Underreporting of Protocol Deviation in Investigator-Initiated Research

Addressing Gaps to Improve Clinical Research Compliance

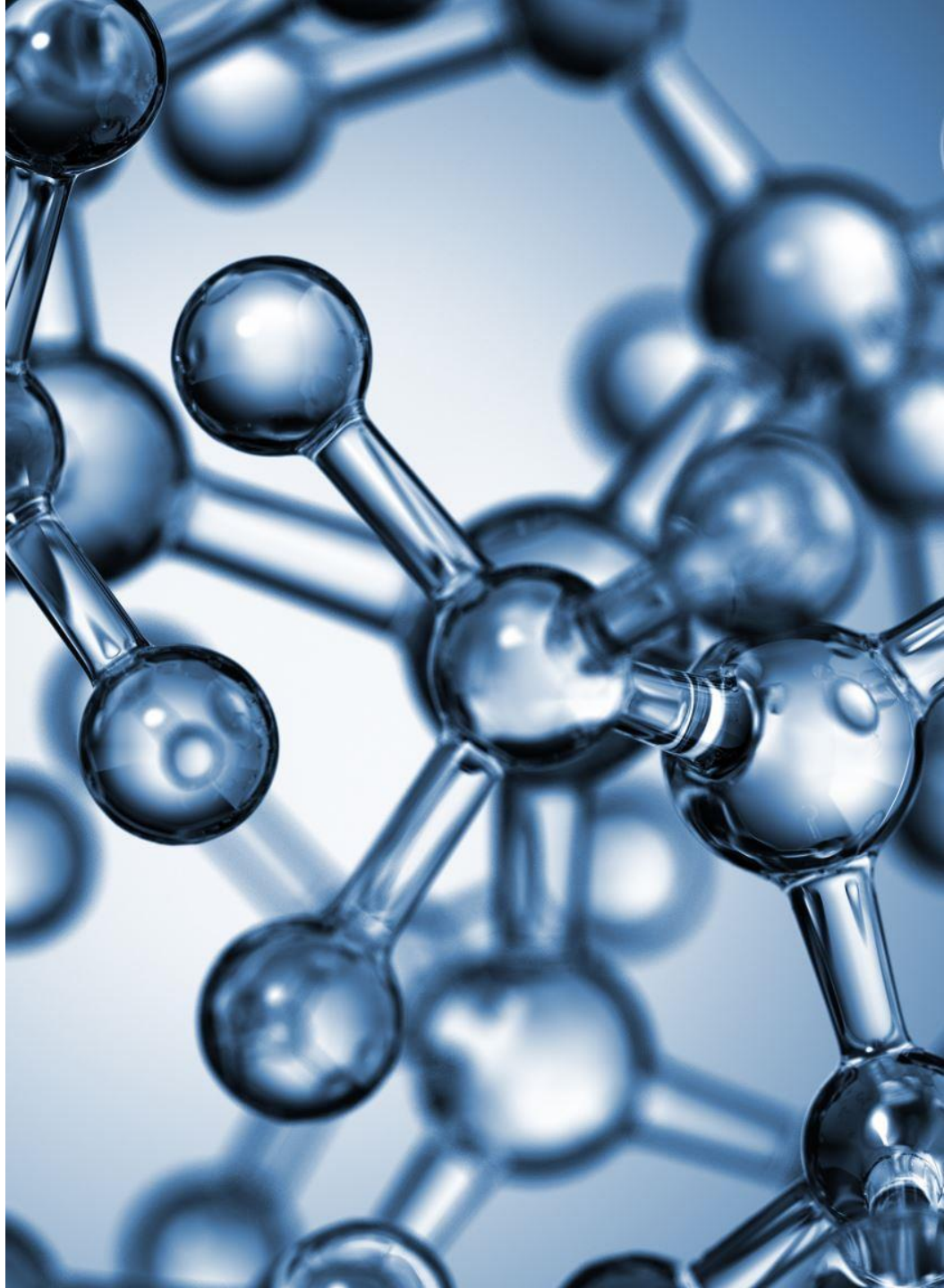
Presented by: Dr. Nurain Md Noor,
Dr. Lee Keng Yee, Sharina Md Nasri
Medical Research & Ethics Committee,
Ministry of Health, Malaysia

Introduction to Protocol Deviation

Definition: A protocol deviation (PD) occurs when there is a departure from approved protocols during a clinical trial, sometimes necessary to eliminate immediate hazards.

Importance of Protocol Deviation Reporting:

- Ensures subject safety.
- Maintains ethical and regulatory compliance.
- Preserves the scientific validity of the study.



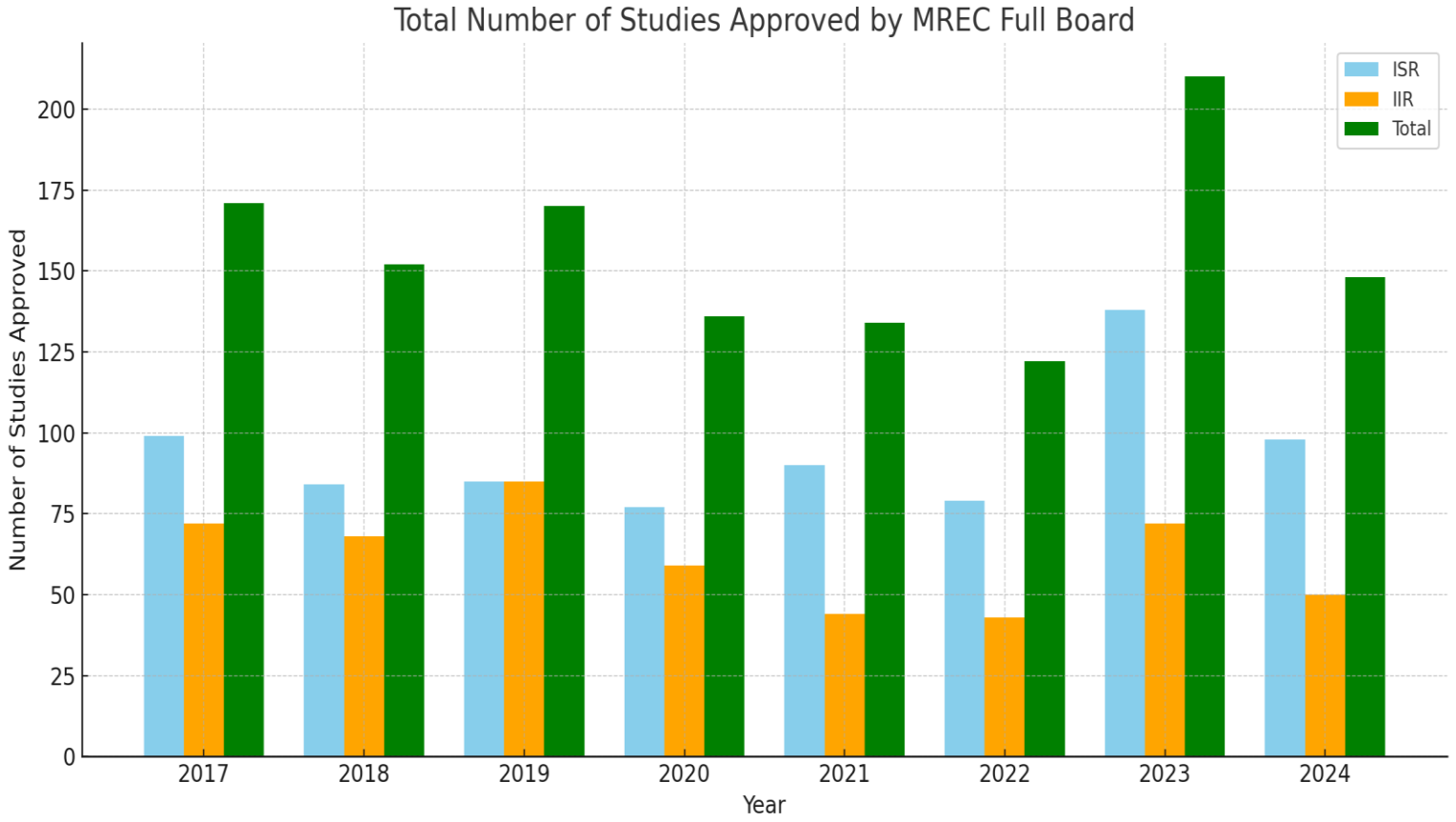
Good Clinical Practice (GCP) Guidelines

- Key Requirements:
  - PDs must be reported promptly to the Institutional Review Board (IRB) or Independent Ethics Committee (IEC).
  - Documentation must include details of the deviation, justification, and proposed amendments if applicable.
  - Purpose: Safeguard participants and uphold research integrity.

Background and Context

- **MREC's Role: to provide an independent ethical review on health research or other research protocols that involve human subjects and are conducted in MOH facilities or using data/ patient/ personnel from the MOH.**
  - Began reviewing PDs through the National Medical Research Registry (NMRR) system in 2017.
  - Conducts compliance reviews to monitor adherence to reporting standards.
  - Scope of Data Analyzed: Reviewed PD submissions from 2017 to July 2024.

Key Statistics



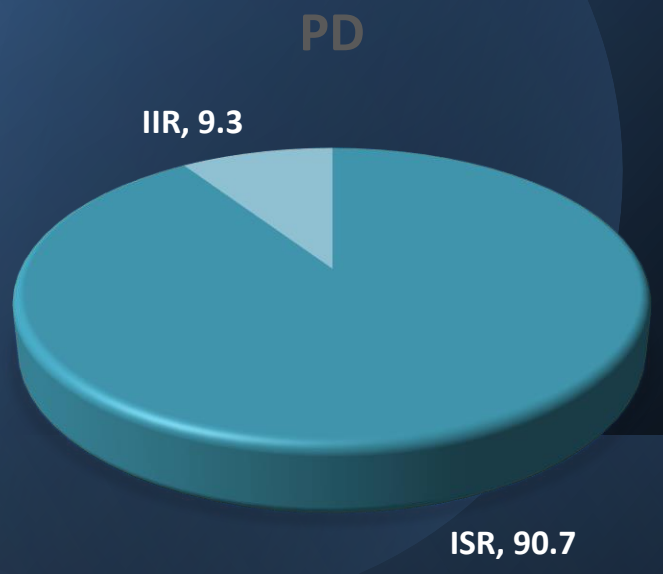
Problem Statement

Observation: Significant underreporting of PDs in IIR compared to ISR.

Implications:

Potential risk to participant safety.	Data integrity and regulatory compliance may be compromised.

Key Statistics



Total Protocol Deviations Reported: 14,029 PD reports between 2017 and July 2024.

Breakdown by Study Type:

- 90.7% from Industry-Sponsored Research (ISR)from **435** studies	- 9.3% from Investigator-Initiated Research (IIR)from **57** studies

Findings from IIR Analysis

Total PD Reports from IIR Studies:
1,032 PD reports analyzed.

Trends Observed:

- Higher compliance in hybrid IIR studies with monitoring systems.

- Gaps identified in fully investigator-driven studies.

Case study from Compliance Review IIR

Conduct of study without ethical approval

- *Principal Investigator had conducted the study without ethical approval (11/19 subjects).*
- *Subjects had their informed consent signed and dated after the expiry of the ethical approval.*

Case study from Compliance Review IIR

Informed consent process

- *No documentation on the informed consent procedures to verify the timing of the consent and the process of obtaining informed consent for all subjects*
- *Signatures for 17 subjects in the informed consent forms are different from the signatures in the case notes.*
- *Copy of informed consent form and any written information were not given to the subjects*

Factors Contributing to Underreporting

1

Lack of Monitoring: IIR studies often lack dedicated study monitors.

2

Limited Awareness: Investigators may not fully understand PD reporting requirements.

3

Systemic Gaps: Absence of a robust framework for institutional oversight in IIR.

Challenges in IIR Protocol Deviation Reporting

Investigator Responsibilities: Balancing clinical and research roles.

Resource Constraints:

Lack of funding for study monitors in IIR.

Inconsistent Reporting Practices:

Varied understanding of what constitutes a reportable PD.

Importance of Reporting PD

Protecting Participant Safety: Ensures immediate hazards are addressed promptly.

Ensuring Data Integrity: Avoids biases or inaccuracies in study outcomes.

Regulatory Compliance: Adherence to GCP standards is essential for ethical research.

Recommendations

Regular Compliance Reviews: Expand MREC's monitoring efforts to include more IIR studies.

Institutional Monitors: Assign dedicated monitors for investigator-driven studies.

Training Programs: Educate investigators on PD reporting requirements and GCP standards.

Simplified Reporting Systems: Enhance NMRR platforms for easier reporting and tracking of PDs.

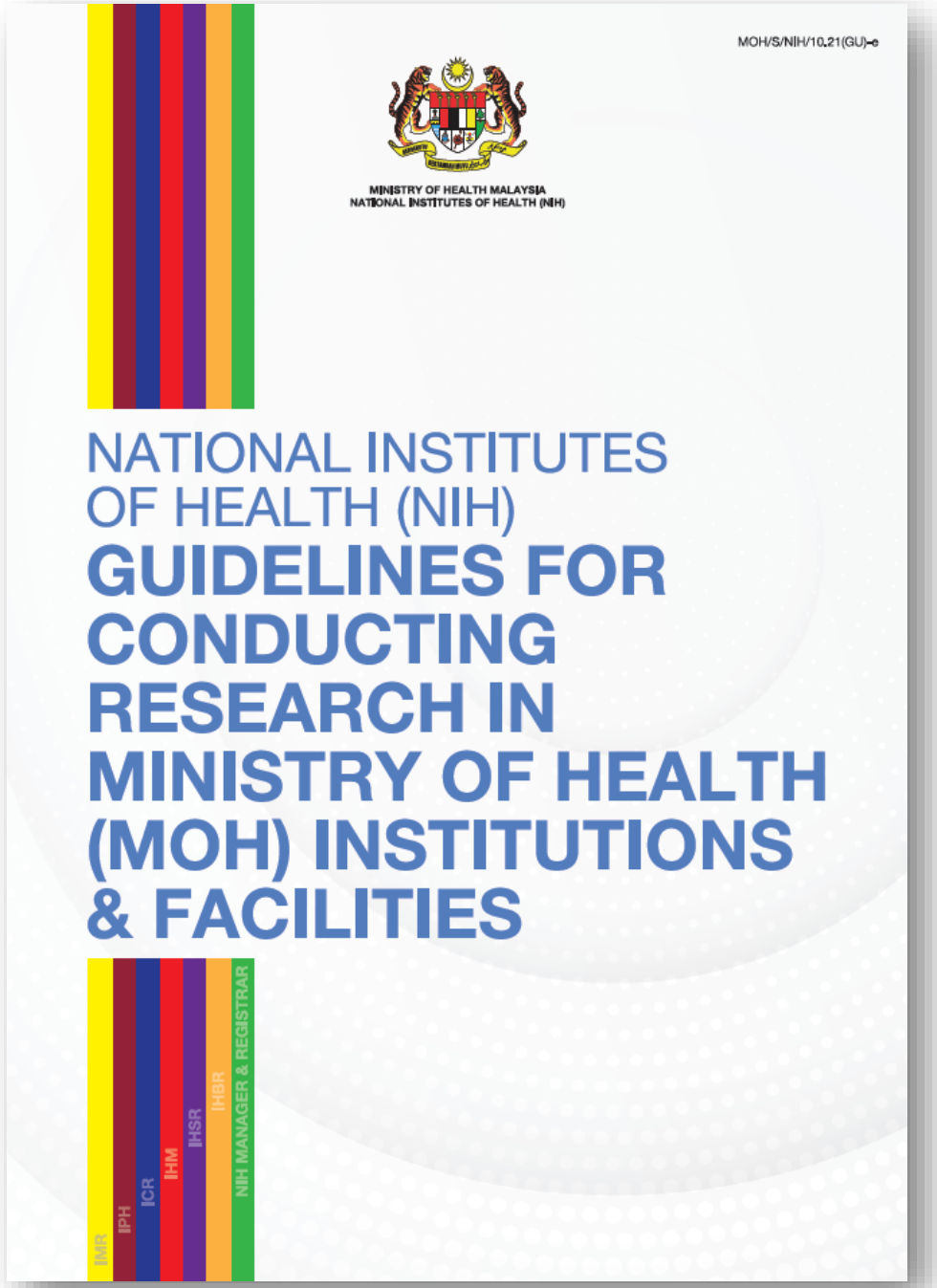
Policy Implications

Policy Changes: Advocate for mandatory monitoring in all IIR studies.

Impact:

- Increased transparency and compliance in IIR.

- Enhanced trust in clinical trial processes.



This updated guideline is officially in use with the release of the Director General of Health Malaysia Circular No 4/ 2022 on 31st January 2022 with regards to the conduct of research in the Ministry of Health (MOH).

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TABLE 1. CRITERIA FOR THE NEED AND VALUE OF A DATA MONITORING COMMITTEE
• When the study endpoint is such (e.g., mortality outcome) that it might be ethically important to stop the trial early if the primary question(s) is/are definitely answered or when there is a finding of futility.
• When there are *a priori* reasons for a particular safety concerns, e.g., the procedure for administrating the treatment is particularly invasive or prior information suggests that there is a potential for serious toxicity with the study treatment.
• The study is being performed on vulnerable populations.
• The study is being performed in a population at a high risk of death or other serious outcomes.
• The study is large and multi-center and requires complex interpretation of data.
• When the study is expected to be long, and compelling new information either external or internal to the trial might require modifications (e.g., to the inclusion criteria or endpoints) in order to help assure the continued scientific value of the trial.

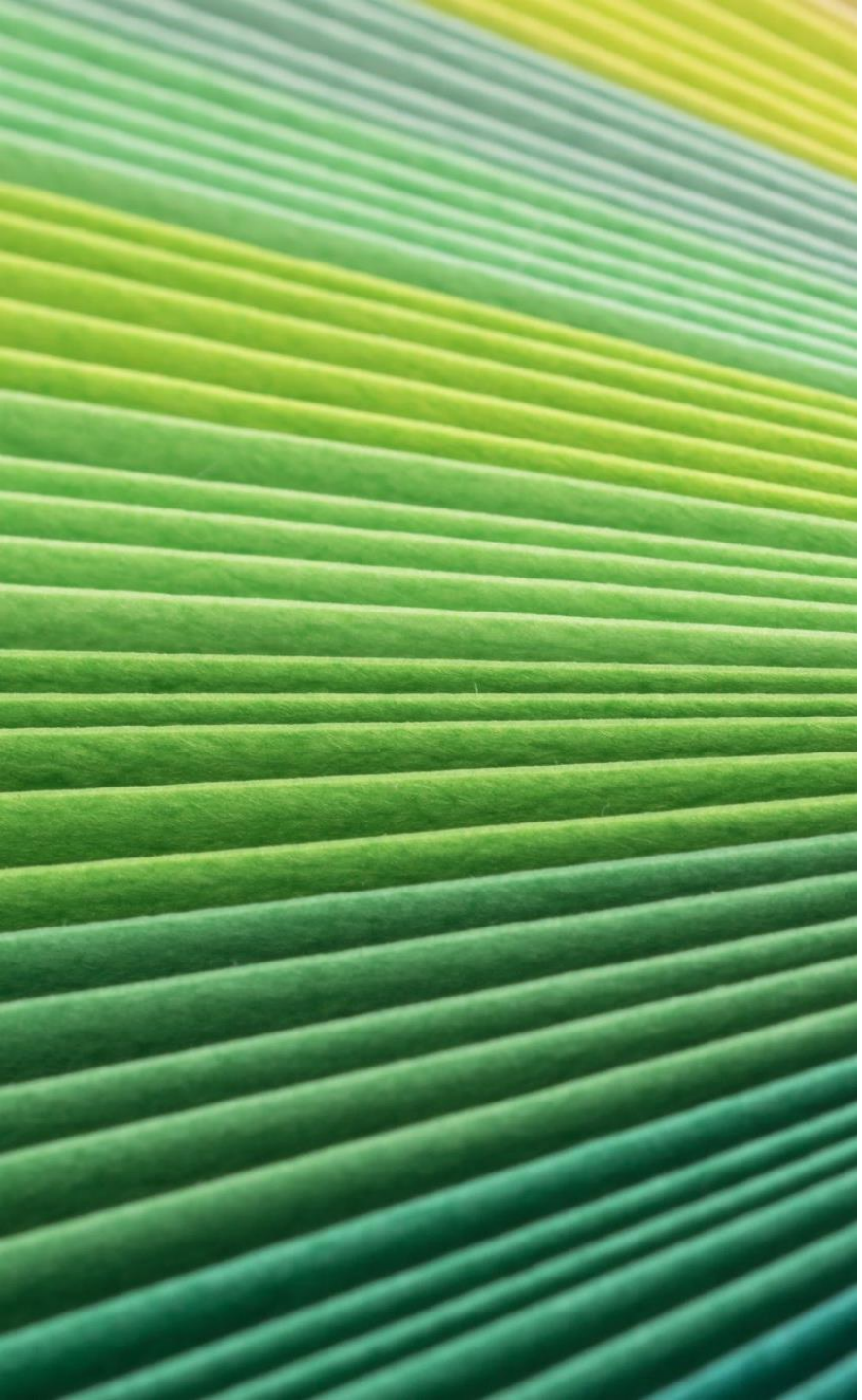
Reference: https://www.atsjournals.org/doi/full/10.1513/pats.200701-010GC

Conclusion

- Underreporting of PDs in Investigator Initiated Research is a significant challenge.

- Enhanced monitoring, education, and streamlined systems are crucial.

- Collaboration between regulatory bodies and investigators is essential to safeguard participant safety and study integrity.



Acknowledgments

Medical Research & Ethics Committee (MREC), MOH, Malaysia.

Protocol Deviation Subcommittee (PDSC) of MREC, MOH Malaysia


Thank you