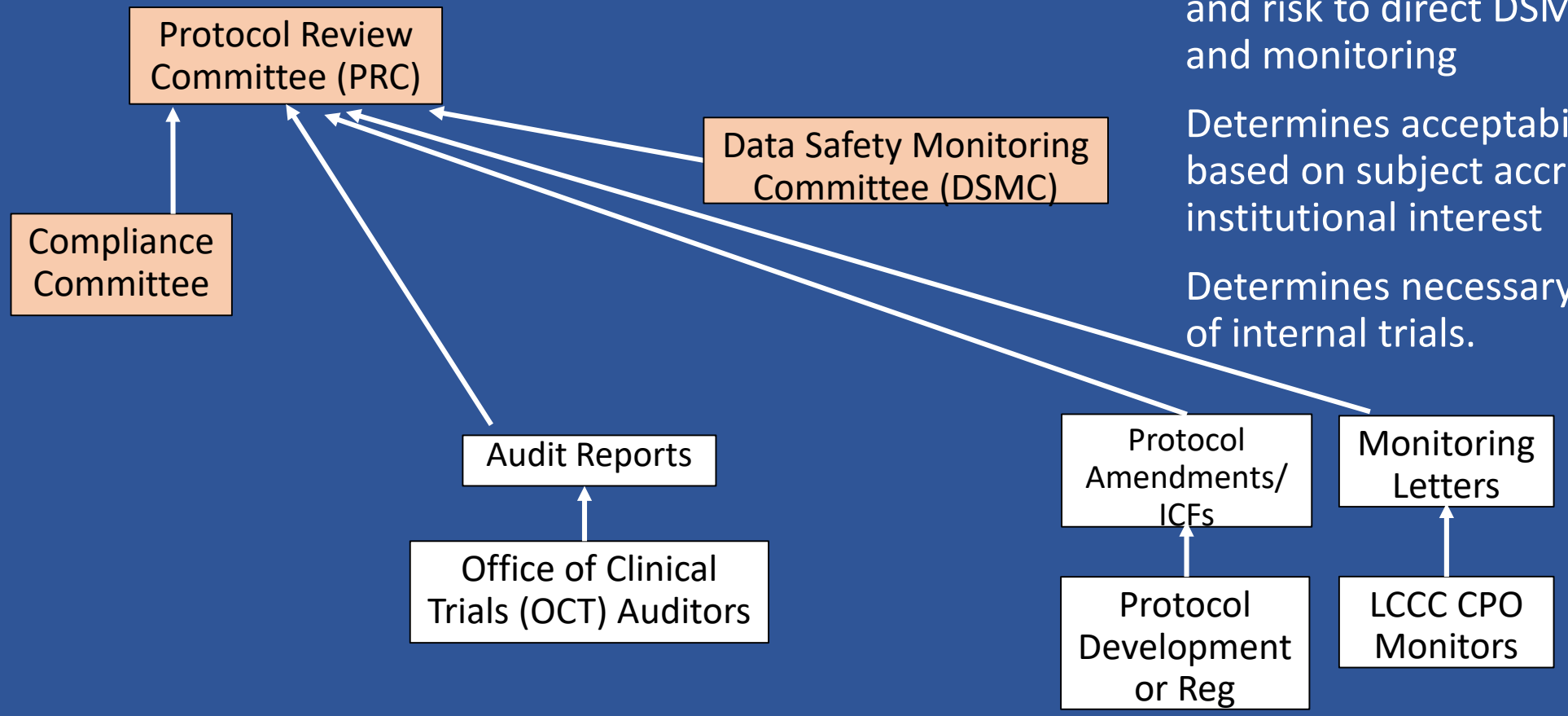
Conducted by OCT under the UNC Clinical Trials Quality Assurance Program (CTQA)

Reviewed by the Committee:

- CAPA Responses
- Audit Trends

Charter for the Compliance Committee UNC Lineberger Comprehensive Cancer Center

Monitor the progress of all clinical investigations being conducted under its IND



PRC: classifies studies by levels of complexity and risk to direct DSMC, Compliance Committee and monitoring

Determines acceptability of continued research based on subject accrual, risk/benefit ratio and institutional interest

Determines necessary actions following audits of internal trials.

Judge acceptability of protocol amendments

- New drug
- Change in primary objective
- Change in stats

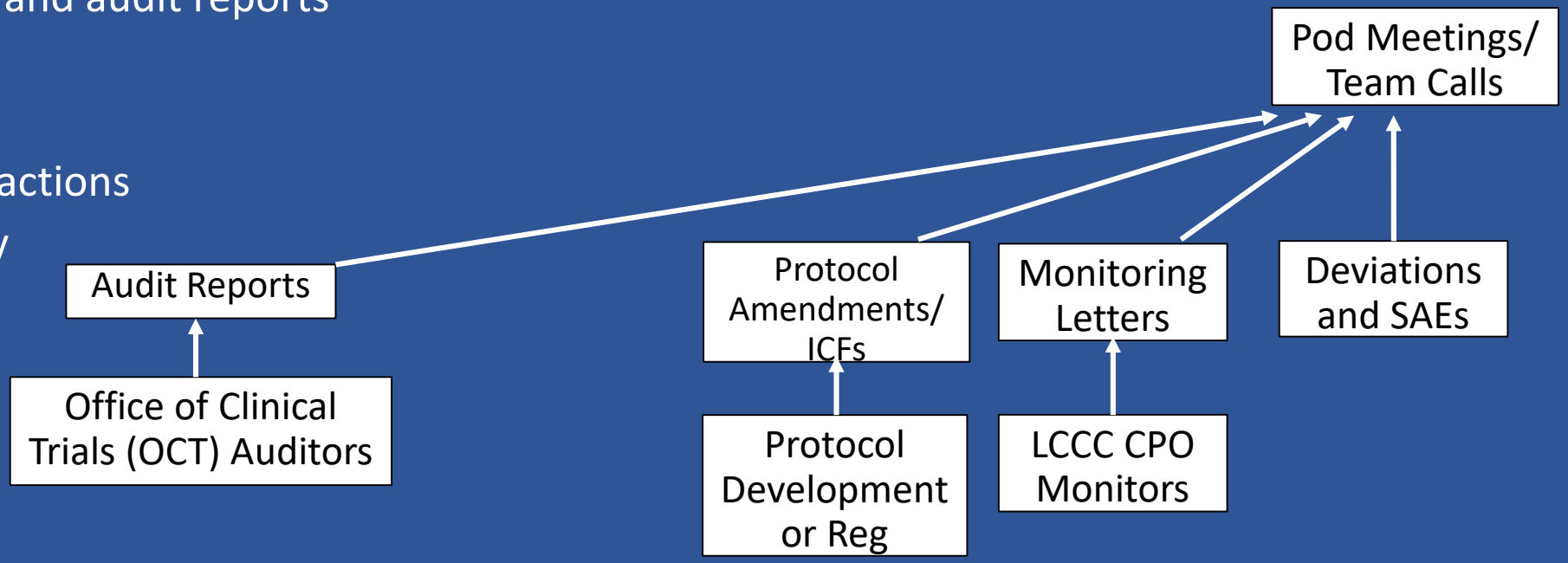
Recommend study closure

LCCC Data and Safety Monitoring Plan (DSMP)

Monitor the progress of all clinical investigations being conducted under its IND

Team (POD) Meetings

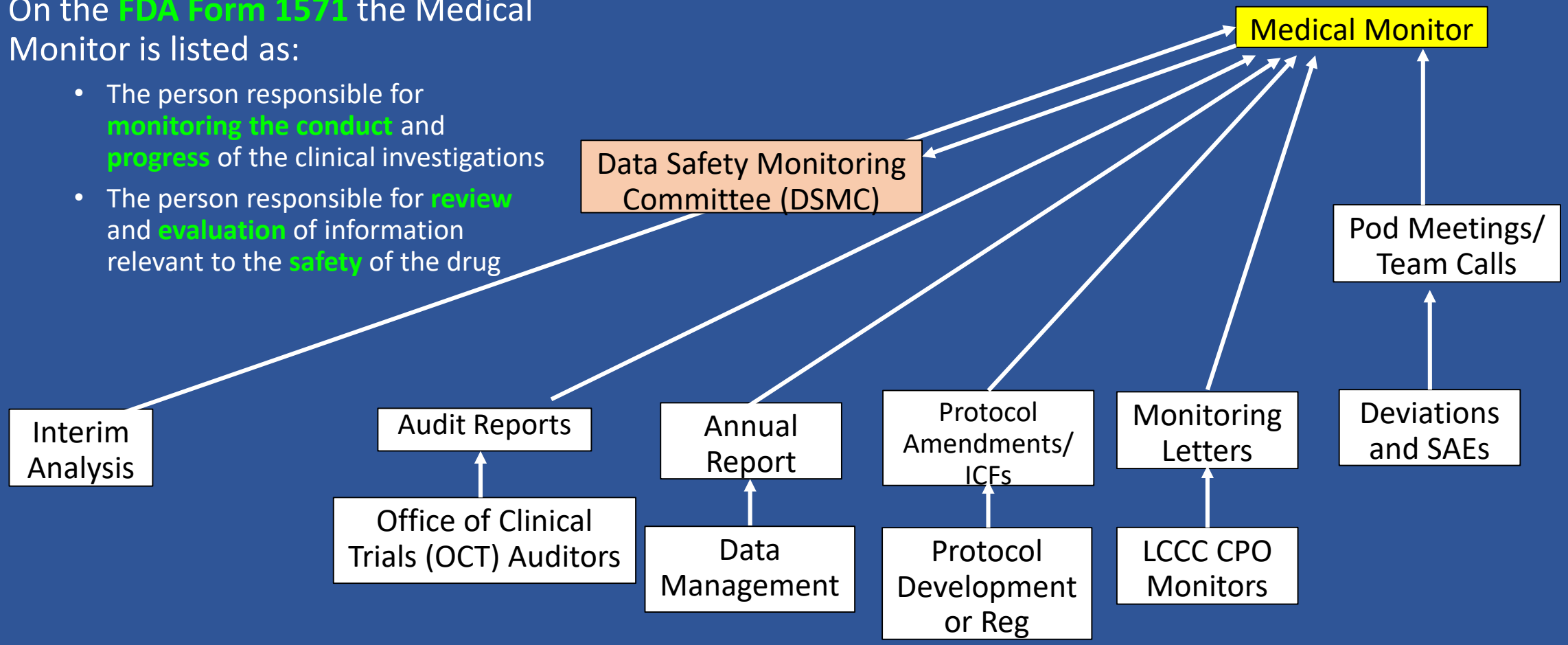
- Current status of trial/patients
- Enrollment
- Monitoring and audit reports
- Deviations
- SAEs
- Regulatory actions
- Data quality



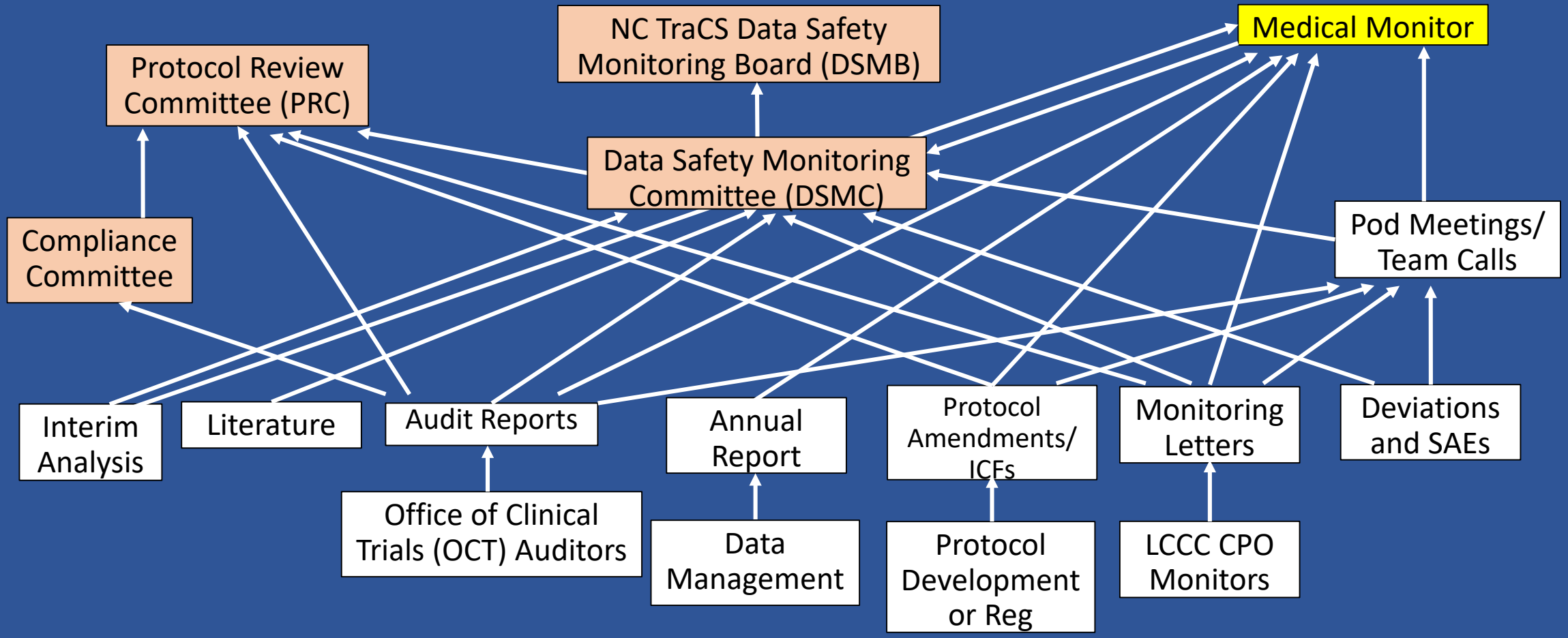
Monitor the progress of all clinical investigations being conducted under its IND

On the **FDA Form 1571** the Medical Monitor is listed as:

- The person responsible for **monitoring the conduct** and **progress** of the clinical investigations
- The person responsible for **review** and **evaluation** of information relevant to the **safety** of the drug

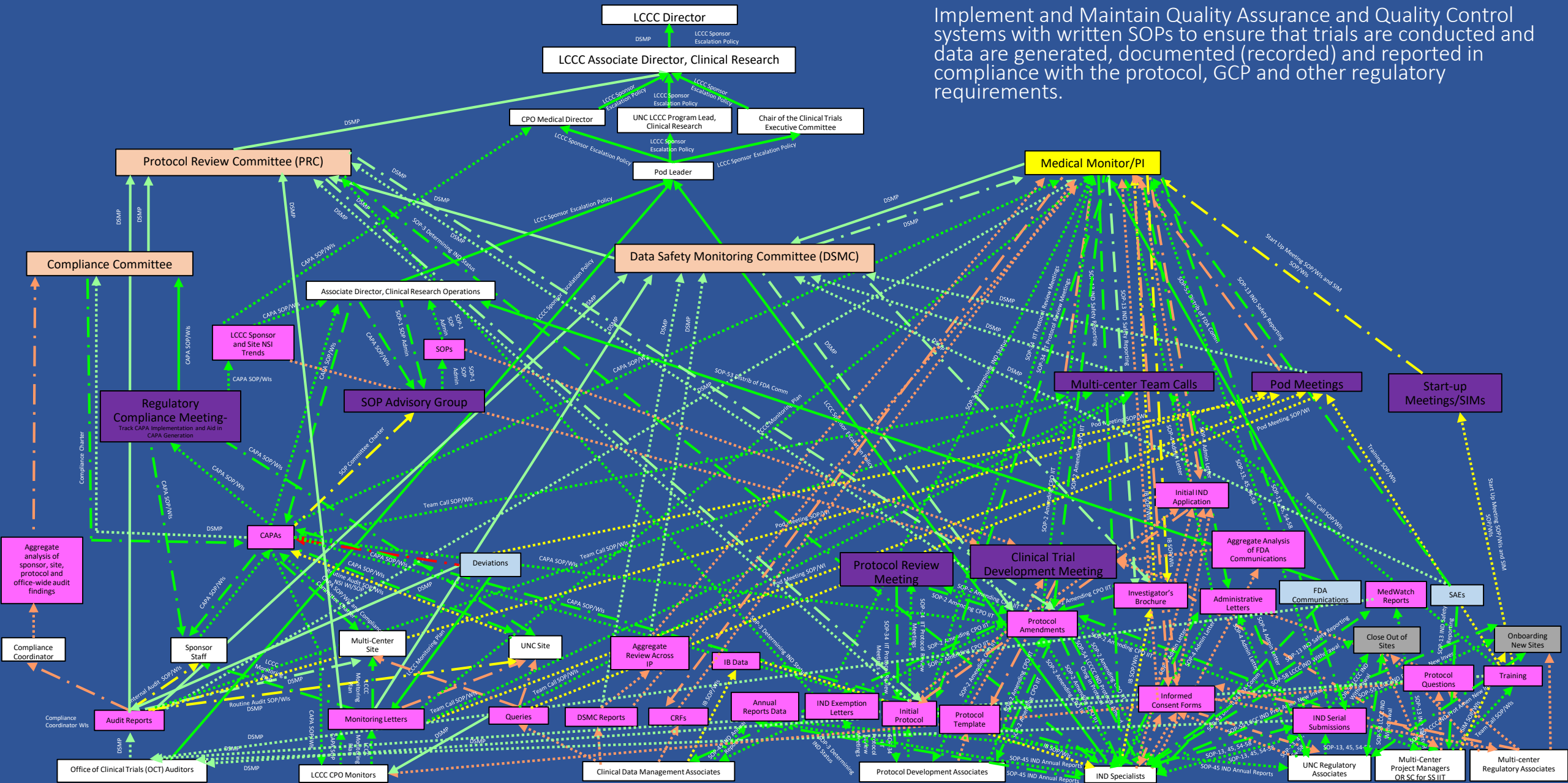


Monitor the progress of all clinical investigations being conducted under its IND



Implementation of a Quality Assurance System

Implement and Maintain Quality Assurance and Quality Control systems with written SOPs to ensure that trials are conducted and data are generated, documented (recorded) and reported in compliance with the protocol, GCP and other regulatory requirements.



Secure Data System

- Maintain security system that prevents unauthorized access to the data
- Maintain a list of individuals who are authorized to make data change
- Ensure data quality
- Ensure audit trails

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- Ensure data quality
- Ensure audit trails

What does it include?: FDA's rules for creating, modifying, maintaining, archiving, retrieving and transmitting electronic records. It requires (among other things):

- Validated computer systems (hardware and software) that are accurate, reliable, consistent, and can discern invalid or altered records
- Easily accessible systems with the stored records so that data can be reviewed and copied by FDA inspectors
- Access to electronic system is limited to authorized individuals
- Education, training and experience for individuals who develop, maintain, sign or use the record
- Adequate controls over the distribution or, access to, and use of documentation for system operation and maintenance
- Secure computer-generated, time-stamped audit trails (shouldn't obscure previously recorded information
- Electronic signatures have:
  - Written policies that hold individuals accountable and responsible for actions initiated under their electronic signature
  - Required elements: printed name of the signer, date/time signed, meaning (review, approve, responsible, authorship), linked…
  - Institutional verification of the signer's identity
  - Documentation sent to FDA verifying that electronic signatures are legally binding and equivalent to handwritten signatures
  - Be based on biometrics OR meet additional

Don't Forget about Part 11 Compliance…

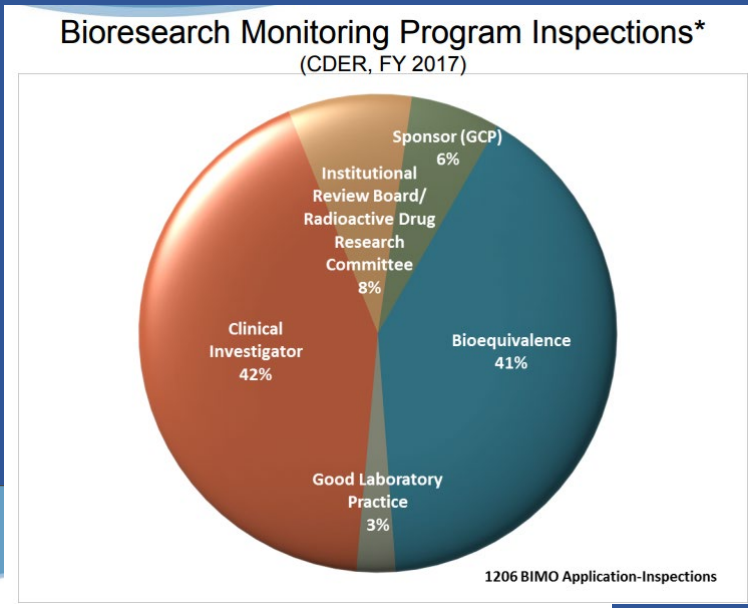
A section of the code of federal regulations that went into effect on August 20, 1997.

Allow Inspections

- Principal Areas covered:
  - Organization and personnel
  - Selection of Clinical investigators
  - Monitors and Monitoring procedures
  - Reporting of AEs
  - Test article accountability and characterization

- Points to remember:
  - Protocol deviations and AEs are expected- a lack of them is a red flag
  - Subject compliance is an uphill battle- a lack of this is a red flag
  - Often protocols will be amended due to problems arising at the site level

FDA's objects are to verify data validity and subject safety



U.S. Food and Drug Administration
Protecting and Promoting Public Health

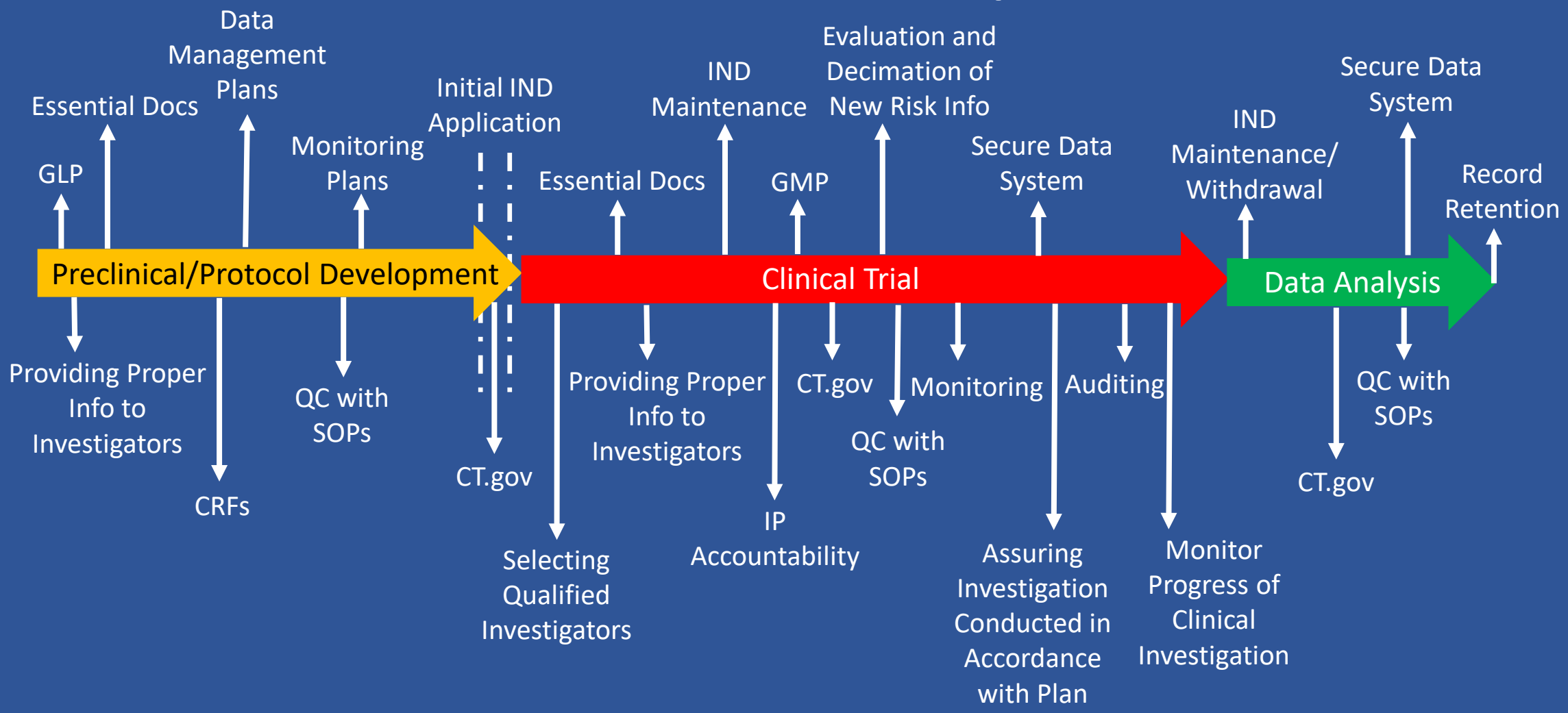
Warning Letters by Program Area*

(CDER, FY 2008 - FY 2017)

Program Area	FY08	FY09	FY10	FY11	FY12	FY13	FY14	FY15	FY16	FY17
Bioequivalence**	0	0	0	1**	0	0	0	0	1**	0
Good Laboratory Practice	0	1	1	0	0	0	1	0	0	0
Clinical Investigator	12	18	13	13	5	5	11	4	7	4
Sponsor-Investigator (GCP)	0	0	2	0	0	0	0	0	0	0
Sponsor (GCP)	3	1	1	0	0	0	3	2	2	2
Contract Research Organization (GCP)	0	0	1	0	0	0	0	0	0	0
Institutional Review Board	3	2	5	2	5	3	1	0	4	0
Radioactive Drug Research Committee	0	0	0	1	0	0	0	0	0	0
Postmarketing Adverse Drug Event***	N/A	N/A	N/A	3	3	0	0	1	3	2
Risk Evaluation and Mitigation Strategy***	N/A	N/A	0	0	0	0	0	0	0	0
Postmarketing Requirements^	N/A	N/A	N/A	N/A	1	0	0	0	0	0

*Based on letter issue date [Complis database as of December 29, 2017]
**Posted Bioequivalence OAI untitled letters.
***As of June 2011, Postmarketing Adverse Drug Event and Risk Evaluation and Mitigation Strategies inspection programs incorporated into OSI.
^Postmarketing Requirements (PMR) includes all required studies and clinical trials that are mandated by statute (e.g., section 505(o)(3) of FDCA, PREA, Animal Rule and 21 CFR 314 and 601 Subparts H and E, respectively.

Data Analysis



ClinicalTrials.gov

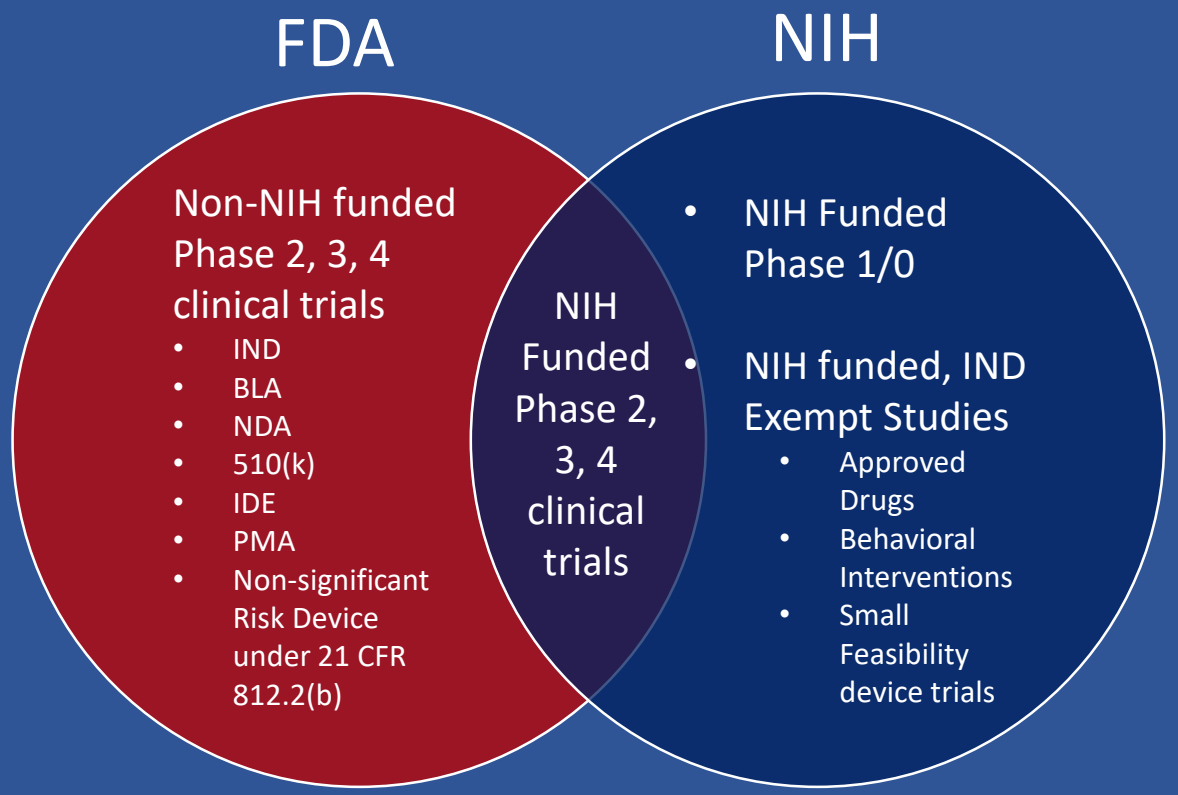
- What is the purpose?
  - Help patients find trials
  - Enhance design of trials
  - Prevent duplication of unsuccessful or unsafe trials
  - Build public trust

- FDA requires Responsible party (**sponsor**) to register with and submit **results** information of applicable trials to clinicaltrials.gov

What types of trials require results reporting?

Not Applicable:

- Non-NIH funded Phase 1 Studies
- Non-NIH funded Studies using Devices/Drugs, but not studying the Device/Drug itself
- Non-NIH funded OTC



UNC has resources to help you:

Contact: Monica Coudurier

https://research.unc.edu/clinical-trials/clinical-trials-gov/

LCCC has specific cancer resources to help you:

Contact: Mary O'Dwyer

https://research.unc.edu/clinical-trials/clinical-trials-gov/

Record Retention

Retain all records and reports required for:

- 2 years after drug approval

OR

- If not approved: 2 years after shipment and delivery of the drug for investigational use is discontinued and FDA has been so notified

Questions???