# Sponsor-Investigator Relationships and Responsibilities

# Agenda

- General Introduction – Gregory Riely
- Conflict of Interest – Erika McCarthy

# Agenda (my section):

- Relationships and Responsibilities in context of a clinical trial
  - What is an investigator
  - Becoming an investigator (on a multicenter sponsored research study)
  - Investigator responsibilities/qualifications
  - Sponsor responsibilities
  - Monitoring
- Relationships and Responsibilities outside of a clinical trial

# E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1)

E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1)
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# Definitions

- Investigator - A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator. (See also Subinvestigator.)
- Sponsor - An individual, company, institution, or organization that takes responsibility for the initiation, management, and/or financing of a clinical trial.
- Sponsor-Investigator - An individual who both initiates and conducts, alone or with others, a clinical trial, and under whose immediate direction the investigational product is administered to, dispensed to, or used by a subject. The term does not include any person other than an individual (e.g., it does not include a corporation or an agency). The obligations of a sponsor-investigator include both those of a sponsor and those of an investigator.

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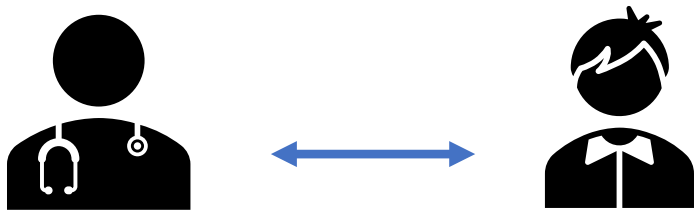
# Being an investigator…
(in a multi-center, industry-sponsored)

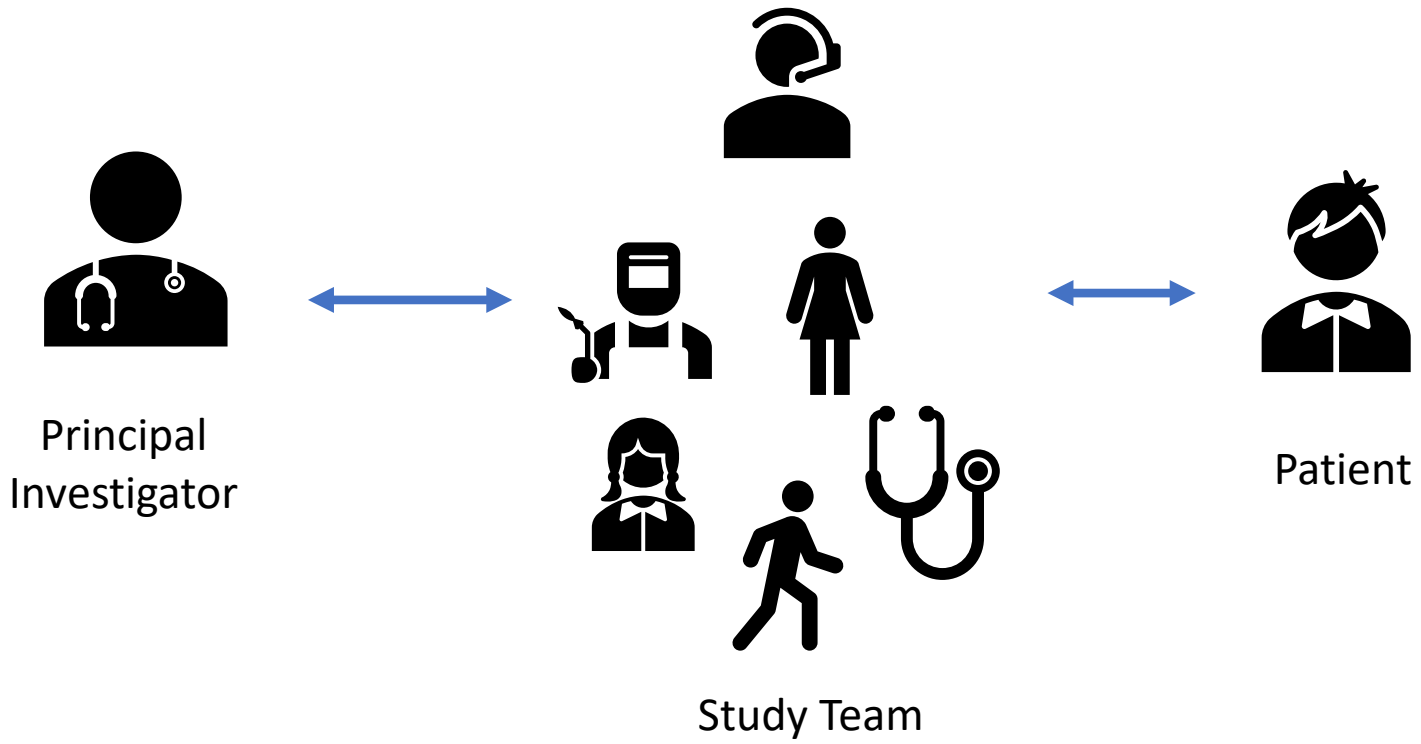
# Investigator-initiated trial



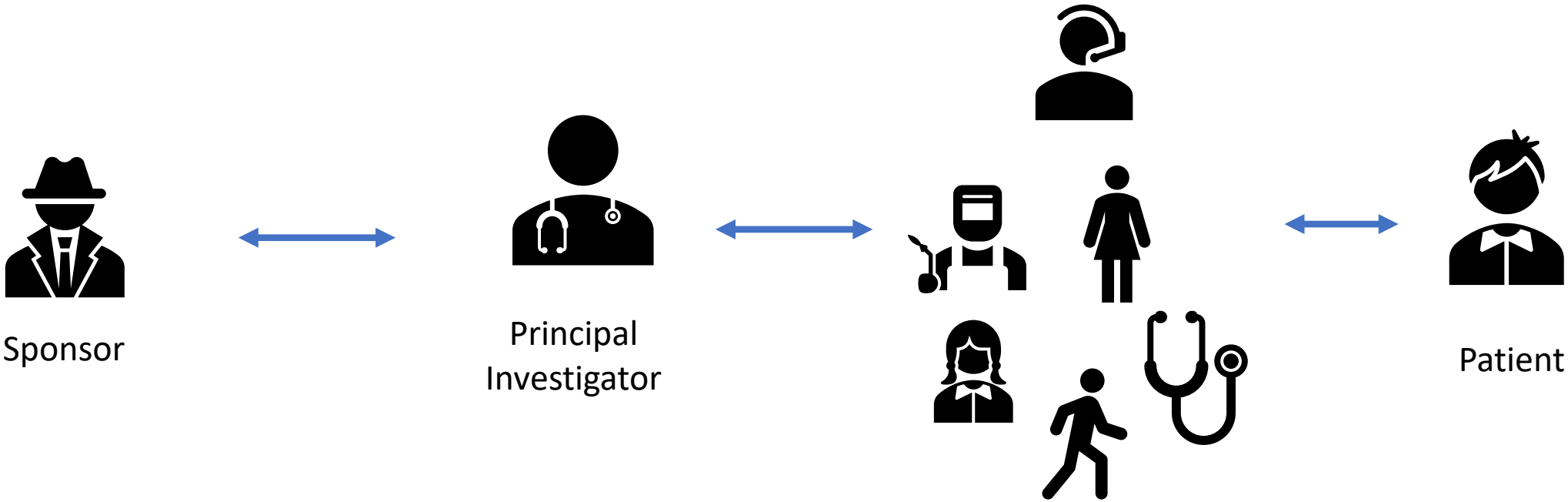
Principal Investigator

Patient

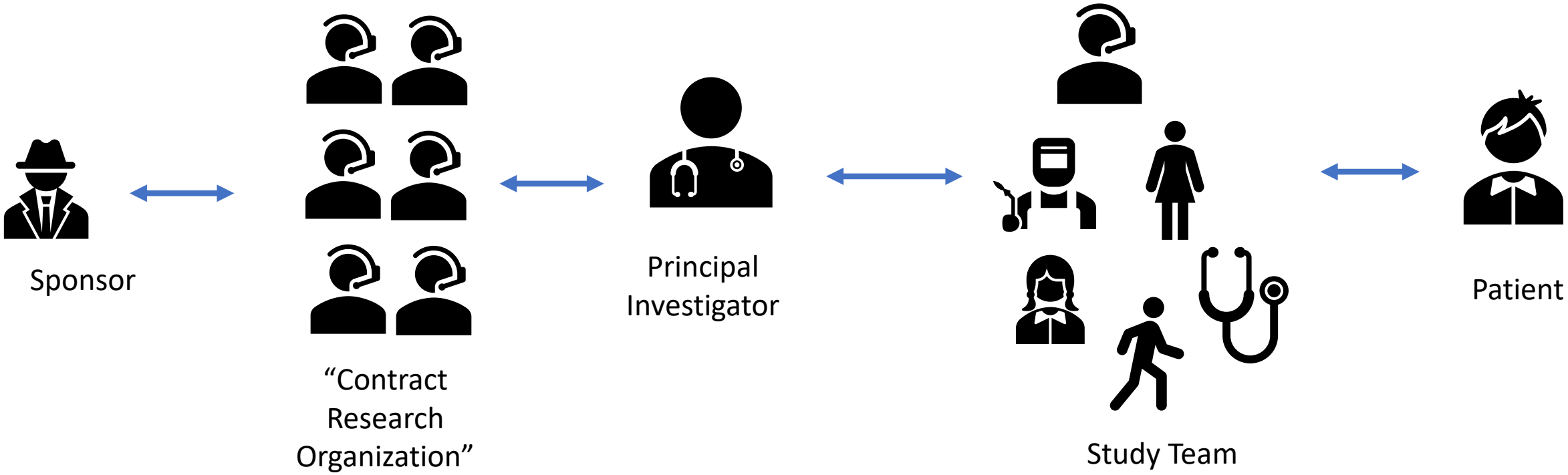
# Investigator-initiated trial



# Multi-center, externally sponsored trial



# Multi-center, externally sponsored trial



# On a practical basis, how do you actually become a site-PI for a multi-center sponsored clinical trial?

A. You serve on a committee for a cooperative group
B. You establish yourself as an investigator who can enroll patients with the condition of interest
C. You meet with the Chief Scientific Officer/Chief Medical Officer of the company and help design the trial
D. You call a phone number to express interest
E. You answer an email from a random company you've never heard of

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# Becoming an investigator…
## (in a multi-center, industry-sponsored)

Dear Dr. Riely,

Fortrea is collaborating with Pierre Fabre Medicament, a French pharmaceutical company, to invite you to assess your interest to conduct a first-in-human phase 1/2 study in Locally Advanced or Metastatic Non-Small Cell Lung Cancer adult patients resistant to third generation EFGR TKIs.

In order to proceed with further assessing your site/PI interest and capabilities to conduct the aforementioned study, we would like to share additional information, once a Confidentiality Agreement (CDA) is fully executed.

Attached you will find the Institution CDA. Please review the attached Institutional CDA and enter your sites correct name and address along with any other additional edits you may need for our review. If you are not authorized to sign on behalf of your Institution, please direct us to the correct authorized Institution signatory to ensure your CDA is executed expeditiously to move through the site selection process.

**Please do not share this information outside of the remit of the signed CDA documents and please direct all inquiries and comments regarding this potential trial to me.**

Thank you for your time and attention.

Kind Regards,

**Nicole Semler**
Start-Up Associate
T: 1-609-419-2938| E: nicole.semler@fortrea.com | fortrea.com
Fortrea Inc.

Fortrea

Dear Investigator,

Mirati has provided your name as a potential investigator for the trial referenced above, and has contracted PRA to perform site feasibility and qualification steps. The final decision about your participation is based on your interest in participating, your recruitment potential, and the ability of your staff and center to fulfill the requirements of the protocol.

**Prior to completing the questionnaire, please review the Protocol Synopsis.**

Please complete this questionnaire within **three (3) business days.** Please also e-mail a signed and dated CV (current within 2 years) of the Principal Investigator to Emily Selinger at PRA Health Sciences: SelingerEmily@prahs.com.

The Phase I Dose Escalation is planned to begin in April 2020 at 3 sites who are able to activate no later than 31Mar2020. Another group of sites will activate to perform the Phase Ib expansion portion of the study. If the study proceeds to Phase II, additional sites will be added.

Thank you for taking the time to complete this questionnaire.

Kind regards,

Amber Beimer, Clinical Team Manager

Q90 How many of the above **KRAS G12C+ patients** with the following tumor types do you see **every 6 months**?

| | Patient count with KRAS G12C+ in 6 months |
|---|---|
| NSCLC | 50 |
| CRC | 50 |
| Pancreatic Cancer | 6 |
| Cholangiocarcinoma | 2 |

# Becoming an investigator…
# (in a multi-center, industry-sponsored)

- PSSV (pre site selection visit)
- SSV (site selection visit)
- SEV (site evaluation visit)
- SQV (site qualification visit)

Typically, a ½ day (virtual) visit by a sponsor representative where they:
(1)tour facilities, including clinic and pharmacy
(2)Review regulatory requirements
(3)Meet with principal investigator

**Mike Thompson, MD, PhD, FASCO** @mtmdphd · 9h

Why are CROs asking to do a pre-site initiation visit (PSIV) even before we have signed a (useless) confidentiality agreement (CDA/NDA) and have not even seen the #ClinicalTrials protocol?

2 2 2

**Alex Spira, M.D.** @AlexSpiraMDPhD · 3h

But why does a  cro ask for a three hour psv on a study with the same sponsor and same cro you've worked with a bajillion times, when they're in the office monthly for visits , for something that could be answered in a two sentence email . "Yes we can do the study".

1 3

# Why do they do a site qualification visit?

# Why do they do a site qualification visit?

A. They are paid by the hour

# Why do they do a site qualification visit?

A. They are paid by the hour
B. They want to torture you

# Why do they do a site qualification visit?

A. They are paid by the hour
B. They want to torture you
C. There is a regulation with which they are complying

## 4.1 Investigator's Qualifications and Agreements

*4.1.1* The investigator(s) should be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial, should meet all the qualifications specified by the applicable regulatory requirement(s), and should provide evidence of such qualifications through up-to-date curriculum vitae and/or other relevant documentation requested by the sponsor, the IRB/IEC, and/or the regulatory authority(ies).

*4.1.2* The investigator should be thoroughly familiar with the appropriate use of the investigational product(s), as described in the protocol, in the current Investigator's Brochure, in the product information, and in other information sources provided by the sponsor.

*4.1.3* The investigator should be aware of, and should comply with, GCP and the applicable regulatory requirements.

*4.1.4* The investigator/institution should permit monitoring and auditing by the sponsor, and inspection by the appropriate regulatory authority(ies).

*4.1.5* The investigator should maintain a list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties.

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# Investigator responsibilities (highlights)

**4.2 Adequate Resources**

*4.2.1* The investigator should be able to demonstrate (e.g., based on retrospective data) a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

*4.2.2* The investigator should have sufficient time to properly conduct and complete the trial within the agreed trial period.

*4.2.3* The investigator should have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely.

*4.2.4* The investigator should ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial-related duties and functions.

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# Investigator responsibilities (highlights)

**ADDENDUM**

*4.2.5* The investigator is responsible for supervising any individual or party to whom the investigator delegates trial-related duties and functions conducted at the trial site.

*4.2.6* If the investigator/institution retains the services of any individual or party to perform trial-related duties and functions, the investigator/institution should ensure this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated.

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# Investigator responsibilities (highlights)

**4.3 Medical Care of Trial Subjects**

*4.3.1* A qualified physician (or dentist, when appropriate), who is an investigator or a subinvestigator for the trial, should be responsible for all trial-related medical (or dental) decisions.

*4.3.2* During and following a subject's participation in a trial, the investigator/institution should ensure that adequate medical care is provided to a subject for any adverse events, including clinically significant laboratory values, related to the trial. The investigator/institution should inform a subject when medical care is needed for intercurrent illness(es) of which the investigator becomes aware.

*4.3.3* It is recommended that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

*4.3.4* Although a subject is not obliged to give his/her reason(s) for withdrawing prematurely from a trial, the investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights.

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**DEPARTMENT OF HEALTH AND HUMAN SERVICES**
FOOD AND DRUG ADMINISTRATION

# STATEMENT OF INVESTIGATOR

***(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) PART 312)***

(See instructions on reverse side.)

Form Approved: OMB No. 0910-0014
Expiration Date: March 31, 2022
*See OMB Statement on Reverse.*

**NOTE:** No investigator may participate in an investigation until he/she provides the sponsor with a completed, signed Statement of Investigator, Form FDA 1572 (21 CFR 312.53(c)).

1. NAME AND ADDRESS OF INVESTIGATOR

Name of Clinical Investigator

| Address 1 | | Address 2 | |
|---|---|---|---|
| City | State/Province/Region | Country | ZIP or Postal Code |

2. EDUCATION, TRAINING, AND EXPERIENCE THAT QUALIFY THE INVESTIGATOR AS AN EXPERT IN THE CLINICAL INVESTIGATION OF THE DRUG FOR THE USE UNDER INVESTIGATION. ONE OF THE FOLLOWING IS PROVIDED *(Select **one** of the following.)*

☐ Curriculum Vitae ☐ Other Statement of Qualifications

3. NAME AND ADDRESS OF ANY MEDICAL SCHOOL, HOSPITAL, OR OTHER RESEARCH FACILITY WHERE THE CLINICAL INVESTIGATION(S) WILL BE CONDUCTED

**CONTINUATION PAGE for Item 3**

Name of Medical School, Hospital, or Other Research Facility

| Address 1 | | Address 2 | |
|---|---|---|---|
| City | State/Province/Region | Country | ZIP or Postal Code |

4. NAME AND ADDRESS OF ANY CLINICAL LABORATORY FACILITIES TO BE USED IN THE STUDY

**CONTINUATION PAGE for Item 4**

# Commitments on FDA Form 1572

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.

Seems like the investigator has a lot of responsibilities…what is the sponsor doing?

# Sponsor responsibilities (highlights)

**5.1 Quality Assurance and Quality Control**

*5.1.1* The sponsor is responsible for implementing and maintaining 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 the applicable regulatory requirement(s).

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# Sponsor responsibilities (highlights)

*5.6.1* The sponsor is responsible for selecting the investigator(s)/institution(s). Each investigator should be qualified by training and experience and should have adequate resources (see sections 4.1, 4.2) to properly conduct the trial for which the investigator is selected. If organization of a coordinating committee and/or selection of coordinating investigator(s) are to be utilized in multicenter trials, their organization and/or selection are the sponsor's responsibility.

*5.6.2* Before entering an agreement with an investigator/institution to conduct a trial, the sponsor should provide the investigator(s)/institution(s) with the protocol and an up-to- date Investigator's Brochure, and should provide sufficient time for the investigator/institution to review the protocol and the information provided.

*5.6.3* The sponsor should obtain the investigator's/institution's agreement:

(a) To conduct the trial in compliance with GCP, with the applicable regulatory requirement(s) (see section 4.1.3), and with the protocol agreed to by the sponsor and given approval/favorable opinion by the IRB/IEC (see section 4.5.1);

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# Sponsor can delegate their responsibilities to CROs

**5.2 Contract Research Organization (CRO)**

*5.2.1* A sponsor may transfer any or all of the sponsor's trial-related duties and functions to a CRO, but the ultimate responsibility for the quality and integrity of the trial data always resides with the sponsor. The CRO should implement quality assurance and quality control.

*5.2.2* Any trial-related duty and function that is transferred to and assumed by a CRO should be specified in writing.

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# Sponsor responsibilities (highlights)

**5.18 Monitoring**

*5.18.1 Purpose*

The purposes of trial monitoring are to verify that:

(a) The rights and well-being of human subjects are protected.

(b) The reported trial data are accurate, complete, and verifiable from source documents.

(c) The conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with the applicable regulatory requirement(s).

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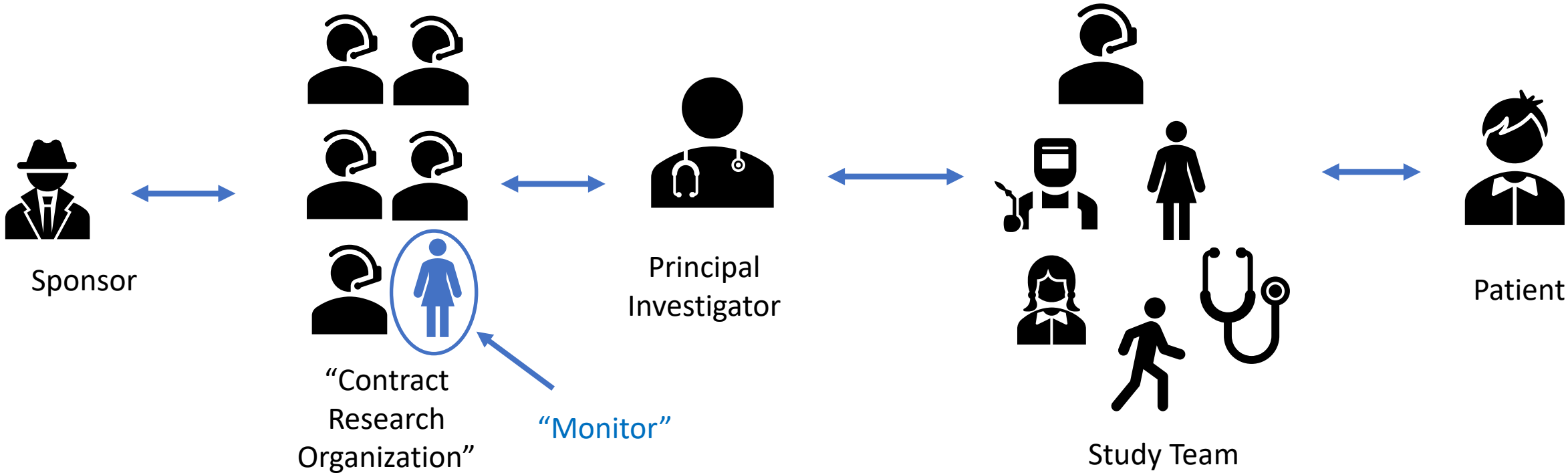
# Multi-center, externally sponsored trial



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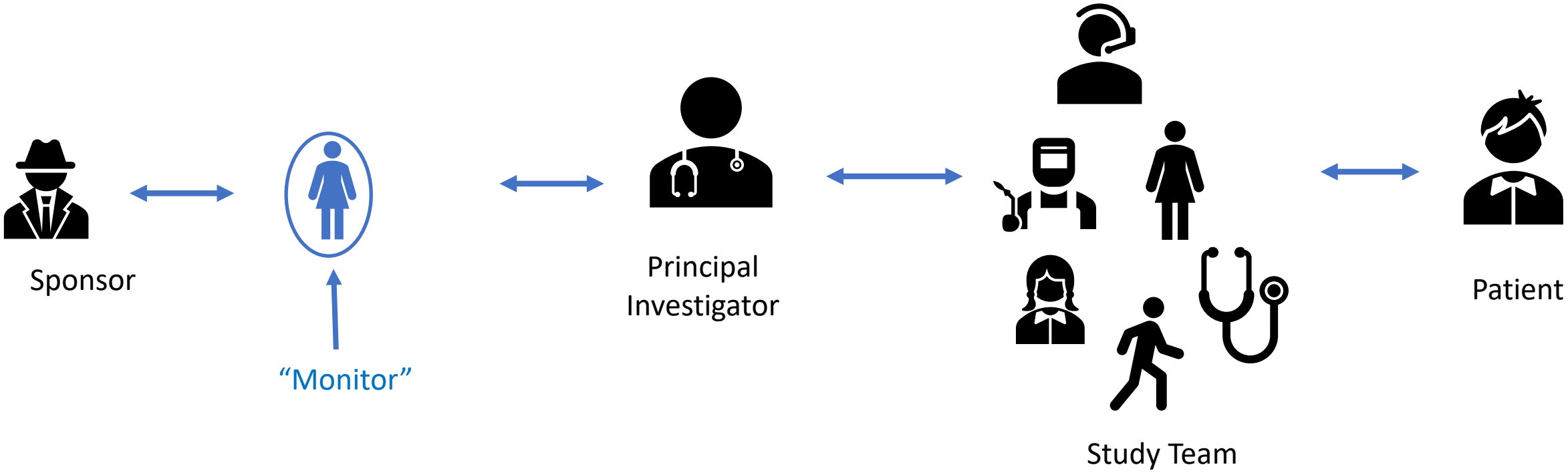

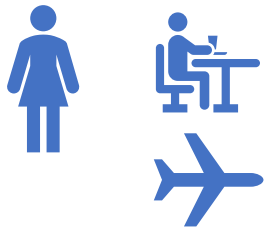

# Monitor Responsibilities (highlights)

*5.18.4 Monitor's Responsibilities*

The monitor(s), in accordance with the sponsor's requirements, should ensure that the tri al is conducted and documented properly by carrying out the following activities when relevant and necessary to the trial and the trial site:

(a) Acting as the main line of communication between the sponsor and the investigator.

(b) Verifying that the investigator has adequate qualifications and resources (see sections 4.1, 4.2, 5.6) and these remain adequate throughout the trial period, that facilities including laboratories and equipment, and staff, are adequate to safely and properly conduct the trial and remain adequate throughout the trial period.

(c) Verifying, for the investigational product(s):

(i) That storage times and conditions are acceptable, and that supplies are sufficient throughout the trial.

(ii) That the investigational product(s) are supplied only to subjects who are eligible to receive it and at the protocol specified dose(s).

(iii) That subjects are provided with necessary instruction on properly using, handling, storing, and returning the investigational product(s).

(iv) That the receipt, use, and return of the investigational product(s) at the trial sites are controlled and documented adequately.

(v) That the disposition of unused investigational product(s) at the trial sites complies with applicable regulatory requirement(s) and is in accordance with the sponsor.

(d) Verifying that the investigator follows the approved protocol and all approved amendment(s), if any.

(e) Verifying that written informed consent was obtained before each subject's participation in the trial.

(f) Ensuring that the investigator receives the current Investigator's Brochure, all documents, and all trial supplies needed to conduct the trial properly and to comply with the applicable regulatory requirement(s).

(g) Ensuring that the investigator and the investigator's trial staff are adequately informed about the trial.

- The monitor is the main line of communication between the sponsor and the investigator
- Verifying that the investigator has adequate qualifications and resources
- Verifying investigational product
- Verifying that investigator follows the protocol
- Verifying that written informed consent was obtained
- Ensuring/verifying all aspects of study conduct

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*5.18.6 Monitoring Report*

(a) The monitor should submit a written report to the sponsor after each trial-site visit or trial-related communication.

(b) Reports should include the date, site, name of the monitor, and name of the investigator or other individual(s) contacted.

(c) Reports should include a summary of what the monitor reviewed and the monitor's statements concerning the significant findings/facts, deviations and deficiencies, conclusions, actions taken or to be taken and/or actions recommended to secure compliance.

(d) The review and follow-up of the monitoring report with the sponsor should be documented by the sponsor's designated representative.

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# Other Sponsor-Investigator Relationships (outside of actual conduct of trials)

Who might you meet with?

- Sales representative
- Medical Science Liaison
- Lead Clinician (can be nurse, pharmacist, or physician)
- Clinical Director, Global Lead, Clinical Scientist, CSO, CEO

How do you interact with them?

What is their goal?

# Sponsor-Investigator Relationships (outside of actual conduct of trials)

- One-on-one meetings
- Advisory boards
- Investigator meetings
- “Investigator” meetings
- Portfolio reviews

# Investigator-Sponsor Interactions… Why do they want to meet with you?

- Sell more approved drug
- Build a relationship
- Make you like them so you will …
- … prescribe more of their drug
- …say nice things about their drug
- …help get drug approved/in guidelines
- Learn from you about their drug/competitor's drugs
- Find a new drug
- Find a new drug target

# Investigator-Sponsor Interactions… Why do you want to meet with them?

- Be a site for a trial (phase 1, 2, 3)
- Be a global/national PI
- Get funding for your own (investigator-initiated) study
- Learn about drugs in development
- Be seen as an influencer

# Agenda

- General Introduction - Gregory Riely
- Conflict of Interest – Erika McCarthy

# Questions?

## 5.19 Audit

If or when sponsors perform audits, as part of implementing quality assurance, they should consider:

### *5.19.1 Purpose*

The purpose of a sponsor's audit, which is independent of and separate from routine monitoring or quality control functions, should be to evaluate trial conduct and compliance with the protocol, SOPs, GCP, and the applicable regulatory requirements.

### *5.19.2 Selection and Qualification of Auditors*

(a) The sponsor should appoint individuals, who are independent of the clinical trials/systems, to conduct audits.

(b) The sponsor should ensure that the auditors are qualified by training and experience to conduct audits properly. An auditor's qualifications should be documented.

### *5.19.3 Auditing Procedures*

(a) The sponsor should ensure that the auditing of clinical trials/systems is conducted in accordance with the sponsor's written procedures on what to audit, how to audit, the frequency of audits, and the form and content of audit reports.

(b) The sponsor's audit plan and procedures for a trial audit should be guided by the importance of the trial to submissions to regulatory authorities, the number of subjects in the trial, the type and complexity of the trial, the level of risks to the trial subjects, and any identified problem(s).

(c) The observations and findings of the auditor(s) should be documented.

(d) To preserve the independence and value of the audit function, the regulatory authority(ies) should not routinely request the audit reports. Regulatory authority(ies) may seek access to an audit report on a case-by-case basis when evidence of serious GCP non-compliance exists, or in the course of legal proceedings.

(e) When required by applicable law or regulation, the sponsor should provide an audit certificate.

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## 4.4 Communication with IRB/IEC

*4.4.1* Before initiating a trial, the investigator/institution should have written and dated approval/favorable opinion from the IRB/IEC for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements), and any other written information to be provided to subjects.



***Contains Nonbinding Recommendations***

*4.4.2* As part of the investigator's/institution's written application to the IRB/IEC, the investigator/institution should provide the IRB/IEC with a current copy of the Investigator's Brochure. If the Investigator's Brochure is updated during the trial, the investigator/institution should supply a copy of the updated Investigator's Brochure to the IRB/IEC.

*4.4.3* During the trial the investigator/institution should provide to the IRB/IEC all documents subject to review.

## 4.5 Compliance with Protocol

*4.5.1* The investigator/institution should conduct the trial in compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authority(ies), and which was given approval/favorable opinion by the IRB/IEC. The investigator/institution and the sponsor should sign the protocol, or an alternative contract, to confirm agreement.

*4.5.2* The investigator should not implement any deviation from, or changes of, the protocol without agreement by the sponsor and prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to trial subjects, or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change in monitor(s), change of telephone number(s)).

*4.5.3* The investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol.

*4.5.4* The investigator may implement a deviation from, or a change in, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB/IEC approval/favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted:

(a) To the IRB/IEC for review and approval/favorable opinion;

(b) To the sponsor for agreement and, if required;

(c) To the regulatory authority(ies).

## 4.9 Records and Reports

**ADDENDUM**

*4.9.0* The investigator/institution should maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial subjects. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (e.g., via an audit trail).

*4.9.1* The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports.

*4.9.2* Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained.

*4.9.3* Any change or correction to a CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry (i.e., an audit trail should be maintained); this applies to both written and electronic changes or corrections (see 5.18.4(n)). Sponsors should provide guidance to investigators and/or the investigators' designated representatives on making such corrections. Sponsors should have written procedures to assure that changes or corrections in CRFs made by sponsor's designated representatives are documented, are necessary, and are endorsed by the investigator. The investigator should retain records of the changes and corrections.

*4.9.4* The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (see section 8.) and as required by the applicable regulatory requirement(s). The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

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