SCARY COMPLIANCE!

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Prologue:
What do we need to be compliant with?

https://PollEv.com/socrabaltimore952

HHS Definition

Non-Compliance – Failure of an investigator to follow the applicable laws, regulations, or institutional policies governing the protection of human subjects in research, or the requirements or determinations of the Institutional Review Board (IRB), whether the failure is intentional or not.

- *Continuing non-compliance* - A pattern of recurring non-compliance that either has resulted, or, if continued, may result in harm to subjects or otherwise materially compromise the rights, welfare and/or safety of subjects, affect the scientific integrity of the study or validity of the results. The pattern may comprise repetition of the same non-compliant action(s), or different non-compliant events. Such non-compliance may be unintentional (e.g. due to lack of understanding, knowledge, or commitment), or intentional (e.g. due to deliberate choice to ignore or compromise the requirements of any applicable regulation, organizational policy, or determination of the IRB).
- *Serious non-compliance* - Non-compliance, whether intentional or not, that results in harm or otherwise materially compromises the rights, welfare and/or safety of the subject. Non-compliance that materially affects the scientific integrity or validity of the research may be considered serious non-compliance, even if it does not result in direct harm to research subjects.

(This definition is cited in Policies 3014-500, 3014-801 and 3014-802)

Chapter 1:
Ghostly Data

By: Scott Wehage, M.S., CCRP

When I realized what was happening, my heart sank....

The fallout and the fix....

Chapter 2: A researcher cuts their R01 teeth

By: Casey Jackson MS, CCRP

In a diabetes clinic, not long ago….

- Junior PI
- Ventured into the foggy fields of investigator-initiated R01 trials….
- HIIT exercise intervention
- Self-quality assurance review plan
- Independent DSMB reviewing AEs, enrollment, safety q6mo

2 years of research go by…

Enrolled 33 out of 60 goal

12 participants withdraw early, citing intervention too tiresome

PI provides QA report: no deviations, minimal AEs

DSMB motioned to continue, suggesting a plan for participant retention

The PI wakes to find they are the lucky winner of a random institutional routine audit, to be received in 2 weeks' time….

The audit report is revealed…

- “It appears the PI did not conduct a full QA review of their study. Multiple missing sections of the regulatory binder; missing participant procedures excessive”
- No manual of procedures or SOPs present. Documentation of protocol procedures inconsistently maintained across 5 different source methods (excel direct entry, excel transcribed from hard copy, REDcap direct entry, hard copy transcribed to REDCap, hard copy only); unclear as to what study team member carried out procedures.
- Non-compliance with federal regulations: “Over 20% of participants enrolled into exercise intervention without evidence of protocol required participant primary doctor approval”
- Multiple procedures carried out by non-delegated study team members.
- Missing documentation of protocol training material for all study team members.

A training session and deep corrective actions commence…

Lessons Learned:

- QA is more than just checking to see if there is something present in the file. Requires critical thinking and cross checking. Every data point has a story.
- Slew of RNIs submitted to the IRB with corrective actions:
  - Manual of Procedures created
  - Study team members re-trained, documentation present, DOA log corrected
  - Assessment of harm conducted on participants included without primary doctor permission, IRB notification, protocol modification to allow for physician PI to assess for exercise appropriateness.
  - PI conduct a full audit of all participants, created roster of missing data, deviations, RNIs, and accountability report to send to DSMB for ad-hoc review.

The study lives on to see another day…

CHAPTER 3: THE COORDINATOR HAUNTED HOUSE

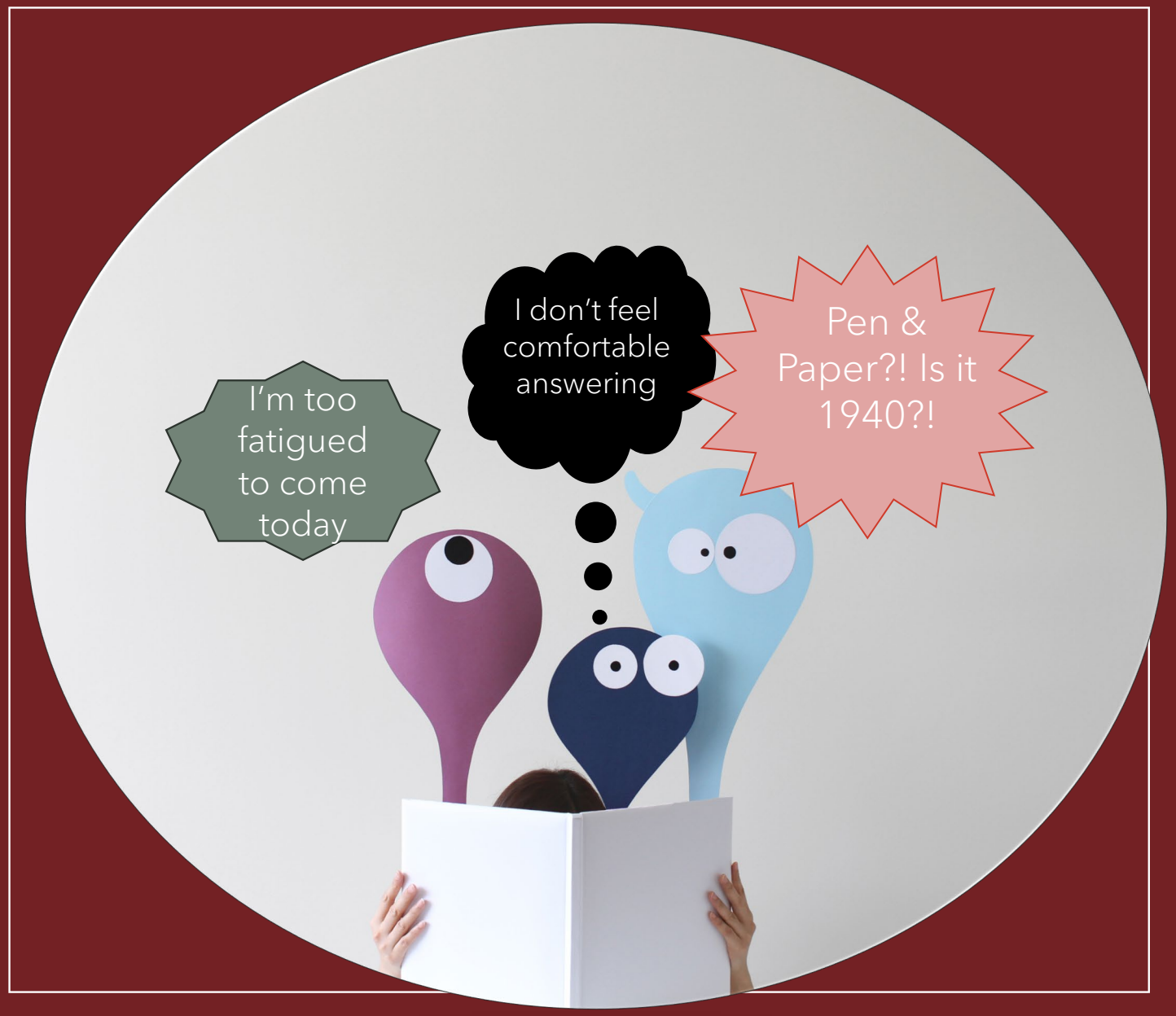
By: Rachel Markley, MPH, CCRP

SOMEWHERE…IN A WORLD OF IITS AND PILOT STUDIES

Eager scientists added to a cauldron…

- A sample size with a neurological disability
- A sprinkling of the perfect endpoints
- Oil of interim analysis
- Root of the Tree of Big Ideas

After simmering for 24-hours, with an occasional sampling by IRB members, emerged



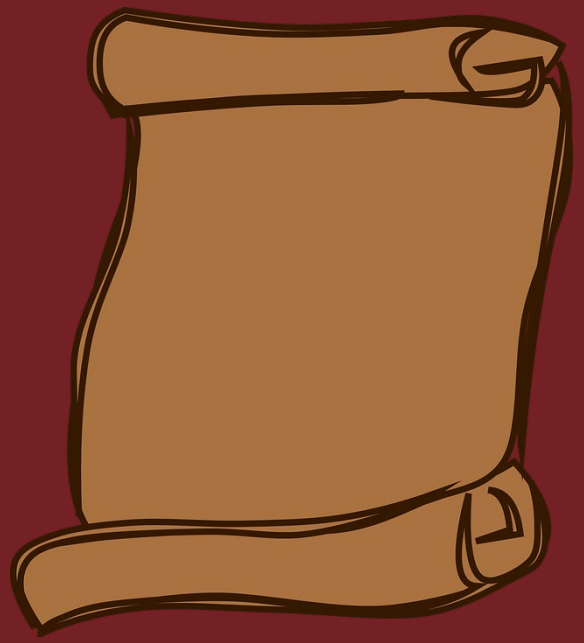
PARTICIPANTS 11-001 & 11-002 EXIT THE STUDY WITH MINOR DEVIATIONS

They are followed by the making of a coordinator' haunted house

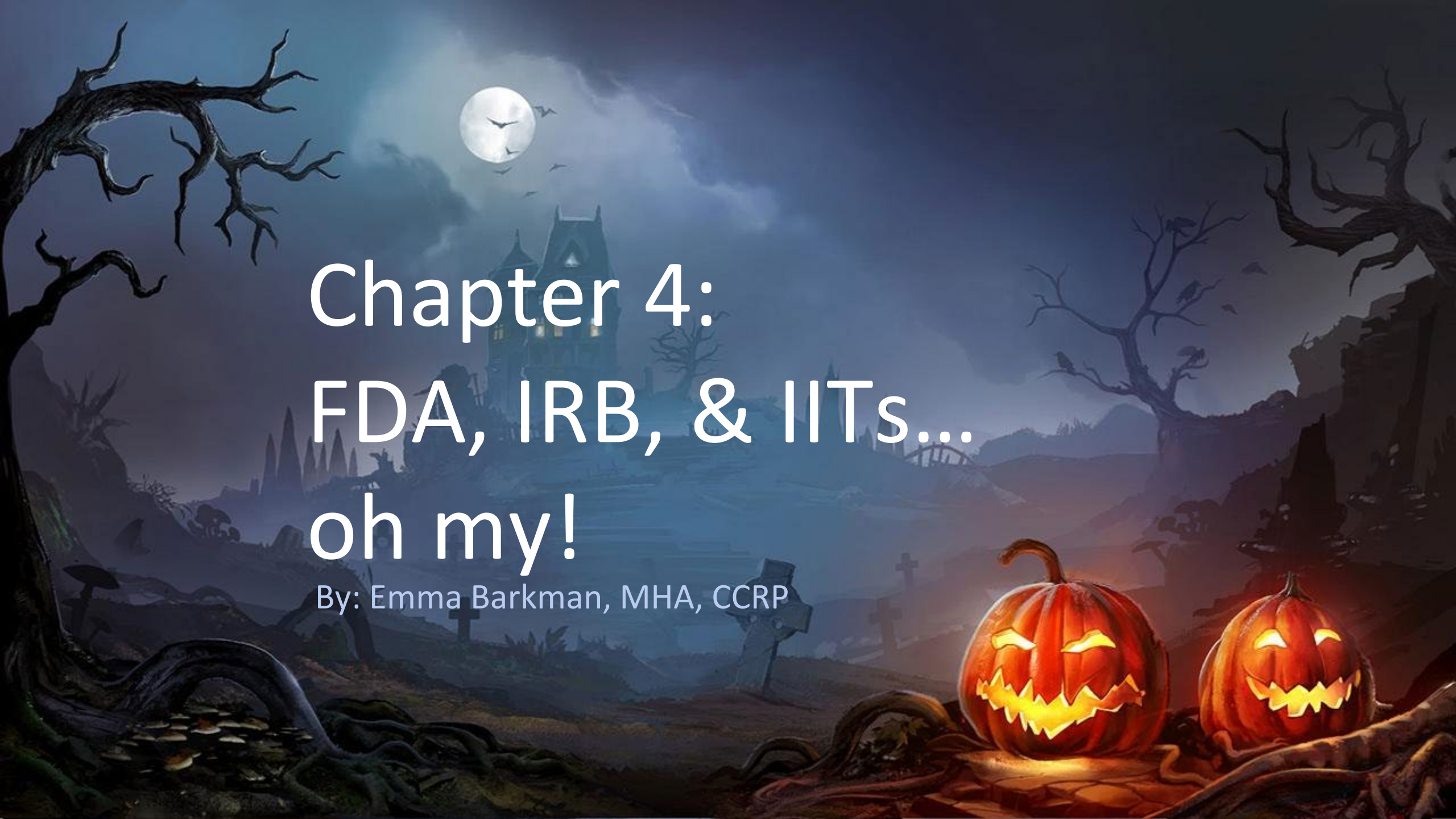
AT THE EXIT OF THE HAUNTED HOUSE APPEARS

The formidable, magical –

Witch of the FDA Consultant



THE RESOLUTION



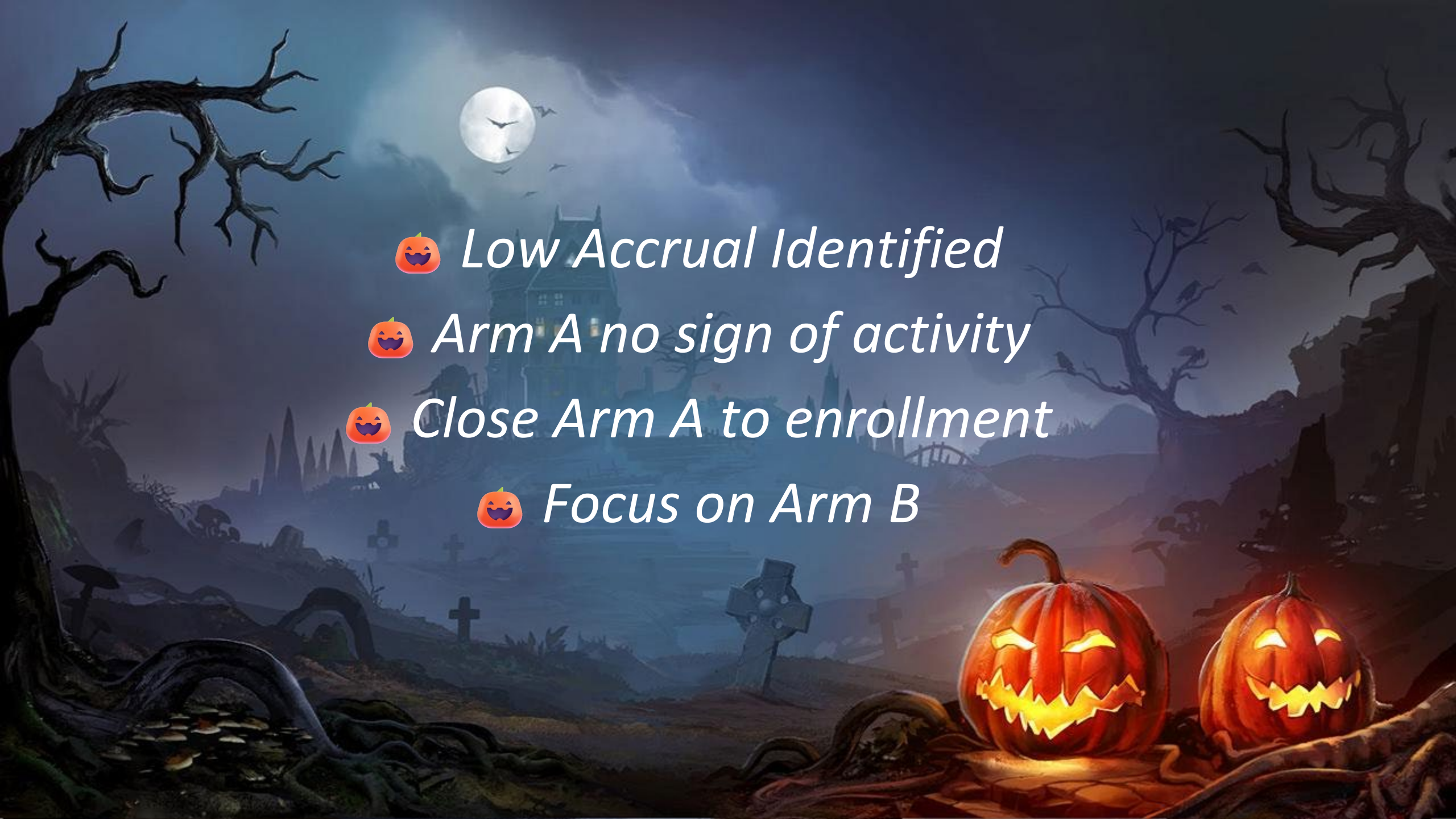
Chapter 4: FDA, IRB, & IITs… oh my!

By: Emma Barkman, MHA, CCRP

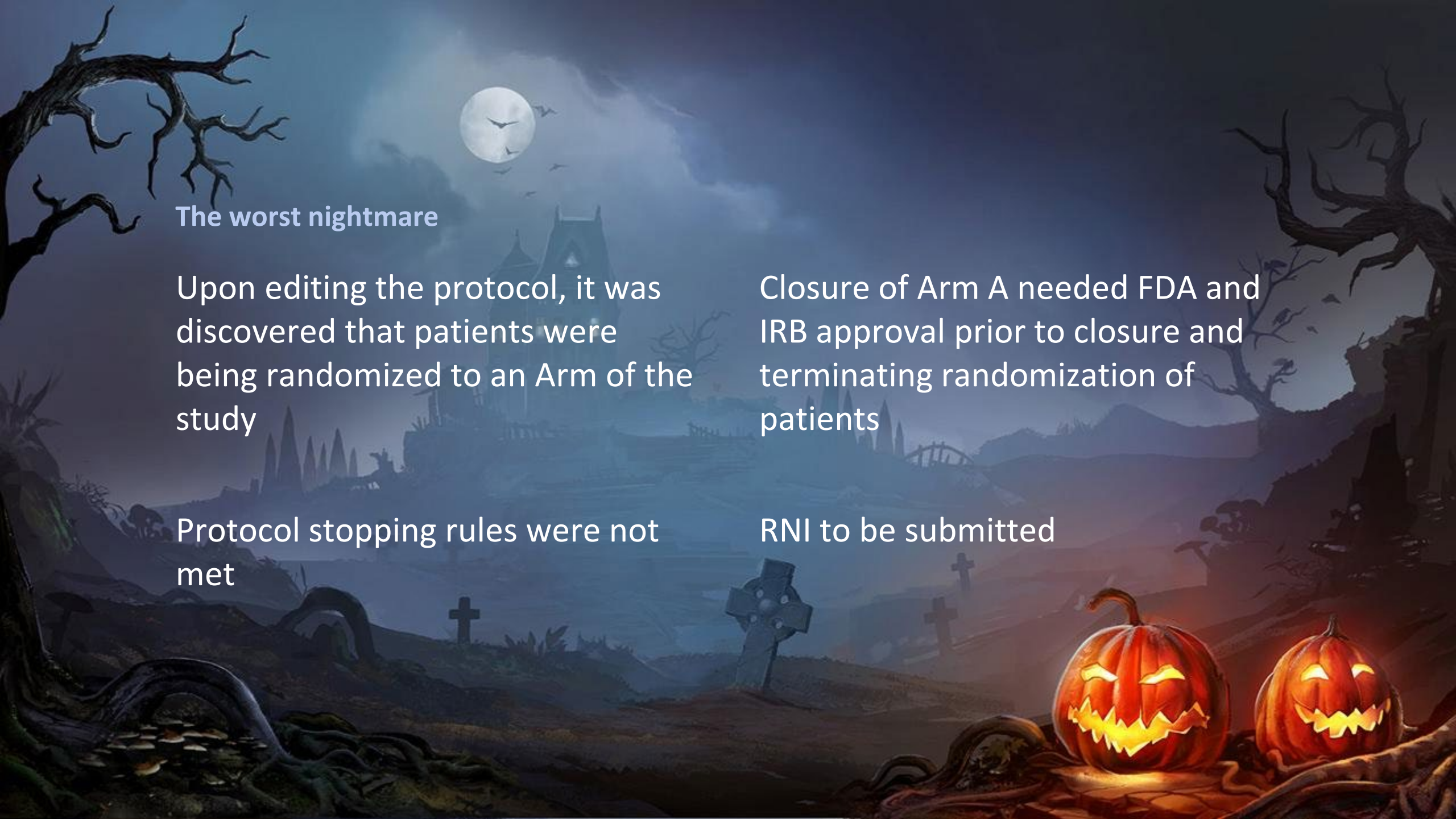
Definitions:

- **Investigator Initiated Trial (IIT):** The investigator conceives the research, develops the protocol, and serves as sponsor investigator.
- **Investigational New Drug (IND):** Application is submitted to FDA if a drug (or biological product) not previously authorized for marketing in the US is intended to be used for the purposes of clinical investigation or, in certain cases, for the purposes of clinical treatment when no approved therapies are available.
- **Protocol Amendment:** Once an IND is in effect, a sponsor shall amend it as needed to ensure that the clinical investigations are conducted according to protocols included in the application.
- **UMGCCC Low Accrual:** Protocols in their annual review cycle that have not accrued 30% of lower target accrual at the open to accrual date and each annual anniversary thereafter will be identified for low accrual review.


It started off like
any typical
request…


Low Accrual Identified
Arm A no sign of activity
Close Arm A to enrollment
Focus on Arm B


But then!!!
Two weeks later…



The worst nightmare

Upon editing the protocol, it was discovered that patients were being randomized to an Arm of the study

Protocol stopping rules were not met

Closure of Arm A needed FDA and IRB approval prior to closure and terminating randomization of patients

RNI to be submitted

The capa

Corrective Action

- Immediately placed protocol on hold
- Protocol amendment and updated ICF submitted to both FDA and IRB
- RNI submitted
- No patients to be enrolled until FDA and IRB approval

Preventative Actions

- Work Instruction Update
- Training
- Ongoing Monitoring

Monitoring & Evaluation

- Follow up Review
- Internal Monitoring/ Auditing

Lessons learned

- Slow down and inspect all aspects of a request
- Communicate!
- Review guidance documents
- Reach out for clarification

Chapter 5: Informed Consent Nightmares

By: Jill Kessler MS, MSL, CCRP

What is informed consent?

Informed consent is one of the founding principles of research ethics. Its intent is that human participants can enter research freely (voluntarily) with full information about what it means for them to take part, and that they give consent before they enter the research.

Signing informed consent

For an oncology trial, the participants are admitted to inpatient service and then once worked up by physicians informed consent can be obtained.

Since the participants are very sick, they are admitted as inpatients and stay for several weeks.

A coordinator didn't want to wake the sick participants and was signing their name and pre-dating ICFs for participants.

What happened?

Coordinator didn't understand that they were being non-compliant. They just wanted to make things easier for the participants.

Corrective action included – retraining on informed consent processes. The coordinator will only sign ICF in presence of participant when they also sign and date.

All pre-signed ICFs were shredded.

What is a screen failure?

Screen failure - occurs when a subject who has given informed consent does not meet the eligibility criteria for a study after undergoing screening procedures. Screen failures are not considered to be enrolled in the study.

What happened?

During an internal audit to prep for a sponsor audit, the QA team requested to review all informed consents.

This was a drug trial, so there were more participants screened than enrolled on the study.

Top enrolling site – audit to review charts and data for our site.

What happened?

Auditor requested the binder with the screen fail participant informed consents to review for compliance.

Coordinator had thrown out all the screen fail informed consents since, "they never went on study".

Corrective action included: Coordinator removed from study team and left the University. States they were never trained on what to do with screen fail consents.

Obscuring information

Using whiteout in a research study is generally not acceptable practice as it obscures the original data, making it difficult to verify and potentially compromising the integrity of the study results.

Obscuring information

Data Integrity Concerns:

Whiteout can hide mistakes or deliberate alterations, making it impossible to trace how the data was originally recorded.

Good Documentation Practices (GDP):

Most research institutions and regulatory bodies adhere to GDP which strictly prohibit the use of whiteout in study documentation.

Proper Error Correction Method:

The standard method for correcting errors in research documents is to draw a single line through the incorrect entry, initial, date, and write the correct information next to it.

What happened?

Participant was enrolled on a study and new guidance from the IRB required re-consent of all enrolled participants.

While reviewing consent forms and re-consents there were signatures that did not match from the previous consent, and there was white out on the consent form and the drug diary.

Corrective action included : retraining on how to correct errors, removal of coordinator from the study team.

Reminder: Inspect your adult candy before you eat it.

Restorative Botanicals LLC

Company products were found to be adulterated because thdy were not prepared, packed or held under conditions that meet GMP.

Violations notes in FDA's warning letter include failure to establish an identifiy specification for each component used in the manufacture of a dietary supplement and failure to establish product specifications for the identity of the finished batch.

The copany relied only on physicial characteristics – color, smell, and taste – for identification of certain ingredients in its products and failed to provide toxic element specifications for each of its mushroom components.

Definitely not a treat!

Chapter 6

Buckle up for a wild Ride!

By: Aryn Knight, BS, CCRP

Meet Jesse Gelsinger

- Jesse was born with Ornithine Transcarbamylase (OTCD) Deficiency.
- A rate genetic defect that interferes with the ammonia being metabolized by the liver.
- Jesse had a mild case and was able to manage daily through restrictive diet and medications.

Meet Jesse Gelsinger

- Jesse was born with Ornithine Transcarbamylase (OTCD) Deficiency.
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- Jesse had a mild case and was able to manage daily through restrictive diet and medications.

The Study....

- **Gene therapy study sponsored by Genovo.**
- **Goal:** To introduce a functional OTC gene into his liver cells using a modified adenovirus as a delivery vehicle.
- **Procedure:** The virus, carrying the correct gene, was injected into his liver.

Biogen

Genovo is a gene therapy company that was founded in 1992 by Dr. James M. Wilson and Marann Grossman.

Penn
UNIVERSITY of PENNSYLVANIA

The Financial Web....

Genovo gave Penn $21 million over 5 years for sponsored research.

Penn holds 5% equity in Genovo.

Dr. Wilson holds 30% equity in Genovo.

Dr. Grossman is the CEO/COO of Genovo.

Penn's IHGT is run by Dr. Wilson and previously Dr. Grossman

But Wait…

There is more!

- Jesse was consented to the study on a consent form that had been altered from the IRB approved consent.
- The altered consent removed the statement that monkeys had died of a clotting disorder and severe liver inflammation after being injected.

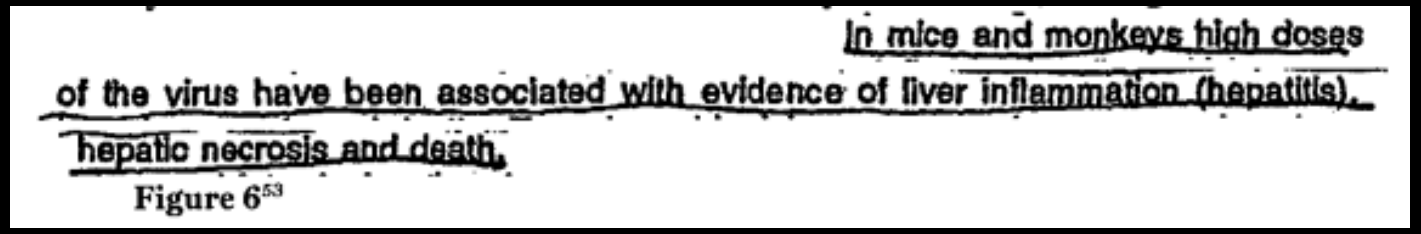
In mice and monkeys high doses of the virus have been associated with evidence of liver inflammation (hepatitis), hepatic necrosis and death.

Figure 6[53]

- PLUS – Jesse's serum ammonia on the day of treatment fell outside the protocol approved inclusion serum. But the PI said his increase level was not clinically significant.
- Dr. Wilson later admitted that he deemed the consent and protocol as "living documents with changes occurring in real time."

The Tragic Outcome:

Adverse Reaction:

- Gelsinger experienced a severe immune response to the adenovirus, leading to multiple organ failure.

Death:

- Four days after the injection, he passed away.
- Jesse died 3 months after turning 18.

The Aftermath:

- **Investigation:** The incident sparked a thorough investigation into the conduct of the trial and the practices of gene therapy research.
- **Ethical Concerns:** The case raised serious ethical questions about informed consent, risk assessment, and the potential conflicts of interest within research institutions.
- **Regulatory Changes:** The FDA and other regulatory bodies implemented stricter guidelines for gene therapy trials to prevent similar tragedies.

Key Lessons:

- **Informed Consent:** The importance of ensuring patients fully understand the risks and benefits of experimental treatments.
- **Risk Assessment:** The need for rigorous evaluation of potential side effects and adverse events.
- **Conflict of Interest:** The potential dangers of financial incentives influencing research decisions.

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▸ CMAJ. 2001 May 29;164(11):1612.

Death but one unintended consequence of gene-therapy tri

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Editorial | Published: 28 June 2016

Gene-therapy trials must proceed with caution

Want to learn more about this case?

Jesse Gelsinger

Article Talk

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The Death of Jesse Gelsinger: New Evidence of the Influence of

Epilogue:

Who dares to ask the speakers questions???