COMMON GCP INSPECTION FINDINGS 2011

Foo Yang Tong
Director
Clinical Trials Branch
Health Products Regulation Group
HEALTH SCIENCES AUTHORITY
SINGAPORE

OUTLINE

- GCP Inspection Framework
- Objectives
- Classification of GCP Inspection Findings
- Common GCP Site Inspection Findings (2011 vs 2009-2010)
- Quality Improvement Initiatives

GCP Inspection Framework

- Launched in Sep 2009
- First GCP Site Inspection done in Nov 2009
- Completed 29 GCP Site Inspections to date:
  - 2009-2010 : 13 (Protocol-specific)
  - 2011 : 15 (Protocol-specific), 1 (Systems on ICF and IP)

Objectives of GCP Inspection

- 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.

GCP INSPECTION CRITERIA

Classification of GCP Inspection Findings

~ adopted from EMEA SOPs on GCP Inspection.

- **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.

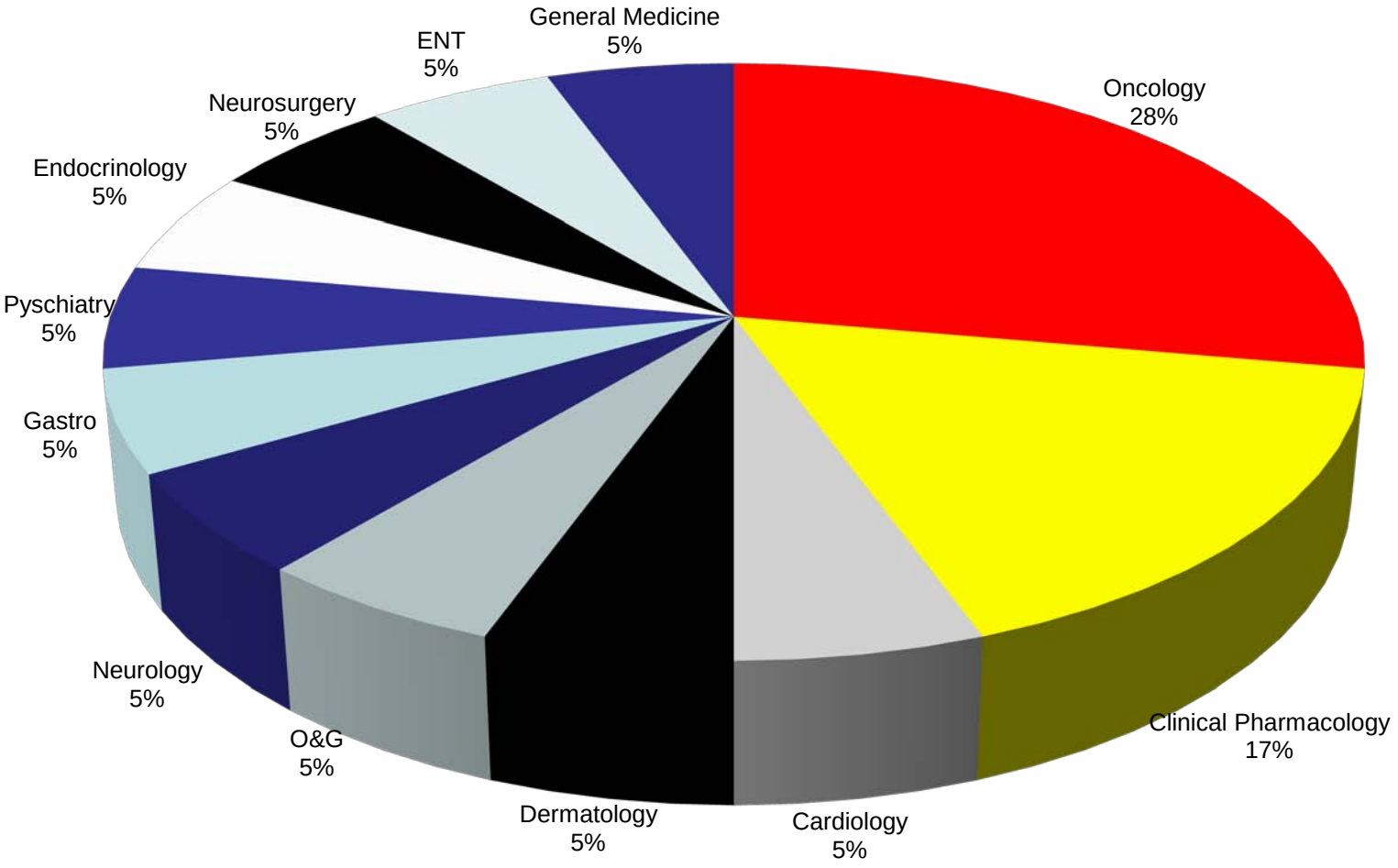
Classification of GCP Inspection Findings

~ adopted from EMEA SOPs on GCP Inspection.

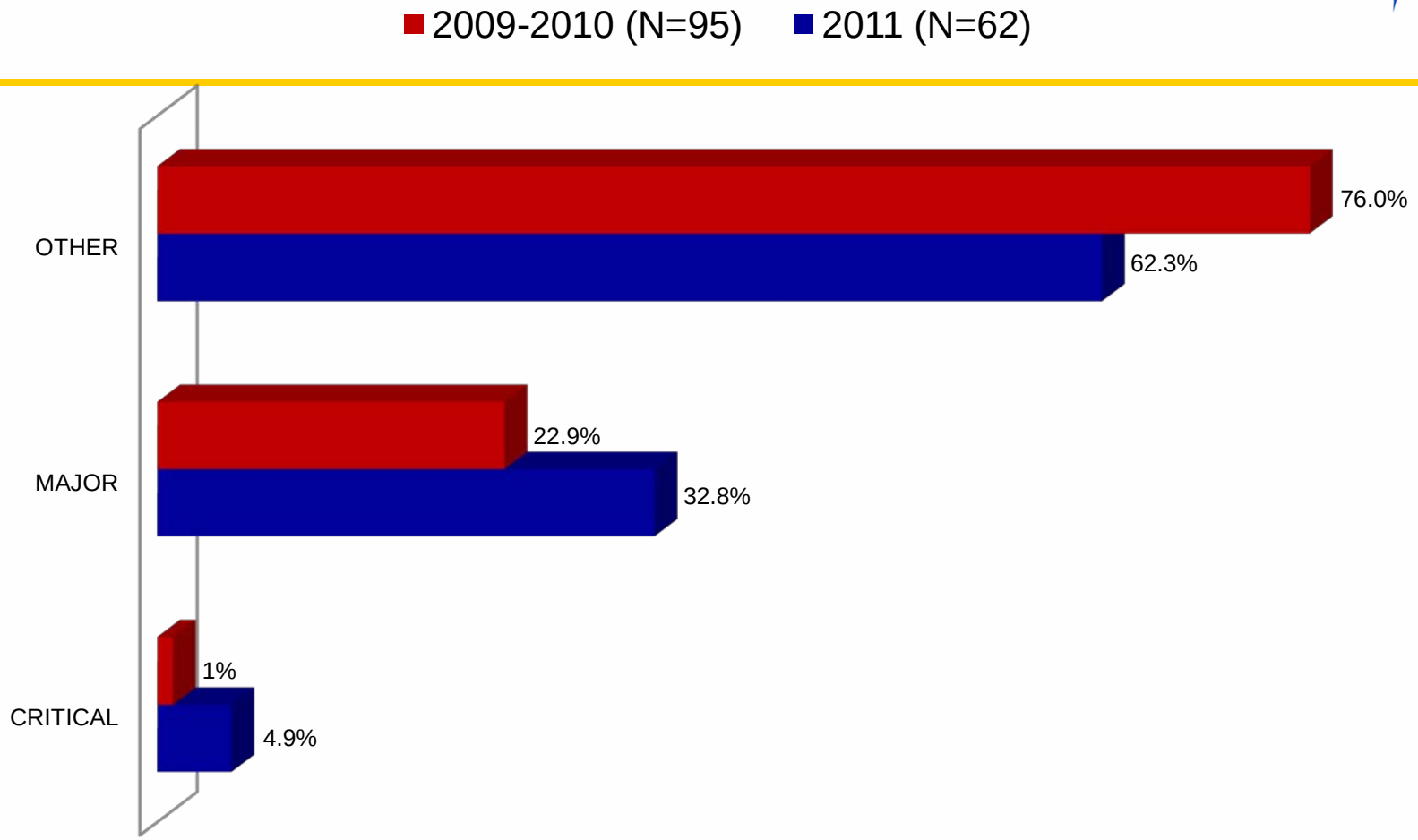
- **Other**: Conditions, practices or processes that would not be expected to adversely affect the rights, safety or well being of the subjects and/or the quality and integrity of data.

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

DISTRIBUTION OF THERAPEUTIC AREAS 2011 (N = 16)



CLASSIFICATION OF GCP INSPECTION FINDINGS



GCP Site Inspections (2011)
CRITICAL GCP Inspection Findings

- **3 CRITICAL GCP Inspection Findings:**
  - Informed Consent
  - Subject Recruitment
  - Investigational Product

GCP Site Inspections (2011)
CRITICAL GCP Inspection Findings

- **Informed Consent**

  Informed consent process was noted to be inadequate:

  - *Use of Short Form Consent for subjects who had been unable to read the English ICF, but able to read the Short Form Consent in another local language.*

    [Ref: Medicines (Clinical Trials) Regulations 11(4), SGGCP 2.9, 4.8.8]

  - *Inappropriate use of impartial witness whereby a Chinese person had acted as an impartial witness to a subject literate in Tamil.*

    [Ref: Medicines (Clinical Trials) Regulations 11(5), SGGCP 4.8.9]

  - *Subjects did not personally date the ICF themselves.*

    [Ref: Medicines (Clinical Trials) Regulation 11(4), SGGCP 4.8.8]

GCP Site Inspections (2011)
CRITICAL GCP Inspection Findings

- **Subject Recruitment**

  Subjects enrolled in a clinical trial were dispensed the Investigational Product prior to confirmation of eligibility.

  [Ref: SGGCP 2.3, 4.5, 4.6.5, 4.7]

GCP Site Inspections (2011)
CRITICAL GCP Inspection Findings

- **Investigational Product (IP)**

  IP management was noted to be inadequate.

  - *Study Pharmacist inadequately qualified to perform randomization and manage IP.*

    [Ref: SGGCP 2.5,2.8,4.2.3]
  - *Active IP was identifiable via code and colour of capsule thereby compromising the study blind.*

    [Ref: SGGCP 5.13.1 and 5.13.4]
  - *CRC had received the bulk Active and Placebo IP bearing different batch numbers and expiry dates despite being blinded to the clinical trial.*

    [Ref: SGGCP 2.12]
  - *Lack of documentation of IP Handling from IP Receipt to IP Destruction.*

    [Ref: SGGCP 2.12, 5.14.3]

GCP Site Inspections (2011)
CRITICAL GCP Inspection Findings

- **Investigational Product (IP) – cont'd**

  IP management was noted to be inadequate.

  - *Lack of SOPs and documentation of IP Re-packaging in accordance with GMP guidelines, where applicable.*

    [Ref: SGGCP 2.12, 5.13.1, 5.13.4, 5.14.3]
  - *Discrepancies noted in design and completion of IP Accountability Logs*

    [Ref: SGGCP 2.10, 4.6.3, 8.3.23]
  - *Lack of documentation of IP Destruction*

    [Ref: SGGCP 4.6.3, 8.4.2]
  - *IP had not been labelled in accordance with applicable regulations and guidelines.*

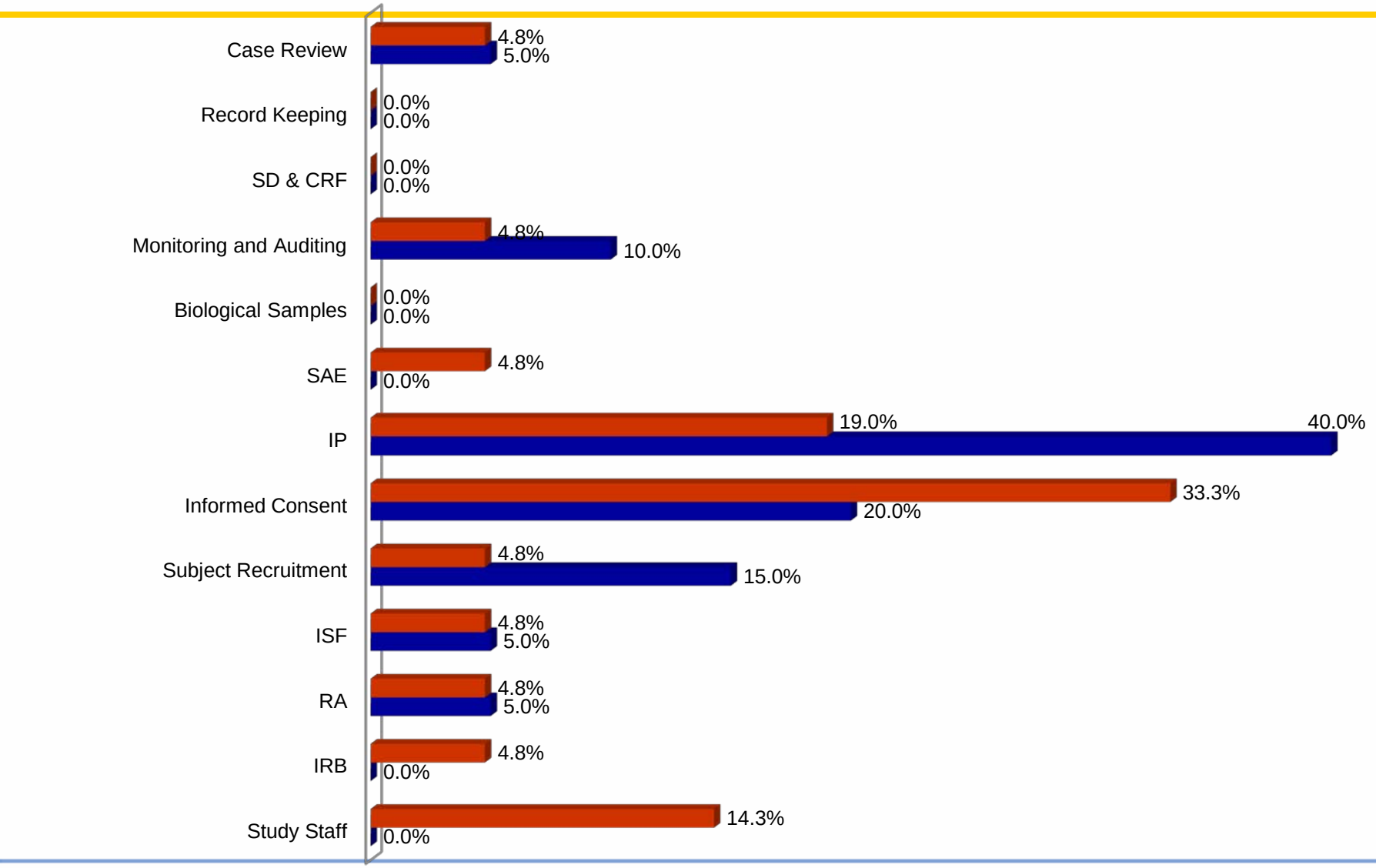
    [Ref: Medicines (CT) Regs 18(1) and SGGCP 4.6.3]

GCP Site Inspections (2011)
CRITICAL GCP Inspection Findings

- Outcome of GCP Site Inspection:
  - PI terminated the clinical trial.

- In comparison with 2009-2010:
  - 1 Critical GCP Inspection Finding
    - Significant protocol non-compliance detected.
    - PI terminated clinical trial.

% MAJOR GCP INSPECTION FINDINGS



GCP Site Inspections (2011)
MAJOR GCP Inspection Findings

- **Investigational Product (IP):**
  - ***For sites involved in IP re-packaging:***
    - *5 out of 8 MAJOR GCP Inspection Findings concerning IP:*
      - *Lack of delineation of roles and responsibilities of blinded and unblinded study staff.*

        [Ref: Medicines (CT) Regs 19(1), SGGCP 4.1.5, 4.2.3, 4.6.2, 4.9.1, 8.3.24]
      - *Lack of written instructions for manufacturing, handling and storage of IP in accordance with GMP guidelines, where applicable.*

        [Ref: SGGCP 2.10, 2.12, 2.13, 4.6.3, 4.6.4, 4.6.5, 5.13.1, 5.13.4, 5.14.3, 8.2.15, 8.3.8]

IP Re-packaging

- ***PICS Annex 13 : Sections 23-25:***

❑ *Delegated and trained study staff*

❑ *Line clearance*

❑ *In-process control checks (e.g. witness)*

❑ *Label re-conciliation*

❑ *Documentation*

GCP Site Inspections (2011)
MAJOR GCP Inspection Findings

- **Investigational Product (IP):**
  - For sites involved in in-patient administration of IP:
    - *Lack of delegation and training of nursing staff involved in in-patient administration of IP.*

      [Ref: Medicines (CT) Regs 19(1), SGGCP 4.1.5, 4.2.3, 4.6.2, 4.9.1, 8.3.24]
    - *Lack of written instructions for handling and storage of IP.*

      [Ref: SGGCP 2.12, 4.6.4, 4.6.5, 5.14.3]

GCP Site Inspections (2011)
MAJOR GCP Inspection Findings

- **Informed Consent:**
  - Subject had signed an unapproved version of the ICF.

    [Ref: Medicines (CT) Regs 11(4), SGGCP 4.4.1]
  - Inappropriate use of impartial witness.

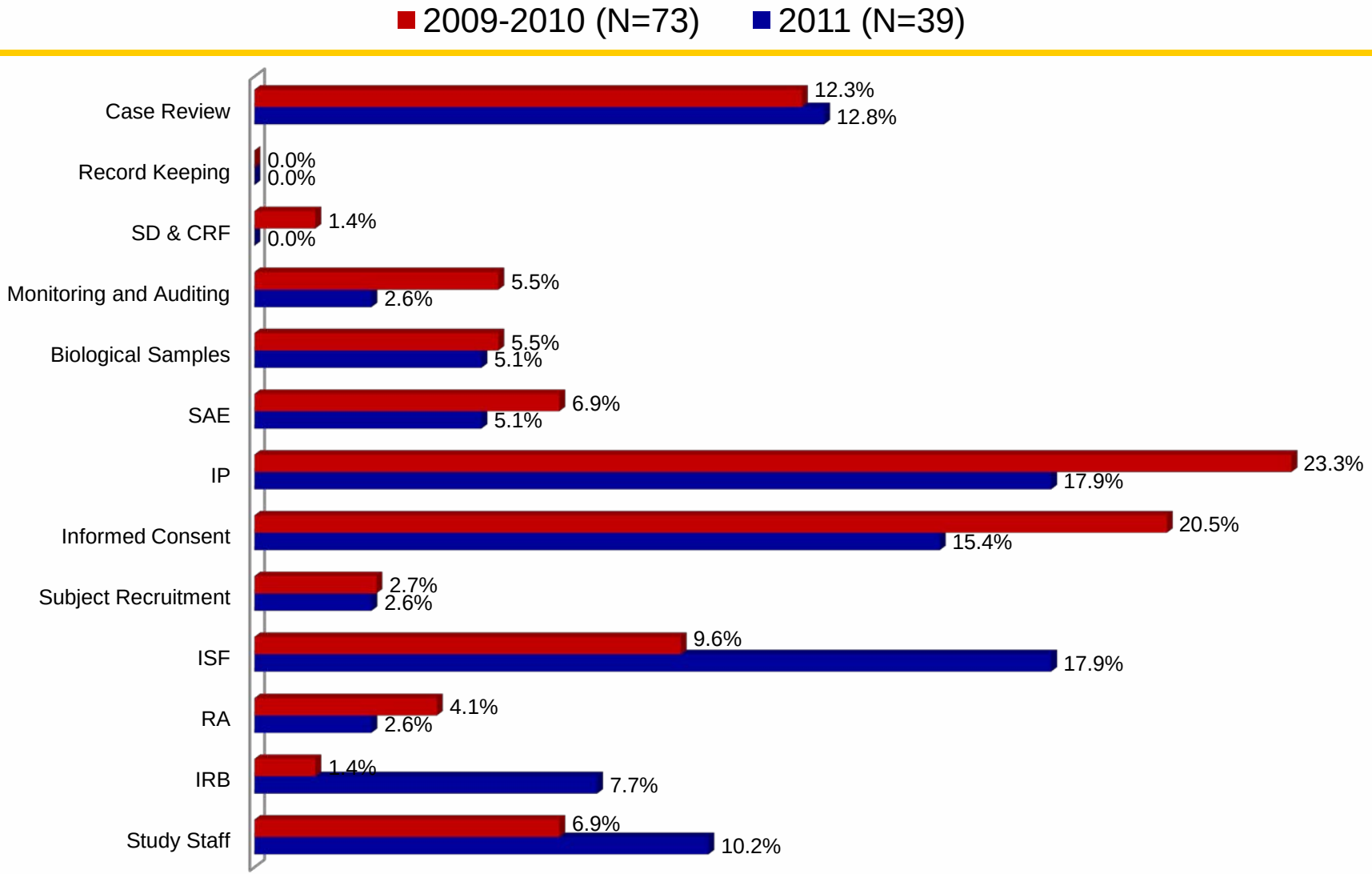
    [Ref: Medicines (CT) Regs 11(5), SGGCP 4.8.9]

GCP Site Inspections (2011)
MAJOR GCP Inspection Findings

- **Subject Recruitment:**
  - ► Breach in subject privacy and confidentiality.

  [Ref: SGGCP 2.11]

% OTHER GCP INSPECTION FINDINGS



GCP Site Inspections (2011)
OTHER GCP Inspection Findings

- **Investigator Site File:**
  - Missing Essential Documents:
    - *Calibration and Maintenance Records for equipment*

    [Ref: SGGCP 8.2.12, 8.3.7]
    - *Record of retained body fluids / tissue samples*

    [Ref: SGGCP 8.3.25]

GCP Site Inspections (2011)
OTHER GCP Inspection Findings

- **Investigational Product (IP):**
  - **IP Documentation did not comply with SGGCP 4.6.3:**
    - *IP Receipts*
    - *IP Inventory Logs*
    - *IP Accountability Logs*
    - *IP Return and / or Destruction Logs*

NB: Include the dates, quantities, batch numbers, expiration dates (where applicable), unique code numbers assigned to the IP and subjects.

  - **Lack of IP Storage Records**

[Ref: SGGCP 2.12, 4.6.4, 5.14.3, 5.14.5, 8.2.15, 8.3.8]

NB: IP Storage temperature should be monitored during IP Shipment and IP storage on site!

GCP Site Inspections (2011)
OTHER GCP Inspection Findings

- **Informed Consent:**
  - **Lack of documentation of the Informed Consent Process.**
    - *SGGCP 4.8.6*
  - **Subject / Impartial Witness / Person Obtaining Consent did not personally date the ICF.**
    - *SGGCP 4.8.8*

Quality Improvement Initiatives

- CTB FAQs uploaded on HSA website
- Meetings with cluster Research QA and monitoring staff
- Observation of GCP Site Inspections
- From The GCP Inspector's Desk Newsletter
- Upstream consultation on IP management

Meeting with Cluster RQA staff

REFERENCES

- **Medicines (Clinical Trials) Regulations**

  http://www.hsa.gov.sg/publish/etc/medialib/hsa_library/health_products_regulation/legislation/medicines_act.Par.41439.File.dat/MEDICINES%20(CLINICAL%20TRIALS)%20REGULATIONS.pdf
- **Singapore Guideline for Good Clinical Practice**
- **CTB FAQs**

  http://www.hsa.gov.sg/publish/hsaportal/en/health_products_regulation/clinical_trials/faqs.html
- **HSA Industry Communication**

  http://www.hsa.gov.sg/publish/hsaportal/en/health_products_regulation/clinical_trials/industry_communication.html
- **PICS Annex 13**

Thank You!

www.hsa.gov.sg