COMMON GCP INSPECTION FINDINGS 2009 - 2010

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OUTLINE

- GCP Inspection Framework
- Objectives
- Classification of GCP Inspection Findings
- Common GCP Site Inspection Findings (2009-2010)

GCP Inspection Framework

- Launched in Sep 2009
- First GCP Site Inspection done in Nov 2009
- Completed 13 GCP Site Inspections to date

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.

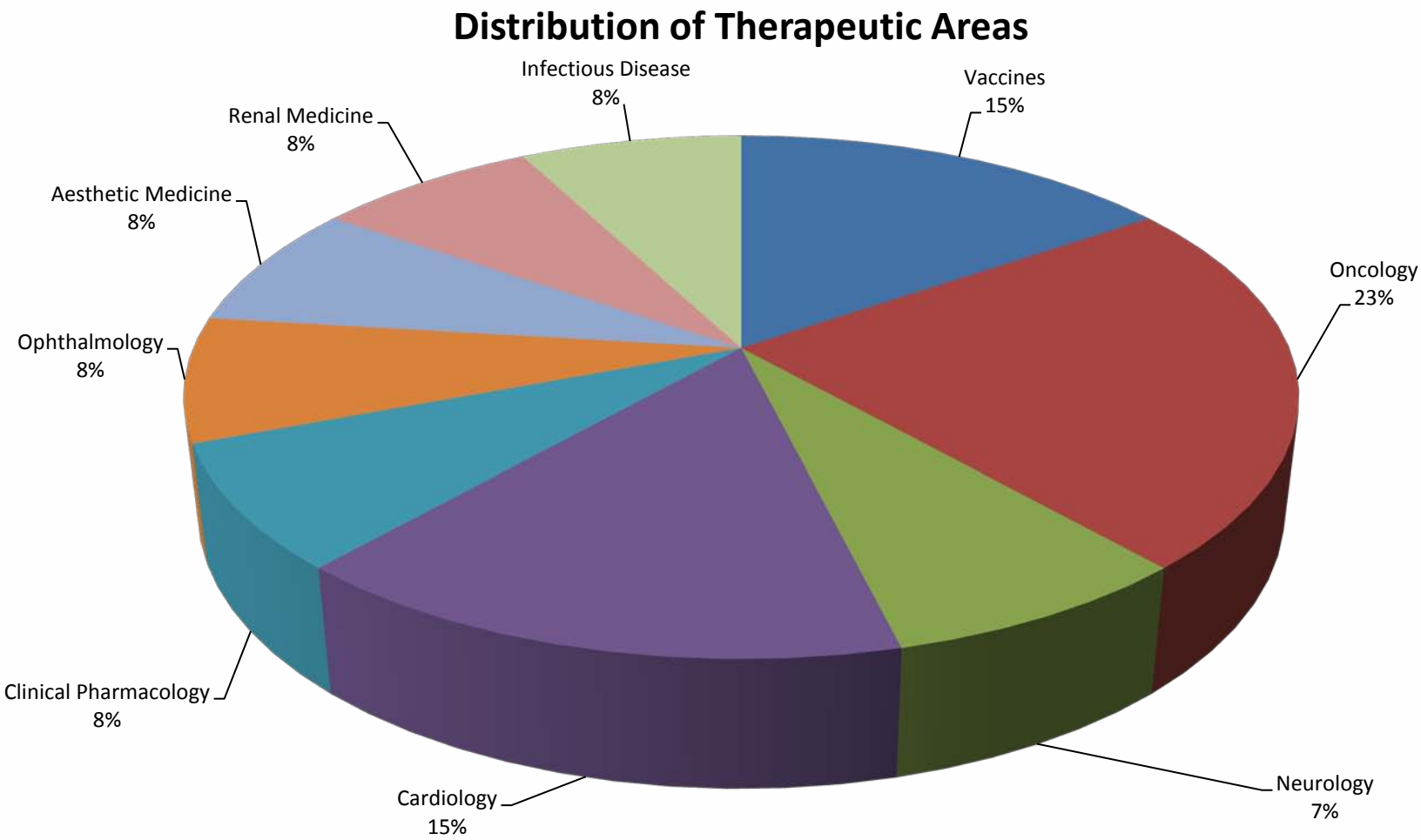
Classification of GCP Inspection Findings

~ adopted from EMEA SOPs on GCP Inspection.

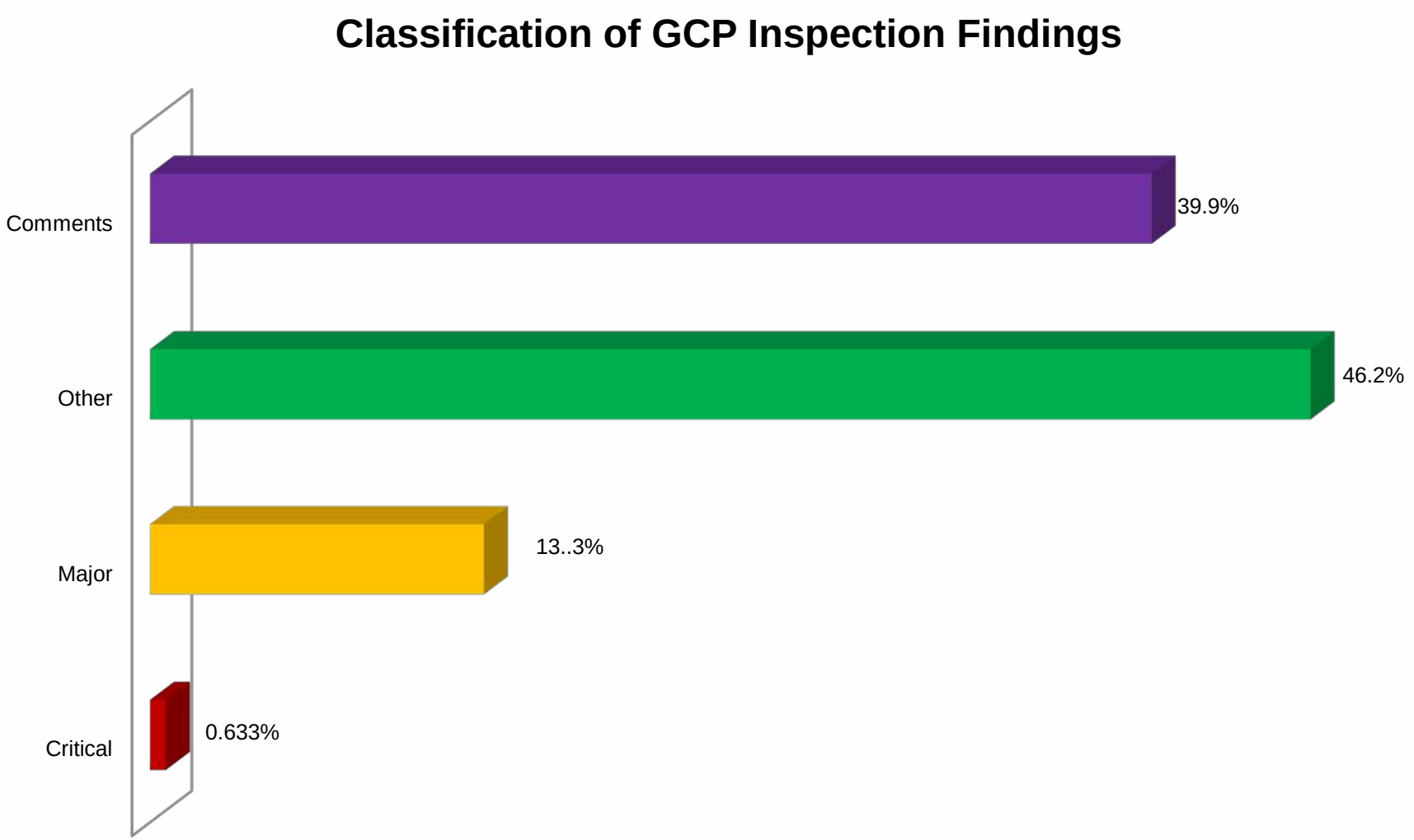
- **Other**: Conditions, practices or processes that would not be expected to adversely affect the rights, safety or well being of the subjects and/or the quality and integrity of data.

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

GCP Site Inspections (2009-2010) N=13



GCP Site Inspections (2009-2010) N=158



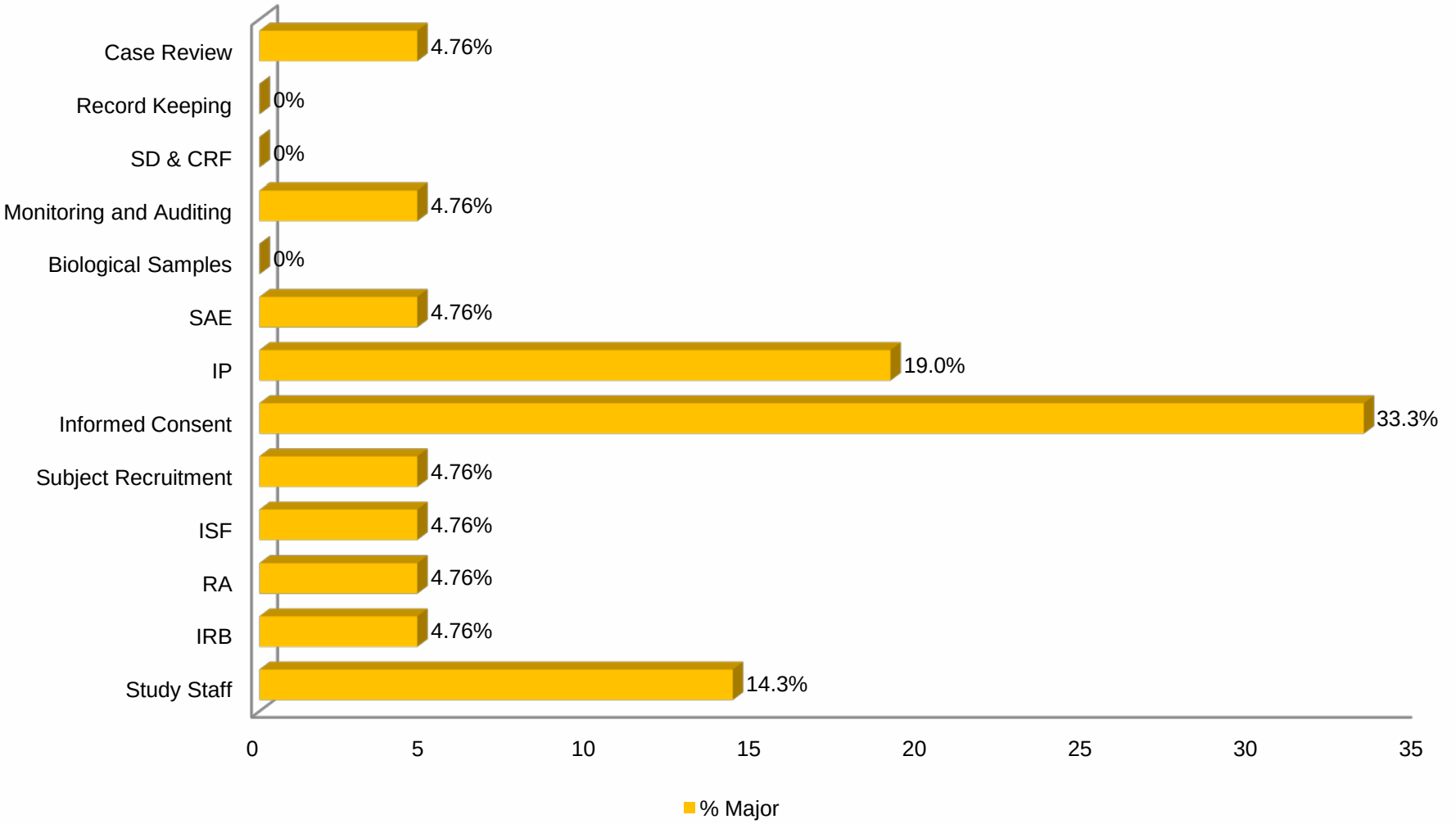
GCP Site Inspections (2009-2010)
Common GCP Inspection Findings

CRITICAL FINDING: 1

Lack of protocol compliance in key aspects of the protocol

GCP Site Inspections (2009-2010)

"Major" GCP Inspection Findings (N=21)



GCP Site Inspections (2009-2010)
"Major" GCP Inspection Findings

- **Informed Consent:**
  - **Subject had signed an amended ICF which had not been approved by the licensing authority.**
    - *Medicines (CT) Regulation 11(4)(a)*

(4) Subject to paragraph (5), consents obtained for the purposes of these Regulations shall be —

(*a*) in written form approved by the licensing authority and signed and dated by the person giving his consent; or

(*b*) if the person giving his consent is unable to sign the written form, in any other form and manner as the licensing authority may approve.

    - *SGGCP 4.4.3*

Additional points to note regarding ICF (1):

- **Administrative changes to protocol and informed consent form do not need to be submitted to HSA for review and approval.**
  - HSA Industry Guidance dated 15 Jun 2009
    - *Applicable to administrative changes to protocol and/or ICF.*
    - *Examples of logistical / administrative changes include:*
      - *Change of contact information, e.g., address, telephone number, fax or email address, except when the change involves the sponsor, principal investigator or address of the trial site*
      - *Change of study coordinator or monitor*
      - *Minor editorial changes e.g., reformatting of document, correction of typographical or grammatical errors*
      - *Addition or deletion of overseas trial sites or collaborating centres*
  - Check IRB submission requirements for administrative changes to protocol and informed consent form.

Additional points to note regarding ICF (2):

- **If subject or subject's legal representative is unable to read the ICF:**
  - Medicines (CT) Regulation 11(5)

> (5) If the person giving his consent for the purposes of these Regulations is unable to read, the consent form referred to in paragraph (4) shall be read and explained to him in the presence of an impartial witness who shall sign and date the consent form to attest that the form was accurately explained to that person and that his consent thereto was freely given.

  - SGGCP 4.8.9

Subject or Subject's Legal Representative Unable to Read the Informed Consent Form

- **Requirement of impartial witness:**
  - *If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion.*
- **Who should sign and personally date the informed consent form:**
  - *After the written informed consent form and any other written information to be provided to subjects, is read and explained to the subject or the subject's legally acceptable representative, and after the subject or the subject's legally acceptable representative has orally consented to the subject's participation in the trial and, if capable of doing so, has signed and personally dated the informed consent form, the witness should sign and personally date the consent form.*
- **Role of an impartial witness:**
  - *By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject or the subject's legally acceptable representative, and that informed consent was freely given by the subject or the subject's legally acceptable representative.*

GCP Site Inspections (2009-2010)
"Major" GCP Inspection Findings

- **Informed Consent (cont'd):**
  - **Substituted consent was considered to be invalid**
    - *Medicines (CT) Regulation 11(1)(b), 11(3), SGGCP 4.8.8*

Medicines (CT) Regulation 11(1)(b)

Consent required to use person as subject in clinical trial

11.—(1) Subject to paragraphs (2) and (3), a holder of a certificate shall not use a person as a subject in a clinical trial unless the following conditions are satisfied:

(*a*) in the case of a person of or above the age of 21 years, or a person below the age of 21 years who is married, with the consent of that person;

(*b*) in the case of a person below the age of 21 years who is not married, with the consent of that person and —

(i) that person's parent or guardian (if there is no parent); and

(ii) if different from sub-paragraph (i), that person's legal representative.

(2) The consent of a person below the age of 21 years who is not married shall not be required under paragraph (1) if —

(*a*) that person lacks sufficient understanding to give such consent; and

(*b*) there is a reasonable prospect that participation in the clinical trial will directly benefit that person.

Medicines (CT) Regulation 11(3)

(3) The consent of a person who is unconscious or incapable of exercising rational judgment shall not be required under paragraph (1) if —

(*a*) the principal investigator and a doctor who is not otherwise participating in the clinical trial certify in writing that —

(i) that person is unconscious or incapable of exercising rational judgment; and

(ii) it is not likely that that person will regain consciousness and be capable of exercising rational judgment within the window period;

(*b*) consent thereto has been obtained from —

(i) that person's spouse, parent, guardian (if there is no parent) or any other person having charge of him; and

(ii) if different from sub-paragraph (i), that person's legal representative; and

(*c*) there is a reasonable prospect that participation in the clinical trial will directly benefit that person.

GCP Site Inspections (2009-2010)

"Major" GCP Inspection Findings (2)

- **Investigational Product:**
  - **IP label did not comply with Medicines (CT) Regulation 18 and SGGCP 4.6.3**

Test materials' particulars, identification and storage

18.—(1) The holder of a certificate shall ensure that all test materials have the following particulars written on the containers:

(*a*) the designation, reference number or other identification mark of each item of such material;

(*b*) the name and address of the manufacturer;

(*c*) the production batch number of the material;

(*d*) the name or other identification mark of the subject for whom the test material is intended;

(*e*) the date of manufacture and the expiry date of the test material;

(*f*) the storage conditions appropriate for each item of test material as may be indicated by the manufacturer; and

(*g*) the words: "This product shall only be used under strict medical surveillance" or "This product shall only be used under strict dental surveillance", as the case may be.

(2) No test material shall be used in a clinical trial if the container in which the test material is stored is not marked and labelled with the particulars specified in paragraph (1).

GCP Site Inspections (2009-2010)
"Major" GCP Inspection Findings

- **Investigational Product (cont'd):**
  - **Lack of traceability and accuracy in IP storage and IP accountability**
    - *SGGCP 2.12, 2.13, 4.6, 5.13.1, 5.14.5, 8.2.14, 8.2.12, 8.2.13, 8.3.23*
    - **IP storage:**
      - *Lack of traceability between thermometers, calibration certificates and IP temperature logs.*
      - *Lack of written procedures for resetting the thermometer.*
      - *Lack of documentation about measures taken post-temperature escalation.*
      - *Lack of written procedures for frequency of temperature monitoring.*
      - *Lack of accuracy in temperature monitoring.*

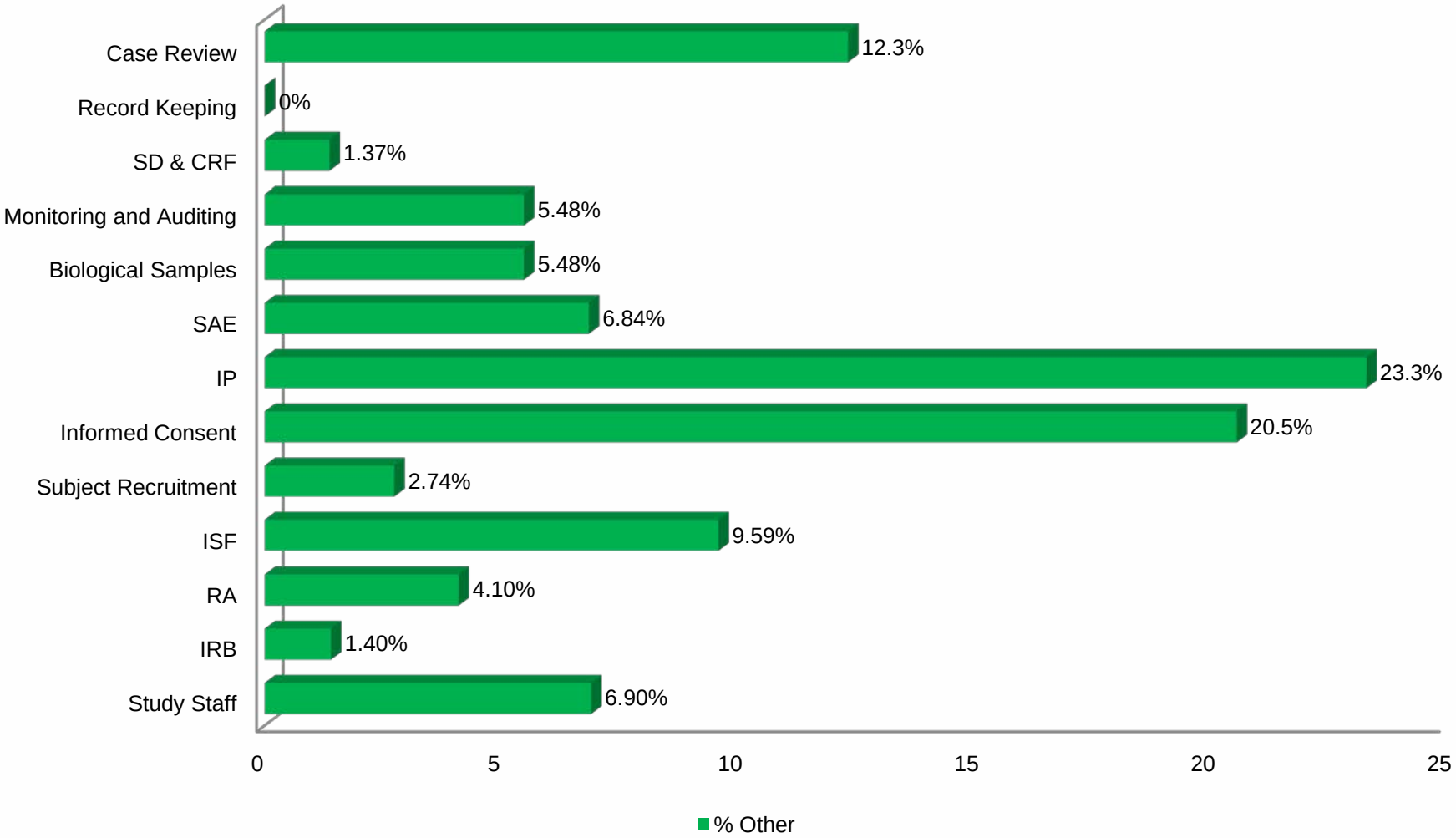
GCP Site Inspections (2009-2010)
"Major" GCP Inspection Findings

- **Investigational Product (cont'd):**
  - **IP dispensing and accountability:**
    - *IP Accountability Log had been typed out instead of manually completed.*
    - *Lack of SOP and documentation for IP re-labelling.*
    - *IP Inventory and IP Accountability logs could not be reconciled.*
    - *Unauthorized amendments made to IP Accountability Logs by CRA.*
    - *IP shipment receipts, IVRS Confirmation Emails, IP Accountability Logs could not be reconciled with regard to the IP receipt date.*
    - *Lack of documentation of dispensing error.*

GCP Site Inspections (2009-2010)
"Major" GCP Inspection Findings (3)

- **Study Staff:**
  - **HSA was not notified about change in Principal Investigator.**
    - *Medicines (CT) Regulation 10 and SGGCP 5.6.4*
  - **Signature Sheet not maintained.**
    - *Medicines (CT) Regulation 19(3) and SGGCP 4.1.5 and 4.9.1*

GCP Site Inspections (2009-2010)
"Other" GCP Inspection Findings (N=73)



GCP Site Inspections (2009-2010)
"Other" GCP Inspection Findings (1)

- **Investigational Product (IP):**
  - **Study staff was not authorized to perform IP accountability.**
    - *SGGCP 4.1.5 and 4.9.1*
  - **Inadequate IP Accountability Records (e.g. IP Inventory Logs, IVRS Confirmation of Randomization Reports).**
    - *SGGCP 4.6.3*

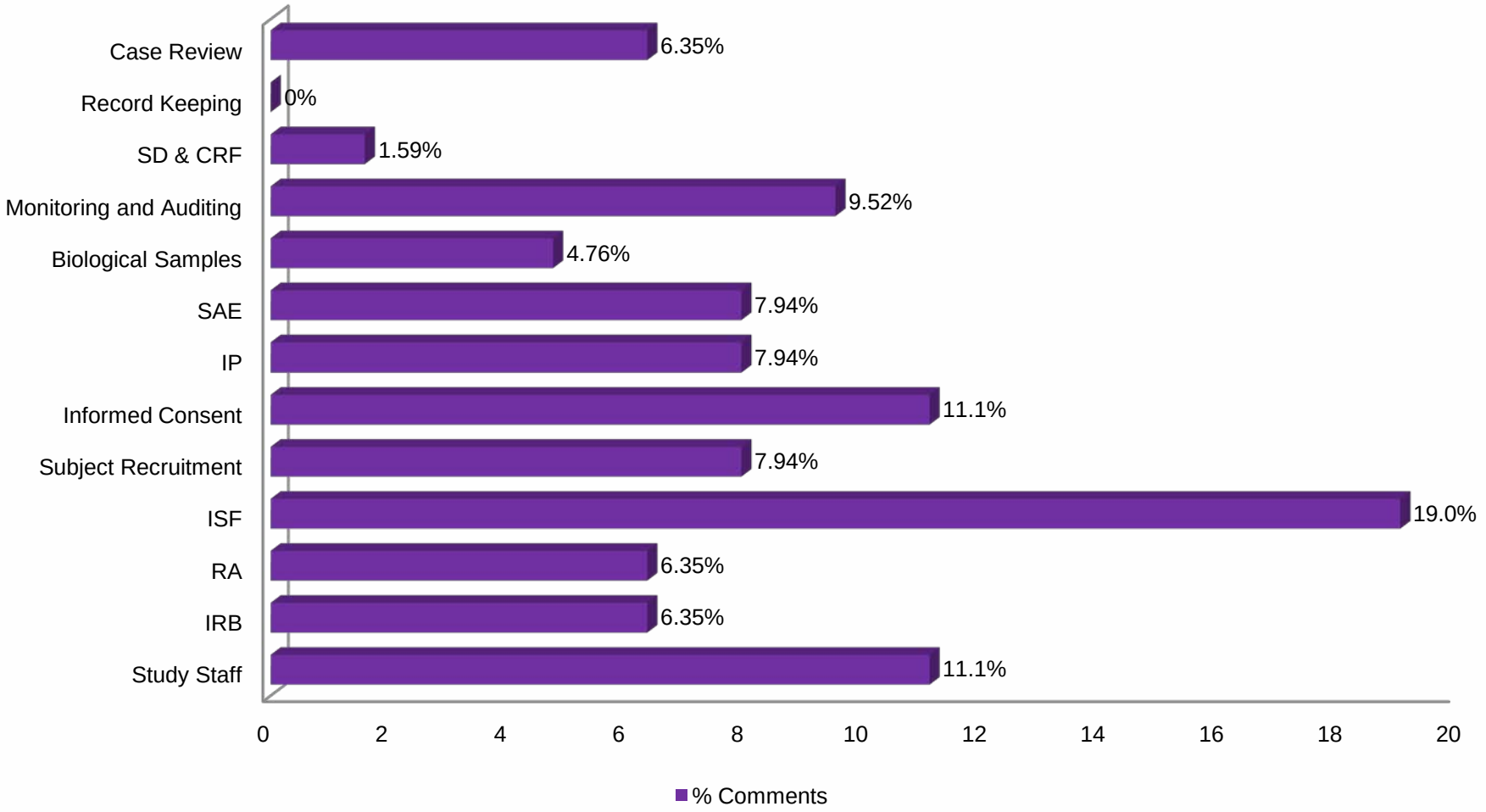
GCP Site Inspections (2009-2010)
"Other" GCP Inspection Findings (2)

- **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*
  - **Amendments to ICF not initialed and dated by individual.**
    - *SGGCP 4.9.2*

GCP Site Inspections (2009-2010)
"Other" GCP Inspection Findings (3)

- **Case Review:**
  - **Inadequate source documentation.**
    - *SGGCP 4.9.2*
  - **Discrepancies in Source Document Verification (SDV).**
    - *SGGCP 4.9.3*

GCP Site Inspections (2009-2010)
"Common" GCP Inspection Findings (N=63)



Recommendations (1):

- **Investigator Site File:**
  - **Tracking Logs**
    - *IRB and HSA submissions and approvals*
    - *UPIRTSO / SAE Reporting to IRB*
    - *Expedited Safety Reporting to HSA*
    - *Re-consent of subjects, if required*
  - **Screening Logs**
    - *Source of subjects*
  - **Monitoring**
    - *Site Visit Log and Follow-up correspondence should be reconciled.*
  - **Good Documentation Practice**
    - *Amendments should be initiated and dated.*
    - *Written clarifications should be made with the current date.*
- **Study Staff:**
  - **Updated training records**

Recommendations (2):

- **Informed Consent:**
  - **Informed Consent Document**
    - *Have all name, signature and date fields been completed accurately, as required?*
    - *Is signature of person obtaining consent consistent with the Signature Sheet?*
    - *Have amendments been initialed and dated, if applicable?*
    - *Has ICF been labelled with Subject ID?*
    - *Is there consistency between different versions of the signed ICF?*
  - **Informed Consent Documentation**
    - *Protocol Reference*
    - *Date of informed consent*
    - *Informed Consent Process*
    - *Signed copy provided to subject*
    - *Signed by person obtaining consent*

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**

- **HSA Industry Communication**

  http://www.hsa.gov.sg/publish/hsaportal/en/health_products_regulation/clinical_trials/industry_communication.html

Thank You!

www.hsa.gov.sg