TWO YEARS SINCE RELEASE OF THE "NEW" OHSRP RESEARCH RELATED EVENT REPORTING POLICIES:

HOW IS THE IRP DOING?

Peg Herbst Sanders, RN, MSN, MA, CIP

OHSRP, Compliance and Training

NIH Office of Intramural Research
Office of Human Subjects Research Protections

OBJECTIVES

- Provide a brief refresher of Policies 801 and 802 and relevant definitions
- Describe the process for review of Reportable Event Forms once they are submitted
- Review metrics for reportable events submitted during CY2020
- Discuss tips for successful completion of the NIH Reportable Event Form (REF)

Policy Release Date: May 14, 2019

- **Policy 801: Reporting Research Events**
  - What events need to be reported
  - When to report events to the NIH IRB
  - IRB vs. RCRC review of reported events
- **Policy 802: Non-Compliance in Human Subjects Research**
  - Investigation of allegations of non-compliance in human subjects research
  - NIH Research Compliance Review Committee's (RCRC) role in reviewing possible serious and/or continuing non-compliance

QUICK REFRESHER: EVENTS THAT REQUIRE EXPEDITED REPORTING TO THE NIH IRB*

- Unanticipated problems involving risks to subjects or others (also referred to as UPs)
- Non-compliance (including major protocol deviations and noncompliance that is not related to a protocol deviation)
- Deaths related or possibly related to research activities
- New information that might affect willingness of subjects to enroll/continue participation on study
- Any suspension or termination of research activities, placed by the study sponsor, NIH or IC leadership, or any regulatory agency

*When NIH is Relying on External (non-NIH) Reviewing IRB:

- The NIH Lead Investigator/NIH PI must report to external IRB in compliance with **their** IRB policies related to event reporting
- External IRB makes determinations of serious/continuing NC, and UPs
- If the event occurred at an NIH site, duplicate reporting to NIH within the same NIH IRB timeframe is required

Unanticipated Problems (UPs)

Must meet ALL 3 criteria

- **Unexpected** in terms of nature, severity, or frequency given (a) the research procedures described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied, and
- It is **related or possibly related** to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research), and
- Suggests that the research **places subjects or others** (which may include research staff, family members or other individuals not directly participating in the research) **at a greater risk of harm** (including physical, psychological, economic, or social harm) than was previously known or expected

Examples of UPs as Related to Unexpectedness

- Unexpected nature: Phase 1 study does not list rash as a possible effect of study drug and subject develops severe rash over entire torso believed to be r/t study drug
- Unexpected severity: protocol lists possible mild elevation of LFTs with study drug and a subject experiences fulminant liver failure after 1 week on study drug
- Unexpected frequency: The protocol and consent list an expected frequency of 10% for serious thrombocytopenia, but after 20 participants have received the study drug, the rate is noted to be 40%

If these unexpected events are thought to be at least possibly related to the research intervention or procedures and also place the participants or others at increased risk of harm, then the event should be submitted as a UP within **7 calendar days**.

Non-compliance & Protocol Deviations

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 IRB, whether intentional or not

Protocol Deviation (PD)

- A PD is any change, divergence, or departure from the IRB-approved research protocol
- PDs can be major vs minor deviation

MAJOR VS MINOR PROTOCOL DEVIATIONS

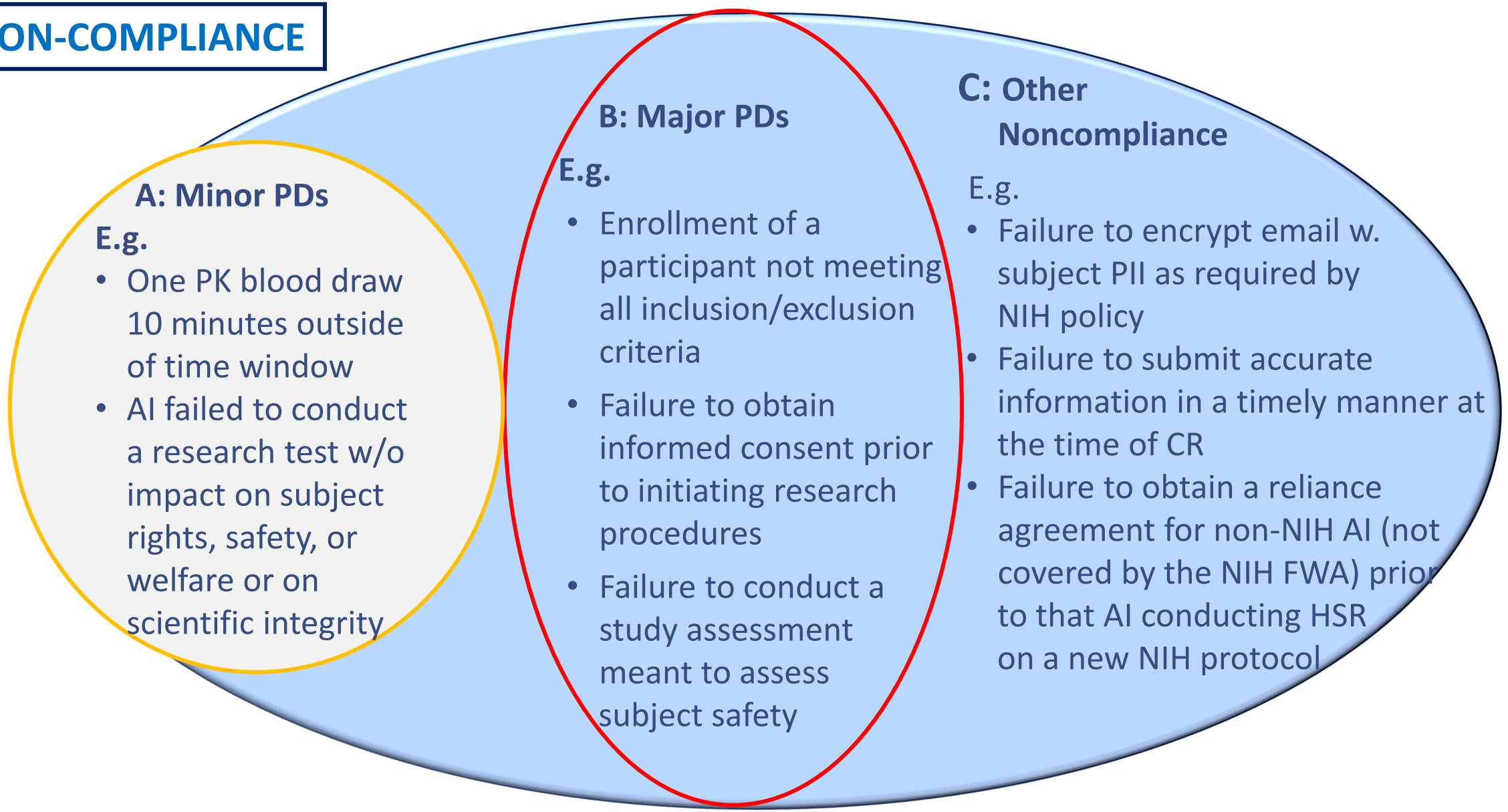
Major Deviation: Deviation from the IRB approved protocol that has, or may have the potential to either:

- negatively impact the rights, welfare or safety of the subject, or
- substantially negatively impact the scientific integrity or validity of the study

Minor Deviation: Deviation that does not have the potential to negatively impact the rights, safety, or welfare of subjects or others, or the scientific integrity or validity of the study

- Minor deviations do not require expedited reporting in iRIS but should be included as part of a high-level summary at the time of the IRB's continuing review (CR)

NON-COMPLIANCE



Only **events in B or C** need expedited reporting within 7 calendar days to the NIH IRB

Additional Reportable Events

- **New information** that might affect the willingness of subjects to enroll or continue participation in the study must be reported to the NIH IRB within **7 calendar days**

- **Deaths that are at least possibly related** (meaning either possibly, probably or definitely related) to the research protocol must be reported to the NIH IRB within **24 hours.** Deaths that do not fall into this category should be reported at the time of CR.

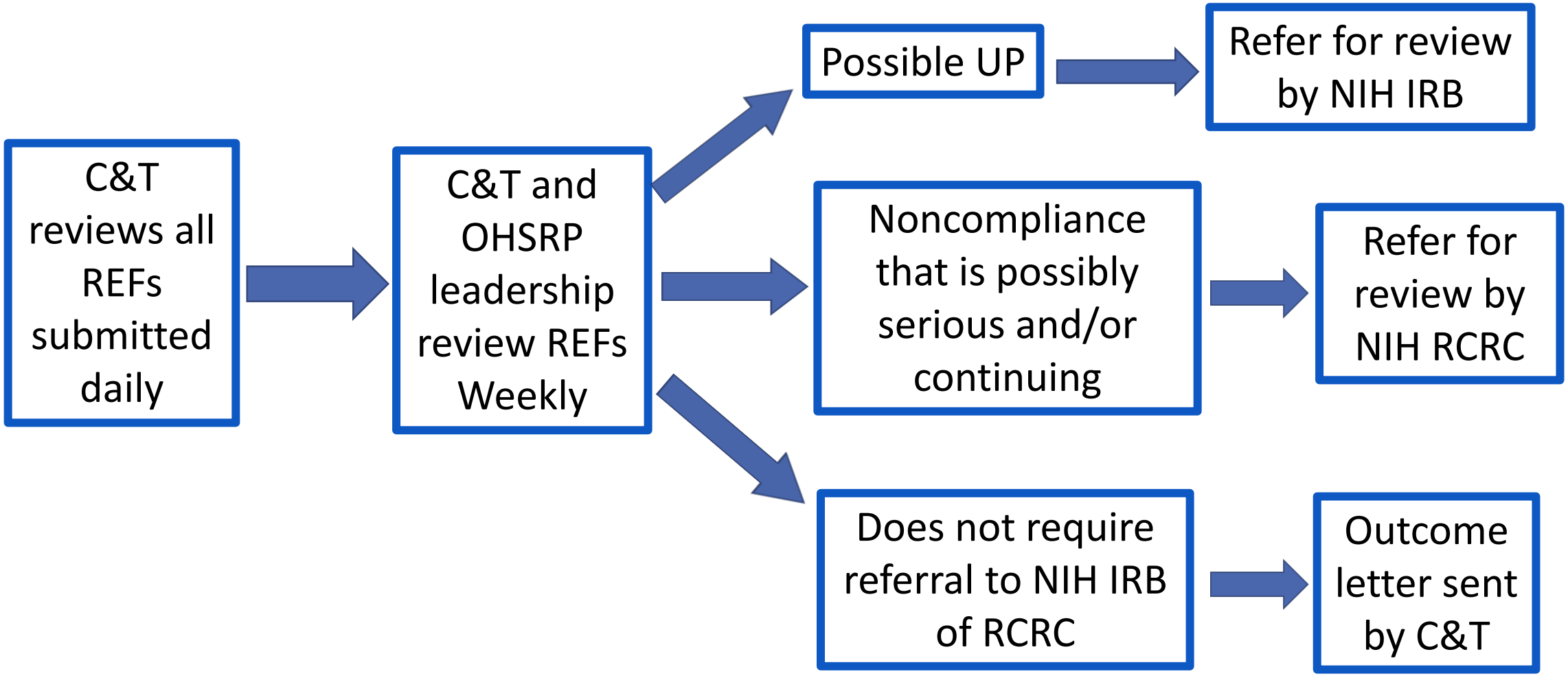
For FDA regulated studies, investigators are also required to report events to the study sponsor as described in the protocol.

Events Requiring Expedited Reporting To The NIH IRB*

Events	Within 24 hours	Within 7 calendar days
Unanticipated problems (UPs)		✓
Non-compliance including major protocol deviations and NC not related to a protocol deviation		✓
New information that might affect willingness of subjects to enroll or continue participation		✓
Suspension or termination of research activities by the study sponsor, NIH or IC leadership, or any regulatory agency		✓
Deaths possibly, probably or definitely related to research	✓	

* Events (AEs, SAEs, minor protocol deviations) that do not fall into the categories above should be reported as part of a high-level summary at the time of continuing review

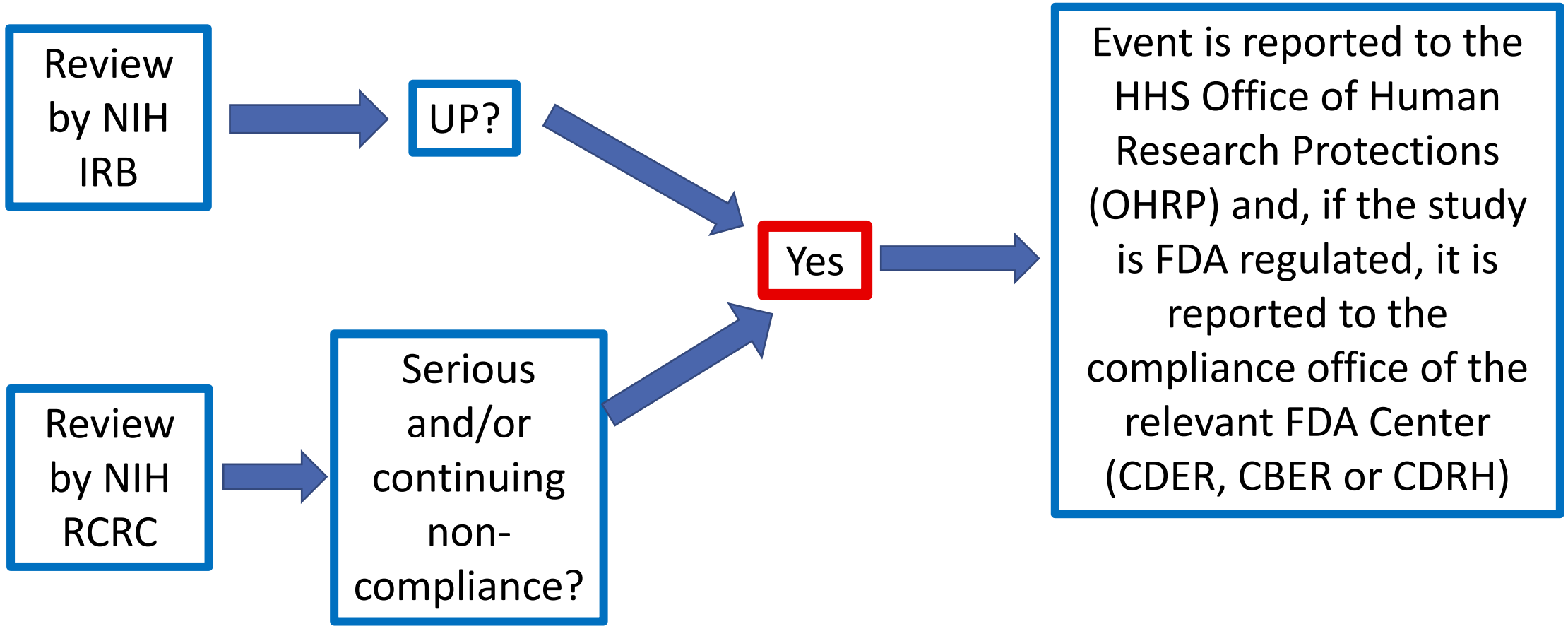
Review Process for REFs Submitted for Protocols Overseen by the NIH IRB



Research Compliance and Review Committee (RCRC)

- Specific role is to review events submitted via REF to determine if they constitute serious and/or continuing noncompliance
- A duly convened NIH IRB
- Has stable membership including IRB members who are experienced clinical researchers
- Focus is on adequacy of the proposed corrective action
- Provides consistency in determinations

REFs Reviewed by the NIH IRB and the RCRC



NIH Reportable Event Forms Report: Calendar Year 2020

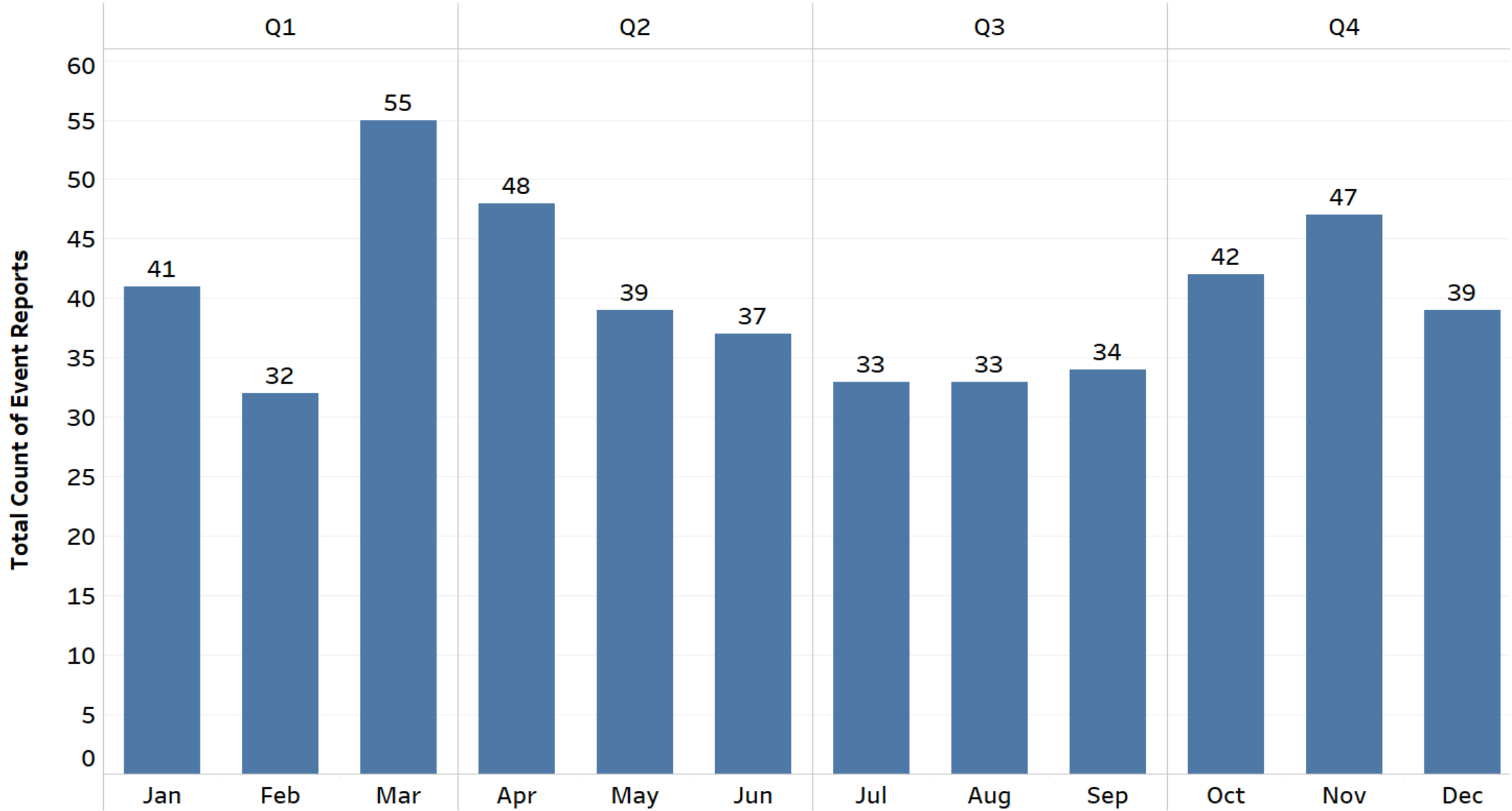
Metrics provided to OHSRP Compliance and Training (C&T) by:

Office of Research Support and Compliance (ORSC), Section for Clinical Research Quality Management (CRQM)

- Darlese Solorzano, MBA, ACRP-CP, ACRP-PM
- Naol Tessema, BS
- Shashi Rudrappa, MS

Thank you!

Event Reports per Quarter



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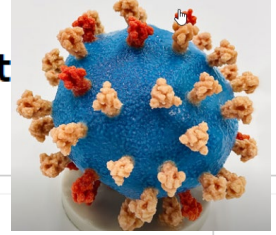
KEY TRENDS

A total of 480 reportable event reports (REF) were reviewed in 2020 by C&T

- On average 40 REFs per month were reviewed in 2020
- Q1 and Q4 had the highest number of REFs reviewed with 128 reports each quarter
- There were a total of 16 ICs who submitted REFs in 2020

Event Reports per Quart



3/11/2020: NIH IRB issues guidelines for protocol deviations during COVID-19 outbreak

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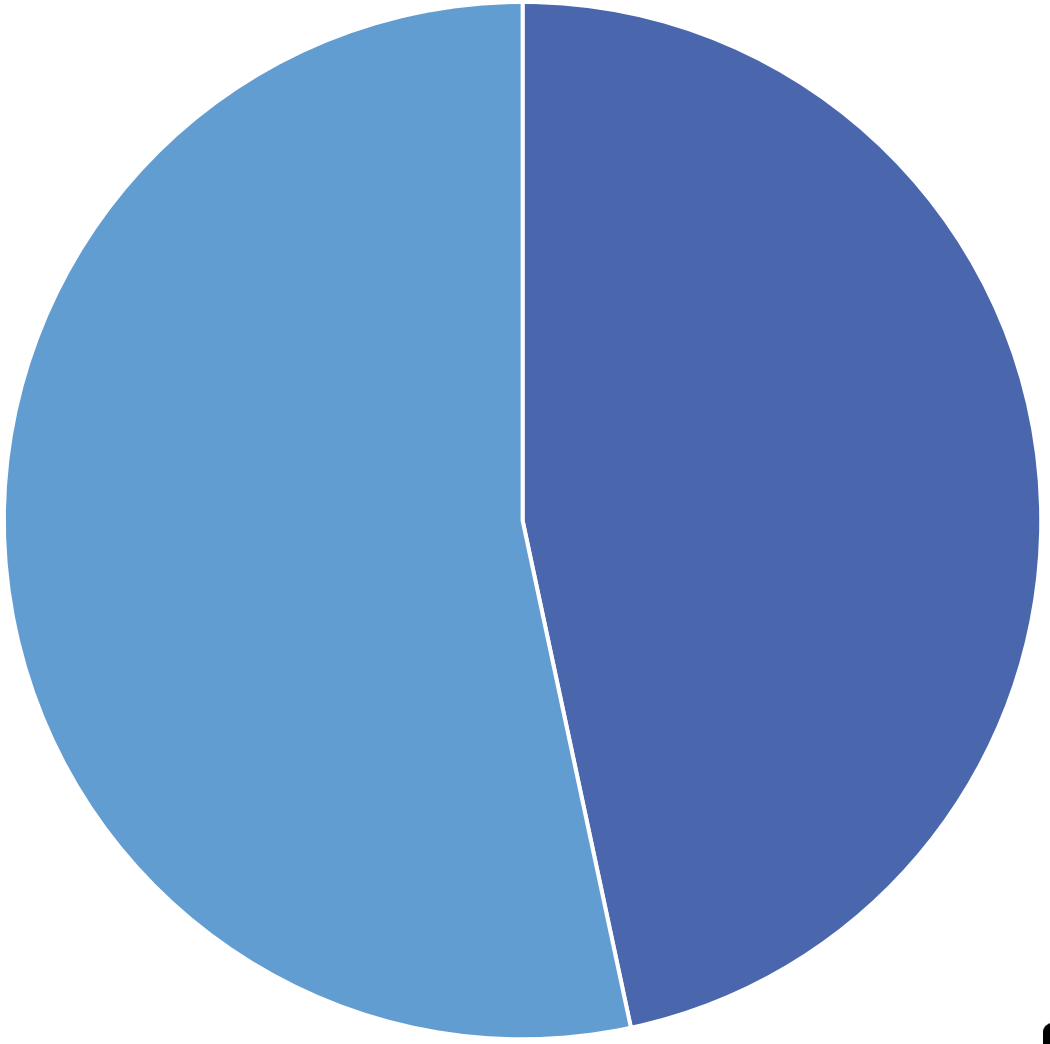
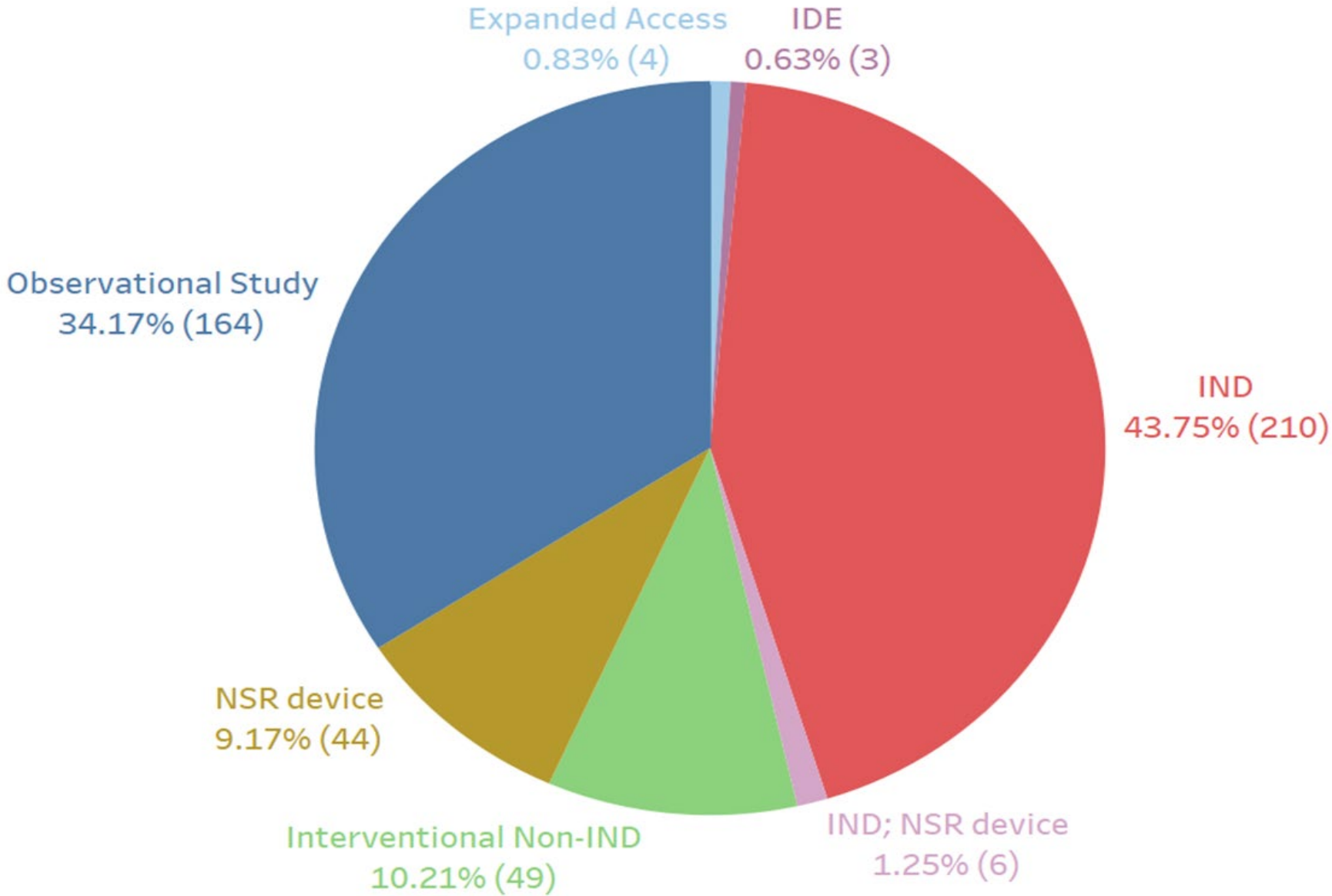
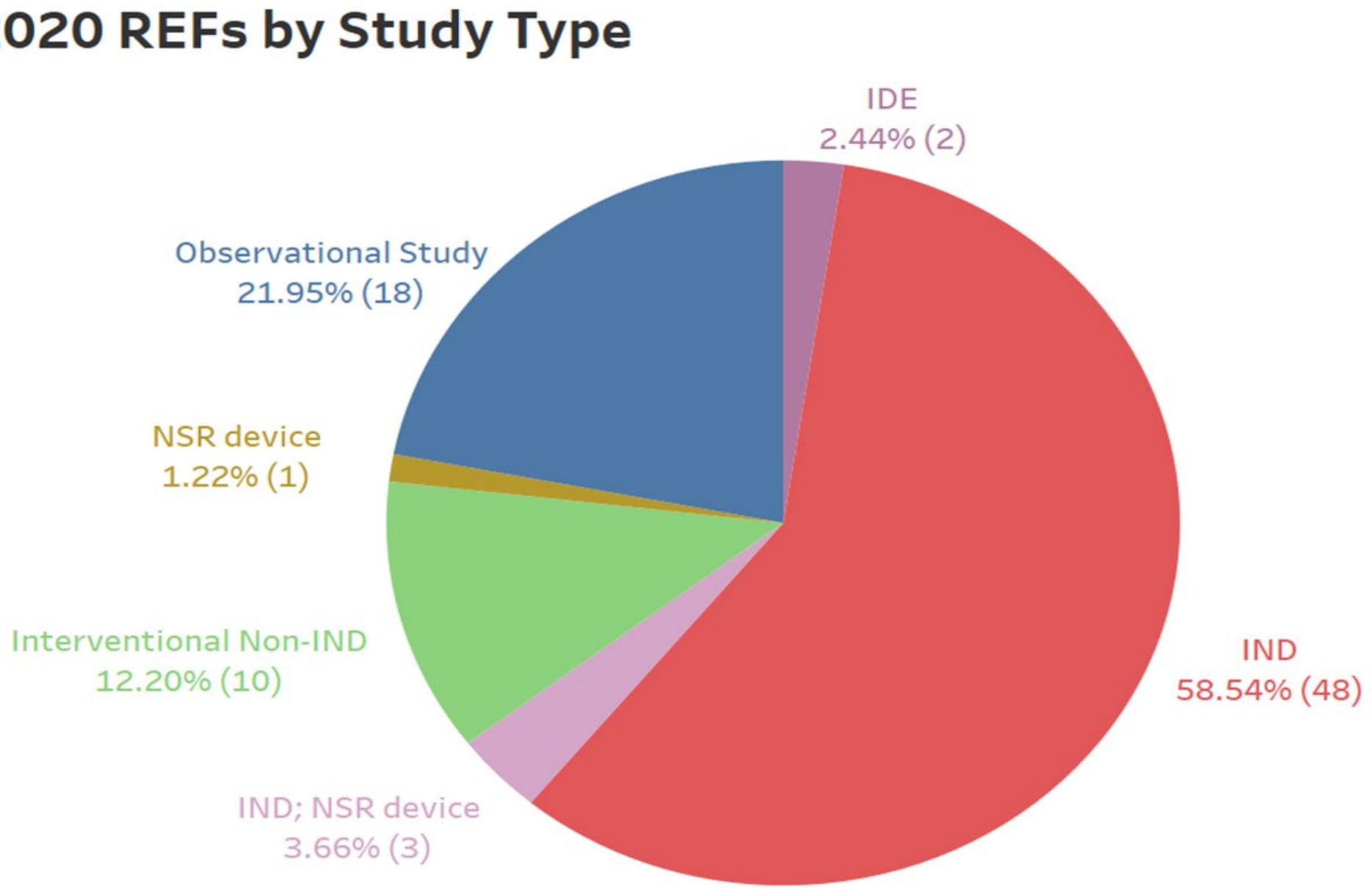
NIH IRB Active Studies By Type
Interventional/Expanded Access vs Observational



2020 REFs by Study Type

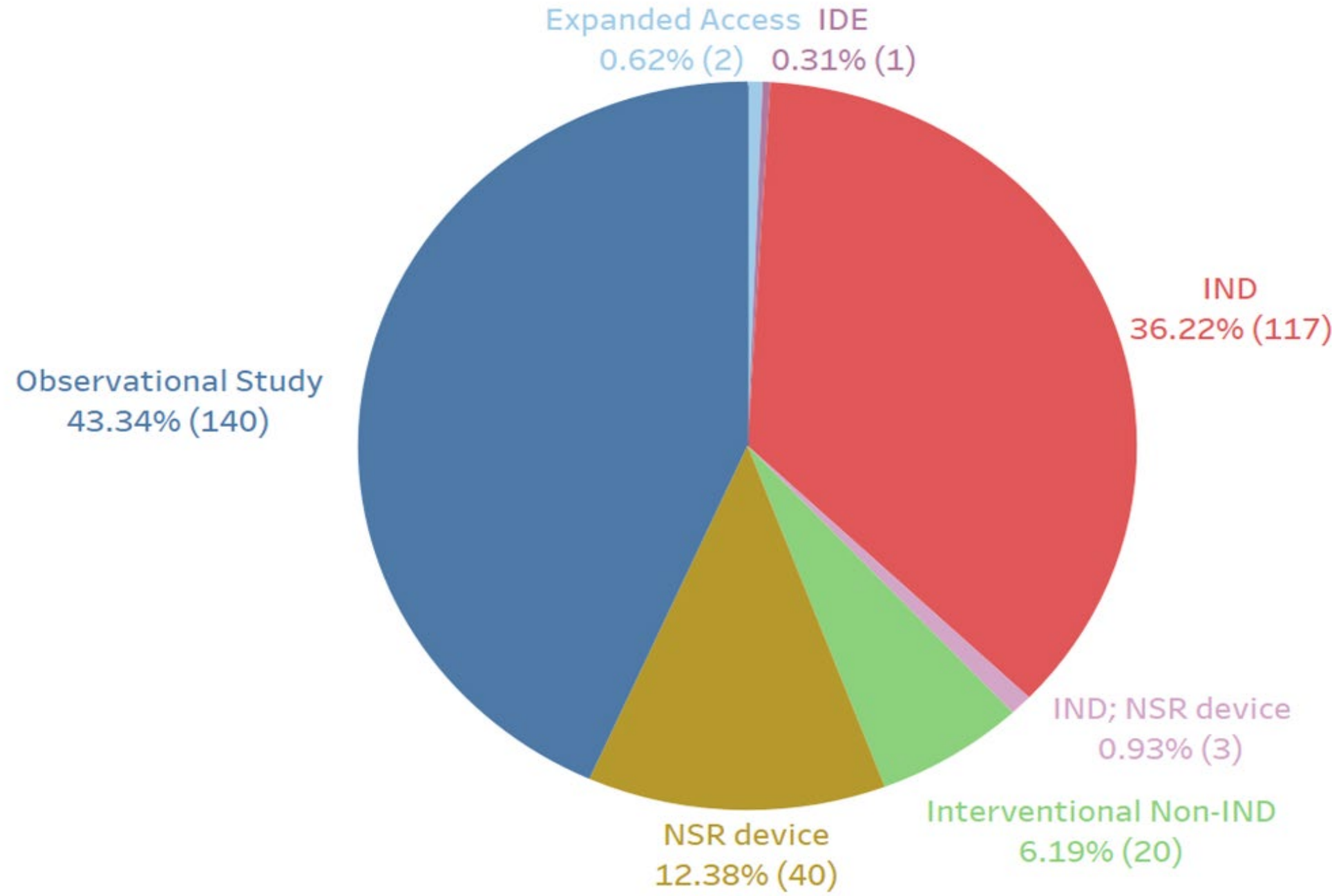


REFs Submitted as UPs

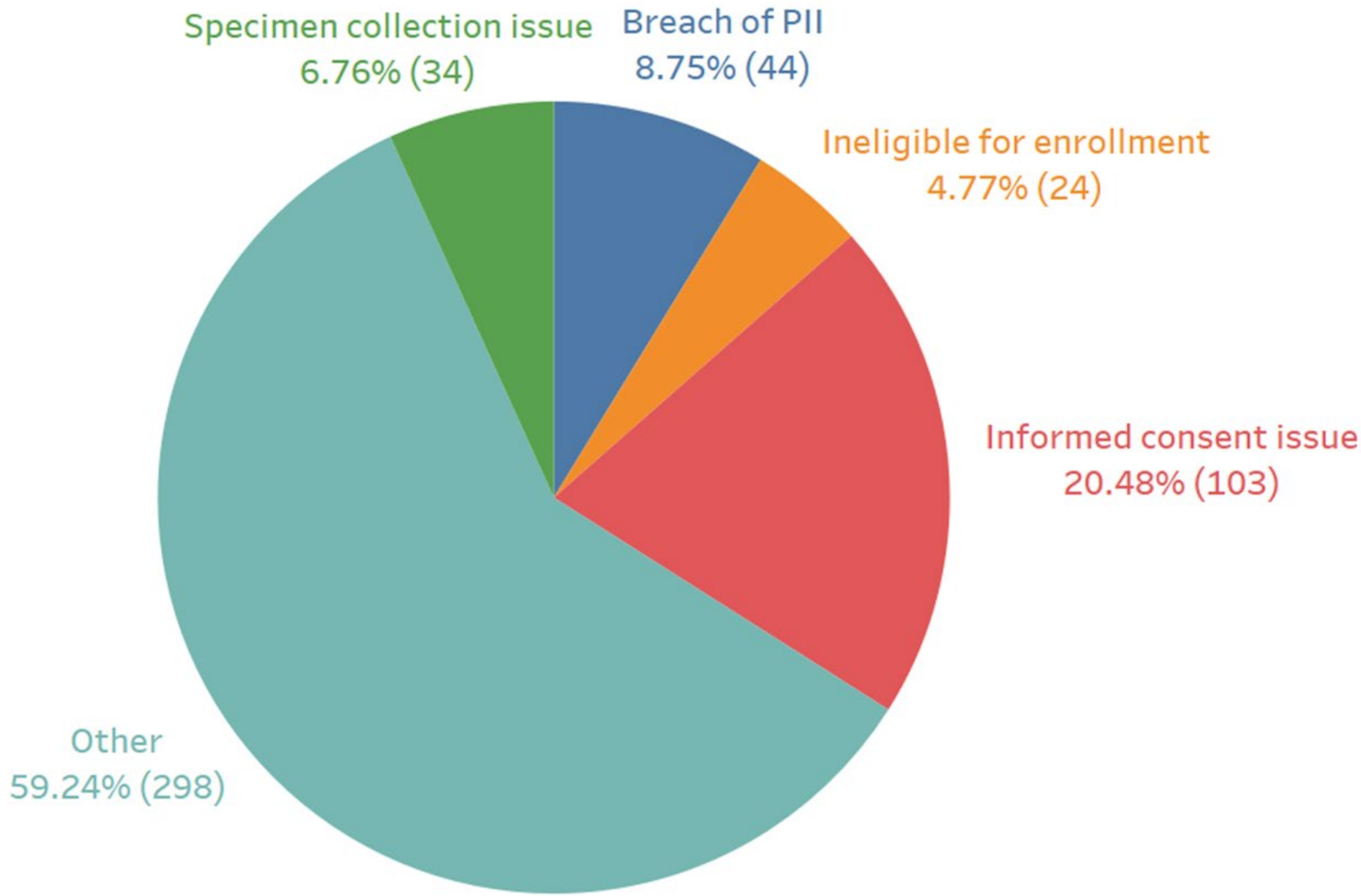


2020 REFs by Study Type

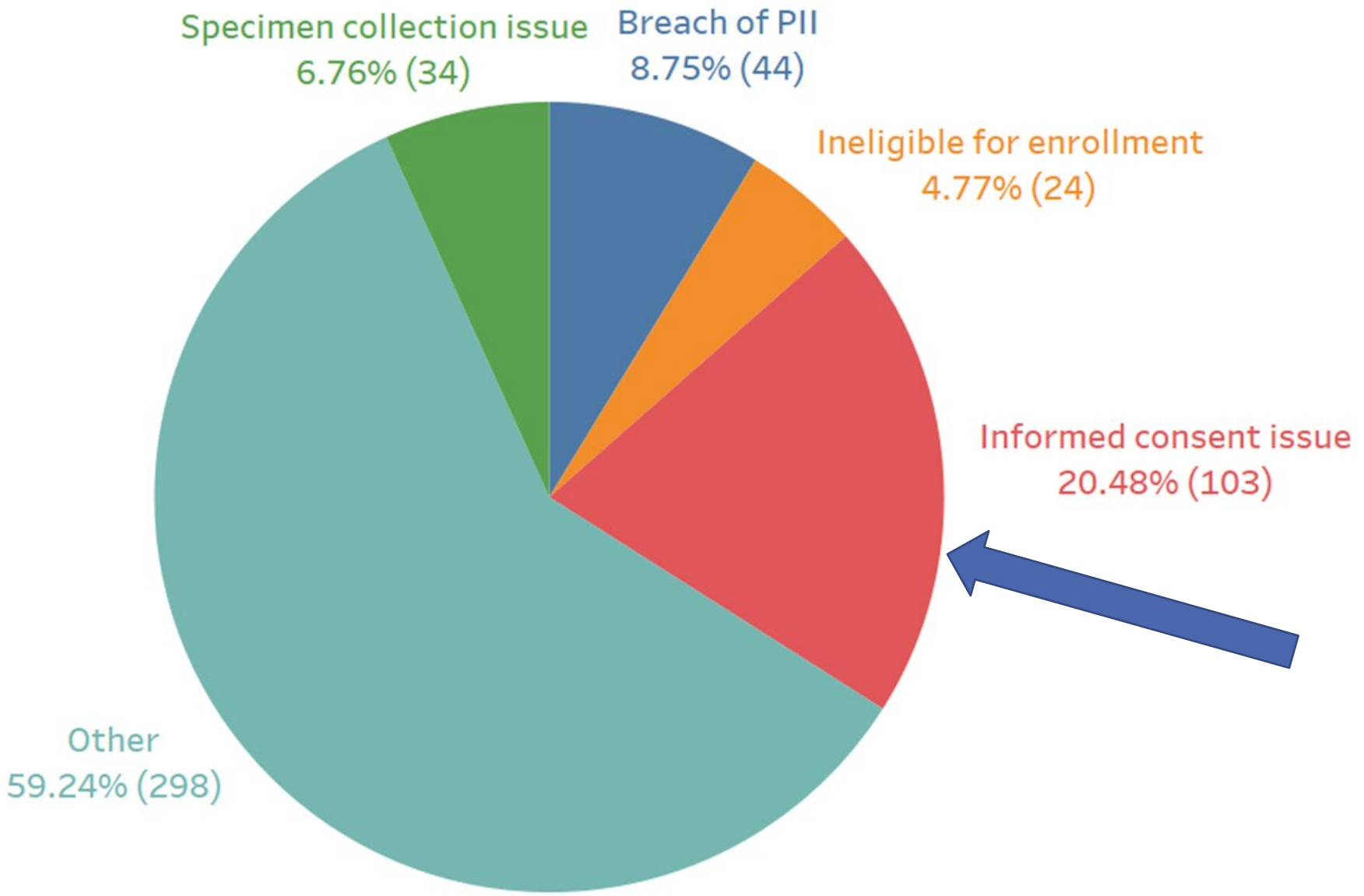
All REFs Submitted as NC (PDs + other NC)



Event Name


Specimen collection issue
6.76% (34)
Breach of PII
8.75% (44)
Ineligible for enrollment
4.77% (24)
Informed consent issue
20.48% (103)
Other
59.24% (298)

Event Name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Common Informed Consent Issues

- Short form process not conducted and/or documented correctly
- Not obtaining written consent or assent as described in the IRB approved protocol prior to conducting research procedures
- Not using the current version of the IRB approved consent (or mistakenly using a consent from a different study!)
- Failure to obtain consent when a participant who is a minor turns 18 and the IRB has not waived the requirement to obtain written consent
- Investigator not approved by the IRB obtains consent
- Not reconsenting subjects after a consent is amended and the IRB required reconsent
- Enrollment of participants not approved by the IRB (e.g., subjects lacking the capacity to consent to research)

Tips for Reporting Deviations Related to Informed Consent

- When submitting the REF for study procedures performed without the required informed consent, please list the procedures performed prior to obtaining consent, whether the subject was notified, and include the plan for obtaining consent
- In cases where an ICF is missing, state if there was a consent note documented in the medical or research record
- OHSRP FAQs related to the consent process have been updated and expanded
  - Change in documentation of consent from subjects who are blind, illiterate or who are non-English speaking individuals for whom no written language exists
    - There still must be a witness (and in the case of the subject for whom no written language exists, there must be an interpreter who may also serve as the witness if they are willing to do so).
    - The ICF templates are being updated to indicate that the line for a witness signature is to be used when there is an oral presentation of the full consent to enroll a blind or illiterate subject

MEDICAL RECORD	CONSENT TO PARTICIPATE IN AN NIH CLINICAL RESEARCH STUDY

Witness should sign below if either:

1. **A short form consent process has been used to enroll a non-English speaking subject or**
2. **An oral presentation of the full consent has been used to enroll a blind or illiterate subject**

Signature of Witness	Print Name of Witness	Date

NIH ADMINISTRATIVE SECTION TO BE COMPLETED REGARDING THE USE OF AN INTERPRETER:

Important Polices Related to the Informed Consent Process

- Policy 301- *Informed Consent*
- Policy 303 - *Intramural Research Program Telehealth Requirements*
- For research at the CC: MAS Policy M20 (internal link)-*Utilization of Telehealth/Telemedicine by NIH Healthcare Providers for NIH Clinical Center Patients*
- Assent requirements-see Policy 402 *Research Involving Children*
- For consent related concerns related to subjects who lack capacity to consent to research, see Policy 403 – *Research Involving Adults Who Lack Decision-making Capacity to Consent to Research Participation*

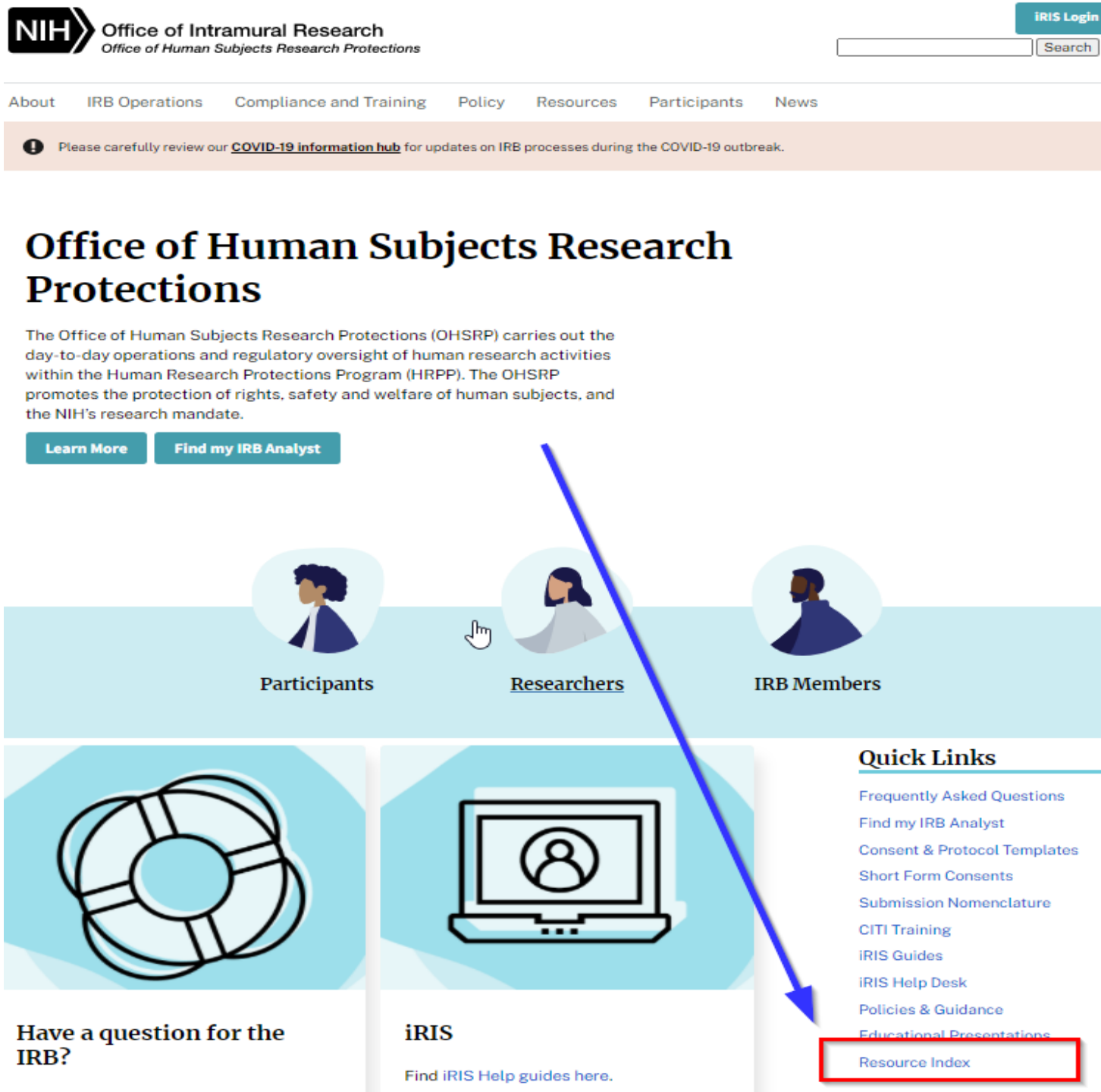
Additional Resources on the OHSRP Website Related to the Informed Consent Process

- Recently updated and expanded OHSRP FAQs related to the consent process will soon be posted on our website
- Consent language library
- Short form consents
- Consent and assent related templates and forms
- Link to the Resource Index section on Informed Consent

Resource Index

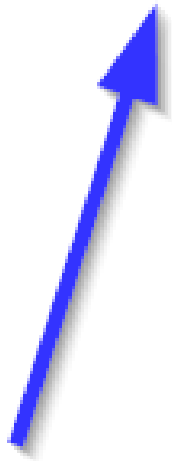
OHSRP website link

https://irbo.nih.gov/confluence/display/ohsrp/



Resource Index-Informed Consent

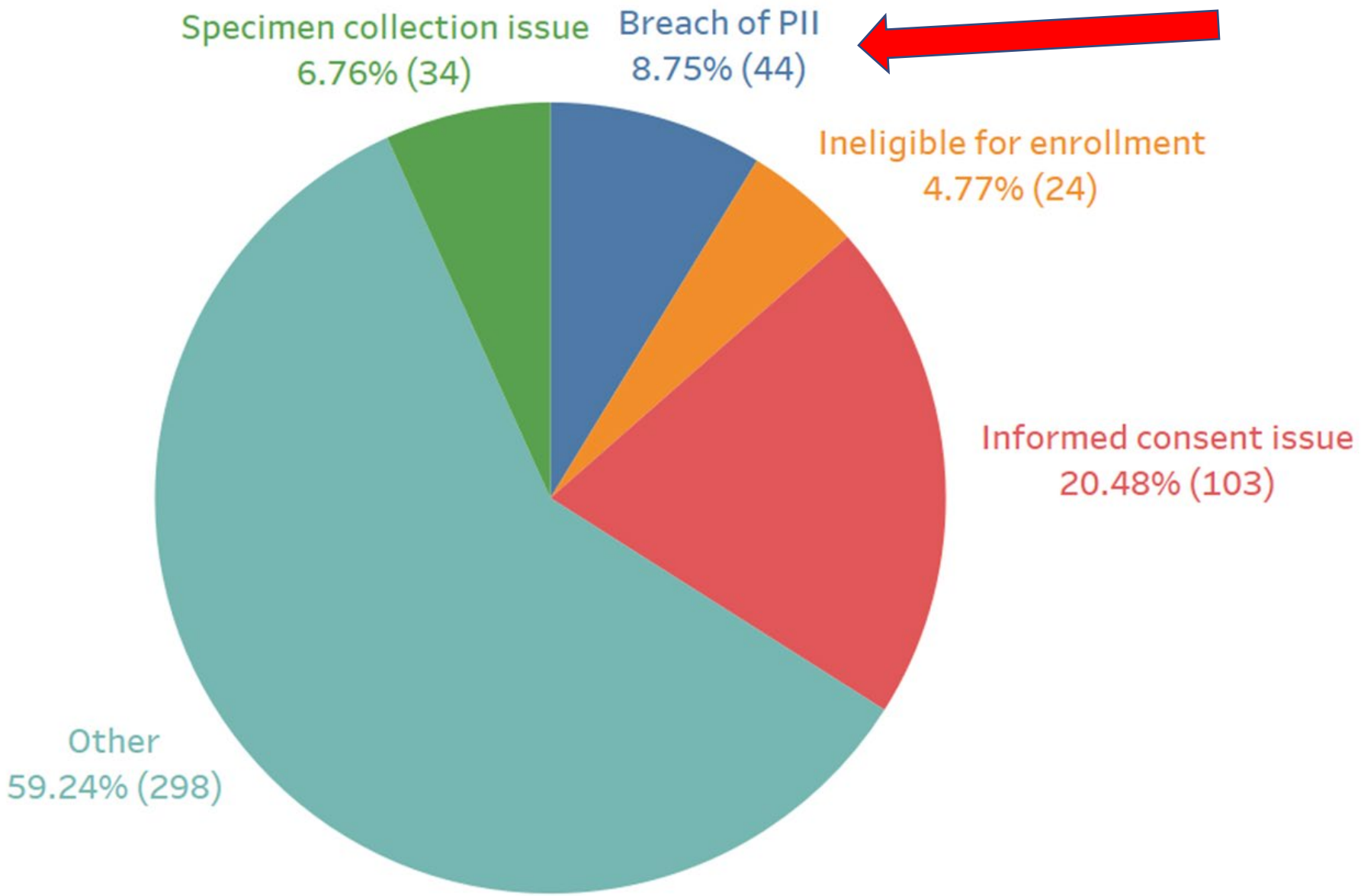
- Accreditation
- Common Rule (Changes Related to the 2018 Common Rule)
- COVID-19
- Exemptions
- FDA Regulated Test Articles, Research With
- Human Subjects Research vs. Not Human Subjects Research
- IND Safety Reporting-Sponsor vs IRB Reporting Policies
- Informed Consent
- International Research
- Investigator education and training requirements
- IRB Member Review Resources
- IRB Review Processes
- Noncompliance
- OHSRP Division of Compliance and Training (C&T)
- Privacy and the Privacy Act of 1974
- Recruitment
- Reliance, FWA Coverage, Single IRB, and Multisite Studies



Informed Consent

- Assent requirements-see Policy 402 Research Involving Children and Policy 402 Change Table and Policy 402 Presentation
- Capacity to give consent: what is it? Who has it? (Bioethics Grand Rounds-02/05/2020) Videocast
- Conducting Informed Consent During the COVID-19 Outbreak (OHSRP Guidance 7/13/2020)
- Consent and assent related templates and forms
- Consent language library
- OHSRP Education Series presentations:
  - Important Changes to Informed Consent: The Regs, the Policies, the Procedures and Forms, Oh My (4/3/2020) Slides and Videocast
  - Informed Consent One Year after the 2018 Common Rule Revisions: Updated Information and Processes (1/14/2020) Slides and Videocast
- OHRP Informed Consent FAQs
- OHRP Simplifying Informed Consent (November 2020)
- OHSRP FAQs
- FAQs as pdf
- Participants lacking capacity to consent to HSR: Policy 403 Research Involving Adults Who Lack Decision-making Capacity to Consent to Research Participation and Policy 403 Change Table and Policy 403 Presentation
- Policy 301 Informed Consent
- Short form consents
- Vulnerable Populations: For consent requirements, see specific policies in 400 Series - Regulatory Protections for Vulnerable Populations

Event Name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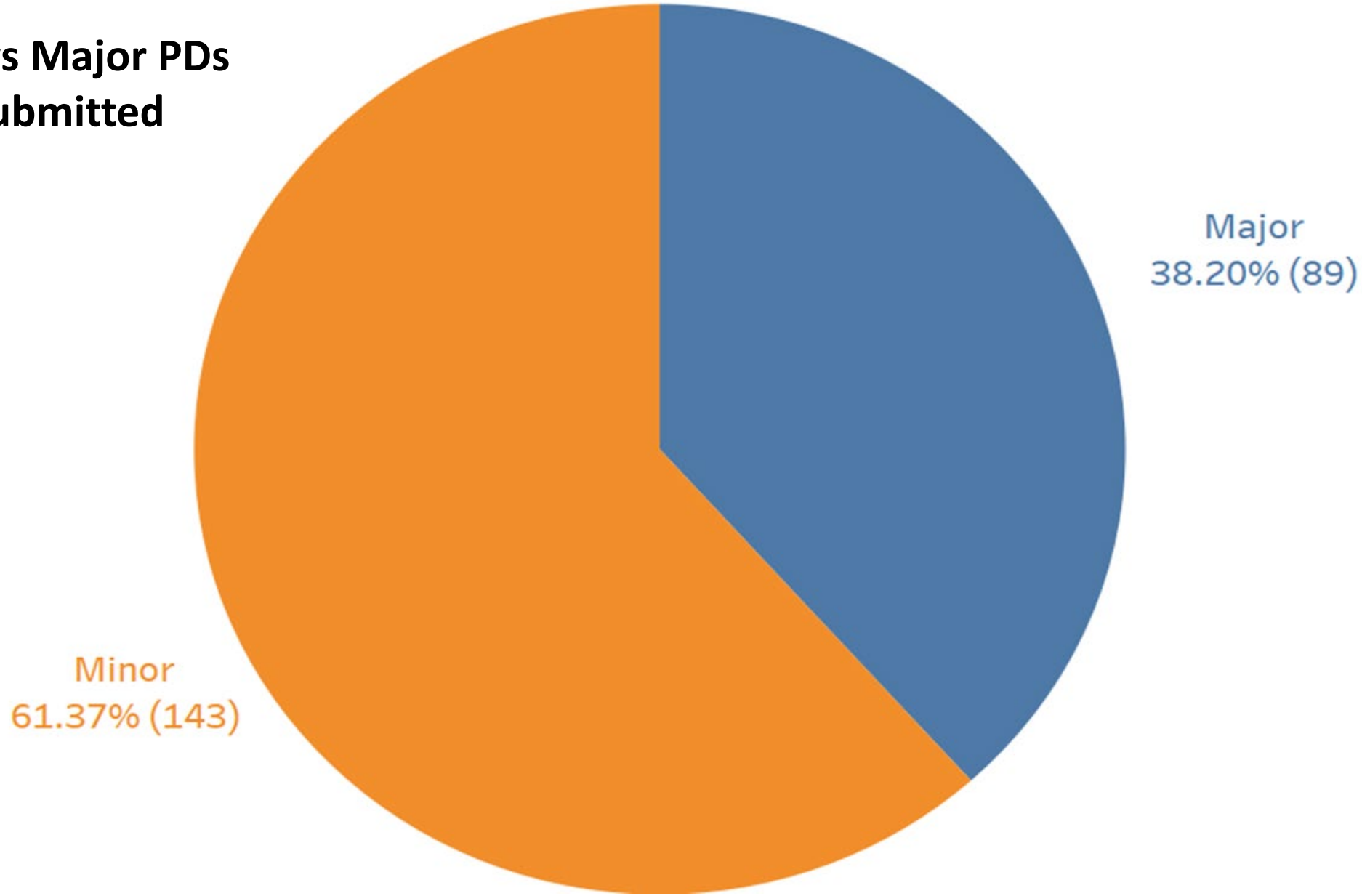
Breach of PII

Reminder: The NIH Privacy Office requires that all potential or actual PII breaches be reported as a security incident, and these events should also be reported via REF in iRIS as noncompliance with NIH policy within 7 days.

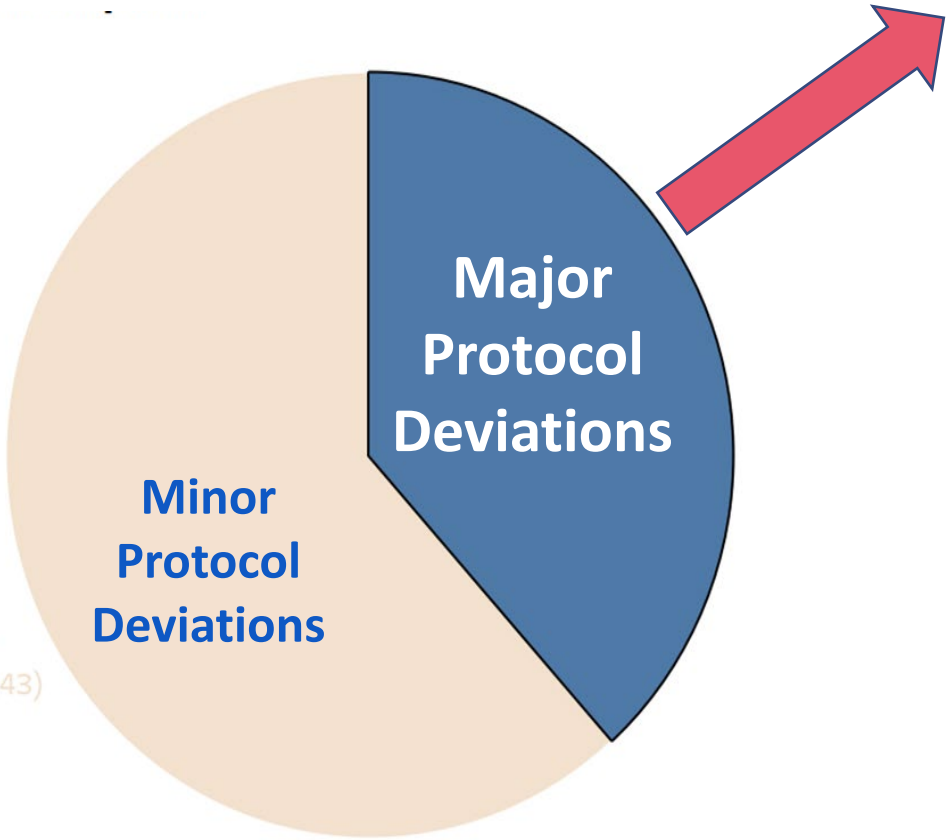
Compliance and Training will stipulate the following at the time the REF is submitted

- Investigators should report potential or confirmed privacy breaches (including unencrypted emails) by contacting their IC Privacy Coordinators and also report NIH security incidents to the Incident Response Team (IRT) at IRT@nih.gov or via Incident Response Team Hotline: 301-881-9726
- The Incident Response Team will do an evaluation and notify the investigator of their risk assessment in a written report
- Upload this report as your response to this stipulation

Minor vs Major PDs as submitted



Further Assessment Of Major Deviations

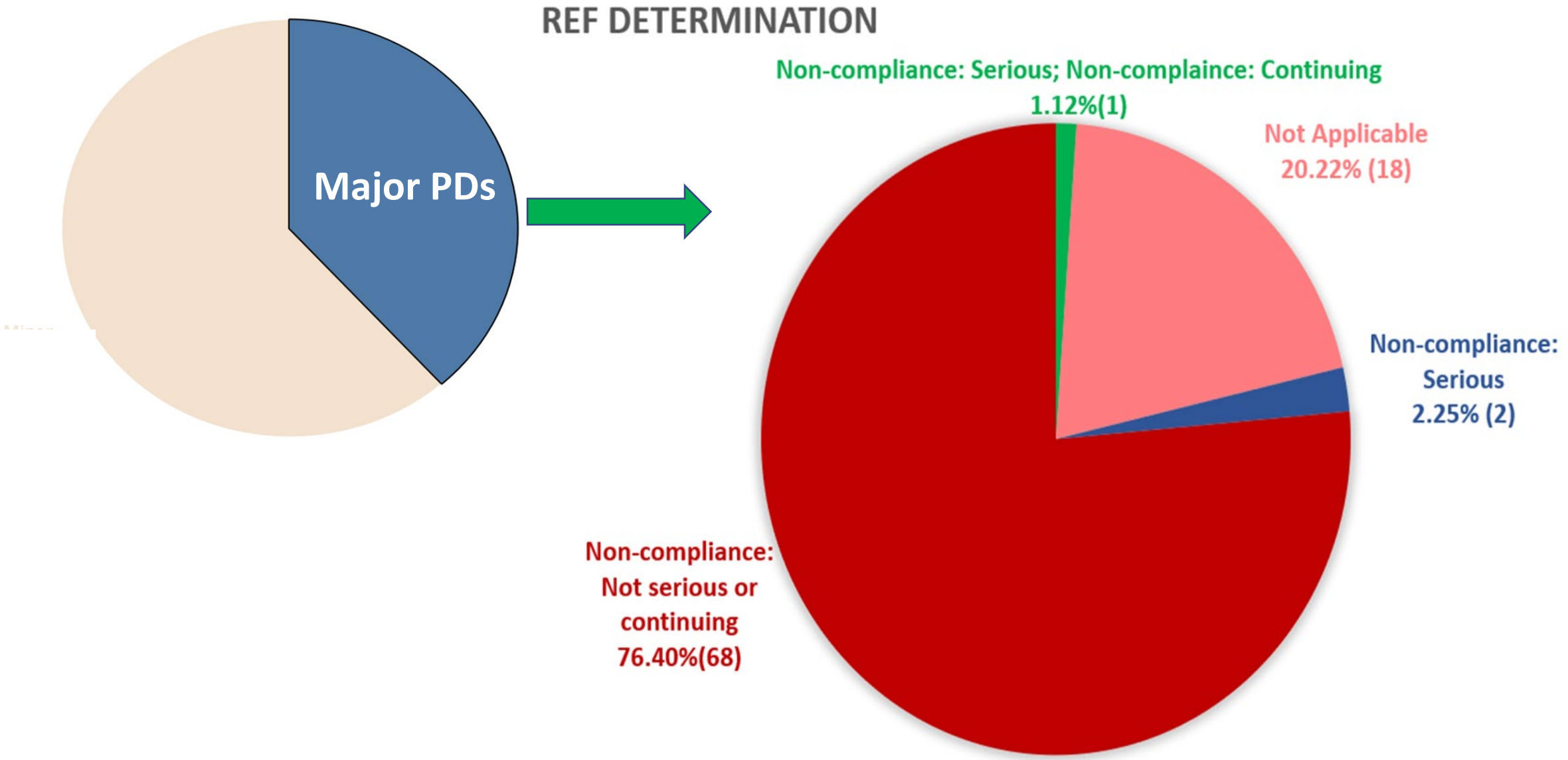


1. Does the deviation meet the definition of noncompliance as defined in our policy?

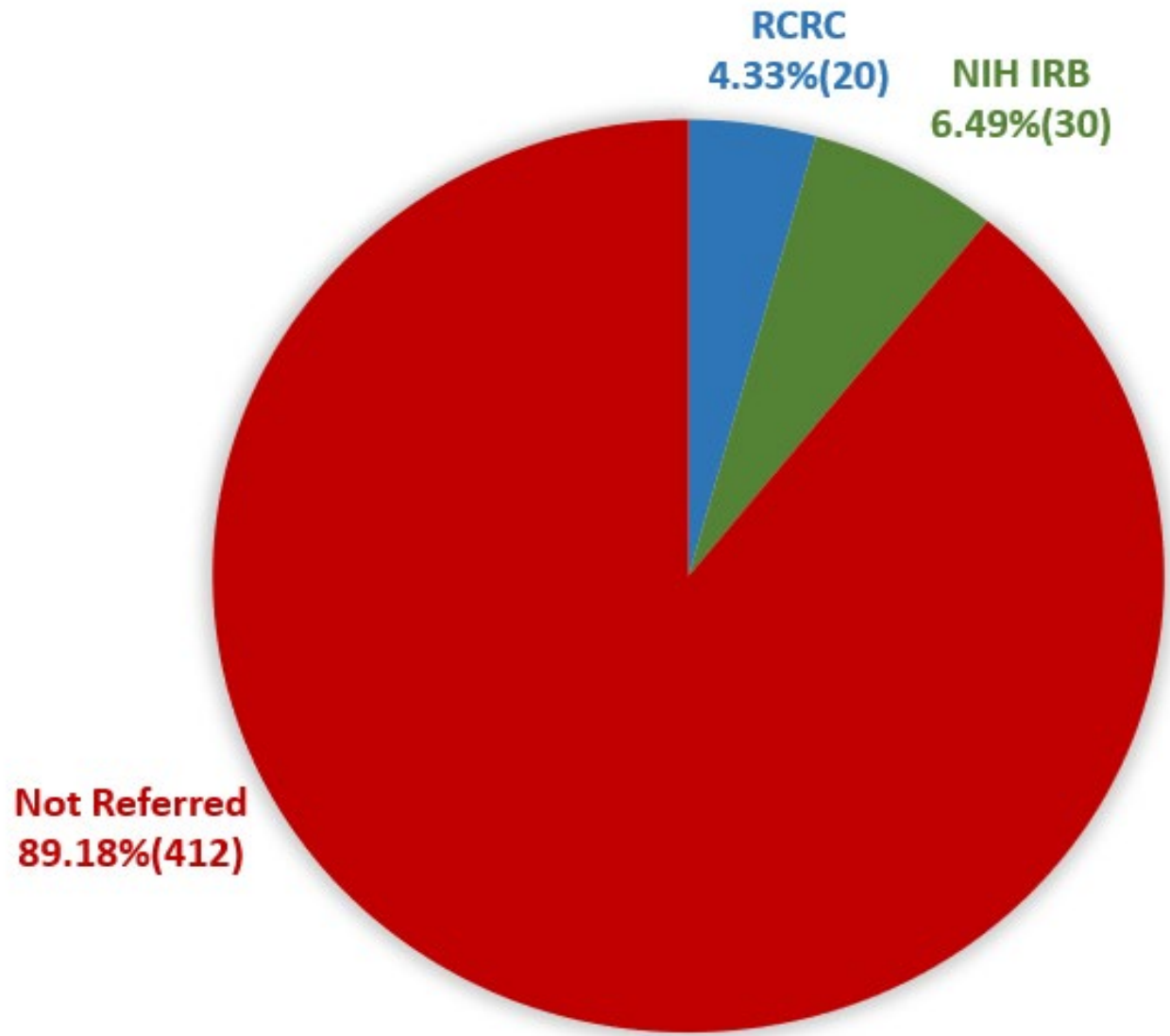
   Non-Compliance: Failure of an investigator to follow the applicable laws, regulations, or institutional policies governing the protection of human subjects in research or the requirements or determinations of the IRB, whether intentional or not

2. ***If*** it meets the definition of NC, does it rise to the level of possible serious and/or continuing NC (which will be forwarded for review by the RCRC?

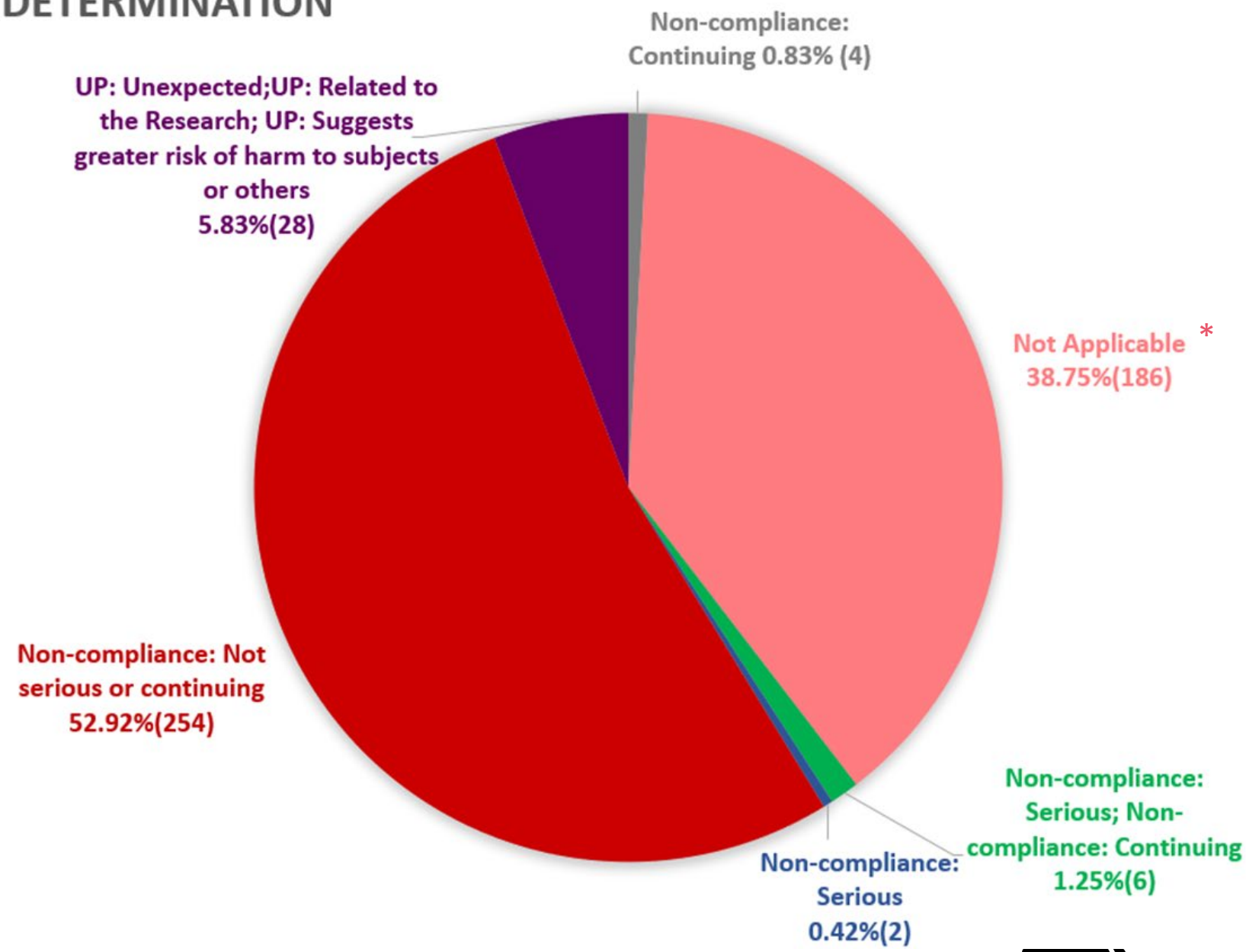
Determination Outcomes for Events Submitted as Major Deviations



EVENT REFERRED TO THE NIH IRB & THE RCRC

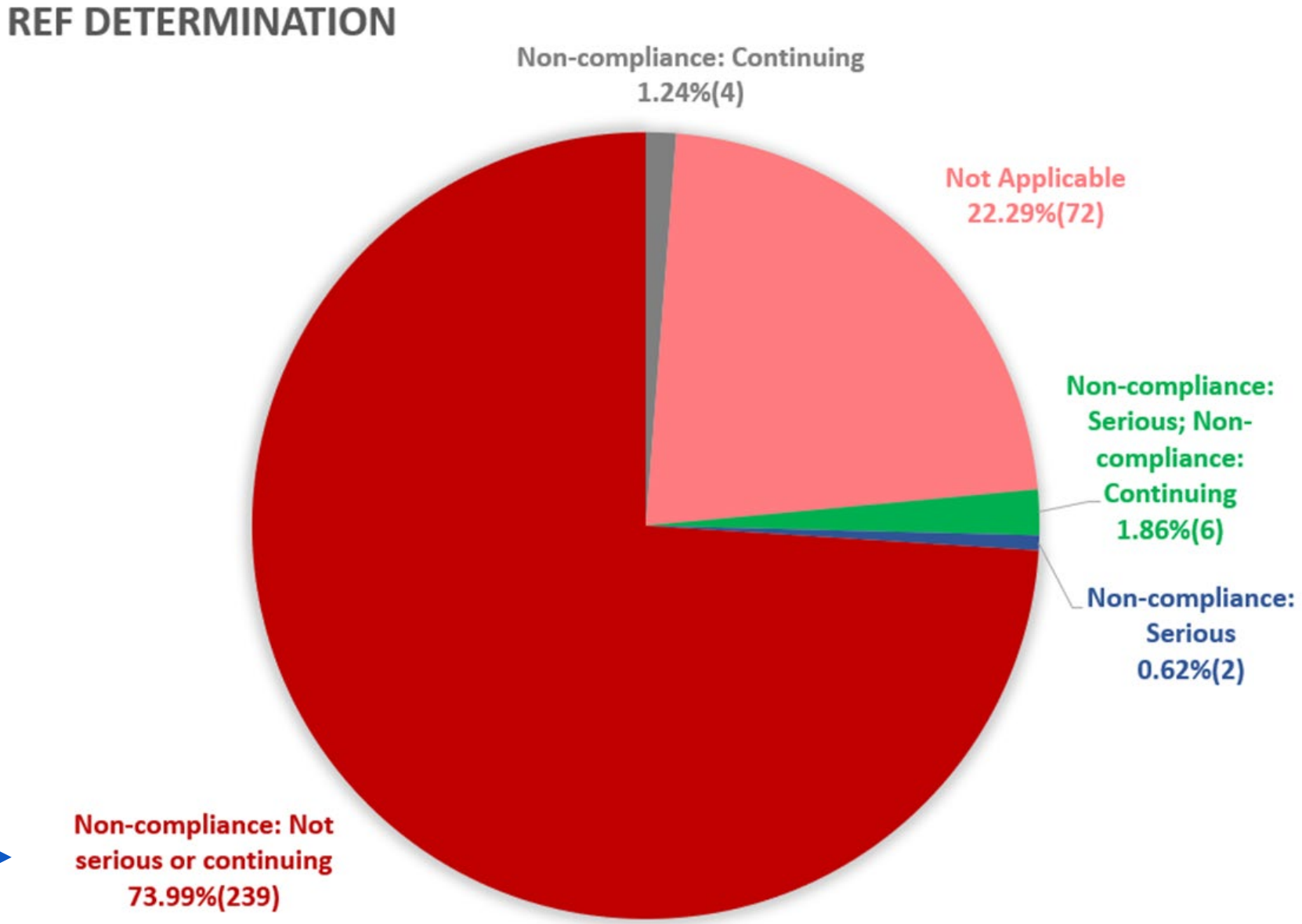


FINAL REF DETERMINATION

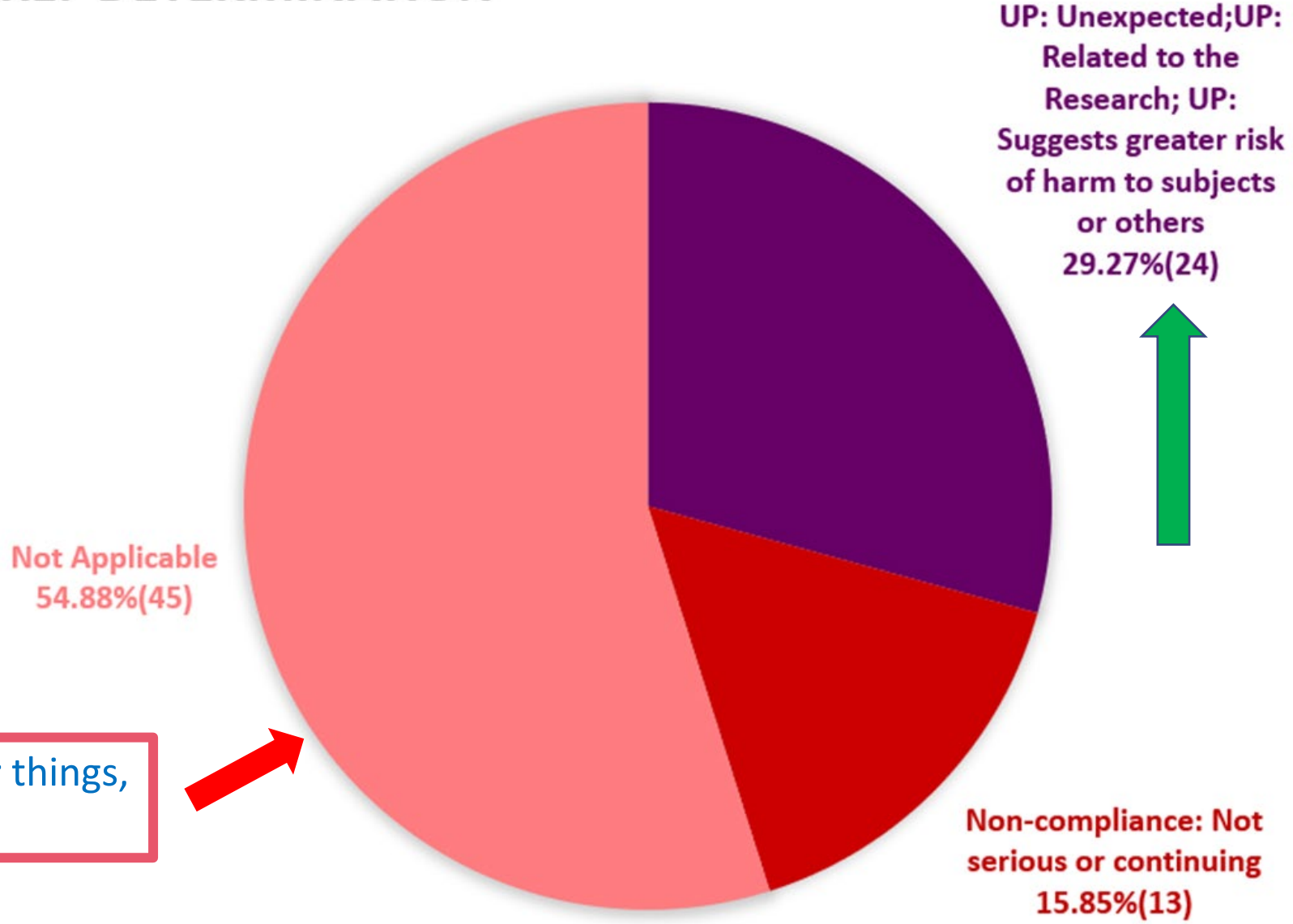


* NA represents PDs that were not determined to be NC

Determinations for All REFs Submitted as PDs or Other NC



Determinations for Events Submitted as UPs



This includes events, among other things, events that are SAEs but not UPs

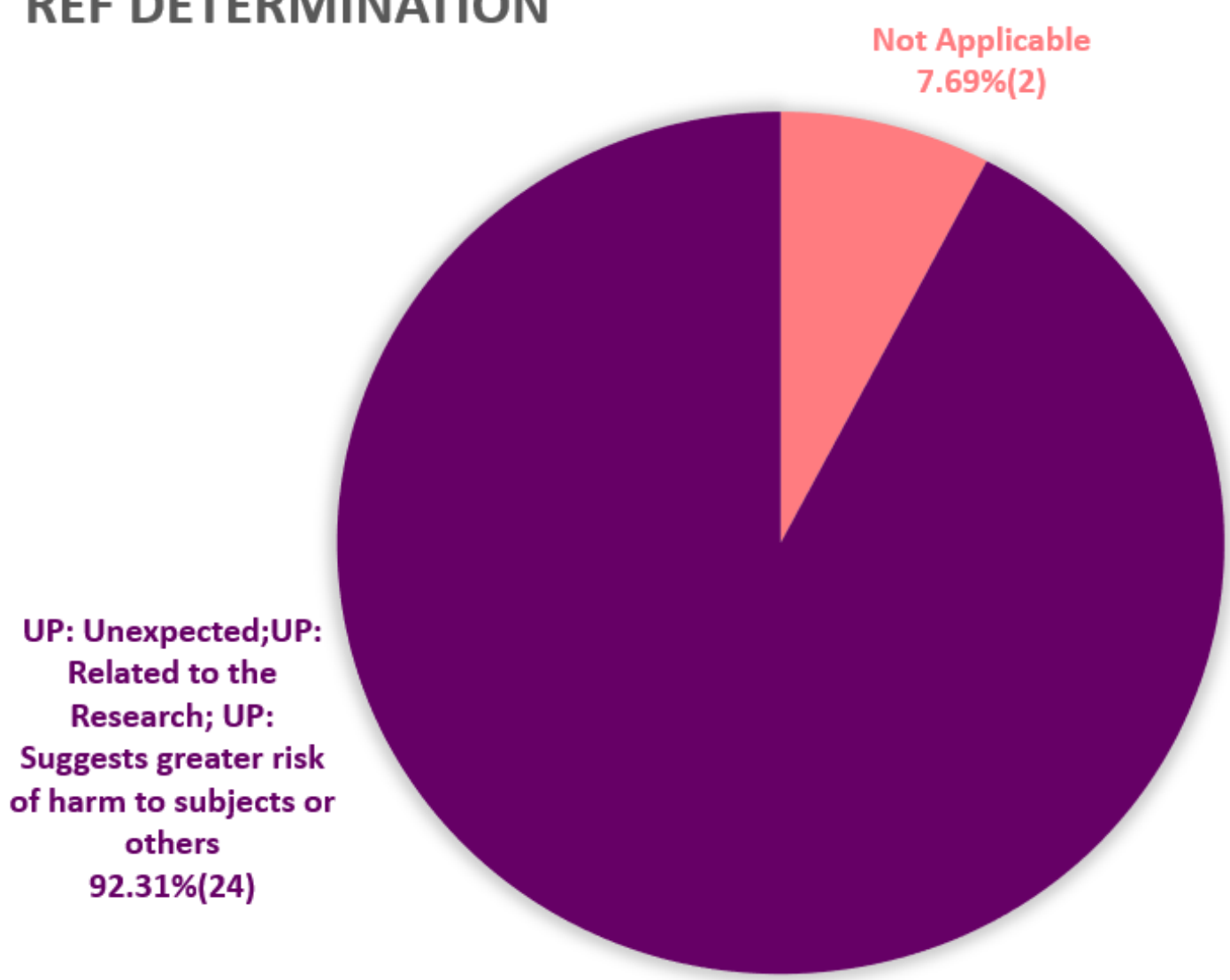
Unanticipated Problem

Reminder: UPs must meet ALL 3 criteria

1. **Unexpected** in terms of nature, severity, or frequency and
2. **Related or possibly related** to participation in the research and
3. **S**uggests that the research **places subjects or others (at a greater risk of harm** than was previously known or expected

If the event does not meet all 3 of these criteria, it is not an unanticipated problem. If the event is an AE or an SAE and not a UP, and it also does not meet the definition of a major protocol deviation or noncompliance, do not report via REF but report it as part of a high-level summary at the time of the IRB's continuing review of the protocol.

Determinations for UPs Referred to the NIH IRB



Examples Of Events Determined by the IRB to be UPs

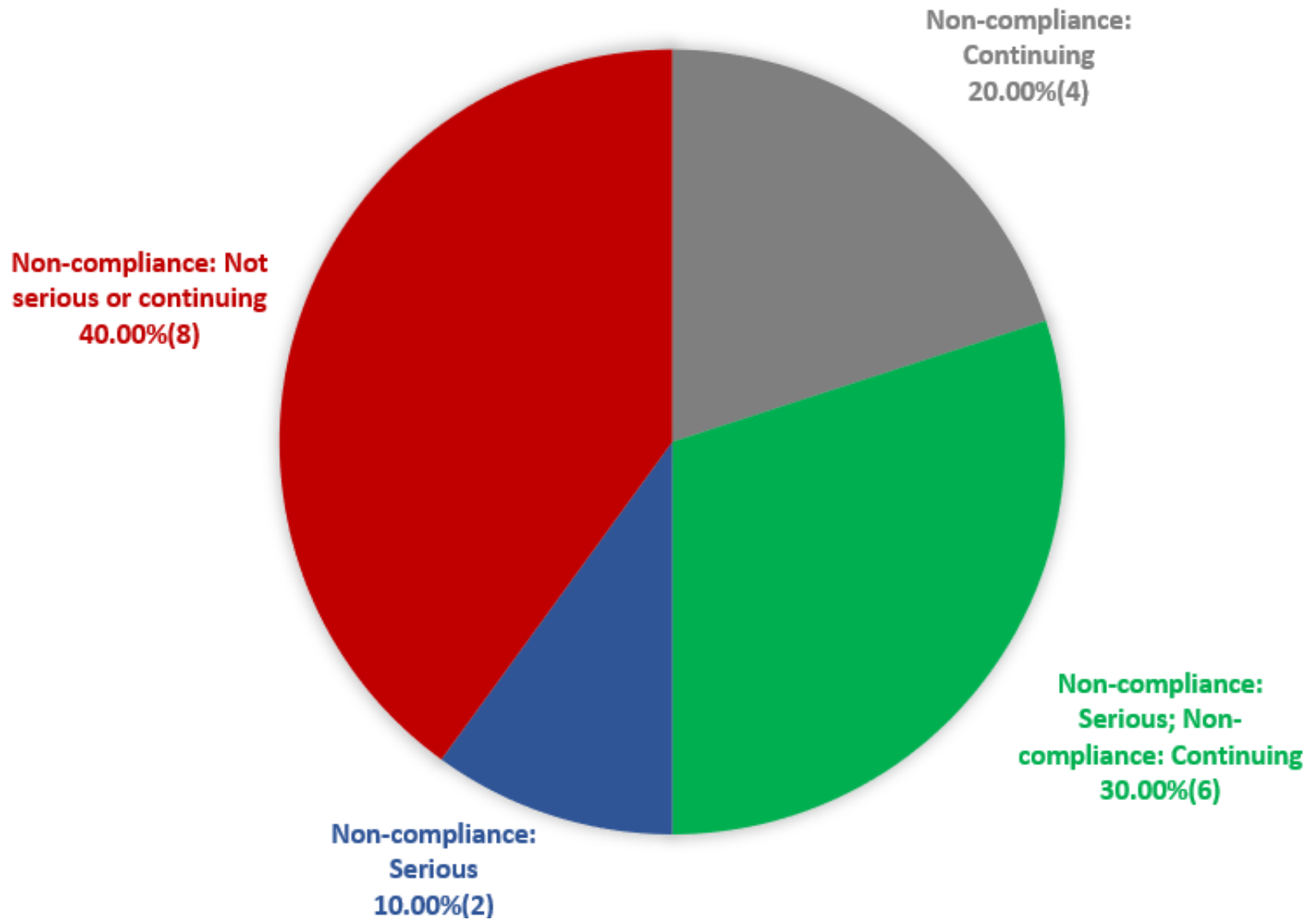
Events r/t process issues

- Investigational product manufacturing and/or processing errors
- Impurities noted in investigational product received from pharma sponsor
- Assay measuring product strength did not meet requirements for use
- PII breach impacting numerous subjects with PII released outside of study sites

Unexpected events post study intervention

- Decreased platelets
- Myocarditis
- Dermatologic: Grade 3 rash, unexpected severity of local skin reaction s/p injection
- Grade 4 CPK increase with rhabdomyolysis
- Grade 4 acute kidney failure
- Neuropathy and muscle weakness
- Increased incidence of significant hematoma
- Subarachnoid hemorrhage secondary to LP
- Significant increase in anxiety and depression associated with questionnaire completion

Determinations for REFs Referred to the RCRC

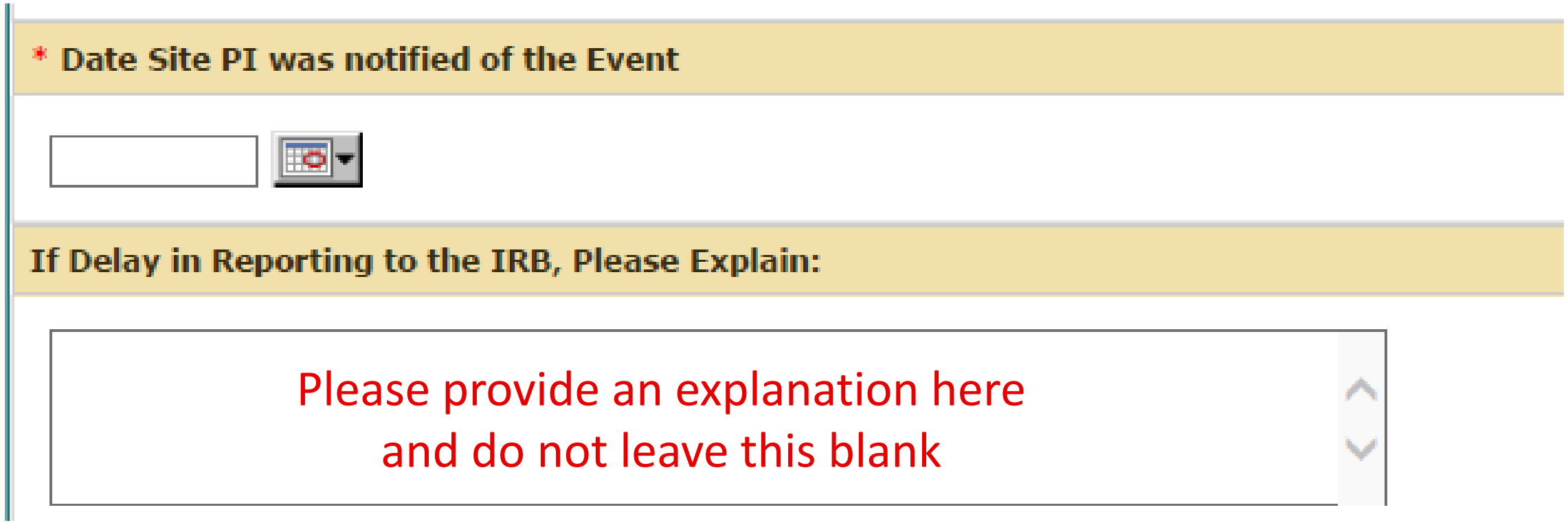


Examples of Events Determined by the RCRC to be Serious and/or Continuing Non-Compliance

- Enrollment of ineligible subjects
- Study procedures performed without required informed consent
- Failure to follow the protocol as written resulting in negative outcomes that were possibly preventable
- Large number of protocol deviations with multiple instances of failure to collect required safety data
- Failure to provide study drug to participants as per protocol
- Lack of appropriate medical oversight of participants receiving study medication

Tips for Completing the NIH REF

When There is a Delay in Submitting the REF



*** Is this Problem "Unexpected"?**

(click on the question mark on the right side to display definitions)

- ◯ Yes
- ◯ No

Please explain:

*** Is this problem related or possibly related to participation in the research?**

(click on the question mark on the right side to display definitions)

- ◯ Yes
- ◯ No

Please explain:

*** Does the problem suggest the research places subjects or others at a greater risk of harm than was previously known or recognized?**

(click on the question mark on the right side to display definitions)

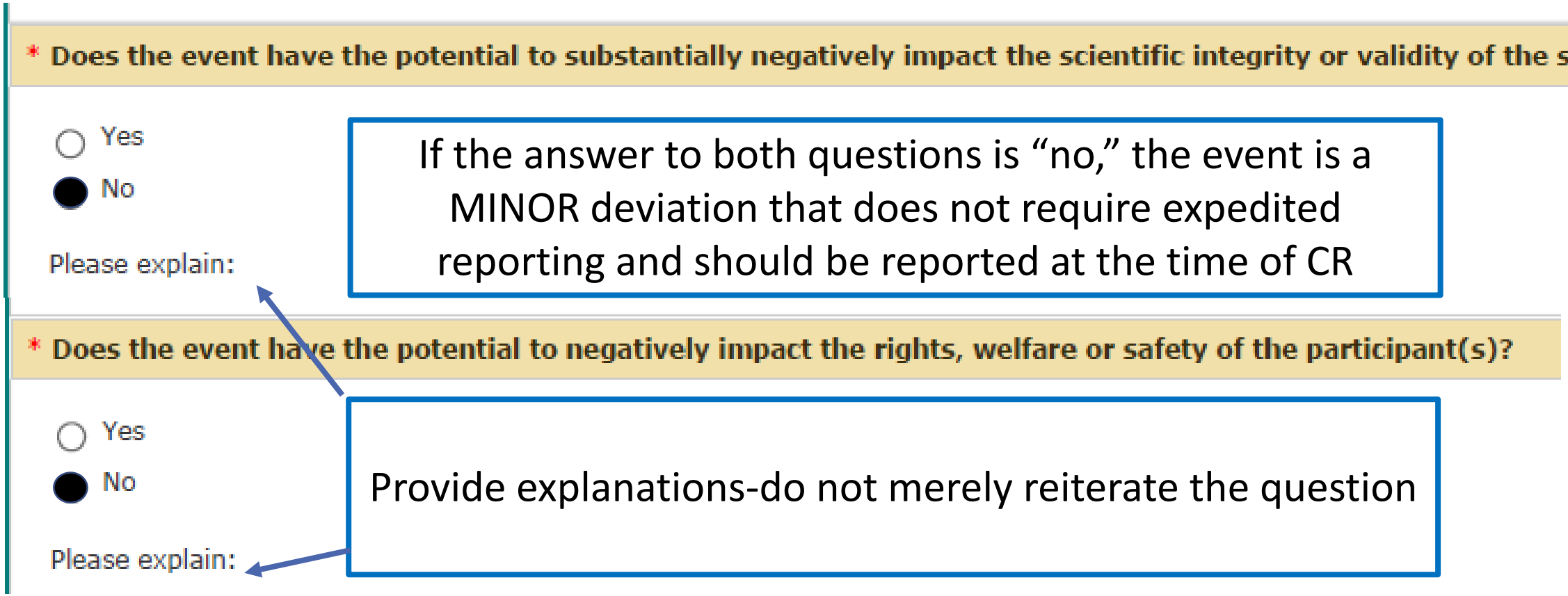
- ◯ Yes
- ◯ No

Please explain:

Section of the REF Relating to Criteria For UPs

Provide explanations- do not merely reiterate the question

Protocol Deviations



If the answer to both questions is "no," the event is a MINOR deviation that does not require expedited reporting and should be reported at the time of CR

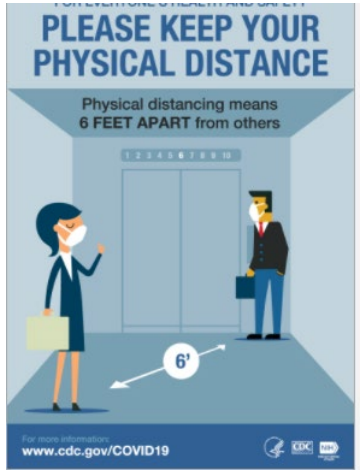
Provide explanations-do not merely reiterate the question

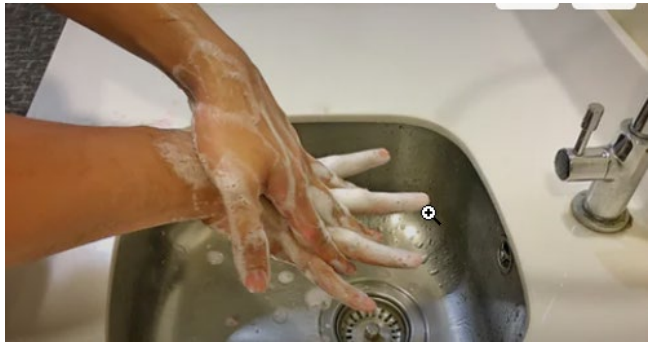
CORRECTIVE ACTION

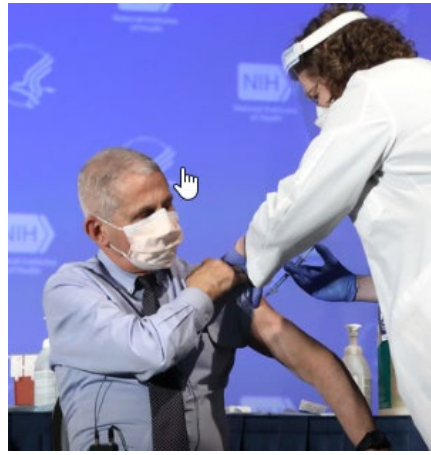
* Describe What Steps have you Already Taken as a Result of this Event?

The PI should provide a robust explanation of what steps have already been taken and what steps are planned to address the problems related to the event being reported. Providing insufficient information in the section will result in a stipulation to provide a more detailed explanation.

SO . . . 2020 WAS QUITE A YEAR!

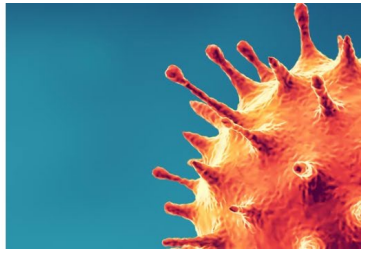






NIH Strategic Response to COVID-19

NIH provides leadership and direction to its institutes, centers, and programs conducting and supporting research on COVID-19.



NIH Office of Intramural Research
Office of Human Subjects Research Protections

WE ARE (STILL) HERE TO HELP IF YOU HAVE QUESTIONS RELATED TO REPORTING RESEARCH RELATED EVENTS

OHSRP office of Compliance and Training

OHSRPCompliance@od.nih.gov

Questions?