GCP Inspection – An Update to CRP 2012

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Outline

- GCP Inspection Framework
- Objectives
- Classification of GCP Inspection Findings
- Common GCP Site Inspection Findings
- Quality Improvement Initiatives
- Sharing of Best Practices

GCP Inspection Framework

- Launched in Sep 2009
- First GCP Site Inspection done in Nov 2009
- Completed 40 GCP Site Inspections to date:
  - 2009-2010 : 13 (Protocol-specific)
  - 2011 : 15 (Protocol-specific), 1 (Systems on ICF and IP)
  - 2012: 10 (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

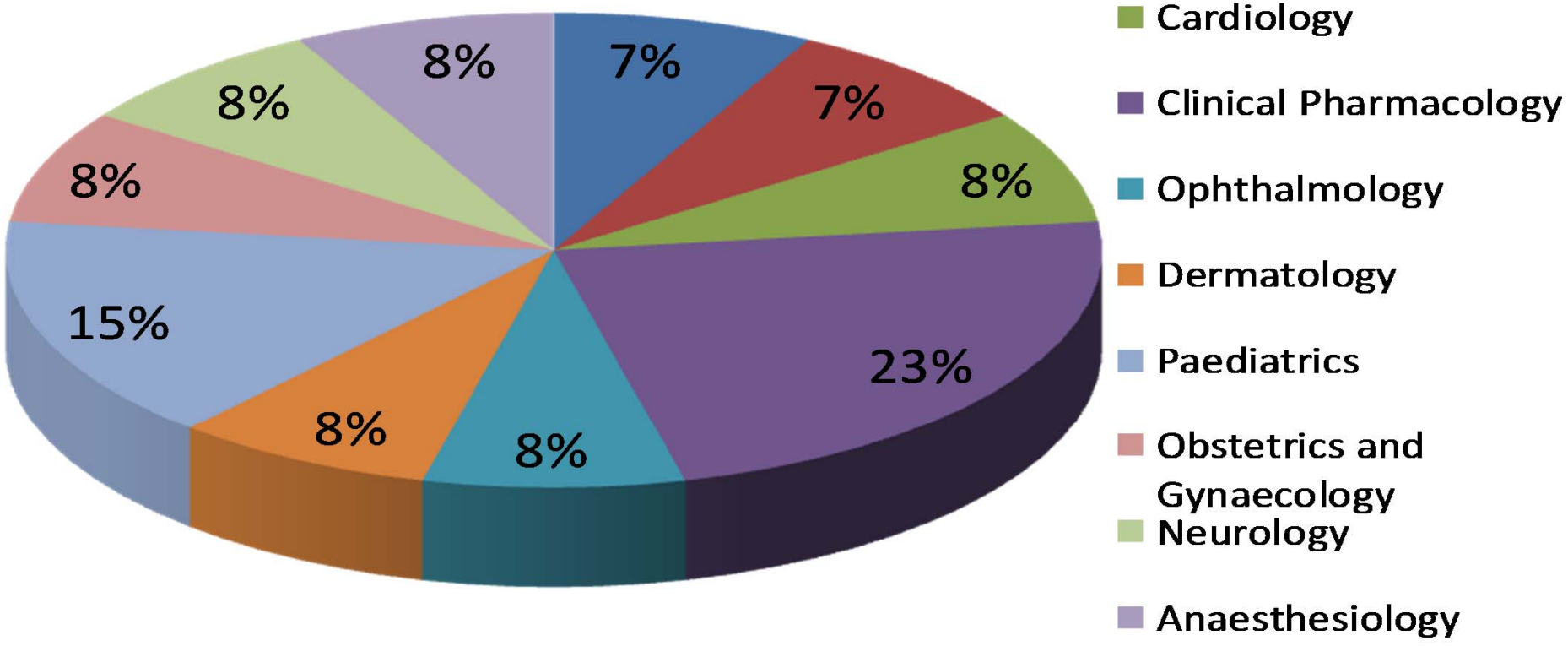
~ adopted from EMEA SOPs on GCP Inspection.

- **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.

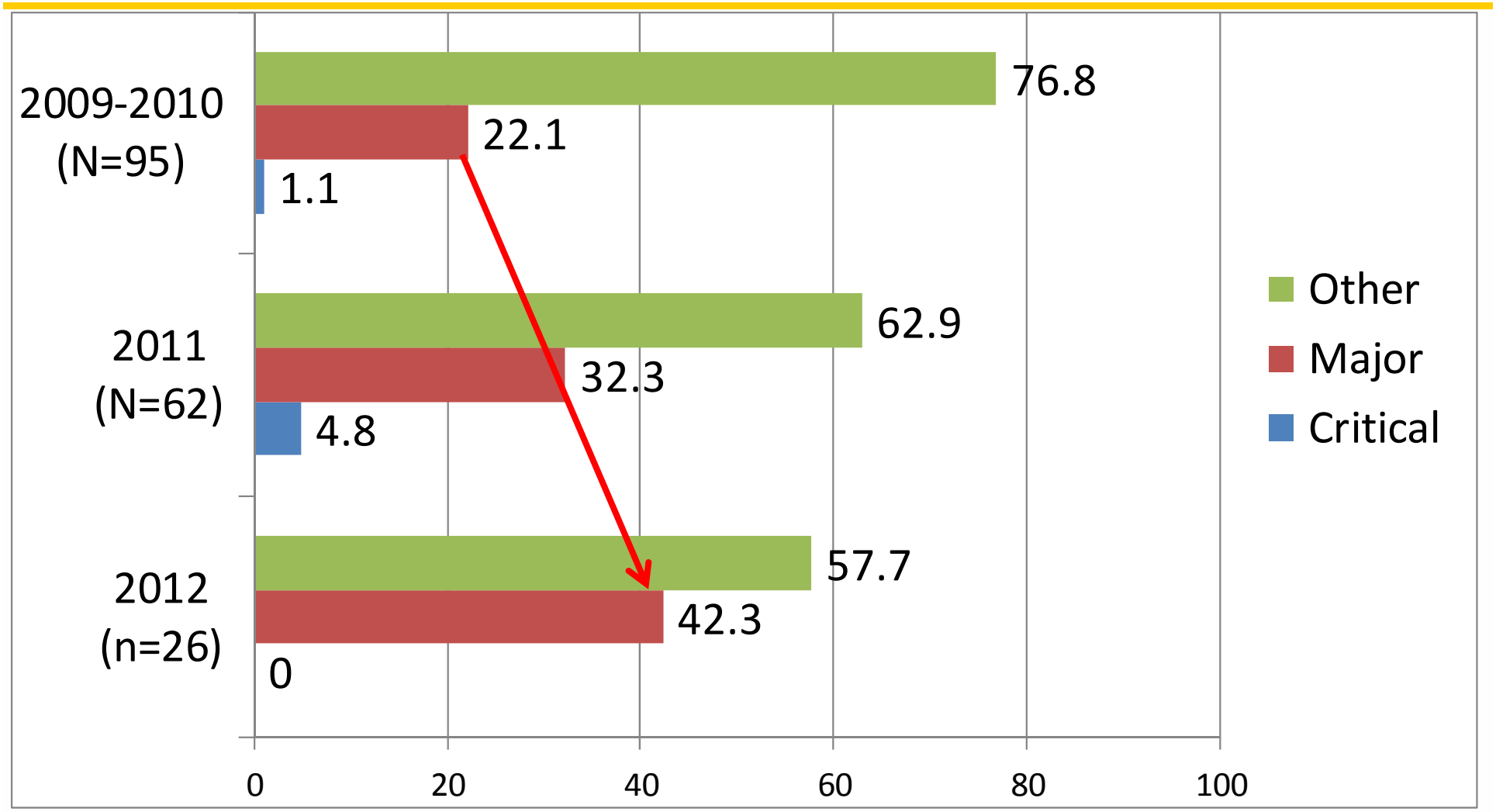
- **Comments**: The observations might lead to suggestions on how to improve quality or reduce the potential for a deviation to occur in the future.

GCP Inspections in 2012

Distribution of Therapeutic Areas
(N=13)



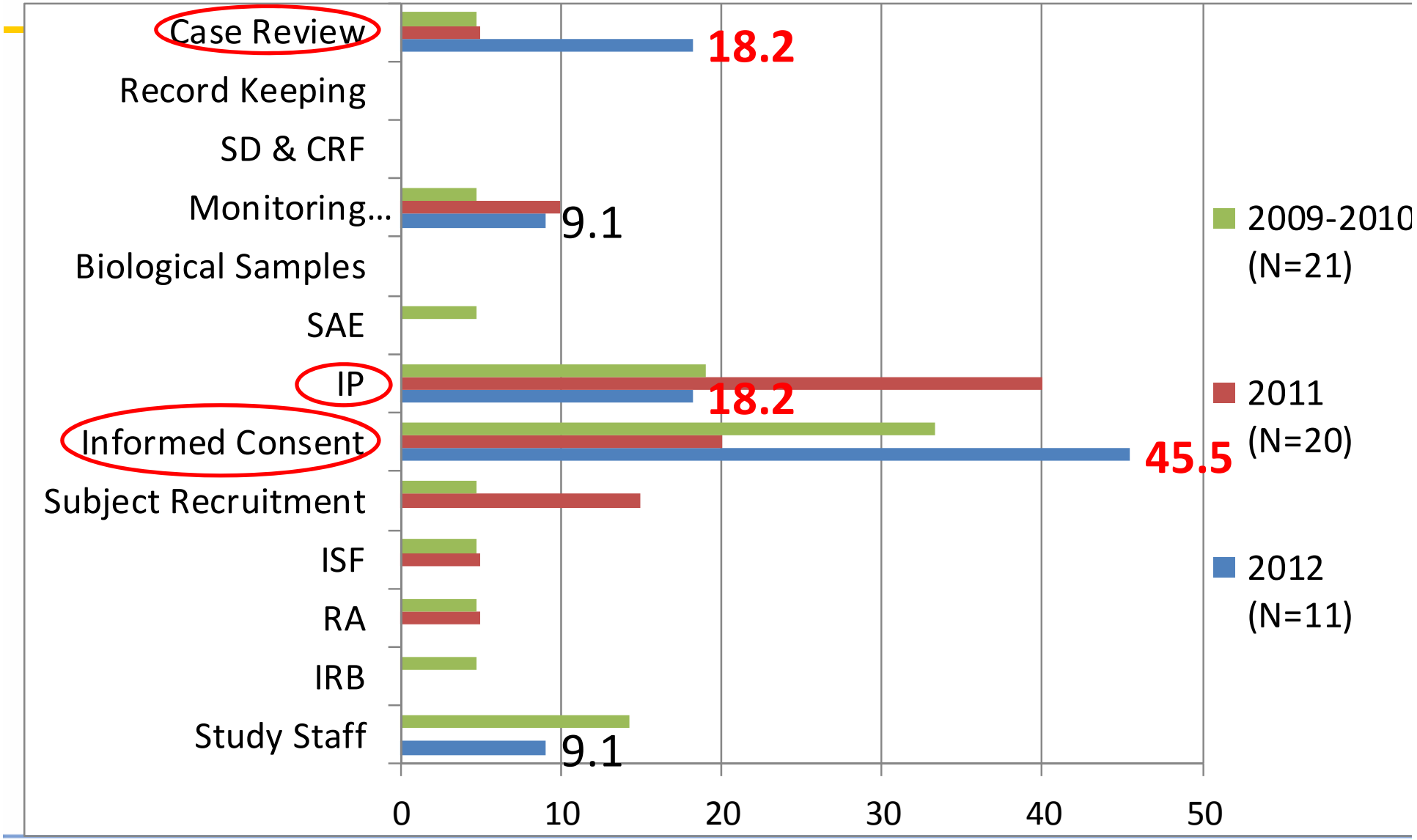
Distribution of Inspection Observations



GCP Site Inspections (2012)
CRITICAL GCP Inspection Findings

None ☺

Distribution of Major Observations



Top 3 Major Observations in 2012

- Informed Consent
- Investigational Product (IP)
- Case Review

Major GCP Inspection Findings
Informed Consent

- Current version of Informed Consent Form was not used to consent subject.
  - *Medicines (Clinical Trials) Regulation 11(4)*, SGGCP 4.4.1 and 4.8.1
    - *Implement revised version of ICF immediately after IRB and HSA approval (if required).*
- Subjects had signed on an amended Informed Consent Form without IRB approval.
  - *SGGCP 4.4.1 and 4.8.1*
    - *Use an ICF **Tracking Log** to track the IRB and HSA submission and approval dates.*
    - *Administrative amendments to ICF do not require HSA submission and approval.*

Major GCP Inspection Findings
Informed Consent

- Substituted informed consent was not obtained from subjects < 21 yrs and not married.
  - *Medicines (Clinical Trials) Regulation 11(1-2), SGGCP 4.8.12*
    - *Retain copy of Birth Certificate / NRIC of subject <21 yrs and not married.*
    - *Document relationship of person providing substituted consent to subject on Informed Consent Form.*
    - *Document details of informed consent process in subject medical records.*
      - *CTB FAQs*
- The identity of persons who had provided substituted consent could not be verified.
  - *Medicines (Clinical Trials) Regulation 11(1-3), SGGCP 4.8.12*
    - *Document relationship of person providing substituted consent to subject on Informed Consent Form.*
    - *Document details of informed consent process in subject medical records.*

Major GCP Inspection Findings
Informed Consent

- Documentation of mental capacity by an independent doctor had been performed by a Sub-Investigator.
  - *Medicines (Clinical Trials) Regulation 11(3), SGGCP 4.8.12*
    - *Documentation of mental capacity is required by an investigator and a non-study doctor.*
    - *Document the informed consent process in the subject medical records.*

Major GCP Inspection Findings
Informed Consent

- Informed consent process for use of translator / impartial witness was not clear.
  - *Medicines (Clinical Trials) Regulation 11(5), SGGCP 2.10, 4.8.6, 4.8.9*
    - *Document the informed consent process involving use of translator / impartial witness in detail.*
    - *Refer to CTB FAQs for further guidance on documentation of consent.*
- Sections of the Informed Consent Form to be completed by the subject were not completed personally by the subject.
  - *Protocol-specific Informed Consent Form*
    - *Determine which sections of the ICF template should be completed by the subject or his LAR in addition to the signature and date fields.*

Major GCP Inspection Findings
Informed Consent

- Consent had been obtained by physicians without prior authorization by the Principal Investigator.
  - *Medicines (Clinical Trials) Regulation 19(3), SGGCP 4.1.5, 4.9.1 and 8.3.24*
    - *Ensure that physicians have been authorized to obtain informed consent on the Signed Signature Sheet.*
    - *Check that IRB has approved the sub-investigator to be involved in the clinical trial.*
- Consent was obtained by CRCs who were not appropriately qualified to obtain consent.
  - *SGGCP 2.8. 4.2.3, 4.8.7*
    - *Consent should be obtained by a physician who has been authorized by the Principal Investigator on the Signed Signature Sheet.*

Major GCP Inspection Findings
Informed Consent

- Individuals did not personally date the Informed Consent Form themselves.
  - *Medicines (Clinical Trials) Regulation 11(4) and SGGCP 4.8.8*
    - *Check the signed ICF to ensure that all individuals have personally signed and dated the ICF themselves.*
    - *Develop an informed consent process for subjects who are unable to sign and / or date the ICF themselves and submit it to IRB and HSA for approval.*
- Consent was not documented in the subject medical records
  - *SGGCP 2.10*
    - *Refer to CTB FAQ for further guidance on documentation of consent.*

Major GCP Inspection Findings
Investigational Product

- Discrepancy in IP use between the protocol (open-labelled) & study conduct (double-blinded)
  - *SGGCP 4.6.5 and Protocol*
    - *Ensure that IP is used in accordance with the protocol.*
- Lack of written procedures for handling & storage of IP
  - *SGGCP 5.14.3*
    - *Develop SOPs for IP management.*
    - *Refer to HSA website for template IP Management SOP.*
- IP repackaging & relabelling was not performed in accordance with GMP requirements
  - *SGGCP 2.12, 5.13.1*
    - *Refer to HSA Guidance on IP Repackaging and Relabelling on Site.*

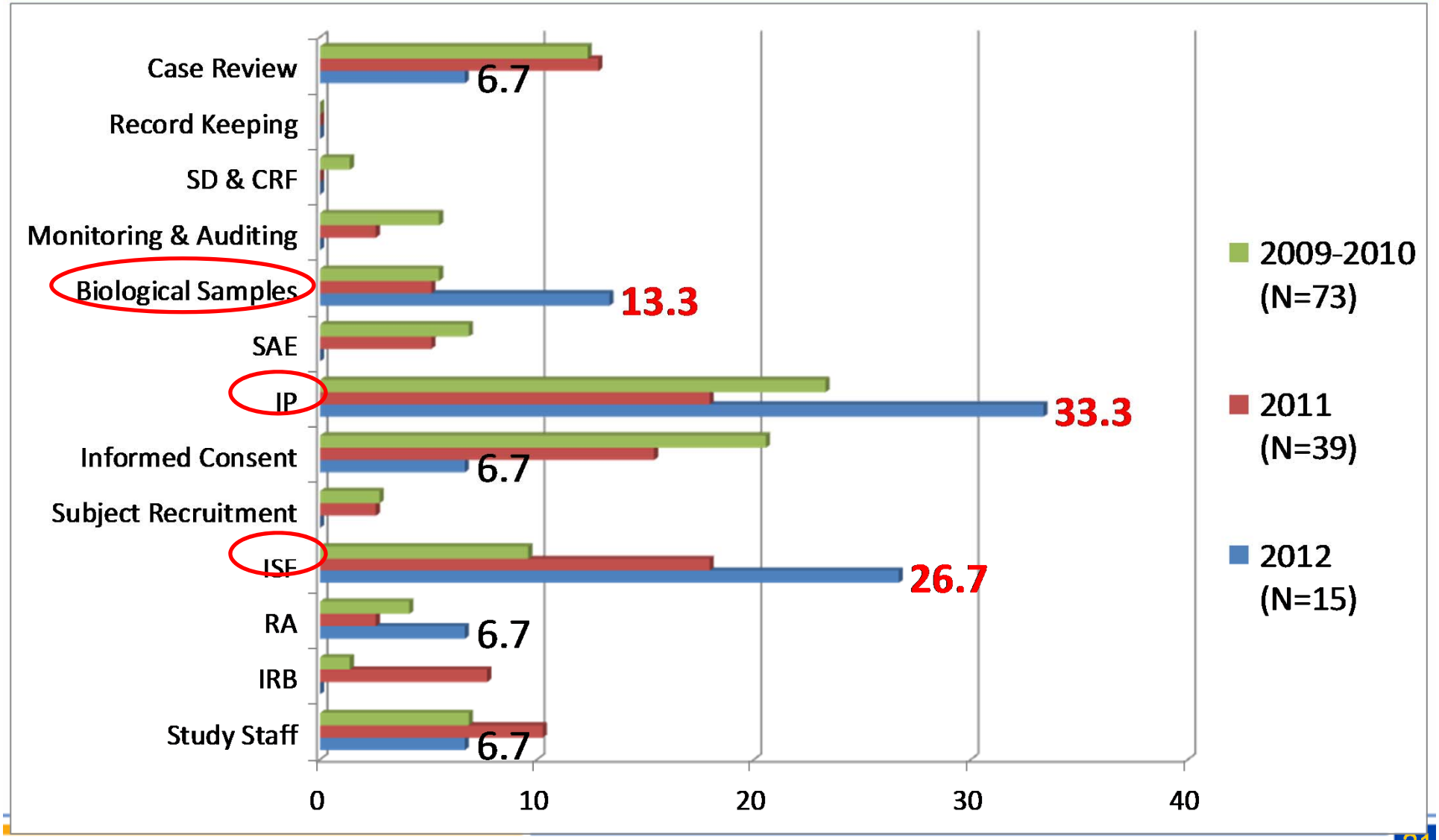
Major GCP Inspection Findings
Investigational Product

- Lack of quality systems in IP Management
  - *SGGCP 2.13*
    - *Ensure that IP Management SOPs are approved by Sponsor.*
    - *Ensure that critical steps in IP management are verified. For e.g. randomization and IP repackaging and relabelling.*
- Study staff was not authorized to perform IP Dispensing
  - *Medicines (Clinical Trials) Regulation 19(3), SGGCP 4.1.5, 4.9.1 and 8.3.24*
    - *Ensure that all study staff involved in IP management are authorized by the PI on the Signed Signature Sheet.*

Major GCP Inspection Findings
Case Review

- Discrepancies noted in source document verification.
  - *SGGCP 2.10, 4.9.2, 4.9.3 and 4.9.4*
    - *Ensure that transcription of source data into CRF is done accurately.*
- Source documents completed retrospectively.
  - SGGCP 2.10
    - *Ensure source data is documented prospectively.*

Distribution of Other Observations



Top 3 Other Observations in 2012

- Investigational Product (IP)
- Investigator Site File
- Biological Sample

Other GCP Inspection Findings
Investigational Product

- IP Documentation for shipment, receipt, dispensing, accountability, return and/or destruction was not laballed in accordance with regulatory requirements.
  - *SGGCP 4.6.3*
    - *Dates, quantities, batch numbers, expiration date (if applicable), unique code numbers assigned to the IP and trial subjects should be included in IP Documentation.*

- IP labelling did not comply with regulatory requirements (e.g. storage condition, For Clinical Trial Use Only).
  - *Medicines (Clinical Trials) Regulation 18(1), SGGCP 4.6.3*
    - *IP must be labelled in accordance with regulatory requirements regardless of whether the IP is a locally registered medicinal product.*
    - *Seek written waiver from HSA if you are unable to fullfill the IP Labelling requirements.*

Other GCP Inspection Findings
Investigational Product

- Transfer of IP was not documented.
  - *SGGCP 4.6.3 and 8.3.23*
    - *Document transfer of IP between storage places.*
- Equipment used to monitor IP storage was not calibrated and maintained.
  - SGGCP 8.2.12 and 8.3.7
    - *Ensure that all equipment used in a clinical trial are calibrated and maintained.*
    - *File calibration and maintenance records in the Investigator Site File.*

Other GCP Inspection Findings
Investigator Site File

- Essential documents were maintained electronically without any audit trail.
  - *SGGCP 2.13*
    - *Ensure that electronic systems used in clinical trials have secure and limited access, and have audit trail.*
- Lack of document control in essential documents.
  - *SGGCP 2.13*
    - *Ensure that all essential documents have document control.*

Other GCP Inspection Findings
Biological Samples

- Calibration and maintenance records were missing for equipment used to handle biological samples.
  - *SGGCP 2.13, 8.2.12 and 8.3.7*
    - *Ensure that calibration and maintenance records are available for all equipment used in a clinical trial.*

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
- Sharing of Best Practices

Sharing of Best Practices

- Informed Consent in subjects who are unconscious or incapable of exercising rational judgment

  Acknowledgement: NNI, TTSH, NUHS and NHG

- IP Repackaging and Relabelling

  Acknowledgement: IMH

Clinical Trials in Subjects Who are Unconscious / Incapable of Exercising Rational Judgment

Two Informed Consent Templates:

- *Substituted Consent from parent / spouse / guardian / person having charge / legally authorized representative*

Microsoft Word
97 - 2003 Document

- *Consent from subject for continued participation*

Microsoft Word
97 - 2003 Document

Major GCP Inspection Findings
Informed Consent

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    - *Document details of informed consent process in subject medical records.*
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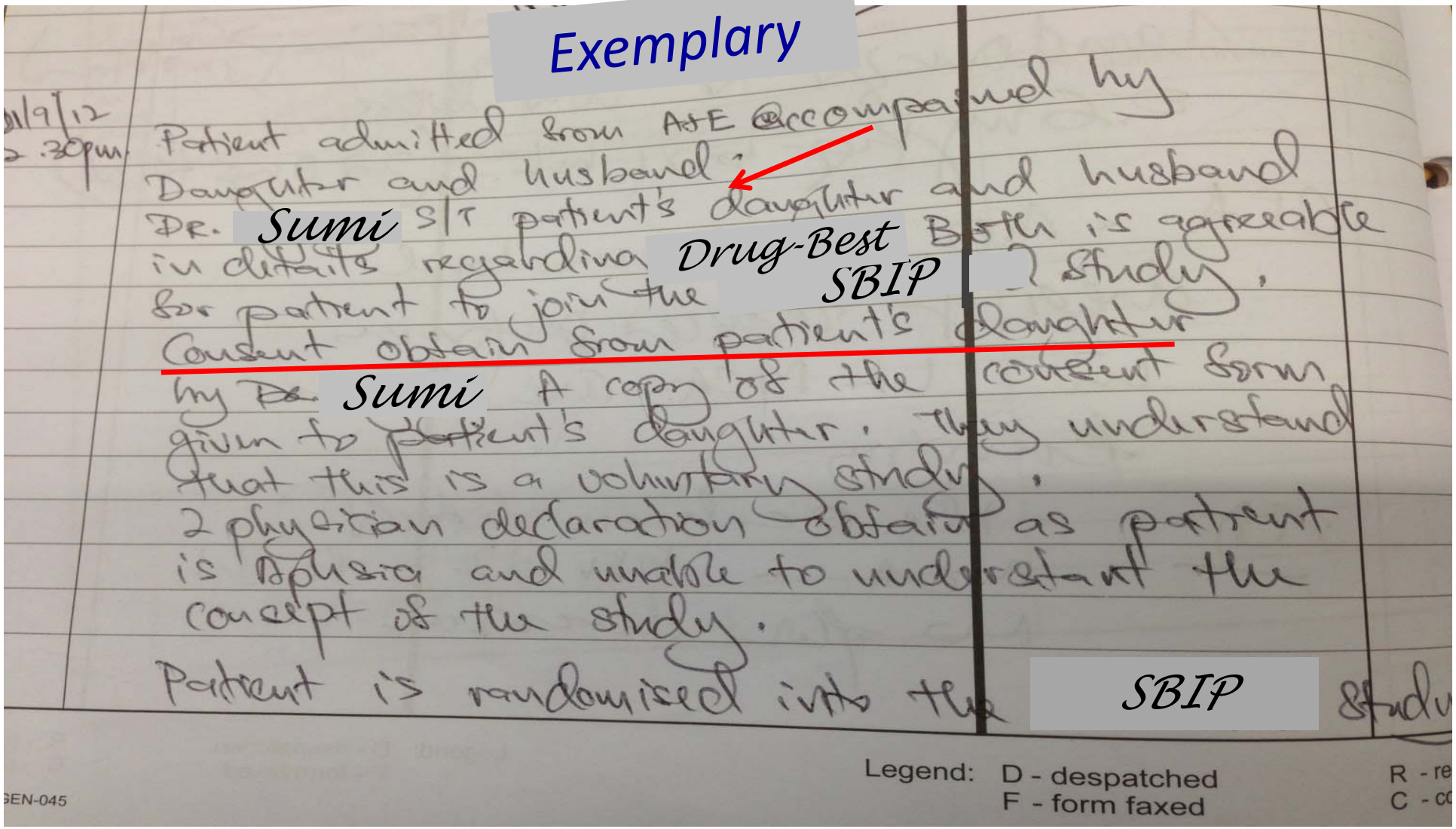
- The identity of persons who had provided substituted consent could not be verified.
  - *Medicines (Clinical Trials) Regulation 11(1-3), SGGCP 4.8.12*
    - *<u>Document relationship of person</u> providing substituted consent to subject on Informed Consent Form.*
    - *<u>Document details of informed consent process</u> in subject medical records.*

Clinical Trials in Subjects Who are Unconscious / Incapable of Exercising Rational Judgment

Documentation of Consent



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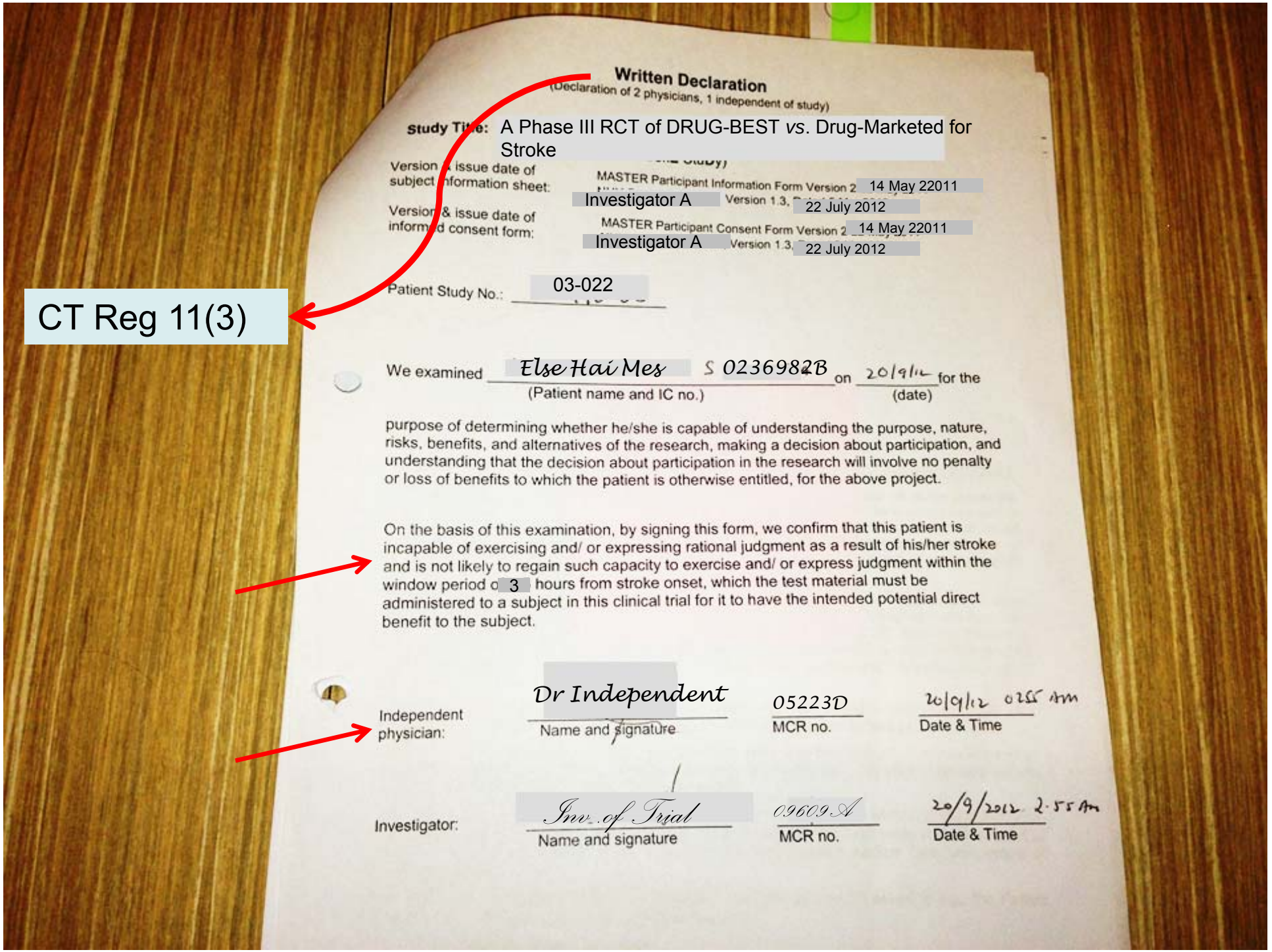
CT Reg 11(3)



Written Declaration
(Declaration of 2 physicians, 1 independent of study)

Study Title: A Phase III RCT of DRUG-BEST *vs*. Drug-Marketed for Stroke

Version & issue date of subject information sheet: MASTER Participant Information Form Version 2 14 May 22011
Investigator A Version 1.3, 22 July 2012

Version & issue date of informed consent form: MASTER Participant Consent Form Version 2 14 May 22011
Investigator A Version 1.3, 22 July 2012

Patient Study No.: 03-022

We examined Else Hai Mes S 0236982B on 20/9/12 for the
(Patient name and IC no.) (date)

purpose of determining whether he/she is capable of understanding the purpose, nature, risks, benefits, and alternatives of the research, making a decision about participation, and understanding that the decision about participation in the research will involve no penalty or loss of benefits to which the patient is otherwise entitled, for the above project.

On the basis of this examination, by signing this form, we confirm that this patient is incapable of exercising and/ or expressing rational judgment as a result of his/her stroke and is not likely to regain such capacity to exercise and/ or express judgment within the window period of 3 hours from stroke onset, which the test material must be administered to a subject in this clinical trial for it to have the intended potential direct benefit to the subject.

	Name and signature	MCR no.	Date & Time
Independent physician:	Dr Independent	05223D	20/9/12 0255 am
Investigator:	Inv. of Trial	09609A	20/9/2012 2.55 Am

Clinical Trials in Subjects Who are Unconscious / Incapable of Exercising Rational Judgment

- Documentation of timing of consent:
  - Is it required for all clinical trials?
    - *Determine how critical it is to capture the time of consent in relation to the protocol requirements.*
      - *For e.g.: If IP has to be administered within a fixed time from symptom onset, it would be recommended to capture the time of consent.*

Written Declaration

(Declaration of 2 physicians, 1 independent of study)

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INFORMED CONSENT

Sharing of Best Practices

- **Informed Consent Process:**
  - **WHO** can obtain informed consent?
  - **WHEN** should informed consent be obtained?
  - **WHICH** version of the informed consent form should be used?
  - **WHERE** should informed consent be explained?
  - **HOW** should the informed consent be explained?
    - Subjects who are illiterate in English but literate in another local language
      - *Use of translated Informed Consent Forms or Use of translator*
    - Subjects who are unable to read the Informed Consent Form
      - *Use of impartial witness*
    - Need for substituted consent?
      - *Paediatric subjects*
      - *Subjects who are unconscious*
      - *Subjects who are incapable of exercising rational judgment*

Ref: Presentation on Case Studies from GCP Inspections 2011

INFORMED CONSENT

Sharing of Best Practices

- **Informed Consent Process (cont'd):**
  - **HOW** many copies of the Informed Consent Form should be signed?
    - *Subject*
    - *Investigator Site Files*
    - *Medical Records?*
  - **HOW** should Informed Consent Process be documented?
    - *Protocol Reference*
    - *Date of informed consent*
    - *Informed Consent Process (e.g. for use of substituted consent / impartial witness / translator)*
    - *Signed copy provided to subject*

Ref: Presentation on Case Studies from GCP Inspections 2011

References

- Medicines Clinical Trials Regulations
- Singapore Guideline for Good Clinical Practice
- HSA CTB FAQs
- HSA Industry Communication
- HSA GCP Compliance Inspection Framework
- PICS Annex 13