Welcome to the RPN Workshop!

- Thank you for joining us. We are glad you are here!
- The RPN Workshop series are peer-led and are based on the Joint Task Force Competencies for conducting clinical research.
- This session will be recorded and posted on the BUMC CRRO website.
- Please participate fully in the workshop activities… everyone will benefit!
- Ask questions by raising your virtual Zoom hand or use the chat.
- If you are having connection issues please try turning off your video – otherwise, please keep your video on if possible.
- Remember to complete the Workshop evaluation!
- **Upcoming RPN Workshops**
  - **Tues, Oct 25:** Multitasking and Managing a Coordinator's Varied Role
  - **Nov:** Project Management with Clinical Research
  - **Dec:** Adverse Events

Sign Up!

BU Clinical & Translational Science Institute

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Back to School: CliffsNotes for Good Clinical Practice and Regulations

Research Professional Network Workshop

September 29th, 2022

3 – 4:30pm

Presenter Bios

Mary-Tara Roth, RN, MSN, MPH
Director, Clinical Research Resources Office. Oversees Regulatory consultations, Research education, and the QA program.

Kimberly Luebbers, MSHS, RN, BSN
Assistant Dean for Clinical Research, Director, Office of Clinical Trials Research & Administrative Director, Clinical Research Center UVM Larner College of Medicine & UVM Medical Center

Sheila Austin, MS, ACRP-CP
Regulatory Specialist, CTSI University of Florida. She has over 20 years of experience in clinical research regulatory affairs, including twelve years as an IRB Administrative Coordinator, and currently provides education and assistance on GCP, clinical research, and IND/IDE application topics.

Rana Leed, MPH
Human Research Education Manager at BU. Primary focus for over 15 years has been regulatory management with a specialty in multi-site and investigator-initiated studies.

Agenda

- The WHAT on regulations
  - What are regulations?
    - Are they the same as law?
    - How do they relate to guidance, policies, best practices, SOPs?
    - ICH GCP
  - What regulations guide my research?
    - FDA, OHRP, Both?
    - How are they the same; how do they differ?
- The WHY on regulations and ICH GCP guidance
- The HOW on regulations and ICH GCP guidance
  - Examples with a focus on relevance and grounding in GCP and the regs
  - Cases for discussion! Find that mic button!

Federal Laws and Regulations ("Civics 101")

- Law:
  - Rule or conduct of action that a nation or group agree to follow
    - What you can do, cannot do, or must do and penalties for not following law
  - US Federal laws created through the Bill process
  - Form basis for regulation, policy, guidance

- Regulations:
  - Agencies have to implement laws and do this by drafting regulation
    - Fill in details of the broad tenants of the law
    - What needs to be done and how will it be enforced
  - Created by a formal rule-making process
  - Regulations are not law, but final rule has "force of law" bc it is implementing law

While we're at it….

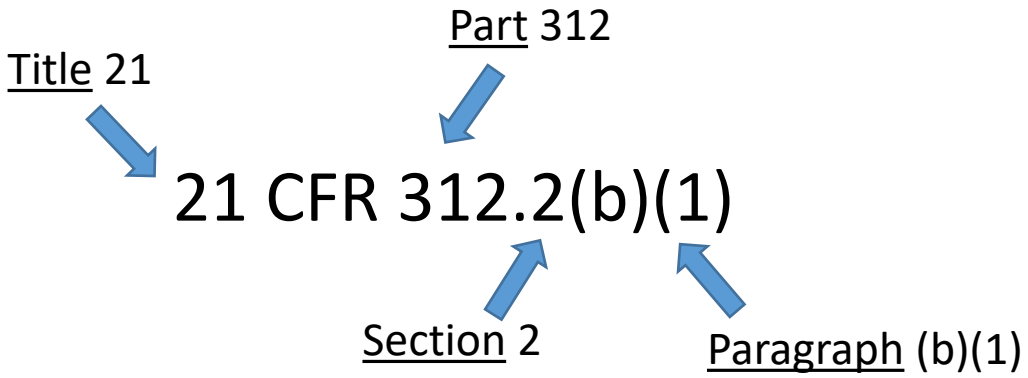
- Guidance:
  - Supplemental material published by an agency
  - Clarifies existing regulations
  - Not binding (doesn't have force of law)
  - In general, should have a good reason for not following guidance
- Policy
  - How an institution interprets and implements regulations and guidance
- SOPs
  - Documents providing step-by-step instructions for members of teams to follow to ensure compliance and consistency in conduct.
- Best practices
  - Procedures or practices that are accepted as being correct and most effective.

Regulation numbering

Helps to find and cite

- Code of Federal Regulations (CFR)
  - Codification of rules published in the Federal Register by executive departments and agencies of the Federal Government
- 50 subject matter Titles
- Titles broken down into Chapters (specific to agency), Parts, Sections and Paragraphs

- Example:



Regulations Guiding Human Research

HHS/OHRP

- IRB Assurance
- Oversight
- Engagement

45 CFR 46, Subpart A (The Common Rule)
Subpart B
Subpart C
Subpart D
Subpart E

Both "Harmonized"

- **Informed Consent**
- **IRB Review/ Functions/ Operations**

FDA

- **Sponsor/investigator roles**
- **Conduct of the research**
- Drug/device dev't & testing process
- Mandatory registration/results reporting

21 CFR 50 Informed Consent
21 CFR 56 IRB review
21 CFR 312 (IND) - drugs
21 CFR 812 (IDE) - devices

Regulations for Clinical/Human Research

- Food and Drug Administration (FDA)
  - Title 21: Food and Drugs
    - 21 CFR 312: Investigational New Drug Application
    - 21 CFR 812: Investigational Device Exemptions
    - 21 CFR 50: Protection of Human Subjects
    - 21 CFR 56: Institutional Review Boards

- Office of Human Research Affairs (OHRP)
  - Title 45: Public Welfare Department of Health and Human Services
  - Part 46: Protection of Human Subjects
    - 45 CFR 46 (including 5 subparts)
      - Subpart A: Basic HHS Policy for Protection of Human Research Subjects
      - Subpart B: Pregnant Women, Human Fetuses and Neonates
      - Subpart C: Prisoners
      - Subpart D: Children
      - Subpart E: requirements for IRB registration

Applicability of the HHS/OHRP and FDA Regs

HHS/OHRP *45 CFR 46.101(a)*	**FDA** *(21 CFR 50.3(c))*
"… all research involving human subjects conducted, supported or otherwise subject to regulation by any Federal department or agency that takes appropriate administrative action to make the policy applicable to such research…." And what about non-funded research? Institutional policies mandate adherence to human subjects protection regulations, with some allowance for relaxing requirements for certain categories of research.	"Clinical Investigation means any experiment that involves a test article and one or more human subjects that either is subject to requirements for prior submission to the FDA under section 505(i) or 520(g) of the act…or… the results are intended to be submitted to FDA… as part of an application for a research or marketing permit…" *Soooo…….. most studies testing drugs/devices, even if they are previously approved and currently marketed….*

FDA regs

- Drug study under an IND
  - 21 CFR 312
  - 21 CFR 50 Protection of Human Subjects (informed consent)
  - 21 CFR 56 IRBs
- Drug study not under an IND (i.e. “IND Exempt”)
  - 21 CFR 50 Protection of Human Subjects (informed consent)
  - 21 CFR 56 IRBs
- Device study under an IDE (Note: Most NSR devices will follow abbreviated IDE requirements)
  - 21 CFR 812
  - 21 CFFR 50 Protection of Human Subjects (informed consent)
  - 21 CFR 56 IRBs

What is ICH GCP?

- International Council for Harmonisation*

  * Note the name formally changed from International Conference on Harmonisation to International Council for Harmonisation in Oct. 2015. More info here, here and here.

- Good Clinical Practice

  … an international ethical and scientific quality standard for **designing, conducting, recording and reporting trials that involve the participation of human subjects.** Compliance with this standard provides public assurance that the rights, safety and well being of trial subjects are well-protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.

  ICH Harmonised Tripartite Guideline, Guideline for Good Clinical Practice, E6

  - Facilitates mutual acceptance of data from clinical trials by regulatory authorities from other jurisdictions.
  - Click this link to ICH GCP guidance E6 (R2).

ICH GCP is <u>FDA Guidance</u>: published in the *Federal Register on May 9, 1997; "*represents the [FDA's] current thinking on good clinical practices".

How do I know if I must follow ICH GCP?

- Look in your protocol: Study Conduct/Ethics/ Regulatory Considerations section(s):

Protocol excerpt:

"This study will be conducted in accordance with the ethical principles that have their origin in the current Declaration of Helsinki and will be consistent with International Conference on Harmonization Good Clinical Practice (ICH GCP) and applicable regulatory requirements."

Should I follow GCP guidance?

"To the extent possible, the principles of GCP should generally apply to all clinical research involving human subjects, and not just research involving pharmaceutical or other medical products…"

Handbook for Good Clinical Practice, WHO, 2002

"Staff at the Division of Scientific Investigations participated in the development of the ICH E6 guideline, which is the official FDA guidance on GCP. Compliance with ICH GCP ensures compliance with FDA regulations."

(Joseph Salewski, CDER DSI deputy director, SoCRA Source, 8/05)

Protocol Compliance

FDA regs	OHRP Regs	ICH GCP
21 CFR 312.60 General Responsibilities of Investigators: An investigator is responsible for ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations; for protecting the rights, safety, and welfare of subjects under the investigator's care…	None	4.5 Compliance with Protocol 4.5.1 The investigator/ institution should conduct the trial in compliance with the protocol, which was given approval/favorable opinion by the IRB. 4.5.2 The investigator should not implement any deviation from, or changes of, the protocol without prior review and documented approval/favorable opinion from the IRB of an amendment.

Investigator Qualifications

FDA regs	OHRP Regs	ICH GCP
21 CFR 312.53 Selecting Investigators and Monitors: A sponsor shall select only investigators qualified by training and experience as appropriate experts to investigate the drug	None	4.1 Investigators 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….. 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,… 4.1.3 The investigator should be aware of, and should comply with, GCP and the applicable regulatory requirements

Reporting Unanticipated Problems/Reportable Events

FDA regs	OHRP Regs	ICH GCP
21 CFR 312.64 Investigator Reports: *(b) Safety reports.* An investigator must immediately report to the sponsor any serious adverse event, whether or not considered drug related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the drug caused the event…..The investigator must record nonserious adverse events and report them to the sponsor according to the timetable for reporting specified in the protocol	45 CFR 46.108 IRB functions and operations a) In order to fulfill the requirements of this policy each IRB shall: (4) Establish and follow written procedures for ensuring prompt reporting to the IRB …. of (i) Any unanticipated problems involving risks to subjects or others or any serious or continuing noncompliance….. OHRP Guidance: Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others	4.11 Safety Reporting 4.11.1 All serious adverse events (SAEs) should be reported immediately to the sponsor except for those SAEs that the protocol or other document (e.g., Investigator's Brochure) identifies as not needing immediate reporting……..The investigator should also comply with the applicable regulatory requirement(s) related to the reporting of unexpected serious adverse drug reactions to the regulatory authority(ies) and the IRB/IEC.

Delegation of Tasks

FDA regs	OHRP Regs	ICH GCP
Nothing in regs about delegation Look to FDA Guidance: Investigator Responsibilities – Protecting the Rights, Safety, and Welfare of Study Subjects, Oct. 2009 "…It is common practice for investigators to delegate certain study-related tasks to employees, colleagues, or other third parties (individuals or entities not under the direct supervision of the investigator). When tasks are delegated by an investigator, the investigator is responsible for providing adequate supervision of those to whom tasks are delegated…."	None	4.1.5 The investigator should maintain a list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties. 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. 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.

Documentation of Informed Consent

FDA regs	OHRP Regs	ICH GCP
21 CFR 50.27 Documentation of informed consent (a) Except as provided in § 56.109(c), informed consent shall be documented by the use of a written consent form approved by the IRB and signed and dated by the subject or the subject's legally authorized representative at the time of consent. A copy shall be given to the person signing the form….	45 CFR 46.117 Documentation of Informed Consent (a) Except as provided in paragraph (c) of this section, informed consent shall be documented by the use of a written informed consent form approved by the IRB and signed (including in an electronic format) by the subject or the subject's legally authorized representative. A written copy shall be given to the person signing the informed consent form….	4.8.8 Prior to a subject's participation in the trial, the written informed consent form should be signed and personally dated by the subject or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion.

Study Documentation

FDA regs	OHRP Regs	ICH GCP
21 CFR 312.62 Investigator recordkeeping and record retention *(b) Case Histories*: An investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered drug or employed as a control in the investigation…. Case histories include the case report forms AND supporting data….	45 CFR 46.117 Documentation of Informed Consent (a) Except as provided in paragraph (c) of this section, informed consent shall be documented by the use of a written informed consent form approved by the IRB and signed (including in an electronic format) by the subject or the subject's legally authorized representative. A written copy shall be given to the person signing the informed consent form….	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). 8.1 Essential documents are those documents that individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced …

GCP in Action!!

ICH GCP 2.8	**"Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s)"**
How to implement	• Records include CVs, licenses, training logs for protocol-specific training • Delegation log that shows that tasks are appropriately delegated (demonstrating oversight of PI)
ICH GCP 2.10	**"All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification."**
How to implement	• Follow ALCOA: Documentation should be Attributable (record identifies who created/modified record), Legible, Contemporaneous (recorded in real-time, and signed/dated accurately), Original, Accurate (collected and recorded honestly and completely) • Source documents must make it clear *who* collected/updated the data and *when*, and reasons for changes if necessary…. • Storing records per protocol and institutional policy • Review and implement GCP Section 8: Essential Documents Before, During, After trial
ICH GCP 2.9	**"Freely given informed consent should be obtained from every subject prior to clinical trial participation."**
How to implement	• Well-trained staff ensuring complete information is supplied to and understood by potential subject

Recap on Regs

Type of study	Regulations that apply
Drug study – under an IND	• 21 CFR 312 IND – Investigational New Drug Application • 21 CFR 50 Protection of Human Subjects (informed consent) • 21 CFR 56 IRBs
Drug study – IND exempt	• 21 CFR 50 Protection of Human Subjects (informed consent) • 21 CFR 56 IRBs
Device study - Significant Risk – IDE - Non-significant Risk – Abbreviated IDE	• 21 CFR 812 IDE – Investigational Device Exemption • 21 CFR 50 Protection of Human Subjects (informed consent) • 21 CFR 56 IRBs
Federally-funded research	• 45 CFR 46 (Common Rule, Subpart A)
Non-federally funded research and not FDA regulated	• 45 CFR 46 (maybe with some requirements relaxed) • If the (US) institution voluntarily extends their FWA to cover all human subjects research at the submitting institution regardless of the source of support for the particular research activity.

Important Guidance (links)

- ICH Good Clinical Practice
- FDA Guidance for Industry: Investigator Responsibilities – Protecting the Rights, Safety, and Welfare of Study Subjects, Oct. 2009
- Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events: OHRP Guidance (2007)
- FDA Safety Reporting Requirements for INDs and BA/BE Studies, Dec. 2012
- Various OHRP Guidance Documents by Topic

slido

You are working on a study that is conducted under an IND. What regulations apply?

ⓘ Start presenting to display the poll results on this slide.

slido

You are looking at the rates of new cases of diabetes at your institution so that you can determine staffing of your diabetes nurse educators.

ⓘ Start presenting to display the poll results on this slide.

slido

You have designed a study, funded by NIH, that will assess effectiveness of yoga to relieve post-traumatic stress disorder in veterans.

ⓘ Start presenting to display the poll results on this slide.

slido

You are conducting a study that assesses long-term outcomes of older patients (65+) who are prescribed “Glowpill” by their PCPs for their clinical care.

ⓘ Start presenting to display the poll results on this slide.

slido

You are conducting an NIH-funded drug study for which the IRB has approved an IND exemption.

ⓘ Start presenting to display the poll results on this slide.

slido

You decide to test a device that you and colleagues have developed to improve surgical outcomes for patients having bariatric surgery.

ⓘ Start presenting to display the poll results on this slide.

How will this work?

We'll present a brief example and provide the relevant regulation or GCP standard – and then we want to hear from you what you think.

It's sometimes hard to understand the **link between regulations and GCP** and what happens **during the day to day activities** of a research study.

Today's activity is designed to make those linkages.

Referenced GCP standard or regulation in following slides should not be assumed to be the only relevant guidance or requirement that may pertain or govern the situation.

Consent – When does it happen if you need to confirm eligibility? KL

- Drug study, has IRB approval
- Eligibility criteria - adequate kidney function
- Timeline:
  - Screening procedure - blood draw to assess kidney function
  - Confirms eligibility and adequate kidney function
  - Consents eligible participants using IRB approved consent process

➢ 45 CFR Part 46 (Common Rule)
  - 46.116 (a)(1) - *before involving a human subject in research covered by this policy, an investigator shall obtain the legally effective informed consent of the subject…*

➢ 21 CFR 50: *no investigator may involve a human being as a subject in research covered by these regulations unless the investigator has obtained the legally effective informed consent of the subject…*

Summary + Regulations/Guidance

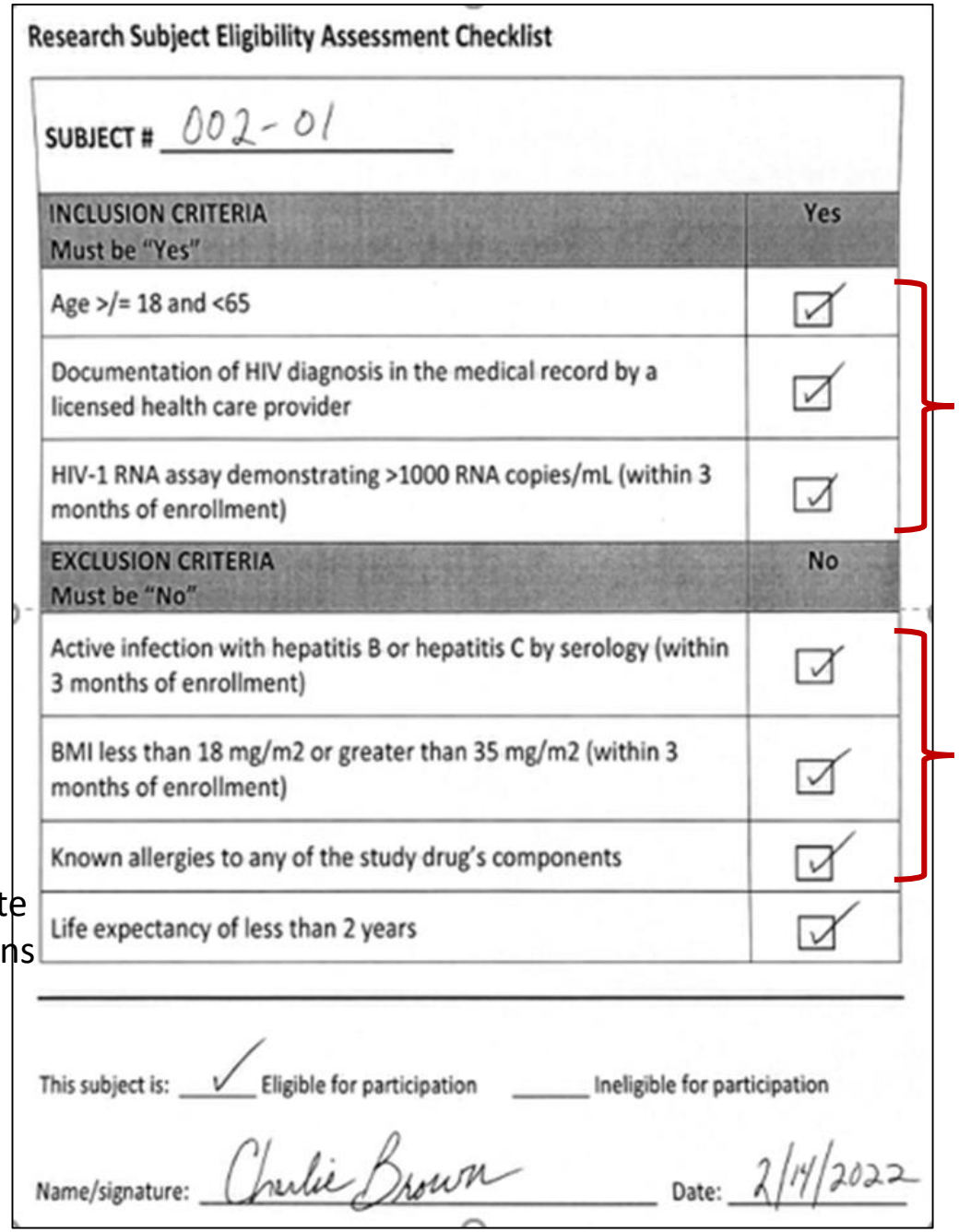
Consent – When does it happen if you need to confirm eligibility?

- Drug study, has IRB approval
- Eligibility criteria - adequate kidney function
- Timeline:
  1. Screening procedure - blood draw to assess kidney function
  2. Confirms eligibility and adequate kidney function
  3. Consents eligible participants using IRB approved consent process

➢ Did the researcher obtain appropriate consent from her participant?

Using Checklists correctly mt

- Study coordinator developed a checklist listing all the inclusion and exclusion criteria for the study to ensure that the subject is eligible.
- The criteria source are either the EMR or the checklist.
- Here is a sample, signed by the study coordinator.



Research Subject Eligibility Assessment Checklist

SUBJECT # 002-01

INCLUSION CRITERIA Must be "Yes"	Yes
Age >/= 18 and <65	☑
Documentation of HIV diagnosis in the medical record by a licensed health care provider	☑
HIV-1 RNA assay demonstrating >1000 RNA copies/mL (within 3 months of enrollment)	☑
EXCLUSION CRITERIA Must be "No"	**No**
Active infection with hepatitis B or hepatitis C by serology (within 3 months of enrollment)	☑
BMI less than 18 mg/m2 or greater than 35 mg/m2 (within 3 months of enrollment)	☑
Known allergies to any of the study drug's components	☑
Life expectancy of less than 2 years	☑

This subject is: ✓ Eligible for participation _____ Ineligible for participation

Name/signature: Charlie Brown Date: 2/14/2022

From EMR

From EMR

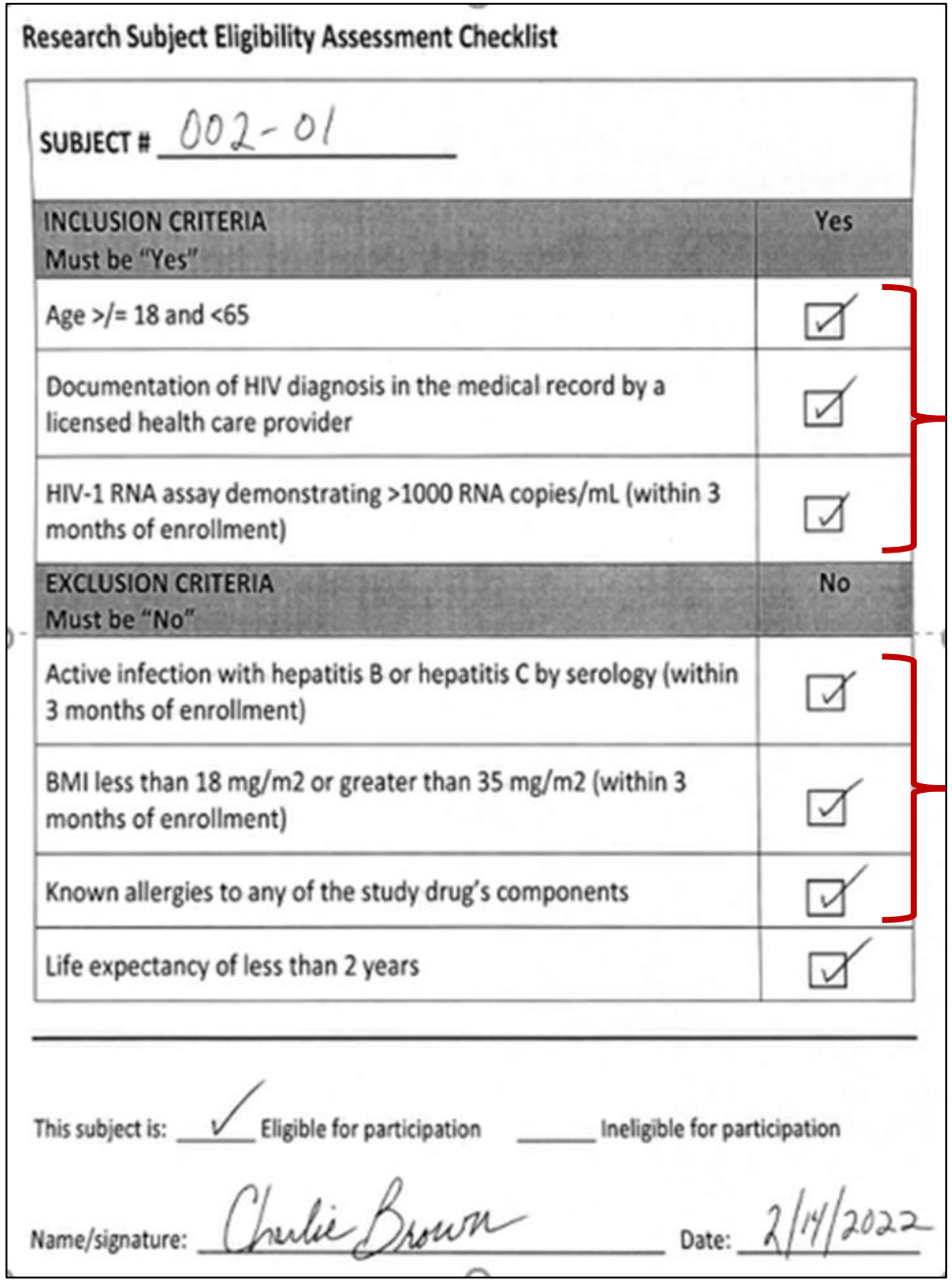
- 21 CFR 312.62 Investigator recordkeeping and record retention
  - *(b) Case Histories*: An investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual
- ICH GCP 4.9 Records and Reports
  - 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).

Summary + Regulations/Guidance

Using Checklists correctly

- Study coordinator developed a checklist listing all the inclusion and exclusion criteria for the study to ensure that the subject is eligible.
- The criteria source are either the EMR or the checklist.
- Here is a sample, signed by the study coordinator.

- ➢ What are some issues here?
- ➢ Is there anything the coordinator should do now, after 10 subjects have been enrolled?
- ➢ What could they have done to avoid the problem before enrolling?



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Life expectancy of less than 2 years	☑

This subject is: ✓ Eligible for participation _____ Ineligible for participation

Name/signature: Charlie Brown Date: 2/14/2022

From EMR

From EMR

Summary + Questions

Complete documentation MT

- The study coordinators have been enrolling subjects into a study testing a medical intervention. The main inclusion criteria include non-Hispanic African Americans or non-Hispanic Caucasians age 30-50.
- A subject was enrolled and the eligibility checklist notes this individual to be non-Hispanic. It is not clear from the documentation who completed the checklist.
- Per the EMR the subject is identified as Hispanic or Latino.
- The study team notes that the individual said he is not Hispanic.

- 21 CFR 312.62 Investigator recordkeeping and record retention
  (b) Case Histories: An investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual

- ICH GCP 4.9.0 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).

Summary + Regulations/Guidance

Complete documentation

- The study coordinators have been enrolling subjects into a study testing a medical intervention. The main inclusion criteria include non-Hispanic African Americans or non-Hispanic Caucasians age 30-50.
- A subject was enrolled and the eligibility checklist notes this individual to be non-Hispanic. It is not clear from the documentation who completed the checklist.
- Per the EMR the subject is identified as Hispanic or Latino.
- The study team notes that the individual said he is not Hispanic

- What are the issues here?
- What would you have advised the study team to do at the time of enrollment?
- What should the study team do when they are made aware of the issue?

Drug Schedules and Providing Information SA/KL

- Osteoarthritis study - drug intervention
- Participant – 8 months into study – Struggling to remember when she took last drug, confusion about schedule
- Review of visit notes reveals repeating pattern of uncertainty
- Initial visit notes include instructions for when and how to take drug - provided verbally and in writing. Also include that Participant was able to repeat back instructions.

➢ICH E6: GCP Guidelines:

- 4.6.6: *The investigator, or a person designated by the investigator/institution, should explain the correct use of the investigational product(s) to each subject and should check, at intervals appropriate for the trial, that each subject is following the instructions properly.*

Summary + Regulations/Guidance

Drug Schedules and Providing Information

- Osteoarthritis study - drug intervention
- Participant – 8 months into study – Struggling to remember when she took last drug, confusion about schedule
- Review of visit notes reveals repeating pattern of uncertainty
- Initial visit notes include instructions for when and how to take drug - provided verbally and in writing. Also include that Participant was able to repeat back instructions.

➢ What red flags does this scenario bring up?

➢ What specific issues about this drug or patient population should have been considered?

Summary + Questions

Collecting All Adverse Events in a Systematic Way RL

- Sildenafil for angina and hypertension → Adverse events → Viagra
- Medicated eye drops for glaucoma → Adverse events → Latisse

➢ 21 CFR Part 312: IND procedures and requirements - definitions: "reasonable possibility" that the drug caused the event – unexpected suspected adverse event: *One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug.*

➢ ICH E6: GCP Guidelines:

- 6.8.3: Protocol should have procedures for…recording adverse event[s]...
- Section 8 Essential Documents for the Conduct of a Clinical Trial

Collecting All Adverse Events in a Systematic Way

- Sildenafil for angina and hypertension → Adverse events → Viagra
- Medicated eye drops for glaucoma → Adverse events → Latisse

- How are you currently collecting Adverse Events?
- Could you see trends in the way you are collecting them?
  Paraphrasing Goldfinger - once is happenstance, twice is coincidence, three times is a trend to be reported.

Consent and Informed Decision Making RL

- Pregnant women - gestational diabetes
- Screening: glucose challenge test, participants compensated $25 for clinical test
- Intervention: randomized to two different diets
- Recruitment: community clinic - African American, lower socio-economic class, young (< 18, late teens, early 20's)
- Comments from participants: "you don't need to tell me about the study/I don't need to read the consent, I have to do this anyway, so might as well do it with you and get the money"
- Participants were enrolled even when making this type of statement

- 45 CFR 46 doesn't make a distinction between consent process and document but Informed Consent FAQ is more explicit.
  - 45 CFR 46.116 and 46.117
- Belmont Report principles of respect: voluntarily and with sufficient information
- ICH E6 (R2):
  - 4.8.5: The investigator, or a person designated by the investigator, should fully inform the subject or, if the subject is unable to provide informed consent, the subject's legally acceptable representative, of all pertinent aspects of the trial including the written information and the approval/ favourable opinion by the IRB/IEC.
  - 4.8.7: Before informed consent may be obtained, the investigator, or a person designated by the investigator, should provide the subject or the subject's legally acceptable representative ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial.
  - 4.8.10: Both the informed consent discussion and the written informed consent form and any other written information to be provided to subjects should include explanations of the following…

Consent and Informed Decision Making

- Pregnant women - gestational diabetes
- Screening: glucose challenge test, participants compensated $25 for clinical test
- Intervention: randomized to two different diets
- Recruitment: community clinic - African American, lower socio-economic class, young (< 18, late teens, early 20's)
- Comments from participants: "you don't need to tell me about the study/I don't need to read the consent, I have to do this anyway, so might as well do it with you and get the money"
- Participants were enrolled even when making this type of statement

➢ What are the red flags in this situation?

➢ Could the study or recruitment have been designed differently?

➢ Was there anything that the coordinator could have done differently?

Summary + Questions

Complete and Accurate Participant Files

- Multi-site, investigator-initiated, NIH-funded, IND
- Monitoring visit → consistent issues with participant files
  - Missing info and forms, data not entered, files in wrong participant
  - Provided guidance on several visits - still issue
  - Site paused for enrollment while Lead Team completed intensive training
- Issue? Staff effort on study
- Issue? Understanding of good data keeping and record maintenance

➢ FDA E6 (R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1): Guidance for Industry

- ➢ Investigator Responsibilities: Many sections in 4.9 Records and Reports
- ➢ Sponsor Responsibilities: 5.11 Confirmation of Review by IRB, 5.16.2 Safety Information, 5.18 Monitoring
- ➢ Section 8 Essential Documents

Summary + Regulations/Guidance

Complete and Accurate Participant Files

- Multi-site, investigator-initiated, NIH-funded, IND
- Monitoring visit → consistent issues with participant files
  - Missing info and forms, data not entered, files in wrong participant
  - Provided guidance on several visits - still issue
  - Site paused for enrollment while Lead Team completed intensive training
- Issue? Staff effort on study
- Issue? Understanding of good data keeping and record maintenance

- How do you organize your files? How do you find time to organize your files? Have you had success with one system or other?
- Have you had sponsors or lead teams require a very specific way of doing things? How do you reconcile that with best practice or local practice?
- What can happen when participant binders are disorganized, messy, missing things?

Summary + Questions

Complete and Accurate Regulatory Files

- Sponsored study (multi-site, IND)
- Regulatory binders were consistent issue - both noticed by monitor and by assigned institutional regulatory specialist
  - Missing documents, misfiled documents
- IRB submissions were particular problem - using chronological filing

➢ FDA E6 (R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1): Guidance for Industry

- ➢ Investigator Responsibilities: Many sections in 4.9 Records and Reports
- ➢ Sponsor Responsibilities: 5.11 Confirmation of Review by IRB, 5.16.2 Safety Information, 5.18 Monitoring
- ➢ Section 8 Essential Documents

Summary + Regulations/Guidance

Complete and Accurate Regulatory Files

- Sponsored study (multi-site, IND)
- Regulatory binders were consistent issue - both noticed by monitor and by assigned institutional regulatory specialist
  - Missing documents, misfiled documents
- IRB submissions were particular problem - using chronological filing

➢ How do you organize your files? How do you find time to organize your files? Have you had success with one system or other?

➢ Have you had sponsors or lead teams require a very specific way of doing things? How do you reconcile that with best practice or local practice?

➢ What can happen when regulatory binders are disorganized, messy, missing things?

Summary + Questions

BU Clinical & Translational Science Institute

The University of Vermont
LARNER COLLEGE OF MEDICINE

UF Clinical and Translational Science Institute
UNIVERSITY of FLORIDA

MUSC Medical University of South Carolina
South Carolina Clinical & Translational Research Institute

Thank you!!

Any Questions?

Upcoming RPN Calendar

Tues October 25 Multitasking and Managing a Coordinator's Varied Role
November (date TBD) Project Management with Clinical Research
December (date TBD) Adverse Events

See BU/BMC Research Professionals Network website

EXTRA CASES

Reporting All Adverse Events to the IRB – Or (?) As the Protocol Says

- Sepsis study - drug intervention
  - 9 deaths in first six months - all due to sepsis, required to be reported per IRB rule. At 10th death report, IRB asked study to update protocol to include sepsis-related death as a specific risk and to specifically state “will not be reported”.
- Infection in cancer patients -biospecimen collection + observational
  - After number of required reporting (hospitalization and deaths - all due to cancer), IRB asked for similar revision.

➢ Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events: OHRP Guidance (2007)

Reporting All Adverse Events to the IRB – Or (?) As the Protocol Says

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  - 9 deaths in first six months - all due to sepsis, required to be reported per IRB rule. At 10th death report, IRB asked study to update protocol to include sepsis-related death as a specific risk and to specifically state “will not be reported”.
- Infection in cancer patients -biospecimen collection + observational
  - After number of required reporting (hospitalization and deaths - all due to cancer), IRB asked for similar revision.

➢ Do you think this would be allowed at your institution’s IRB? Why or why not?

➢ Have you seen studies like this?

➢ What would be the pros or cons of a study protocol written like this?

Summary + Questions

Consent – Changing the process but not the document? KL

- Minimal risk study
- IRB approved protocol and consent
  - Consent process includes documenting consent on IRB approved consent form
- Eligible participant but investigator didn't have a consent form
- Explained study procedures, risks, etc.; provided time to consider
- Participant says they don't need anything in writing and agrees to participate

➢ 45 CFR Part 46 (Common Rule)

- 46.116 General Requirements for Informed Consent – specifically subsection B – basic elements of informed consent
- 46.117 Documentation of Informed Consent

➢ 45 CFR Part 46 and 21 CFR 56: Both contain language on IRB required procedures for ensuring that changes in approved research may not be initiated without IRB review

➢ ICH GCP E6(R2)

- 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…*

Summary + Regulations/Guidance

Consent – Changing the process but not the document?

- Minimal risk study
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  - Consent process includes documenting consent on IRB approved consent form
- Eligible participant but investigator didn't have a consent form
- Explained study procedures, risks, etc.; provided time to consider
- Participant says they don't need anything in writing and agrees to participate

➢ Is it okay to continue with the research activities with this participant?

➢ What specific issues about this drug or patient population should have been considered?

Recruitment, Screening, Consent

Study enrolling females age 16-45. Subjects will receive a new vaccination which is FDA-approved, but a new dosing schedule will be tested: 2 doses (experimental dosing) vs. 3 doses (FDA-approved dosing).

- Inclusion criteria: age 16-45; patient at Super City Hospital; Not yet received vaccine; afebrile 24 hours before injection
- Exclusion criteria: pregnant/nursing, allergy to yeast, immunocompromised (treatment within last 30 days); coagulation disorder

- 21 CFR 312.62 Investigator recordkeeping and record retention
  - *(b) Case Histories*: An investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual
- 21 CFR 50 Subpart D – Additional Safeguards for Children in Clinical Investigations
- ICH GCP 4.4 Communication with IRB
  - 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
- ICH GCP 4.8 Informed Consent of Trial Subjects
- ICH GCP 4.9 Records and Reports
  - 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.

Summary + Regulations/Guidance

Recruitment, Screening, Consent

- Study enrolling females age 16-45. Subjects will receive a new vaccination which is FDA approved, but a new dosing schedule will be tested: 2 doses (experimental dosing) vs. 3 doses (FDA-approved dosing).
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➢ What are some considerations on 1) consent and 2) screening that the study team should take into account and develop processes for prior to enrolling?