LOOKING BACK AT 2018

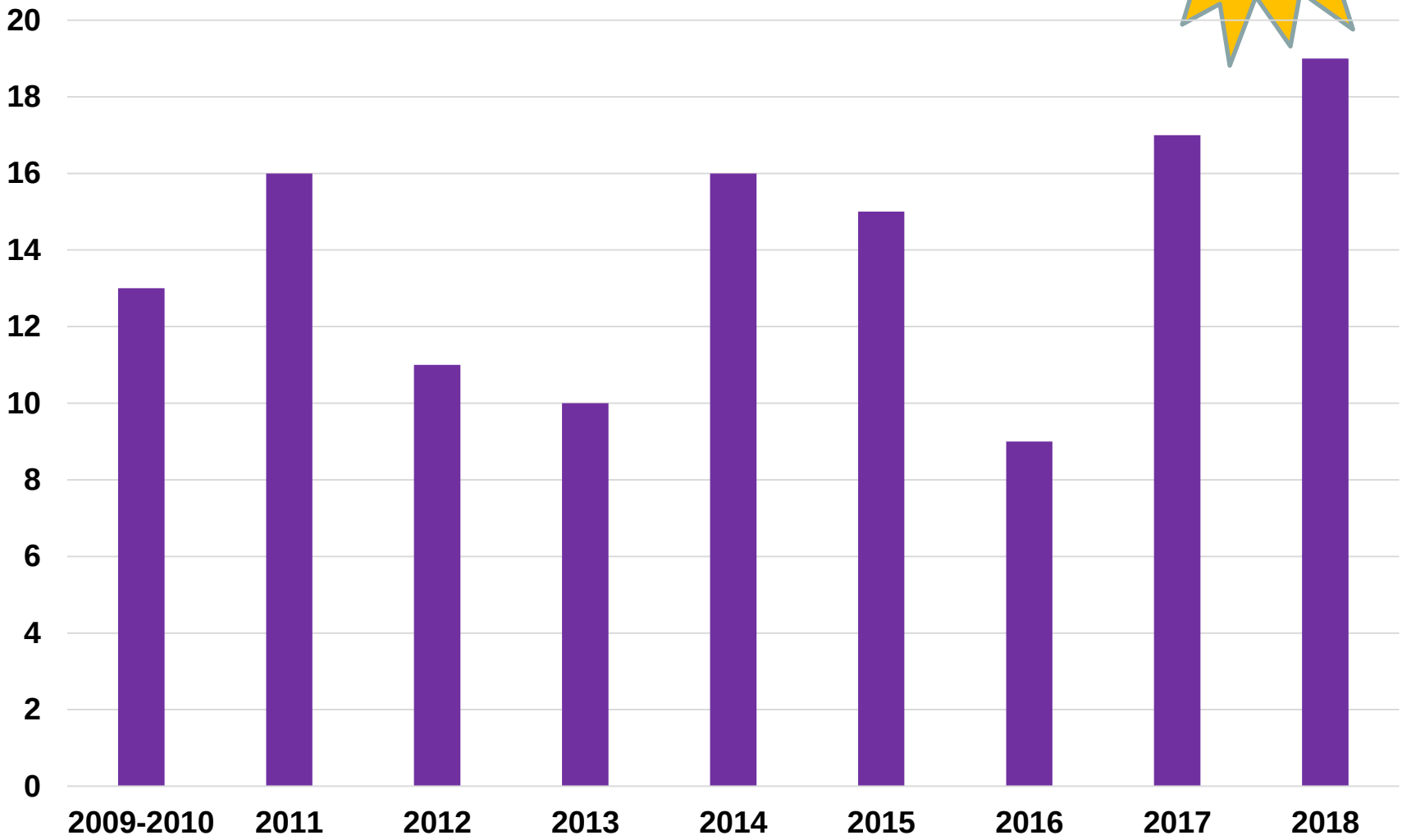
Sumitra Sachidanandan
Regulatory Consultant
Innovation Office & Clinical Trials Branch
Health Products Regulation Group
Health Sciences Authority Singapore

OUTLINE

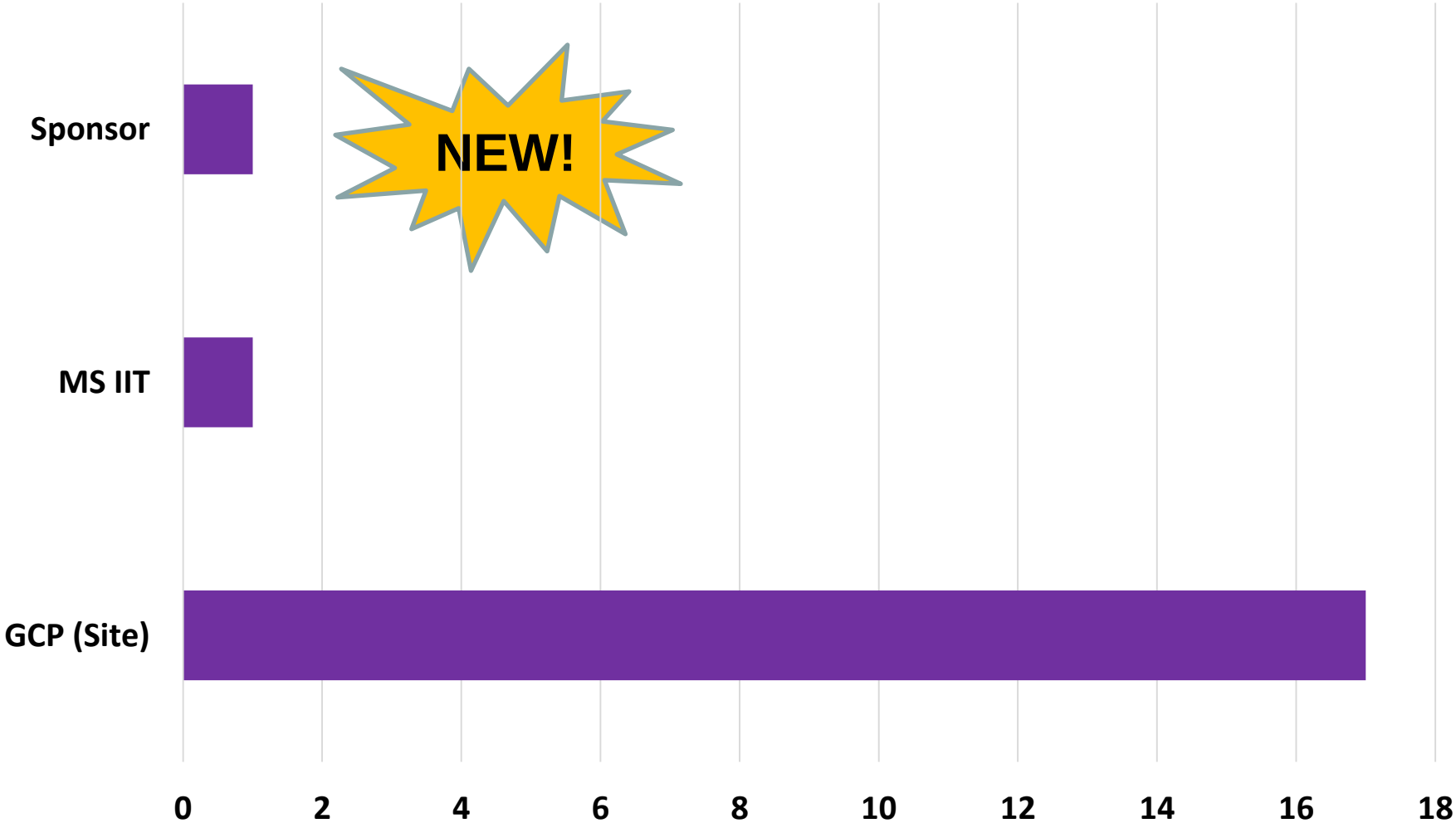
- General Overview
- GCP Inspections
- MS IIT Inspections
- Sponsor Inspections

HSA Inspections over the past 9 yrs

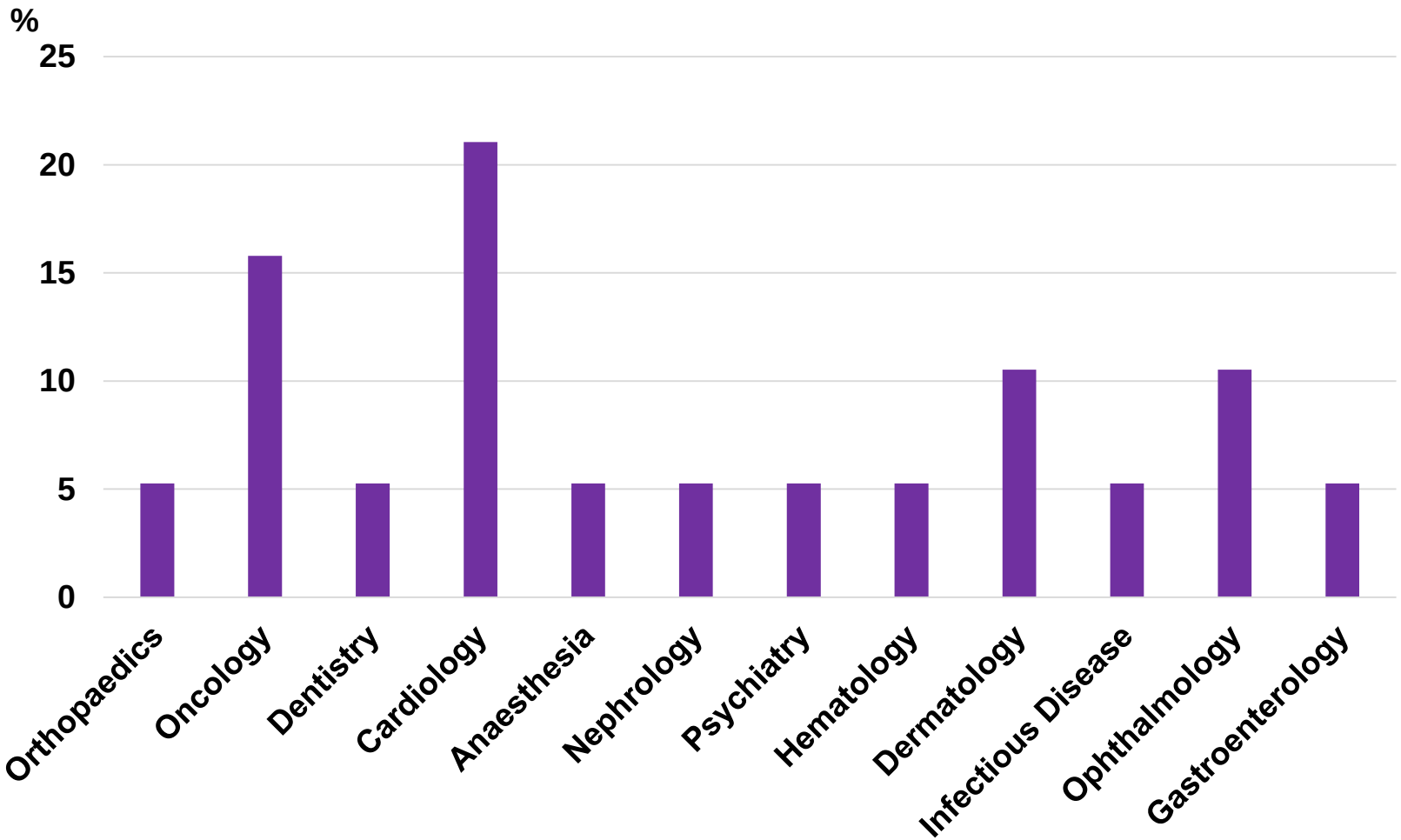
126



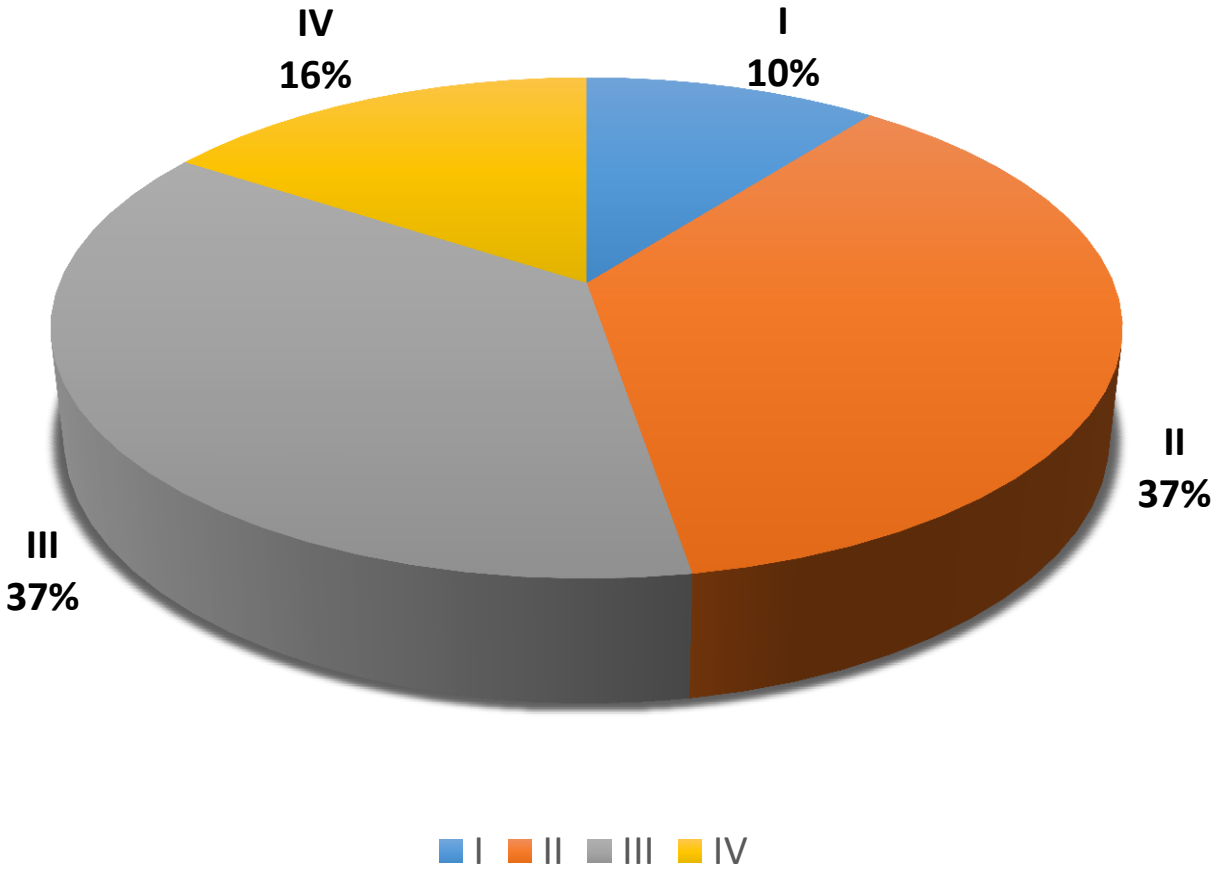
Types of Inspections in 2018 (N=19)



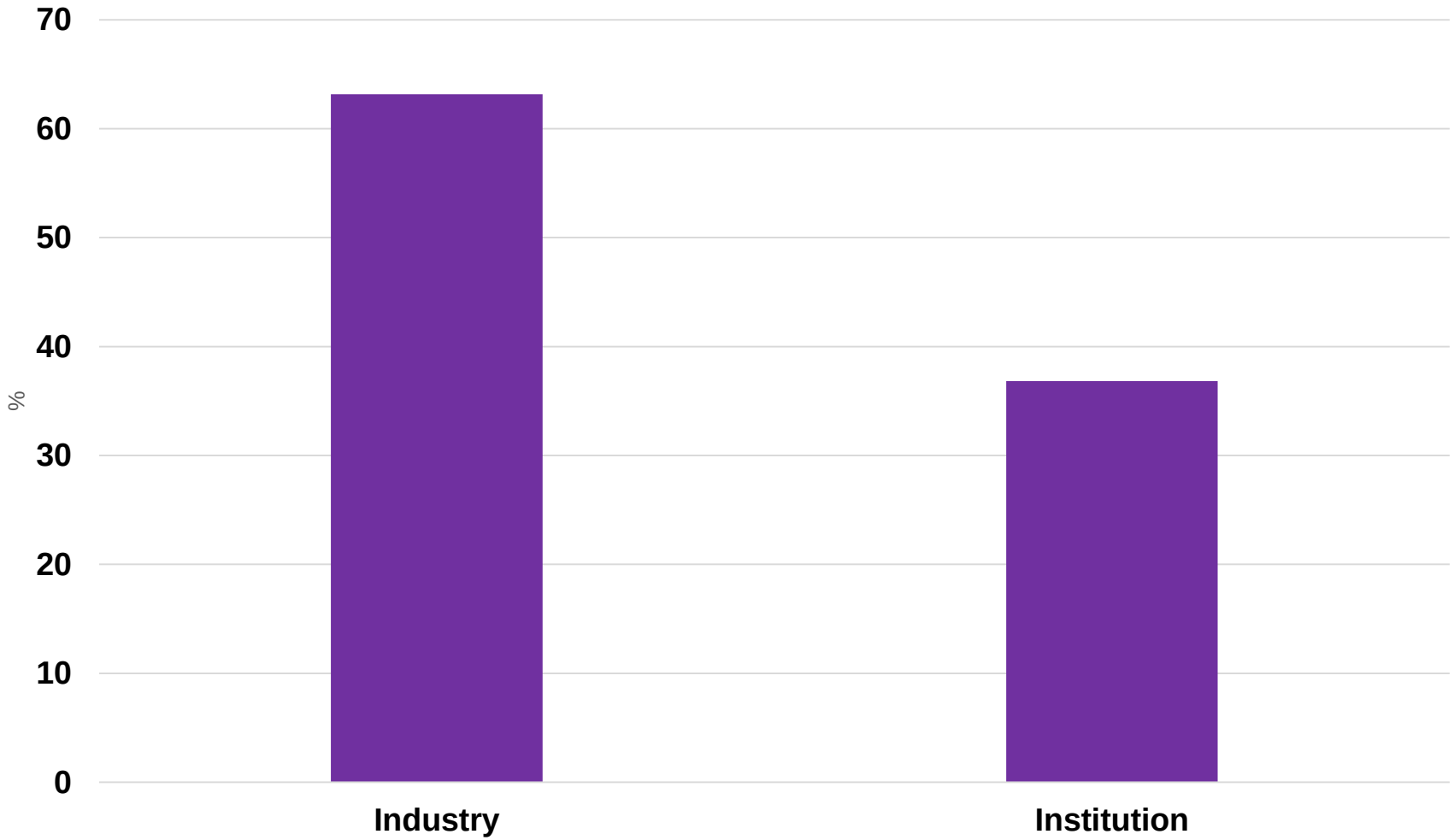
Distribution by Therapeutic Area (N=19)



Distribution by Phase of Clinical Trials (N=19)



Distribution by Sponsor (N=19)



OUTLINE

- General Overview
- GCP Inspections
- MS IIT Inspections
- Sponsor Inspections

Objectives of GCP Inspections

- To safeguard the Rights, Safety and Well-Being of trial subjects.

- To verify the Quality and Integrity of the clinical trial data submitted to the Regulatory Authority.

- To assess Compliance to protocol and applicable regulations, guidelines and standard operating procedures for clinical trials.

Classification of GCP Inspection Findings

- **Critical:** Conditions, practices or processes that adversely affect the rights, safety or well being of the subjects and/or the quality and integrity of data.

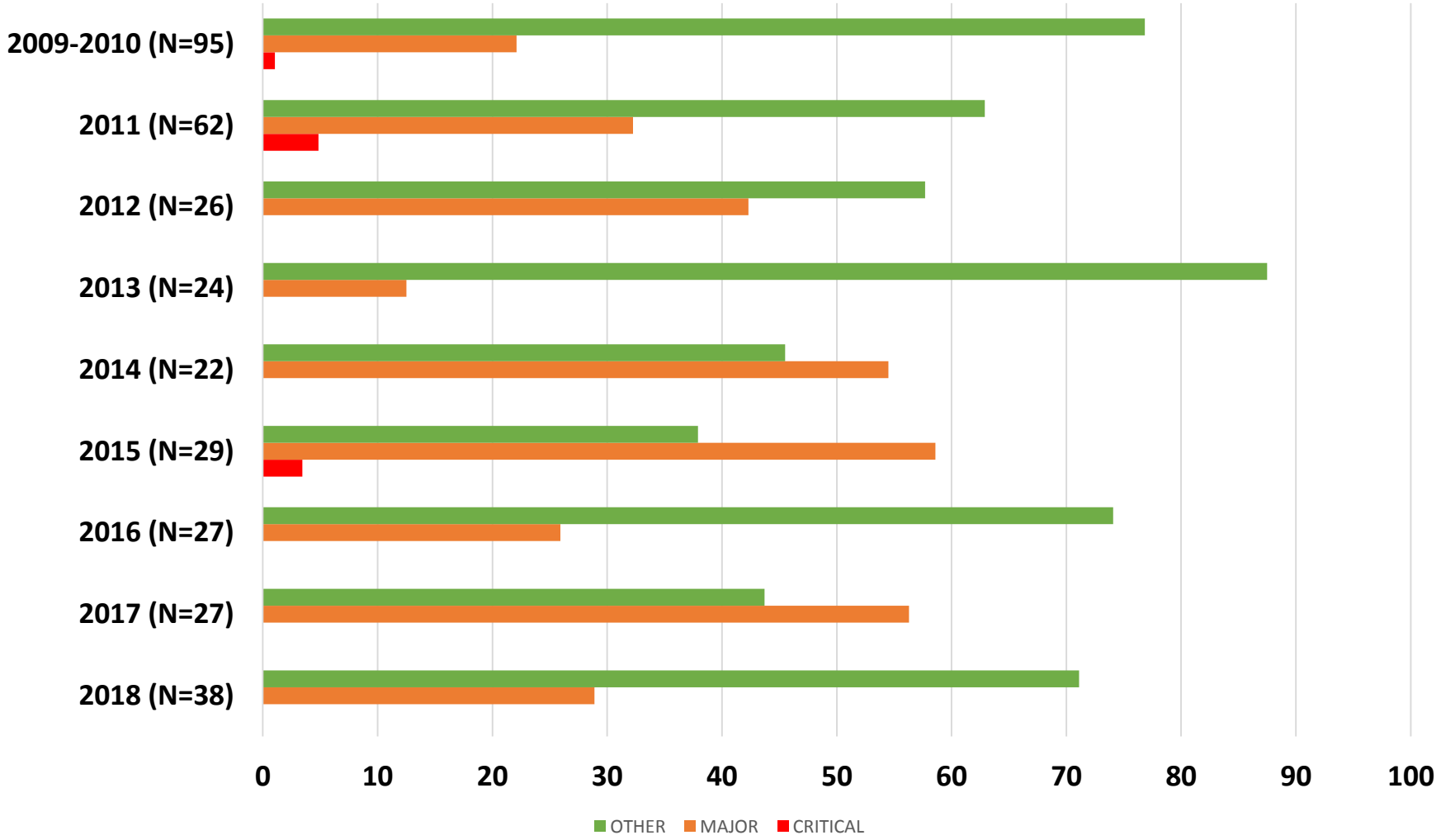
- **Major**: Conditions, practices or processes that might adversely affect the rights, safety or well-being of the subjects and/or the quality and integrity of data.

Classification of GCP Inspection Findings

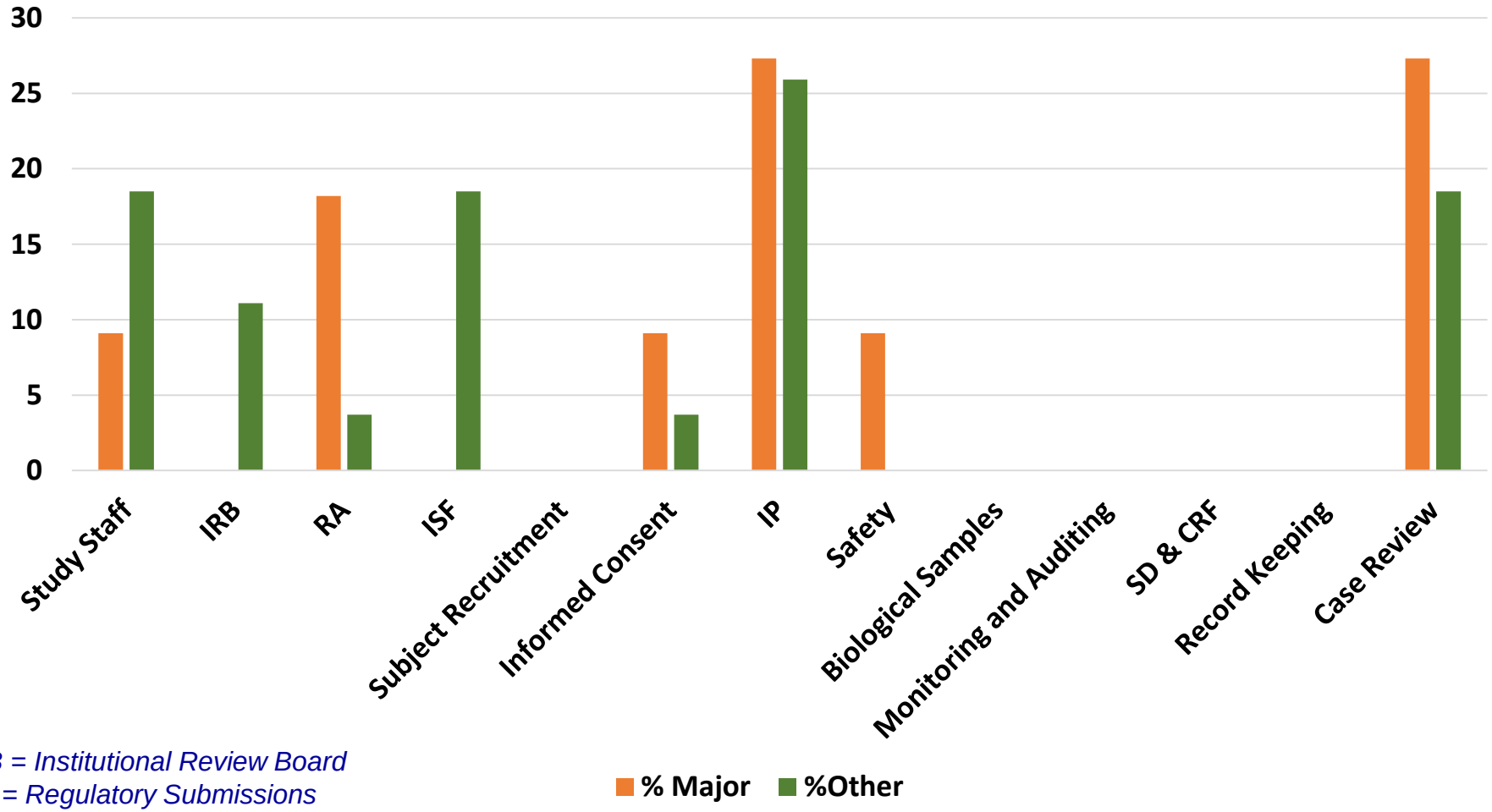
- **Other**: Conditions, practices or processes that would not be expected to adversely affect the rights, safety or well being of the subjects and/or the quality and integrity of data.

- **Comments**: The observations might lead to suggestions on how to improve quality or reduce the potential for a deviation to occur in the future.

Classification of GCP Inspection Findings



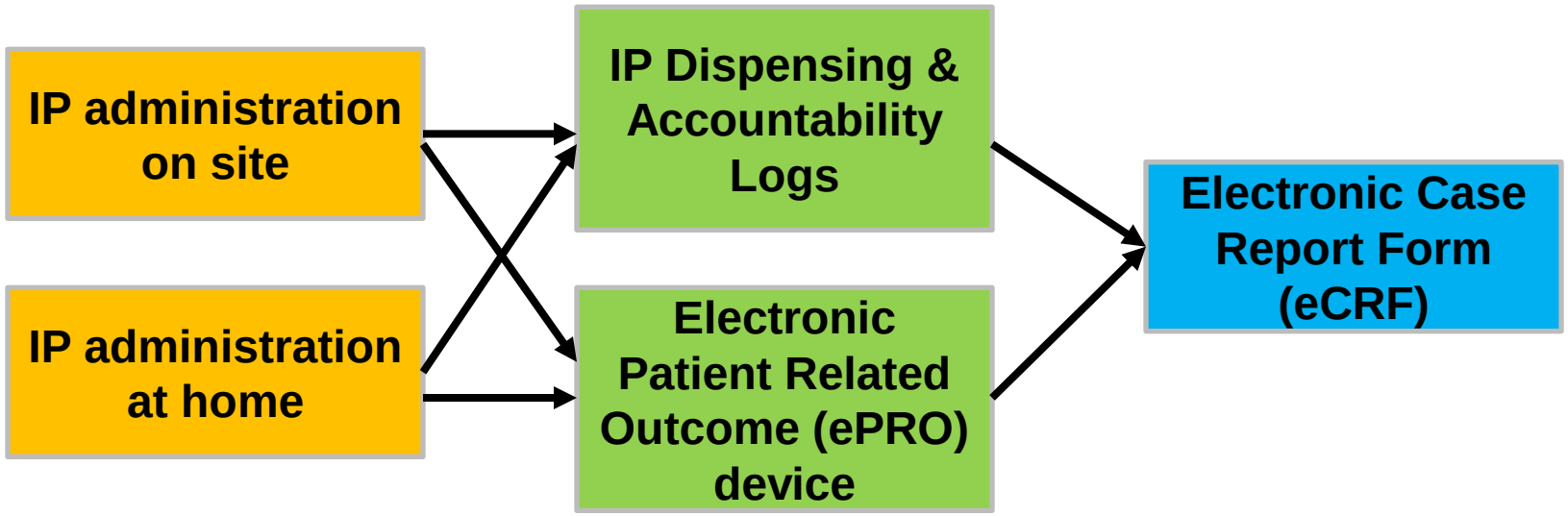
Distribution of GCP Inspection Findings in 2018 (N=17)



IRB = Institutional Review Board
RA = Regulatory Submissions
ISF = Investigator Site File
IP = Investigational Product
SD & CRF = Source Document & Case Report Form

GCP Inspection Findings in 2018

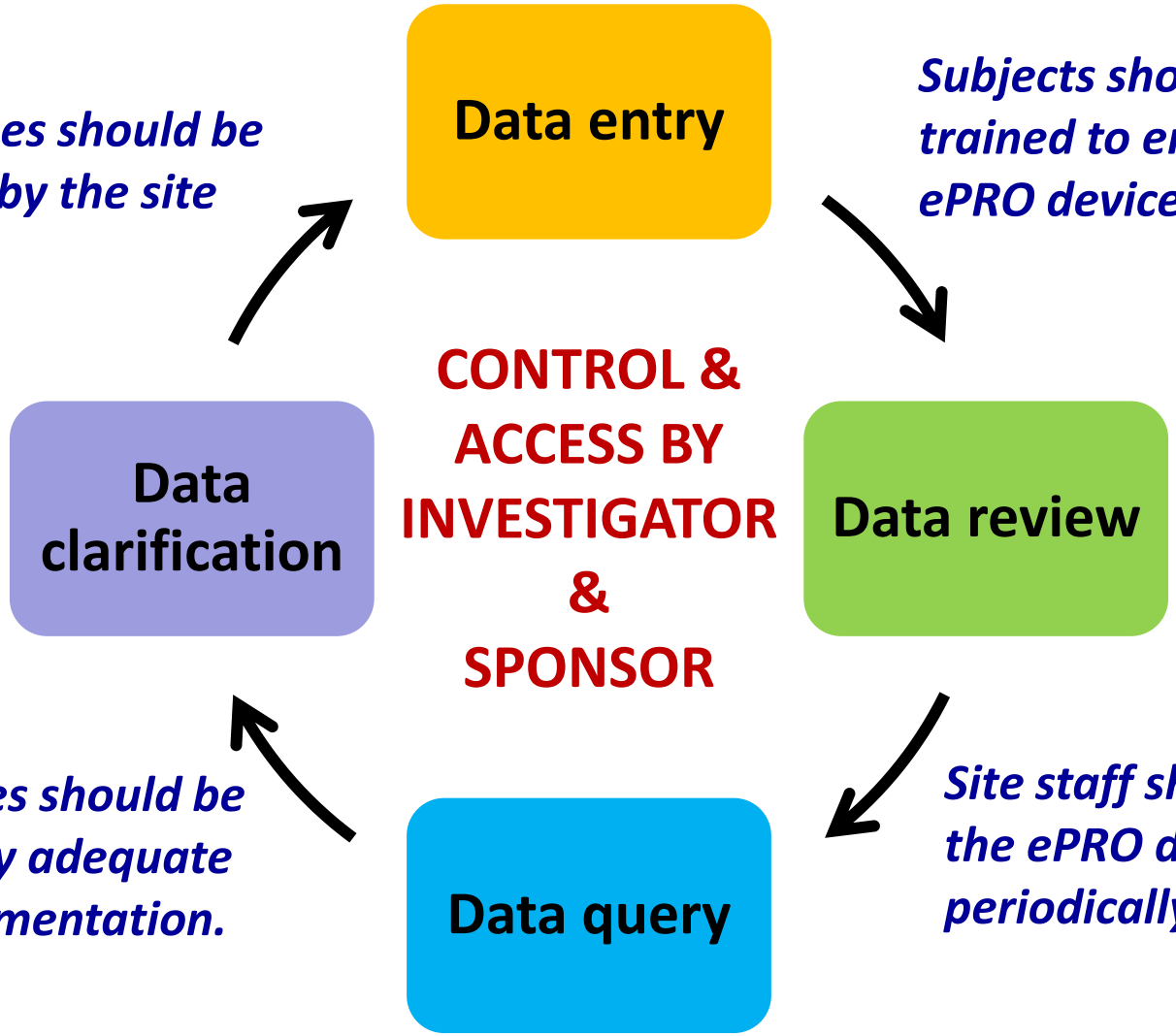
INVESTIGATIONAL PRODUCT (IP)



- **Discrepancies concerning ePRO data for IP administration:**
  - Missing entries in ePRO device
  - Lack of traceability between ePRO data, IP docs and eCRF
  - Lack of review of ePRO data by study staff

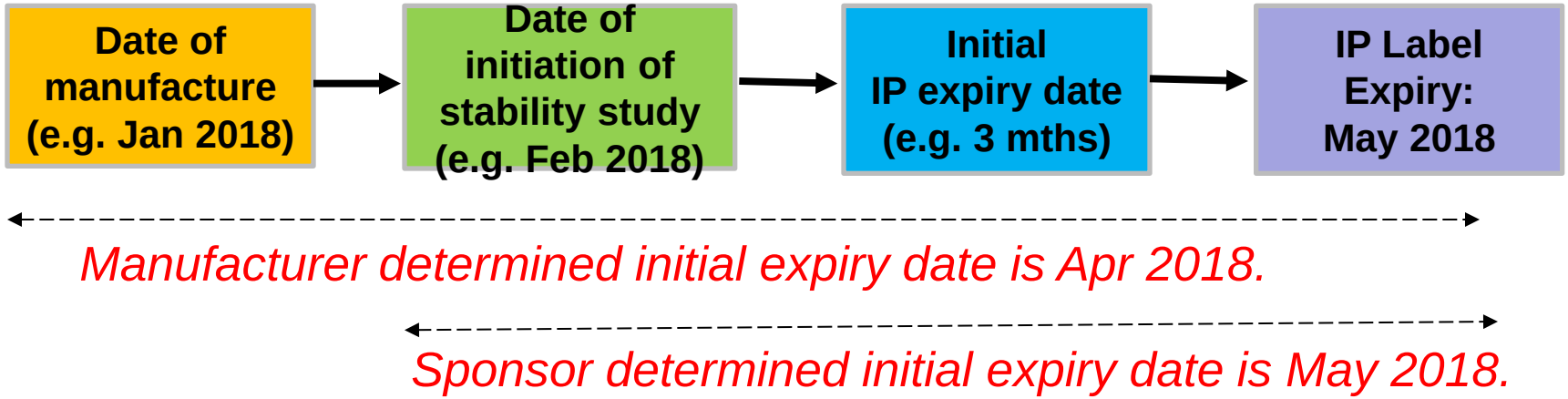
➔ *Ref.: Section 4.9.0 of ICH E6 (R2) GCP Guidelines*

Electronic Patient Related Outcome (ePRO) devices



GCP Inspection Findings in 2018

INVESTIGATIONAL PRODUCT (IP)

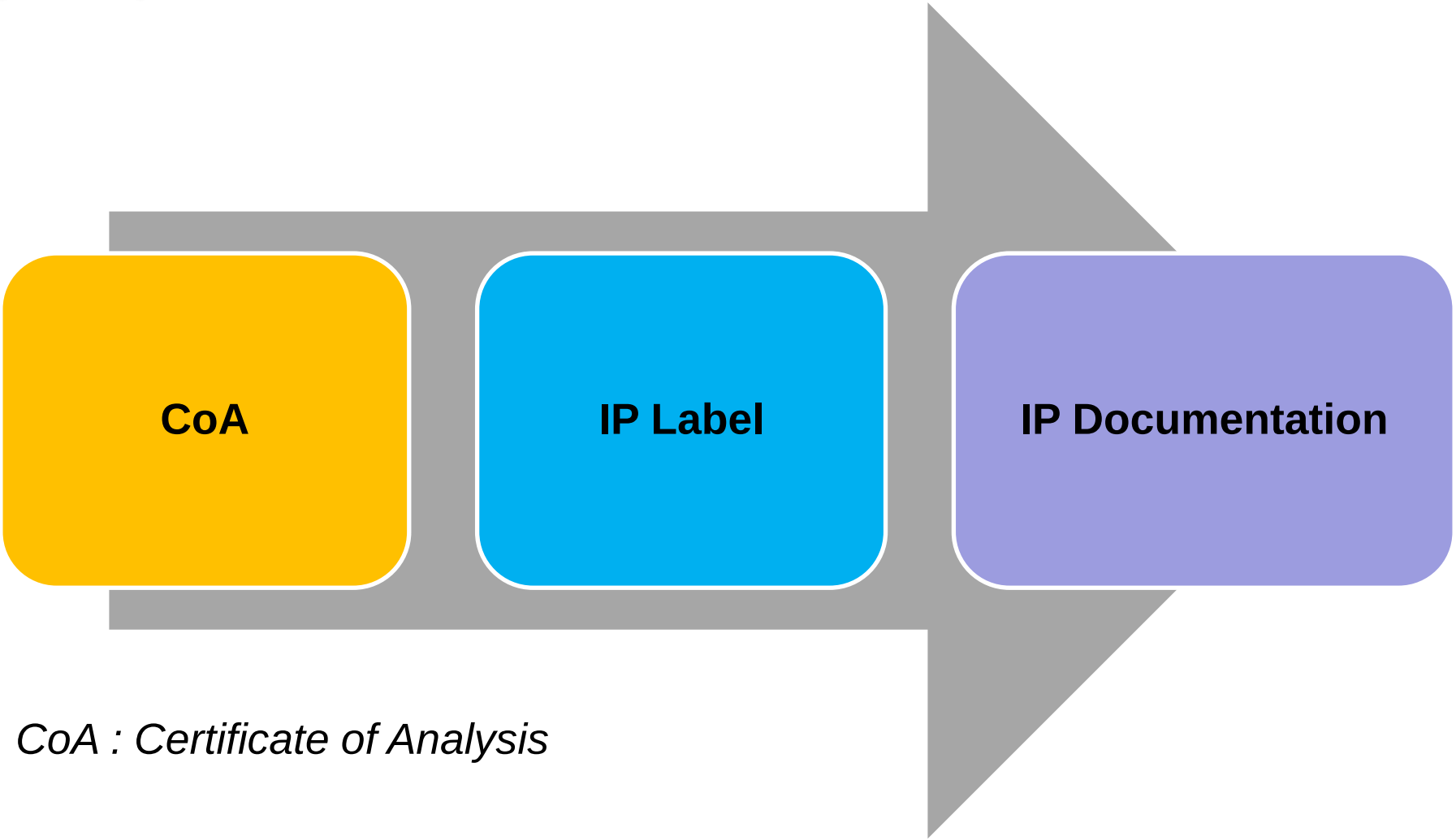


- Inadequate quality control in the management of the IP expiration date, resulting in ambiguity in the assignment of the initial expiry date and labelling error.

➔ *Ref.: Section 2.13 of ICH E6 (R2) GCP Guidelines*

TIP

Determination of IP expiry date



CoA : Certificate of Analysis

GCP Inspection Findings in 2018
INVESTIGATIONAL PRODUCT (IP)

- **Discrepancies in IP labelling:**
  - Reasons for Labelling Omissions Form had not been submitted to request for waiver of Subject ID on IP label.
  - IP expiry date had not been updated on the primary packaging. It had only been updated on the secondary packaging.
  - Vial ID had been used as the Subject ID, as Study Pharmacist was unaware of the actual Subject ID.

➔ *Ref.: Paragraph 1(2) of the Second Schedule of the Health Products (Clinical Trials) Regulations*

IP Labelling

- Check if the IP label is compliant with applicable clinical trials and clinical research materials regulations.
- Refer to HSA Guidance on Labelling of TP and MP Used in Clinical Trials for further guidance.
- Submit a Reasons for Labelling Omissions Form to request for a waiver, if applicable.
- Subject ID should be communicated to the Study Pharmacist.
- IP relabelling applies to all types of IP packaging.

GCP Inspection Findings in 2018

CASE REVIEW

- Lack of adequate source documentation.

  ➔ *Ref.: Section 4.9.0 of ICH E6 (R2) GCP guidelines*

- Source documents were not attributable.

  ➔ *Ref.: Section 4.9.0 of ICH E6 (R2) GCP guidelines*

- Eligibility criteria in Eligibility Checklist did not co-relate with study protocol.

  ➔*Ref.: Study protocol*

- Study discontinuation procedures were not included in study protocol.

  ➔ *Ref.: Study protocol*

ALCOA principles

- Accurate
- Legible
- Contemporaneous
- Original
- Attributable

GCP Inspection Findings in 2018

REGULATORY SUBMISSIONS

- Trial Status Reports were not submitted to HSA.

  ➔*Ref.: Regulation 12(1) of the Health Products (Clinical Trials) Regulations*

- Substantial amendments to the protocol / ICF had not been submitted to HSA.

  ➔*Ref.: Regulation 10(2) of the Health Products (Clinical Trials) Regulations*

Regulatory Submissions to HSA

- Refer to the HSA Guidances:
  - *Regulatory requirements for new applications and subsequent submissions to HSA.*
  - *Determining whether an amendment to a clinical trial is a substantial amendment.*
- Consult HSA when in doubt.
- Be familiar with the timelines for regulatory submissions to HSA.

TIP

Regulatory Submissions to HSA

Subsequent Submission to HSA	Submission Timeline
Substantial amendments	Prior to implementation
Serious Breaches	As soon as possible, but no later than 7 calendar days
Urgent Safety Measures	As soon as possible, but no later than 7 calendar days
Trial Status Reports	6 monthly (+ 14 calendar days)
Unexpected Serious Adverse Drug Reactions (USADR) - Fatal or life threatening events	Initial report: As soon as possible, and not later than 7 calendar days from sponsor's first awareness of the USADR; Follow-up report: As soon as possible, and not later than 8 calendar days following the initial report.
Unexpected Serious Adverse Drug Reactions - Non-fatal or non-life threatening events	Initial report: As soon as possible, and not later than 15 calendar days from sponsor's first awareness of the USADR; Follow-up report: As soon as available
Updates to the Investigator's Brochure (IB) or new safety information	As soon as available
Suspension of clinical trial	15 calendar days from date of trial suspension
Termination of clinical trial	15 calendar days from date of trial termination
Completion of clinical trial	30 calendar days from date of trial completion
Final Report	1 year from date of trial completion

HSA Health Sciences Authority

GCP Inspection Findings in 2018

STUDY STAFF

- Study staff had performed IP administration without being delegated by the PI. CVs and training records had also not been maintained.

➔*Ref.: Section 4.1.5, 4.2.4, 8.3.24 of ICH E6 (R2) GCP guidelines*

- Study staff had received IP prior to delegation by PI.

➔*Ref.: Section 4.6.2 of ICH E6 (R2) GCP guidelines*

Study Staff

- Prior to conducting any study procedures, study staff should be:
  - *Adequately qualified*
  - *Trained on study protocol, CITI, GCP (mandatory for PI)*
  - *Delegated by PI on Signature Sheet*
- Maintain a Study Staff Tracking Log to track:
  - *Start date and end date*
  - *IRB approval (for investigators)*
  - *CV*
  - *Medical Licence (for investigators)*
  - *Financial Disclosure Forms*
  - *CITI*
  - *GCP (mandatory for PI)*
  - *Study-specific training*

TIP

Study Staff

Investigators

SIGNATURE SHEET				IRB	ML#	CV*	For IND Study		TRAINING RECORDS						Comments
Name of Investigator	Start Date	PI Authorisation Date	End Date	Approval Date	ML	CV	FDA 1572	FD#	GCP	CITI	Study training				
					☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
					☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
					☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
					☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
					☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
					☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

Other study staff

SIGNATURE SHEET					FD#	CV*	TRAINING RECORDS						Comments
Name	Role	Start Date	PI Authorisation Date	End Date	FD	CV	GCP	CITI	Study training				
					☐	☐	☐	☐	☐	☐	☐	☐	
					☐	☐	☐	☐	☐	☐	☐	☐	
					☐	☐	☐	☐	☐	☐	☐	☐	
					☐	☐	☐	☐	☐	☐	☐	☐	
					☐	☐	☐	☐	☐	☐	☐	☐	
					☐	☐	☐	☐	☐	☐	☐	☐	

OUTLINE

- General Overview
- GCP Inspections
- MS IIT Inspections
- Sponsor Inspections

MS IIT Inspection Findings 2018

INVESTIGATIONAL PRODUCT (IP)

- **IP receipt**
  - Inadequate documentation of IP receipt and inventory.

  ➔*Ref.: Section 4.6.3 of ICH E6 (R2) GCP guidelines)*

- **IP repackaging and relabelling**
  - *No documentation of IP repackaging and relabelling process.*
  - *No witness to verify the repackaging process.*

  ➔ *Ref.: Section 5.14.3 of ICH E6 (R2) GCP guidelines)*

MS IIT Inspection Findings 2018

INVESTIGATIONAL PRODUCT (IP)

- **IP Preparation**
  - *Blinded investigators had signed off on the IP Preparation Form that had been completed by the unblinded study team, thereby potentially compromising the study blind.*

  ➔ *Ref.: IP Management SOP*

- **IP Administration**
  - Baseline weight for calculation of IP dose could not be traced to source documents.

  ➔ *Ref.: Section 4.9.2 of ICH E6 (R2) GCP Guidelines*
  - Nurses had not been trained on IP administration.

  ➔ *Ref.: Section 4.2.4 of ICH E6 (R2) GCP Guidelines*

MS IIT Inspection Findings 2018

INVESTIGATIONAL PRODUCT (IP)

- **Blinding**
  - *File note regarding treatment assignment for a subject had been signed off by the blinded PI.*
  - *Blinded investigator had been given access to the randomisation system.*

➔ *Ref.: Section 4.2.4 of ICH E6 (R2) GCP Guidelines*

IP Management for MS IIT studies

- Develop an IP Management SOP for the clinical trial.
- Same IP Documentation templates should be used across all trial sites.
- Site staff involved in IP management from various trial sites should be in regular contact.
- Consider cross-institution monitoring of IP management for quality control purposes.

OUTLINE

- General Overview
- GCP Inspections
- MS IIT Inspections
- Sponsor Inspections

SPONSOR INSPECTION

- **Scope**
  - Quality Assurance and Quality Control
  - Outsourced services
  - Investigator Selection
  - Investigational Product management
  - Safety Reporting
  - Monitoring
  - Data Collection and Handling
  - Essential Document management

Sponsor Inspection

- **Objectives**

1. To evaluate the quality assurance and quality control systems established by the sponsor / CRO in order to assure that clinical trials are conducted and data are generated, recorded and reported in compliance with the protocol, applicable regulations, guidelines and standard operating procedures for clinical trials.

Sponsor Inspection

- **Inspection Criteria**

(i) Protocol
(ii) Applicable clinical trials and clinical research materials regulations*
(iii) ICH E6 (R2) Good Clinical Practice Guidelines [ICH E6 (R2) GCP]
(iv) Applicable Sponsor / Contract Research Organization (CRO) / Site Standard Operating Procedures for clinical trials

** Health Products (Clinical Trials) Regulations, Medicines (Clinical Trials) Regulations, Health Products (Therapeutic Products as Clinical Research Materials) Regulations, Medicines (Medicinal Products as Clinical Research Materials) Regulations, Health Products (Medical Devices) Regulations*

- **Inspectee**
  - Local Sponsor

Sponsor Inspection Process

Preparation

- Notice of Sponsor Inspection sent to local sponsor within 30 working days of sponsor inspection.
- Sponsor should complete and send the Sponsor Inspection Dossier to HSA within the stipulated timeline.

Conduct

- Sponsor inspection will be conducted at local trial site(s), CRO (if applicable) and local sponsor office.
- Access to IWRS, electronic Trial Master Files (eTMF), electronic Case Report Forms (eCRFs) required before sponsor inspection.

Follow-up

- Sponsor Inspection Report will be sent to local sponsor within 20 working days of Sponsor Inspection.
- Sponsor should complete and submit the Corrective Action and Preventive Action (CAPA) Plan to HSA within 30 working days.

Grading of Sponsor Inspection Findings

- Similar to grading of GCP Inspection Findings.

(A) Sponsor Inspection Findings will be classified as Critical, Major or Other, which are defined as follows:

1. **Critical:** Conditions, practices or processes that adversely affect the rights, safety or well-being of the subjects and/or the quality and integrity of data.

   1.1. Observations classified as critical may also include several major observations.

2. **Major**: Conditions, practices or processes that might adversely affect the rights, safety or well-being of the subjects and/or the quality and integrity of data.

   2.2. Observations classified as major may also include a several other observations.

3. **Other**: Conditions, practices or processes that would not be expected to adversely affect the rights, safety or well being of the subjects and/or the quality and integrity of data.

(B) Comments are observations might lead to suggestions on how to improve quality or reduce the potential for a deviation to occur in the future.

Conclusions

- Be familiar with the study protocol, regulations, GCP and SOPs.
- Quality systems should be implemented in every aspect of the clinical trial.
- Risk-based approach should be adopted in quality systems.
- Think outside the box.
- Rules of thumb:
  - *If it was never documented, it was never done.*
  - *It is always better to prepare than repair.*

We welcome your enquiries and feedback!

HSA_CT@hsa.gov.sg

THANK YOU!