Protocol non-compliance monitoring: a retrospective review of submitted protocol deviations and EC decisions

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Introduction

- Post-approval review include assessment of protocol non-compliance/deviations (NCs/PDs).
- ICH-GCP and WHO clearly defined the roles and responsibilities of the investigator/institution, sponsor & ethics committees in the reporting, management, and recommending actions on NCs/PDs.
- Very few published studies looked at protocol non-compliance monitoring, while none for EC assessment

Compliance

adherence to the trial-related requirements, GCP requirements

(ICH GCP E6(R3))

Protocol non-compliance/ deviation

any change, divergence, or departure from the study design or procedures defined in the protocol

(US DHHS, FDA, Guidance for industry E3 Q&A(R1)

Important protocol deviations

those that impact rights, safety, and well-being of trial participants, and reliability of results

(ICH GCP E6(R3))

Protocol non-compliance monitoring:
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OBJECTIVES

METHODOLOGY

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- Review the protocol non-compliance/deviations
  - Categorize deviations
  - Identify patterns
  - Identify gaps in reporting
  - Identify gaps in assessment

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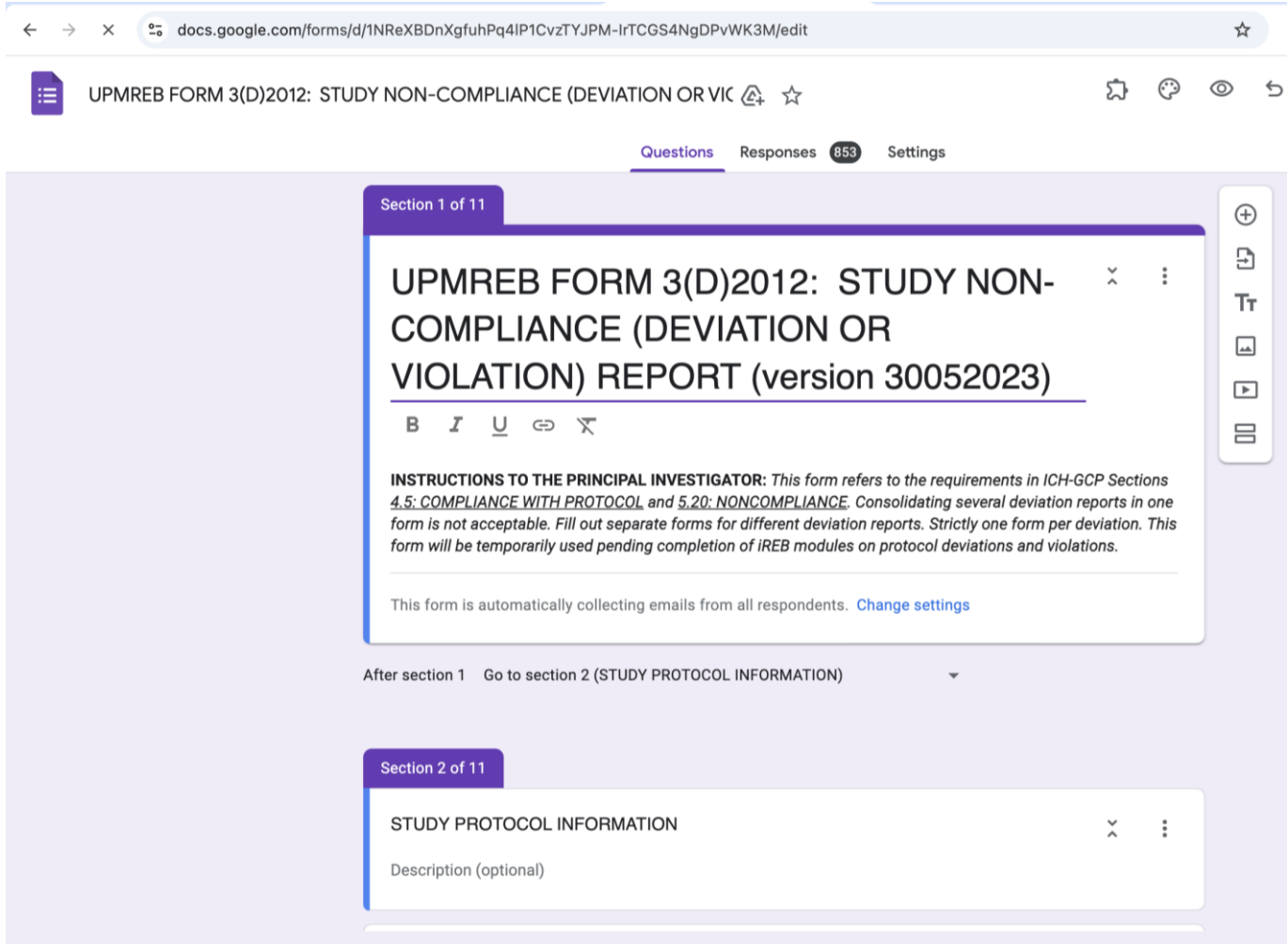
- Retrospective review of NC/PD database



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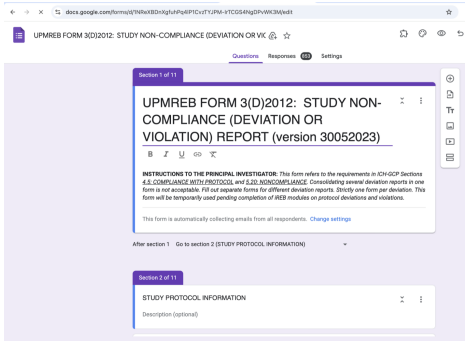
UPMREB Form 3D Sections:



- Protocol Info
- Investigator, Sponsor details
- Deviation attribution (Subject, PI, Sponsor)
- Description of the NC/PD
- PI/sponsor assessment (minor/major; impact on safety/data)
- CAPA
- Submission details
- REB Assessment (impact on data quality or patient safety)

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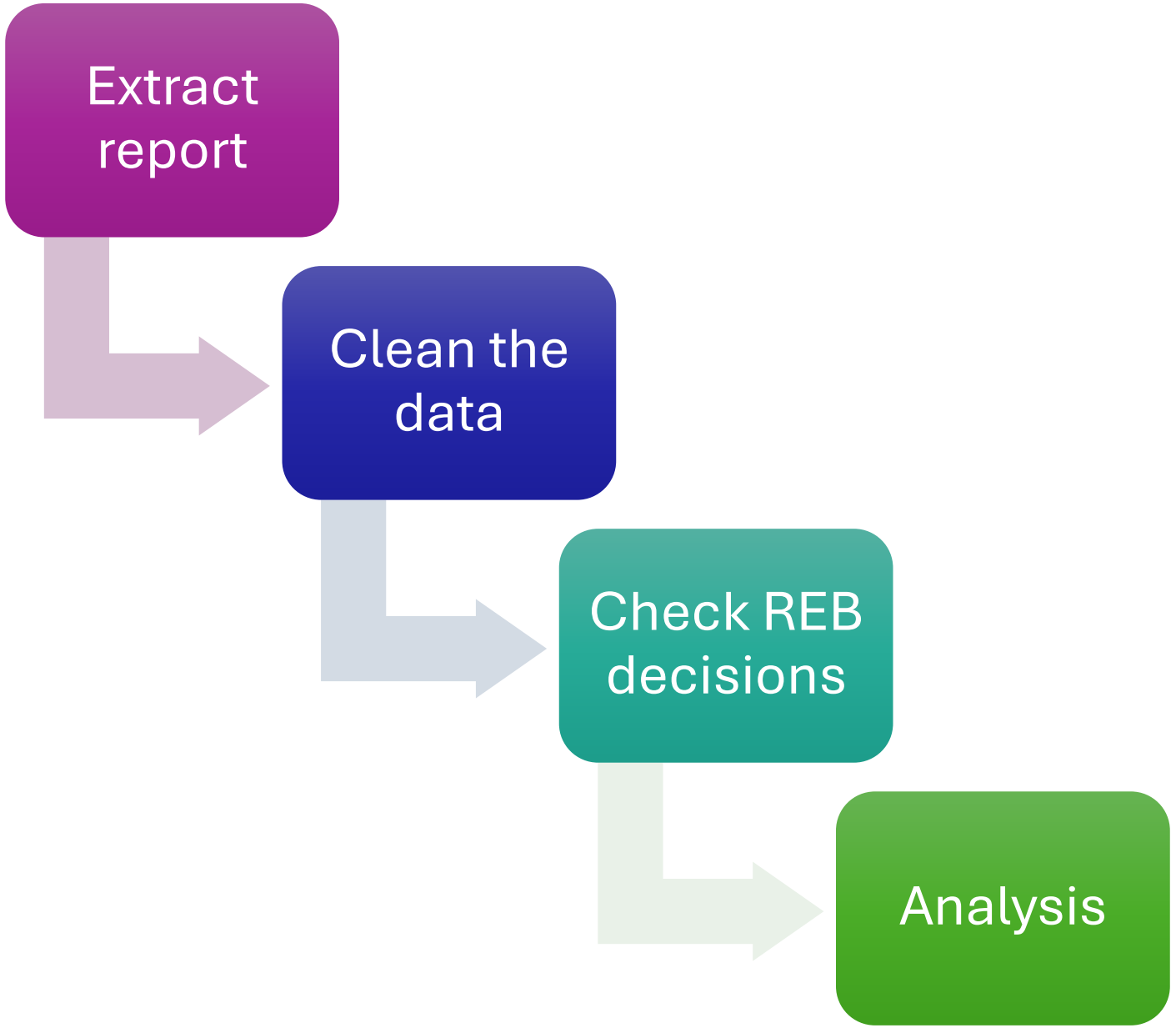

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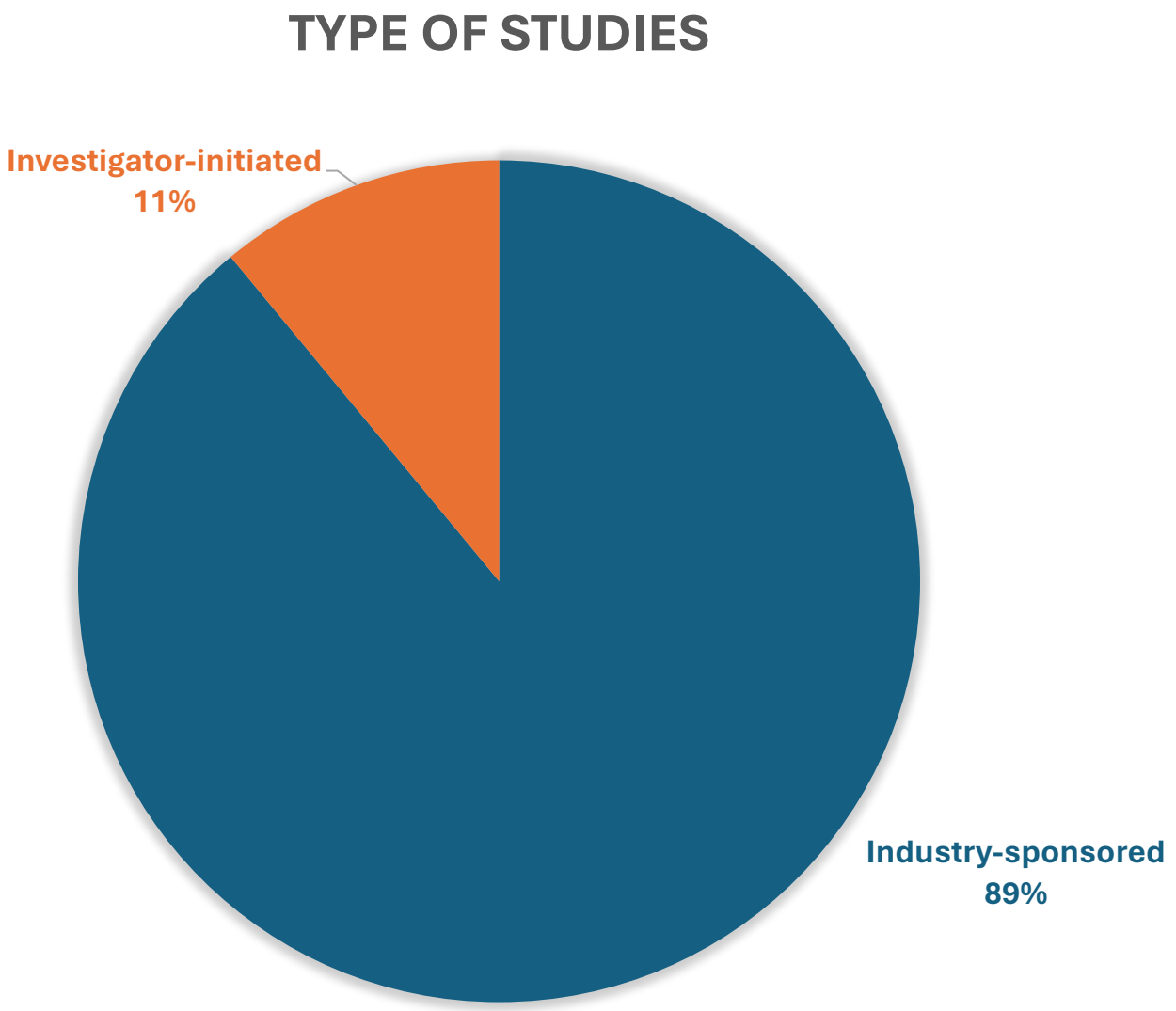

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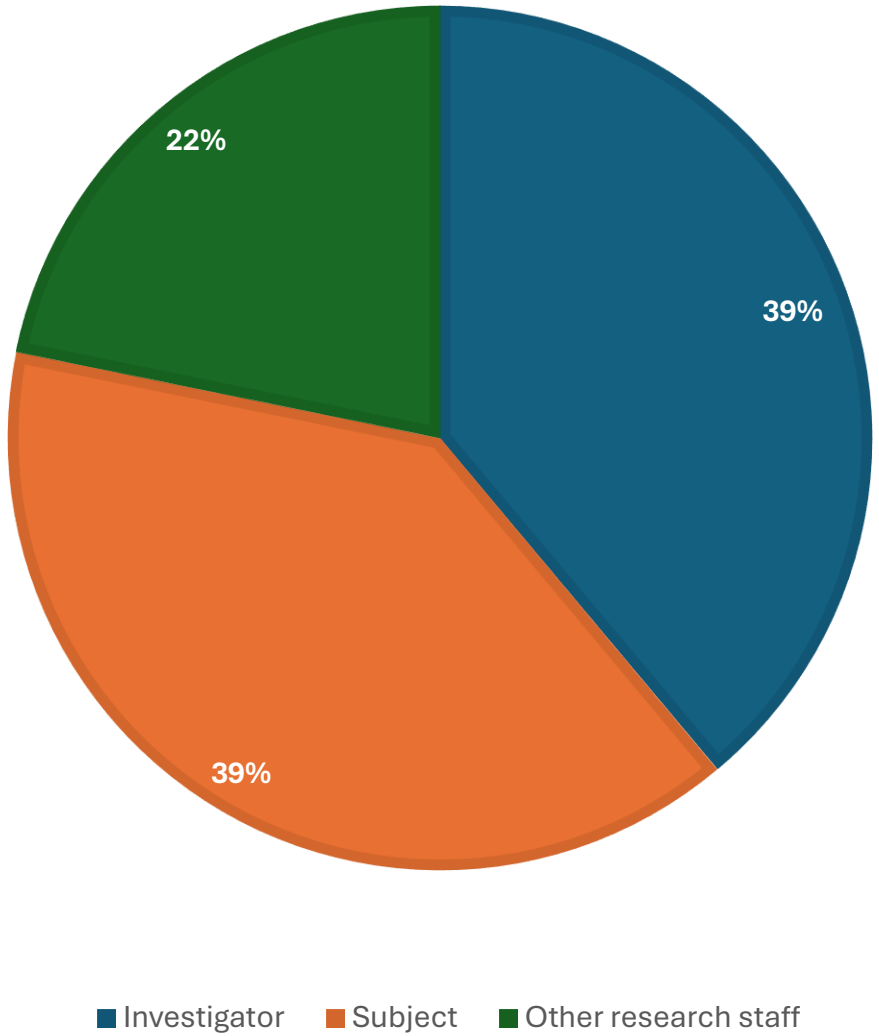

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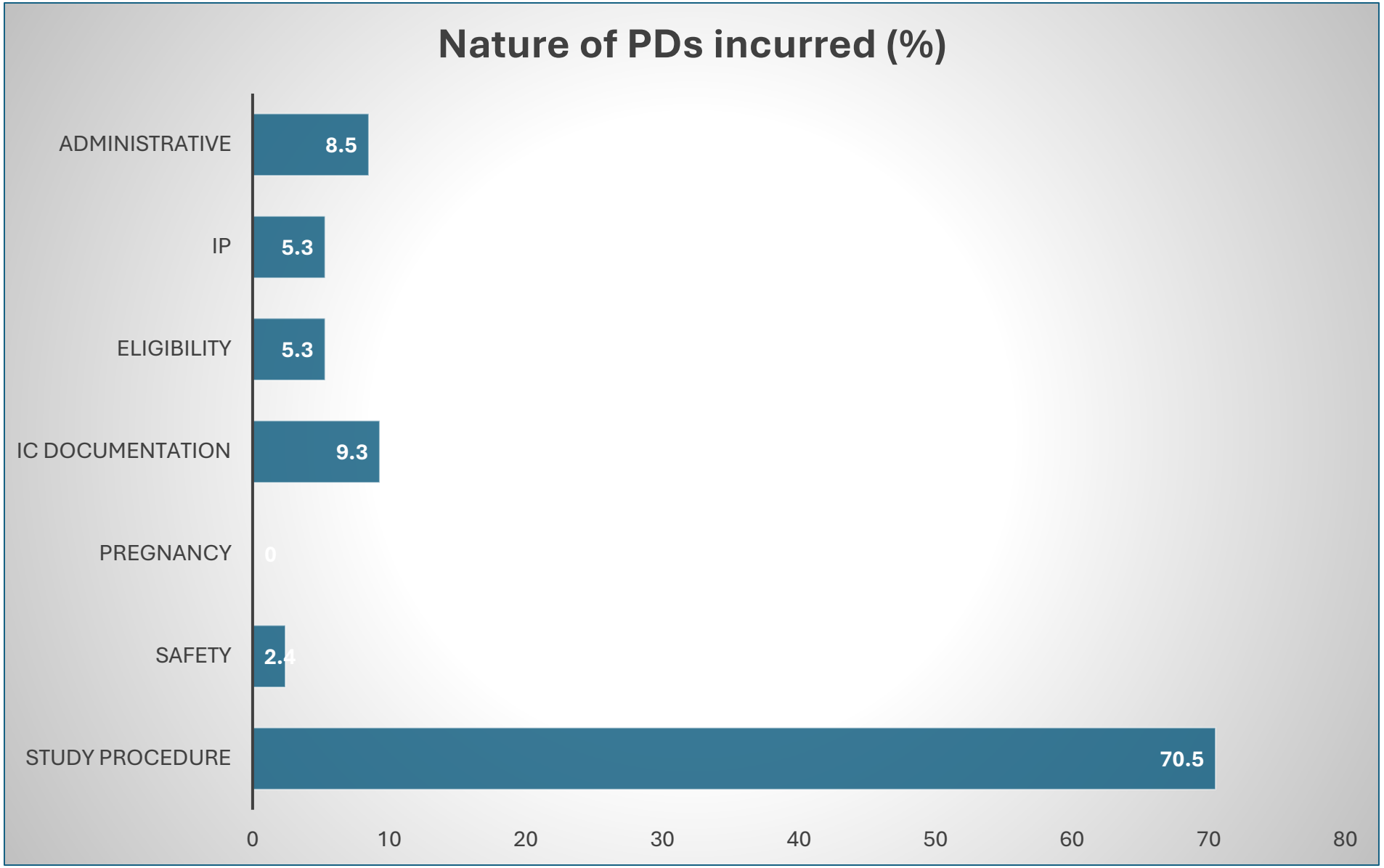

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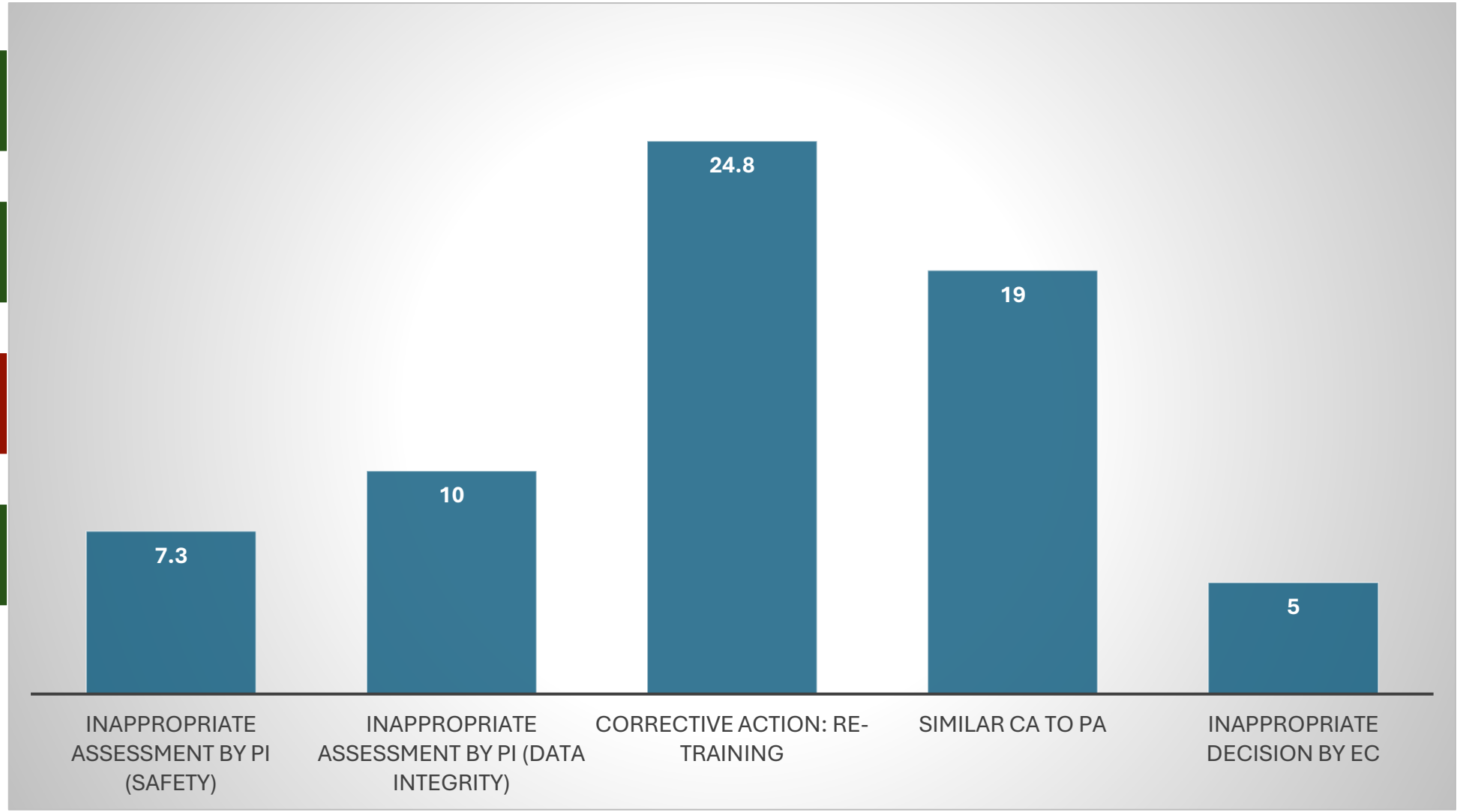

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Deviation:

Plasma sample for ctDNA/MRD and blood-borne biomarkers was not collected at Week 1 Day 1

PI Assessment: No impact on credibility of data

REB Decision: No further action

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Deviation:

Vital signs was obtained before the ICF was signed.

Corrective Action: All site staff to synchronize their time

Preventive Action: The site staff confirmed in the source document that the vital signs measurement was done after the ICF was signed.

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Deviation:

*Subject 3*****'s Covid 19 vaccine history included mRNA vaccine. However, the subject still proceeded with the enrolment last 23 Dec 2022 and received 2nd dose of vaccine last 24 Jan 2023.*

PI Assessment: No impact on credibility of data

CA/PA: Reminded all sub-investigators to review and checked the inclusion-exclusion criteria in adherence to the latest approved protocol prior to enrollment of the subject

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Deviation:

ECG was performed on Day 1 instead of performing ECG during the screening

Corrective Action: retraining of study personnel

Preventive Action: retraining of study personnel

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Deviation:

a. *ECG was performed on Day 1 instead of performing ECG during the screening*

b. *ECG was ordered but was not performed*

Corrective Action: retraining of study personnel

Preventive Action: retraining of study personnel

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- Protocol non-compliance/deviations are often committed by the site (PI, other research staff).
- Most of the deviations are related to the study procedures.
- There is room for improvement in terms of reporting and analyzing the PDs submitted by the PI as well as the assessment by the Ethics Committee.
- As part of quality assurance in reviews, regular analysis of assessment and decisions on PDs by the EC should be done.
- Regular training of both the researcher and EC members on PD management is needed.

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