Oh my! The Unique Challenges of Monitoring Investigator Initiated Trials (IITs)

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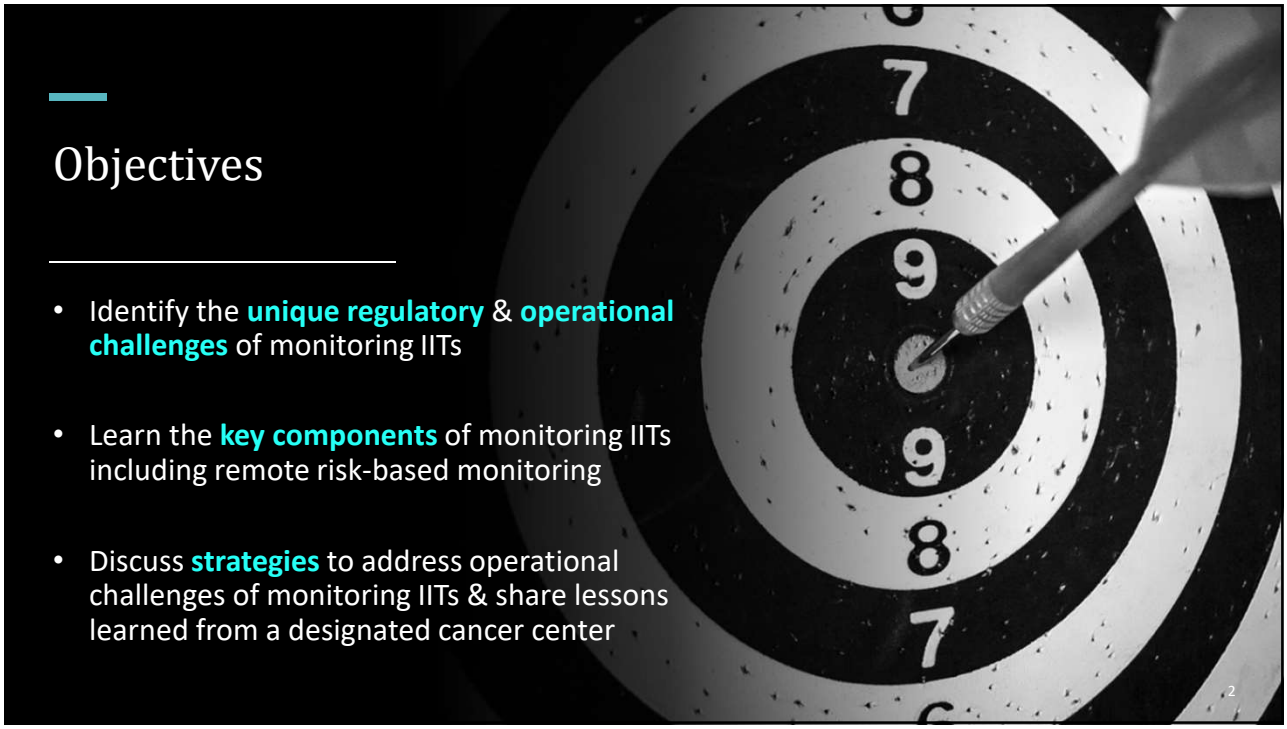
1

Objectives



- Identify the **unique regulatory** & **operational challenges** of monitoring IITs
- Learn the **key components** of monitoring IITs including remote risk-based monitoring
- Discuss **strategies** to address operational challenges of monitoring IITs & share lessons learned from a designated cancer center

2

Investigator Initiated Trials (IITs)

- Are clinical studies initiated and managed by **non-pharmaceutical company researchers**, like individual investigators, institutions, collaborative study groups or cooperative groups

> ***Sponsor-Investigator*** means an **individual** who both **initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed.**
>
> **Food and Drug Administration 21CFR312.3**

- May or may not involve an Investigational New Drug Application **(IND) or** Investigational Device Exemption **(IDE)** with FDA
  - 21CFR312, 21CFR812, 45CFR46
- May or may not be **funded / supported** by industry, such as: drug product, comparator drug, financial support

3

Principal Investigator

- **Overall study conduct**
- Medical oversight, maintain case histories, reports
- Informed consent & source documentation
- Subject eligibility, data integrity, delegation of authority
- Protect rights and safety of subjects
- Control investigational product, protocol adherence
- Training, regulatory
- More…

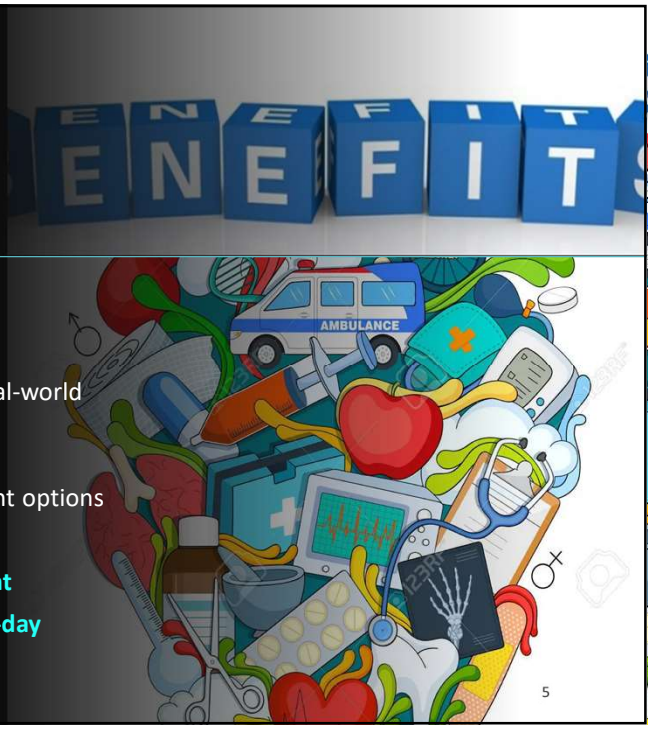
Responsibilities

Sponsor

- Select qualified investigators
- Provide Investigators with necessary information
- **Ensure proper monitoring**
- Ensure ethical (IRB) review and approval
- Prepare and submit applications to regulatory agencies
- Inform IRBs and regulatory agencies of significant new information
- Ensure Good Clinical Practices
- More…

4

IIT Benefits



- Expand product **knowledge**, including **safety**
  - Greater weight give to **non-industry data**
  - Study use in different indication (**off-label use**)
  - **Safety** and **effectiveness** data generated in a real-world setting
  - Comparison of two different treatment options
- Evaluate **cost-effectiveness** of two or more treatment options
- Potentially fewer **conflicts of interest**
- Assists in hospital /state / nation **policy development**
- Answers research questions for physicians in **day-to-day practice**
- **More….**

5

IIT Selected **Challenges & Risks:** Regulatory, Compliance & More

Lack of:

- **Resources**
- **Monitoring / monitoring plan**
- **Investigational product** oversight
- Adherence to **institutional policies**
- Of / maintaining an **IND/IDE**
- **Regulatory documents**
- **Insurance** coverage / **indemnification**

- Inadequate **funding**
- Unclear **protocols**
- **Ghost**-written **protocols**
  - **Phase IV "marketing studies"**
- **Adverse event** reporting to funder & IRB inconsistencies
- Inconsistent **documents**

6

When do IITs need an IND?

A clinical investigation of a marketed drug is **exempt from the IND requirements** if **ALL** of the following criteria for an exemption in 21CFR 312.2(b) are met:

- The drug product is **lawfully marketed** in the U.S.
- The Investigation is **not intended to be reported to FDA** a well-controlled study in support of a **new indication**, and no there is **no intent** to use it to support any other significant **change in labeling of the drug**
- In the case of a prescription drug, the **i**nvestigation is **not intended to support** a significant **change in advertising** for the drug
- Investigation **does not involve a different route of administration, dose, patient population, or significant increased/decrease of risk** (or decreases the acceptability of the risk) associated with the sue of the drug product (21 CFR 312.2(b)(1)iii))
- The investigation is conducted in compliance with the requirements of § 312.7 (i.e., the investigational is **not intended to promote or commercialize** the drug product)
- The investigation is **conducted in compliance with** requirement for review of **IRB** (21 CFR part 56) and with the requirements for **informed consent** (21 CFR part 50)

7

FDA IIT Related Warning Letter Citations….

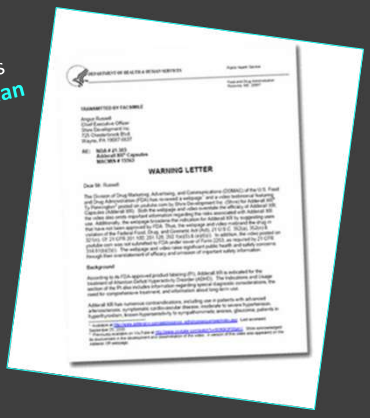
In FY 2021, FDA issued 80 warning letters and 43 import alerts related to drugs. [1]

"**You failed to submit an IND** for an investigational new drug 21 CFR 312.2(a) [21 CFR 312.20(a), 312.20(b), and 312.40(a)]."

"**Not all changes** in research activity were **approved** by an **IRB** prior to implementation"

"An investigation was **not conducted** in accordance **with the signed statement of investigator** and investigational plan."

"**You did not ensure** that the investigation was conducted according to the **investigational plan** (21CFR312.60)"


WARNING LETTER

"**Failure to ensure proper monitoring** of the study…… "

"…**Adverse Events** and deaths occurred…and **were not included** in the **Annual Report**…."

"You were **unable to provide any documentation** which demonstrates what this study was **monitored** to ensure it was conducted in accordance with the general investigational plan."

8

FDA Warning Letter Re: Fatal Experiment: Hexamethonium Inhalation

"Mechanisms of Deep Inspiration-Induced Airway Relaxation"

Funded by the National Institutes of Health (NIH)

Ellen Roche

Violations:

- **"causing the introduction or delivery of an unapproved new drug in interstate commerce"**
- **Failure to:**
  - **Submit an IND**
  - **Provide adequate animal toxicity data**
  - **Provide a summary of previous human studies with hexamethonium**
  - **Provide dosing rationale**
  - **Describe procedures for identifying, collecting/reporting AEs**
  - **Notify & obtain IRB approval for changes in protocol**
  - **Promptly report unanticipated problems**

https://ahrp.org/fda-warning-letter-re-fatal-experiment-hexamethonium-inhalation_johns-hopkins/ 9

FDA Warning Letter Re: (b)(4)

"An Open-label Pilot Study to Assess the Efficacy and Safety of (b)(4) in Subjects and Their Quarantined Close Contacts Who Test Positive for COVID-19."

Kimberly Dunn, PI

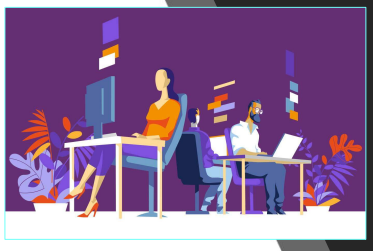
Violations:

- **Failure to:**
  - **Submit an IND**
  - **Retain records (case histories, informed consent)**
  - **Maintain adequate records of shipment**
  - **Obtain appropriate informed consent – exculpatory language "waive, release, hold harmless"**

10

https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/kdunn-and-associates-pa-dba-healthquilt-611864-02162021

What is Monitoring?



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,
  - Standard Operating Procedures (SOPs),
  - Good Clinical Practice (GCP), and
  - The applicable regulatory requirement(s)."
  - **ICH/GCP E6 (R2) 5.18 Monitoring**
- Monitoring is ongoing!
- Monitoring is NOT auditing.

12

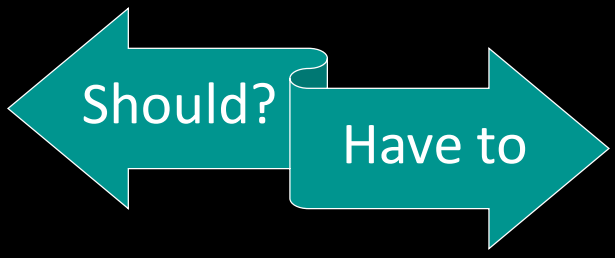
Purpose of Monitoring

- The purposes of trial monitoring are to **verify** that:
  - The rights and **well-being of human subjects** are protected.
  - The reported trial **data** are **accurate, complete, and verifiable** from **source documents**.
  - The conduct of the trial is in **compliance** with the currently approved **protocol**/amendment(s), with **GCP**, and with the applicable **regulatory requirement(s).**
  - **ICH GCP 5.18.1**

13

Monitoring IITs

Risk Decision



IND / IDE

14

Monitoring Essentials

- Standard Operating Procedures (SOPs)
- Individualized Monitoring Plans
- Risk-Based Monitoring
- Remote versus On-site Monitoring
- Schedules
  - Coordination with auditing/quality assurance
- Follow-Up
- Report(s)
- Tools needed

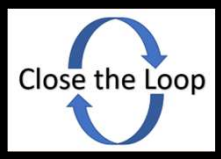
15

IIT Monitoring Common Oversights & Challenges

- Protocol design & conflicting language
- Monitoring plan or an individualized monitoring plan
- Data capture alignment
- Adverse Event (AE) / Serious Adverse Event (SAE) / Unanticipated Problems (UP)
- Source documentation

16

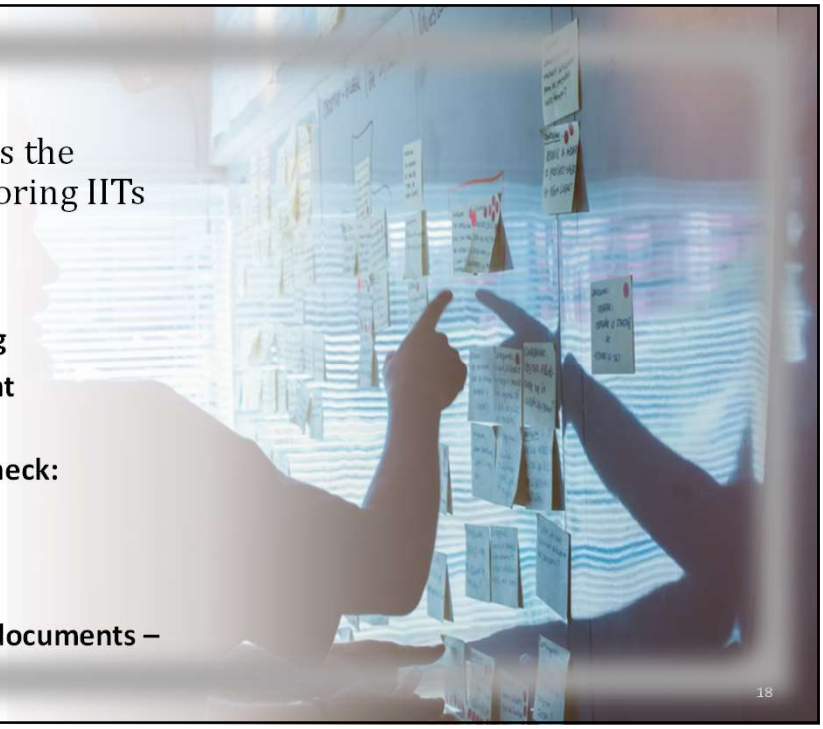
IIT Monitoring Common Oversights & Challenges



- New - Working remotely
  - Delegation of Authority & Training
  - Informed Consent
  - Investigational product monitoring
- Regulatory maintenance / Institutional Review Board (IRB)
- IND / IDE maintenance (Annual Reports)
- **Monitoring reports – close the loop**
- More….

17

Strategies to Address the Challenges of Monitoring IITs



- **Management of Monitors**
  - **Insourcing vs. outsourcing**
- **Budget for monitoring upfront**
- **Involve monitors in protocol development & start-up to check:**
  - **Protocol**
  - **Data points**
  - **Case Report Forms**
  - **Consistency between all documents – "document concordance"**

18

Strategies to address the challenges of monitoring IITs

- Create a monitoring plan before start-up
  - Revisit monitoring plan during the study lifecycle
- Monitor early…
- Schedule meetings / enhanced communication with study teams

19

Monitoring – Where We Are, Where We Came From

Monitoring Function Observation	Correction
1. Plans not tailored	1. Develop risk-based plans
2. Processes inefficient, long, inconsistent	2. Revise process to shorten monitoring visit
3. Reports too long, confusing, inefficient, too many	3. Streamline to 1 report & revise process to close-out visit sooner
4. Oversight inefficient – Protocol Management Committee	4. Revise reporting process to PMC
5. Organizational structure flat	5. Restructure department- hire new staff, supervisors
6. Other duties disrupt monitoring activities	6. Remove/revise other duties to not interfere with monitoring duties

20

Questions to ask…

- Do we conduct any IITs?
- Who determines if IITs need an IND / IDE?
- Who submits / maintains the IND /IDE with the FDA?
- Do we have monitors and monitoring plans for IITs?
  - Are the monitoring plans tailored to individual IITs?
- How often are IITs monitored?
- How is the data captured and analyzed?
  - Are Case Report Forms (CRFs) tailored for each study?
- What people and departments and people are
- involved in IIT planning, oversight and execution?
- More…

21

Summary

01	02	03	04	05	06
Knowing your universe!	Planning for monitoring is critical • Using a risk-based approach • Involving monitoring from the start	Budgeting for monitoring	Determining and maintaining IND/IDE	Aligning IIT with data capture, analysis and study objectives	Closing the loop • Follow-Up! Follow-Up! Follow-Up!

22

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Thank You!

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23

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- FDA Guidance for Industry: Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring, August 2013
- A Risk-Based Approach to Monitoring of Clinical Investigations Questions and Answers Guidance for Industry – Draft FDA Guidance, March 2019
- FDA Guidance for Industry: Investigational New Drug Applications Prepared and Submitted by Sponsor-Investigators – Draft Guidance May 2015
- FDA Guidance for Industry: E6 (R2) Good Clinical Practice: Integrated Addendum to ICH E6 (R1), Procedural, March 2018
- 21 CFR 312; 21 CFR 812; 45 CFR 46
- International Council for Harmonization / Good Clinical Practices (ICH/GCP) E6(R2)
- TransCelerate: https://www.transceleratebiopharmainc.com/initiatives/risk-based-monitoring/

24