Essential Documents, SAE Reporting, PI and Study Staff Considerations for QA / Monitoring Visits

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Learning Objectives

1. Essential document review and importance during life of study
2. SAE Reporting
3. Preparing for a successful remote site visit
4. Common findings during monitoring visits and how to prevent or resolve
5. FDA 483 review / case study.

Overview

- What are essential documents?
- What documents are essential?
- How do these tie into the monitoring visit?
- SAE Reporting
- Preparing for a monitoring visit
- Monitoring v. Auditing
- Risk Based Monitoring
- FDA warning letter
- Dr. Giron

What are Essential Documents?

- International Conference on Harmonization (ICH) Good Clinical Practices (GCP) guidance defines essential documents as:

“those documents which individually and collectively permit evaluation of the conduct of the clinical trial and the quality of the data produced."

What are Essential Documents?

- **Translation:** Essential documents are the regulatory source documents for the study.
- Just like you need confirmatory labs and visit notes for the study, these are equally as important.
    - Without these, we cannot ensure the qualifications of the investigator, the approved protocol being used for the site (and correct version on file), approved consent forms…
- Think about what are the most important documents that a site needs to conduct a clinical trial.

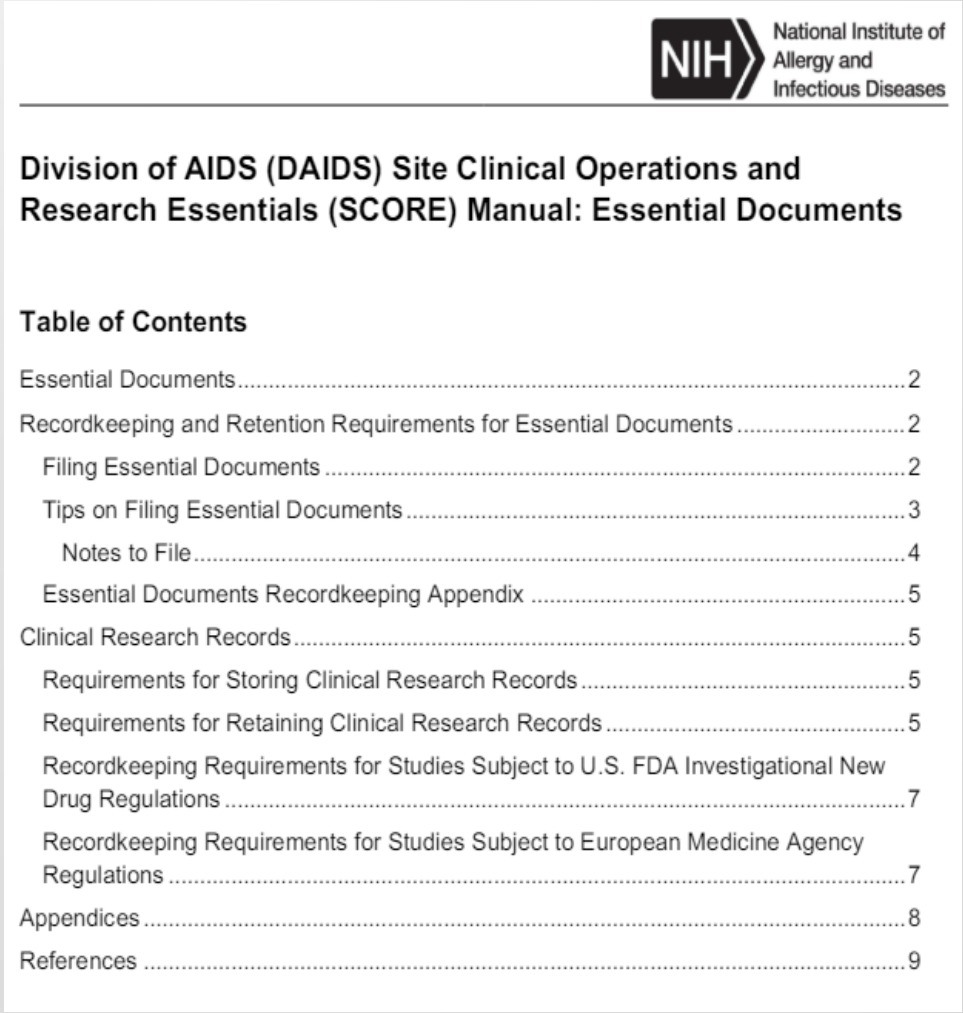
What Documents are Considered Essential?

- Protocols
- Consent Forms
- Case Report Form (CRFs)
- Investigator information
  - (CV, MD license)
- Lab Normal for each lab
- CAP, CLIA - lab accreditation information with dates
- Shipping records
- GCP training confirmation / CITI Certificates
- Current IRB approval documents
- 1572 / IoRA
- Investigator Brochure
- Delegation of Authority Logs
- Monitoring reports
- Enrollment /Randomization Logs

NIH Review of Essential Documents

- It is good practice to review guidelines for essential documents - the NIH/NIAID has helpful information.

https://www.niaid.nih.gov/sites/default/files/score-essential-documents.pdf



National Institute of Allergy and Infectious Diseases

Division of AIDS (DAIDS) Site Clinical Operations and Research Essentials (SCORE) Manual: Essential Documents

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Essential Documents are used to ensure -

- Adherence to ethical principles
- Risk minimization
- Subject's rights, safety, and well-being
- Adequate drug information
- Scientifically sound protocols
- IRB/IEC review and approval and protocol adherence
- Involvement of qualified physicians and support staff

How Do I Keep These Documents up to Date?

- When a new study member is added to the protocol, this is a great time to check the rest of the study teams documents and the delegation log.
- Be aware of dates for continuing reviews – then you can be prepared for an updated IRB letter to file.
- You can keep a tracker with consent form versions and dates. This way you can be sure you are using the correct version, and if anyone needs re-consented you have this information easily available.
- Keeping these in a clearly labeled Regulatory binder (paper or electronic) is critical.
    - During a monitoring visit, you don't want to be unprepared and have to scramble for signatures on a DOR log or find an IRB letter.

Serious Adverse Event (SAE)

- A Serious Adverse Event (SAE) is any unfavorable medical occurrence in a human study participant that is related to their involvement in the research. SAEs are a subset of adverse events.
- The **FDA defines an SAE as an adverse event or suspected adverse reaction** that results in any of the following outcomes:
  - Death
  - A life-threatening adverse event
  - Inpatient hospitalization or prolongation of existing hospitalization
  - A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
  - A congenital anomaly/birth defect

SAE Reporting Timeline

- Reporting period is 24 hours (to IRB, Sponsor and/or FDA) after you **LEARN** of the event. These can be in real time, discovered after the event, found at monitor visits, or when coordinator reviews participant charts.

SAE - Death

- Death of a research participant.

  Participant is on a study with 10 years follow up.

- When there is a long term follow up period and the protocol requires you to reach out every 6 months, you may find out when you reach out to the participant 6 months later that they have died. You have 24 hours to report from when you **learn** the participant has died.
- Participants partner calls you 3 months after participant had died to let you know. You have 24 hours to report from when you **learn** the participant has died.

SAE - Life Threatening

- An SAE is considered life-threatening when the patient is at risk of death at the time of the event. It does not refer to an event that might have hypothetically caused death if it were more severe.
  - Participant A goes to appointment after leg surgery and due to excessive movement, the wound has completely separated. At the visit the surgeon rates this as grade 4 wound separation and the participant is rushed to surgery for amputation.

Investigations					
CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Wound dehiscence	Incisional separation, intervention not indicated	Incisional separation, local care (e.g., suturing) or medical intervention indicated (e.g., analgesic)	Fascial disruption or dehiscence without evisceration; revision by operative intervention indicated	Life-threatening consequences; symptomatic hernia with evidence of strangulation; fascial disruption with evisceration; major reconstruction flap, grafting, resection, or amputation indicated	Death
Definition: A finding of separation of the approximated margins of a surgical wound.					
Navigational Note: Also consider Infections and infestations: Wound infection					

SAE – Hospitalization

- Participant A is admitted to the hospital with amputation later that day. They are hospitalized for 3 weeks.
  - The event lasts until the participant has recovered from the SAE.
  - Participant A sees how bad the wound is and goes to the ED and are admitted to an outside hospital. They call you a week later to update you– reporting is 24 hours after you **learn** of the admission.

Queries

Monitor

Coordinator

Queries

Queries are a means of communicating issues that could interfere with the statistical analysis of the data being collected.

- If the wording of queries is not effective, then communication will not be effective either – this is for both monitor and coordinator.
- You should be able to have honest conversations about queries with your monitor and ask questions if anything is unclear.
  - This helps clear up misunderstandings on either part and is beneficial to the study.
  - **It isn't personal.** Issuing queries and responding to them is a team effort.

Queries Can Do a lot of Things

Quality issues may be isolated, or they may have a broad impact across trials / programs and can represent:

- A single occurrence or a cluster of occurrences / trends.
- Gaps indicating noncompliance with regulations, policies, and/or procedures
- Risk to subject safety and/or data integrity, and, as a result, risk to the company's license to operate.

Evaluation of Query / Issue

After identifying the issue, one must evaluate its severity and impact by considering:

- The potential for a broader impact across clinical trials
- The impact on company processes and procedures
- How the issue will impact other departments
- Whether the issue requires immediate action

Some Query Categories

Safety	•Outliers/trends in number of adverse events or SAEs per subject visit/site
Protocol & Study Compliance	•Number of significant protocol deviations per subject visit/site compared to average
Enrollment	•Number of screen failures compared to average across sites ; enrollment rate vs. average
Discontinuation	•Total number of discontinuations compared to average across all sites
Data Entry	•Total number of critical data fields entered vs. expected compared to the average across all sites
Data Quality	•Total number of queries; number of queries outstanding for X days & overall response time
Essential Documents	•Number of overdue or missing documents
On Site workload	•Staff turnover, PI presence

Monitoring

Monitoring is the act of overseeing the progress of a clinical trial and ensuring it is conducted, recorded and reported in accordance with the protocol, standard operating procedures (SOPs), GCP, and the applicable regulatory requirement(s). (ICH GCP 1.38).

- High-quality monitoring and trial oversight procedures are essential for avoiding the serious consequences that come from protocol deviations, poor data quality, and regulatory issues.
- Without adequate monitoring there is no assurance that your study conduct is compliant and that any instances of noncompliance are resolved properly.

Auditing

Auditing is a systematic and independent examination of trial-related activities and documents to determine whether the evaluated trial-related activities were 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). (ICH GCP 1.6)

- Think of it as a monitoring visit focused on the entirety of the study and drug, not just focused patient visits. Helps find systemic issues that need review.
- The **goals of both auditing and monitoring are the same**: to ensure that the trial is conducted properly, that participant safety is protected, and that data integrity is secured.

What Does Risk-Based Monitoring Mean?

- Risk based monitoring is an adaptive approach that **directs monitoring focus** and activities to the **evolving areas of greatest need** which have the **most potential to impact patient safety and data quality.**
- **Critical data that deserve the most attention relate to:**
  - Eligibility criteria, informed consent, primary and secondary endpoints, safety, investigational product accountability, HIPAA compliance, and data that would be the focus of an FDA inspection.

https://www.transceleratebiopharmainc.com/rbminteractiveguide/what-is-risk-based-monitoring-rbm/introduction/

Risk Based Monitoring

If site performance improves or diminishes, the amount of data monitored should change accordingly.

- A site might be very good at data collection, but lack experience with regulatory documents, so the focus of the monitoring visit should be adjusted and monitor may provide training / guidance for the site.
- Likewise if the site is strong with regulatory processes, but are making continued data entry errors, the focus would be on resolving the underlying problem with data entry.

Risk Based Monitoring

- Risk Based Monitoring makes the work of monitors more interesting, because it enables them to focus on data and processes most important to project success.
- Risk Based Monitoring allows monitors to function more as site managers and less as data checkers.
- Monitoring data that indicate the presence of a systemic risk, as opposed to random human error.
  - For example, if the instructions for an assessment are ambiguous, inter-rater reliability may be unacceptably low, jeopardizing the entire study.

Preparing for a Successful Remote Site Visit

- Monitor should be aware of time restrictions to obtain access and schedule accordingly. (EMR access, share drive access)
- Coordinators should close out queries from the previous visits.
- Be aware of any issues that might come up during the visit.
  - Reviewing deviations / SAEs and notes to file.
- Coordinators / sites are the experts on their participants. This knowledge helps fill in any gaps about missing visits or issues. These aren't always clear to people outside the site that don't know the participants (the monitor/sponsor).

Preparing for a Successful Remote Site Visit

- Have any questions ready to ask your monitor.
  - This is your scheduled time with the monitor and your site is the focus of the visit, so don't hesitate to ask.
  - It is likely that if you have a question other sites may have it too.
- If there is an SOP that helps explain a process have these available to the monitor. These may vary from site to site and may help avoid unnecessary queries.
- Arrange time for monitor to speak with PI.

Understanding the Monitoring Visit

- IMV findings are part of the process. It helps sites and monitors understand what to focus on and how to improve.
- Reviewing site specific procedures and providing guidance.
- Answering questions about data and resolving queries.
- Discussion about Corrective Action Preventative Action (CAPA) plan if needed.
- Debrief / close out for the visit.

The entire goal is to ensure patient safety.

What is a CAPA?

A corrective and preventive action (CAPA) plan is a series of actions taken to resolve a compliance issue, and most importantly, to prevent further recurrence.

How do I write a CAPA?

- A CAPA plan will focus on the immediate noncompliance and the broader scope of the problem.
- It involves investigating and understanding the issue, correcting the issue, and preventing the root cause. CAPAs can be used for audit or inspection observations, compliance improvement, or risk mitigation.
- Be realistic about what you include in the CAPA.

FDA Warning Letters - Form 483

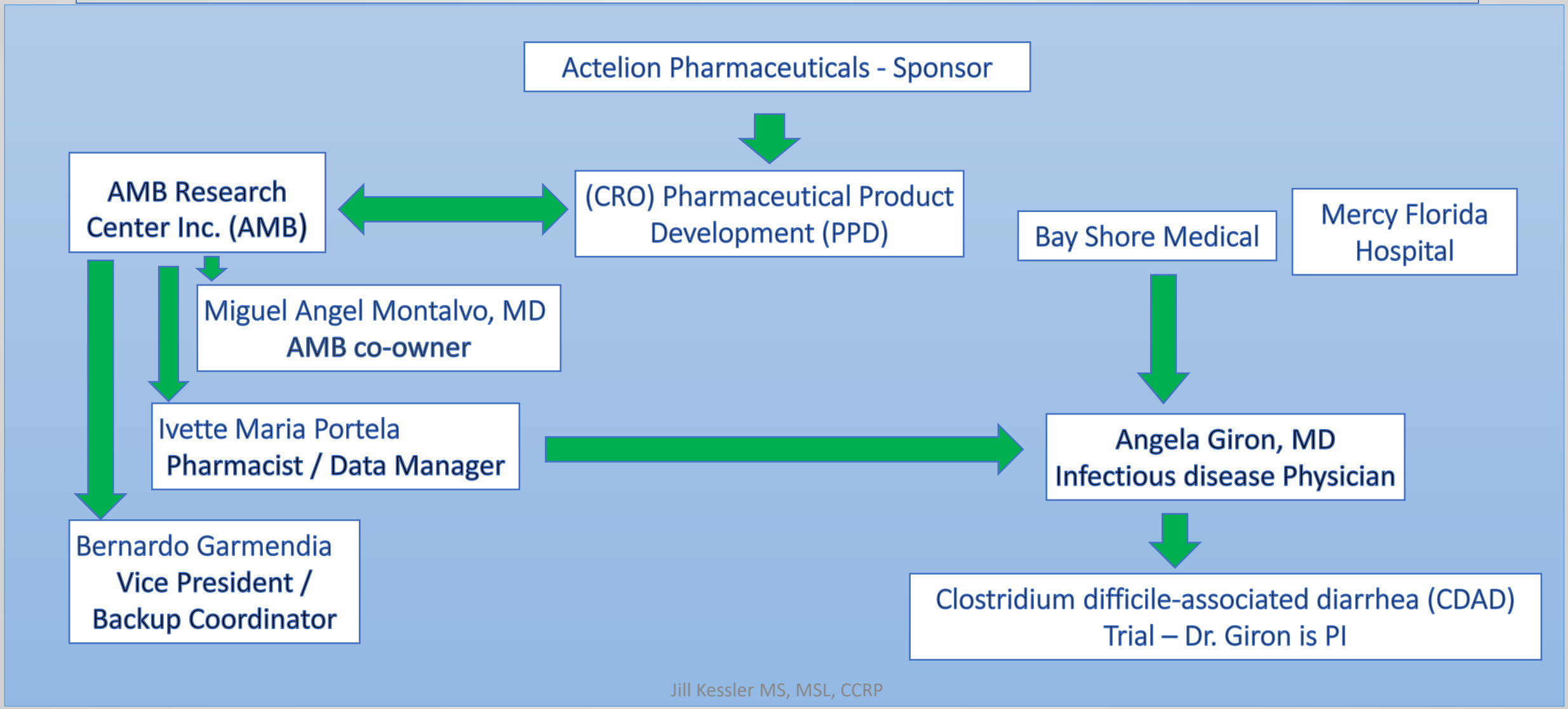
Failure to select qualified investigators and monitors by training and experience for conducting of a study [812.43(a) and (d)].

As a sponsor, you are responsible for selecting qualified investigators and monitors. Examples of your failure include, but are not limited to, the following:

a. You failed to ensure that **clinical investigators were qualified by training and experience** to conduct the study. During the inspection, you **did not provide documentation, such as a curriculum vitae, to show that the clinical investigators were qualified** to conduct this study.
b. You did not provide documentation to support that you have the **proper training and experience to appropriately monitor the study**.

https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/compliance-actions-and-activities/warning-letters

Case Study


Actelion Pharmaceuticals - Sponsor
AMB Research Center Inc. (AMB)
(CRO) Pharmaceutical Product Development (PPD)
Miguel Angel Montalvo, MD
AMB co-owner
Ivette Maria Portela
Pharmacist / Data Manager
Bernardo Garmendia
Vice President / Backup Coordinator
Bay Shore Medical
Mercy Florida Hospital
Angela Giron, MD
Infectious disease Physician
Clostridium difficile-associated diarrhea (CDAD) Trial – Dr. Giron is PI

Angela Giron, MD

Dr. Angela Giron graduated from Universidad Del Valle Escuela De Medicina, Colombia.

- She completed residency at the University of Pennsylvania, and a fellowship at Jackson Memorial Hospital in Miami.
- Dr. Giron has been board-certified in internal medicine and infectious disease physician since 2007.
- Dr. Giron's practice is affiliated with Bay Shore Medical Center which is adjacent to Mercy Hospital.

Clostridium Difficile-Associated Diarrhea (CDAD) Trial

- In September 2015, while working in an office on campus at Mercy Hospital in Miami, Ms. Portela (pharmacist/data manager) learned about an upcoming clinical trial for treatment of symptoms of Clostridium difficile infections and decided that AMB Research Center Inc. (AMB) should participate.
- Ms. Portela needed a doctor to sign on as the principal investigator (PI) for the trial sponsored by Actelion Pharmaceuticals and run by the clinical research organization (CRO) Pharmaceutical Product Development (PPD).

CDAD Trial Finding an Investigator

- Ms. Portela's husband is AMB co-owner Dr. Montalvo, (not practiced medicine since leaving Cuba in 2011), and his business partner, Mr. Garmendia, AMB's vice president and backup study coordinator, (had no medical training at all).
- Dr. Montalvo and Ms. Portela researched infectious disease doctors. They found and then targeted Dr. Giron - whose practice was adjacent to Mercy.

CDAD Trial Finding an Investigator

- Dr. Giron met with Ms. Portela and Dr. Montalvo where they discussed AMB, and clinical trial opportunities.

- After these meetings, Dr. Giron agreed to be the PI on the Clostridium difficile-associated diarrhea (CDAD) trial. A Clinical Trial Agreement and supporting documents, **including 1572 were signed and submitted.**

CDAD Trial Study Start up

- A week before they met, **unbeknownst to Dr. Giron, Dr. Montalvo falsified Dr. Giron's resume to indicate that she had been employed by AMB since 2014 and had clinical trial experience**—the first of many fabrications.

- Ms. Portela **emailed the doctored resume to PPD**, indicating that Dr. Giron was working with AMB.

CDAD Trial

- The next month, Ms. Portela assured Dr. Giron the trial would have no more than eight participants and would conclude in 2016.

- Dr. Montalvo convinced her that she would be able to **delegate responsibility to him to conduct the patient examinations, obtain the necessary samples, interview the patients for any adverse effects and other matters** that were important to the study. He would share that information with her, and **she would be able to sign off.**

CDAD Trial

- The CDAD trial didn't start until 2016, at which time AMB faced another problem: finding participants with the type of diarrhea the study drug was designed to treat.
- Dr. Montalvo and AMBs solution to enrollment was to dip into their database from previous trials, screen and pay family and friends and even use their own stool and blood samples—**fabricate the data, hide the falsehoods from Dr. Giron (and the CRO) and get her to unwittingly sign off on the fraud.**

CDAD Trial

- Under Dr. Montalvo's guidance, **falsified informed consent forms** (using the names and personal identification information) of individuals who had previously been screened and thus had no knowledge they were being potentially enrolled in the CDAD trial, government court records show.
- The AMB staff also **used their own specimens and those of friends** and family, some of whom were paid $120.

Sponsor / Actelion Audit Findings CDAD Trial

Actelion's concerns with AMB's clinical trial data included:

1. "all 22 randomized subjects reached clinical cure at approximately the same time;
2. the start of onset of diarrhea was almost the same for every randomized subject;
3. every randomized subject had the same number of bowel movements within 24 hours of randomization;
4. the drug kits, questionnaires, and diaries were neat and clean and showed no signs of use;
5. all medication sachets were opened in the same manner; and
6. the validity of the signatures on the informed consent forms."

Actelion then sent FDA "written notification of possible scientific misconduct by AMB."

Essential Document Findings

Unfortunately for Dr. Giron was the issue of the informed consent to the patients, **which was not delegable, but she did delegate this task.**

- The linchpin of the case against her - she signed the 1572.

- U.S. Department of Justice, Office of Public Affairs, "Florida Medical Clinic Owner and Pharmacy Technician Sentenced to Prison in Clinical Trial Fraud Scheme," news release, November 30, 2023, https://bit.ly/3IIssSS.

This order is applicable May 2, 2024.

- The Food and Drug Administration (FDA) is issuing an order under the Federal Food, Drug, and Cosmetic Act (FD&C Act) **permanently debarring** Angela Maria Giron, M.D. from providing services in any capacity to a person that has an approved or pending drug product application.
- FDA bases this order on a finding that Dr. Giron was convicted of a **felony** under Federal **law for conduct relating to the development or approval, including the process for development or approval, of any drug product**.

https://www.jdsupra.com/legalnews/AngelaGiron

I. Background

Section 306(a)(2)(A) of the FD&C Act requires debarment of an individual from providing services in any capacity to a person that has an approved or pending drug product application if FDA finds that the individual has been convicted of a felony under Federal law for conduct relating to the development or approval, including the process of development or approval, of any drug product. On September 11, 2023, Dr. Giron was convicted as defined in section 306(l)(1) of the FD&C Act in the United States District Court for the Southern District of Florida-Miami Division when the court accepted her plea of guilty and entered judgment against her for one count of Conspiracy to defraud the United States in violation of 18 U.S.C. 371. The underlying facts supporting the conviction are as

Florida pharmacist and clinic owner found guilty in clinical trial data fabrication scheme

By NICEVILLE.COM – September 17, 2023 No Comments 4 Mins Read

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/ Physicians / Dr Angela Maria Giron MD

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HCA Florida Mercy Hospital

NATIONAL ARCHIVES

FEDERAL REGISTER

The Daily Journal of the United States Government

Notice

Angela Maria Giron: Final Debarment Order

A Notice by the Food and Drug Administration on 05/02/2024

Lessons Learned from Case

- First and most importantly (especially for a principal investigator) is do not delegate non-delegable things!
- If you are unsure about the validity of your data, compare this to suspicious data and it can assist you in making a determination of whether fraud may be happening. (Same dates, times, are things too perfect?)

The majority of clinical research facilities, especially on the university level are doing legitimate research.

Conclusion

- Essential documents are as important to the study as data input.
- Monitoring visits are not intended (and should not be) used to intimidate staff.
- Monitors have been study coordinators / data managers themselves, so there should be a level of understanding and respect for the work your site does.
- Speak up anytime something seems off and contact your manager. There should be transparency on both parts.
- You can also notify your compliance team for assistance.

Questions?

Thank you for inviting me to give this presentation today.

Thank you to everyone in attendance!

Jill Kessler

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