GCP excellence in clinical trials-

the inspector's expectation

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Quality can not be guaranteed via guidelines, rules, regulation and laws

But they give

a system of criteria/standards accepted internationally

Definition GCP

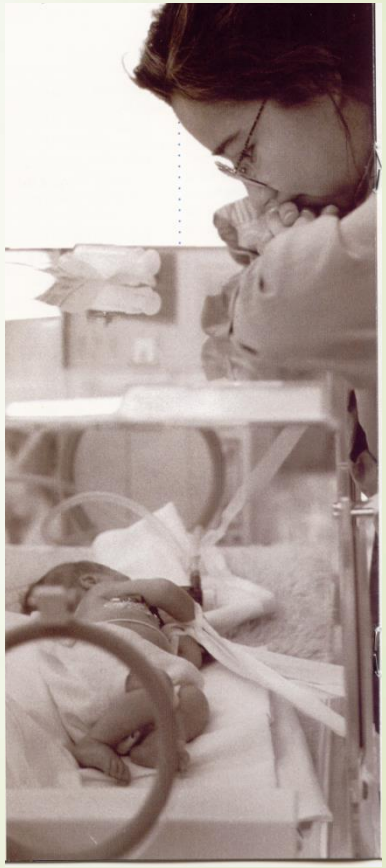
A standard for the design, conduct, performance, monitoring, auditing, recording, analyses and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity and confidentiality of trial subjects are protected.

Good Clinical Practice

A set of responsibilities

- Shared responsibilities
- Individual responsibilities

'a process that makes all parties to a study responsible for patient safety and study quality'



Regulatory framework

- Declaration of Helsinki
- CIOMS International Ethical Guidelines for Biomedical Research Involving Human Subjects
- GCP (ICH, WHO or other)

- Local laws and regulations
  - Clinical trial
  - Ethics
  - Medical care and records
  - Secrecy and confidentiality

The 13 Principles of ICH GCP

ICH GCP Guidelines (CPMP/ICH/135/95)

1. Declaration of Helsinki
2. benefits must outweighed risks
3. rights, safety, and well-being
4. non clinical and clinical information investigational should be adequate
5. scientifically sound, clear and detailed protocol
6. conducted in compliance with the protocol that has received prior IRB/IEC approval/favourable opinion

The 13 Principles of ICH GCP
ICH GCP Guidelines (CPMP/ICH/135/95)

7. the medical care and medical decisions should always be the responsibility of a qualified physician
8. study staff to be qualified
9. freely given informed consent
10. documentation recorded, handled, stored and reported accurately
11. confidentiality of records
12. GMP
13. systems of quality

Compliance with GCP standard provides public assurance that

- the rights, safety and well-being of trial subjects are protected
- the clinical trial data are credible
- laws and regulations are compiled with

Trial subject

- Declaration of Helsinki
- Ethics Committee approval
- Confidentiality
- Informed consent
- Medical care and decisions by qualified physician
- Handling of Investigational Medicinal Product

Data

- Can we rely on the credibility of the data

- Application to Regulatory Authorities for permission to start clinical trails
- Clinical Trial Report
- Application to Regulatory Authorities to obtain registration (market authorization)

Quality control is a shared responsibility

- Investigator
  - Adherence to protocol
  - Correct documentation
- Sponsor
  - manuals and instructions
  - Identified problems are followed up
  - All systems used are acceptable
- Monitor
  - verification of the conduct of the study with specific control of patient safety and integrity and the quality of the data

GCP defines the responsibilities for:

- Institutional Review Board/Independent Ethics Committee /(IRB/IEC)
- Investigator
- Sponsor

3 key elements of a Clinical study

- Delegation
  - Who's doing what in the study
- Source data
  - Where are the results documented
- Quality control
  - How is the data controlled

Investigator's responsibilities

- Resources and qualification

  time, facilities, personnel, subjects, CV

- Information to

  subjects (informed consent), IRB/IEC (approval), personnel, sponsor, authority

Investigator's responsibilities

- Handling of

  subjects, protocol (adherence), data, adverse events (serious and non-serious), IB, investigational product

- Acceptance of

  quality control and quality assurance procedures, record retention

Sponsor's responsibilities

- To investigator

  selection, IB, safety information, monitoring, medical expertise, investigational products, insurance/indemnification

- To subjects

  insurance/compensation, direct access to medical records

Sponsor's responsibilities

- To authorities

  clinical trial permission, safety reporting, clinical trial report

- Within the organisation

  SOPs, quality control and quality assurance systems, trial design, investigational product, monitoring, data handling, statistical analysis, reporting and record retention

How do you achieve quality in clinical trials?

- Quality is fundamental when conducting clinical trials

but

Quantity is not equal to Quality

Is quality a problem?

- 20 % of all applications for clinical trials are not valid, e.g. do not contain all requested documentation.
- Inspections of 100 Bioequivalance studies resulted in rejection of MAA in 50 studies (25 due to fraudulent data).
- EMA inspections of MAA for centralised procedure lead to withdrawal or rejection in 15-20 % of the applications.

Risk Based Quality management

Purpose of risk assessment - facilitate the development of a more:

- systematic,
- prioritised,
- risk-based approach to quality management of clinical trials,
- to support the principles of GCP and to complement existing quality practices, requirements and standards.

Problem can be summarised:

- current practices are not proportionate
- nor well adapted to achieving the desired goals
- generally very costly,
- resulting either in success at an unnecessarily high cost or failure which is also very costly.

The origins of the problem are multifactorial.

Risk based approach to clinical trials

- What are the risks?
  - To trial participants'
    - Rights
    - Safety
    - Integrity
  - To data quality, and hence robustness of future decision making based on that data
    - Next protocol, continued development or not
    - Marketing authorisation CSR, database
    - Medical practice, treatment strategies and guidelines

Risk based quality management

- How do we evaluate the appropriateness of risk based monitoring?
  - What level of risk to the patient do we accept?
  - What level of risk to data quality do we accept?
  - What level of "mistakes" do we accept?
  - What level of quality do we request?

Quality control

It's not just about on-site monitoring

– Protocol and Case Report Form design

– Investigator training and communication

- Centralized data review and evaluation

– Sponsor oversight of monitoring delegated to a CRO

– Site Selection

Clinical

- The protocols of all clinical studies, finished or ongoing, should be reviewed with regard to design, statistical power and endpoints.

  Were the studies adequately designed to achieve the intended goal?

  Were the endpoints appropriate?

  Were endpoints discussed with regulatory authorities?

  Has the indication been identified which may facilitate the fastest way to approval?

  Did the studies have adequate quality to achieve trustworthy results?

Risk based quality management

- A systematic process in order to:

  - Identify and asses risks
  - Control/ prevent the risks – up a plan
  - Communicate the plan and work according to the plan
  - Continuous review in order to assess if the risks have changed

Risk assessment

- What can go wrong?
- What is the likelihood that something will go wrong?
- Will we discover if anything goes wrong?
- What would the consequences be for
  - Patient integrity and safety?
  - Reliability of the data?

- Focus on risks with great possibility and great consequences.

Outcome of risk assessment

- Reduced
  - Limited SDV
- Targeted
  - Emphasis on relevant data
- Triggered
  - Identification of risk indikators

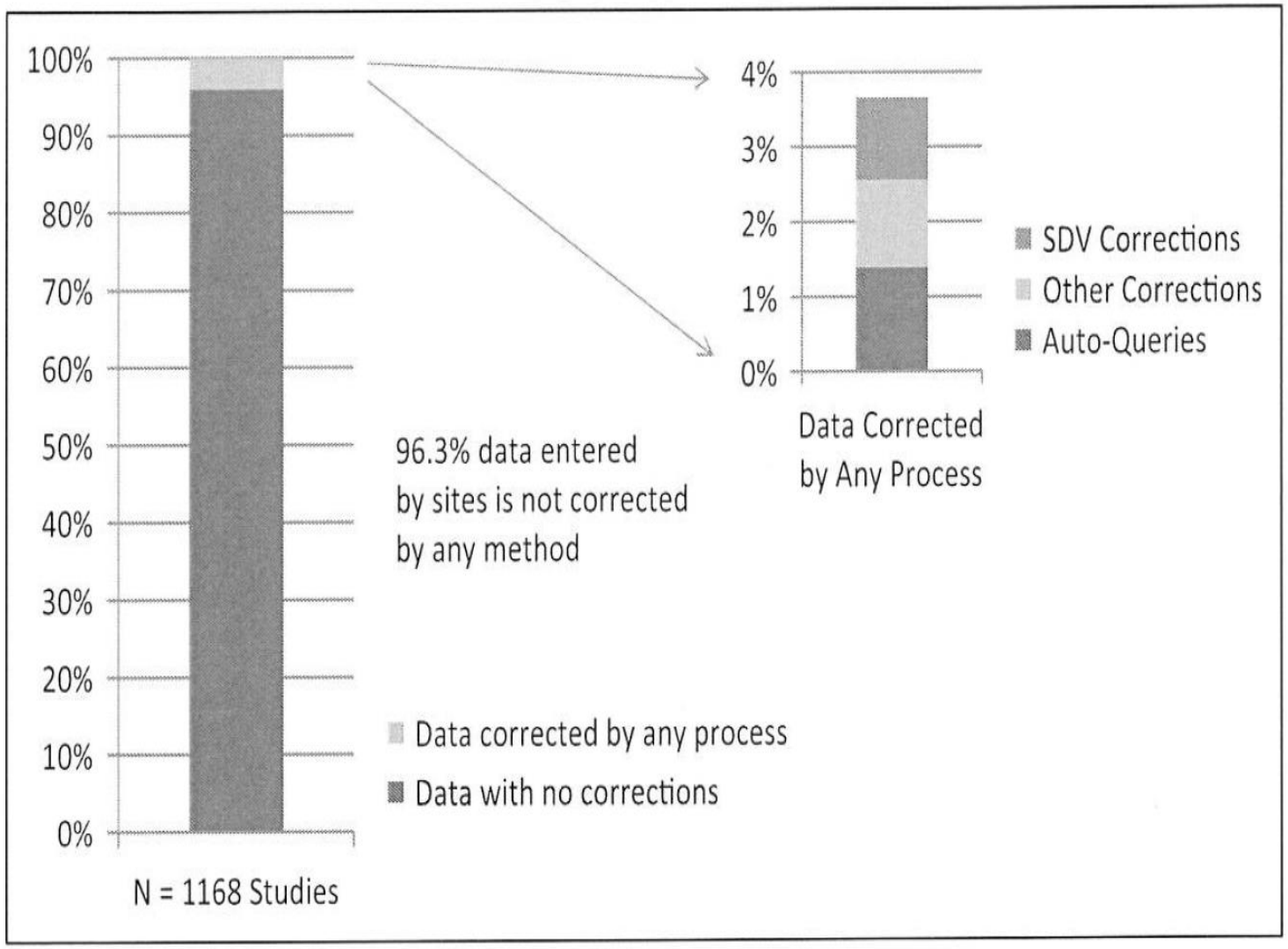
And remember

Quantity can never replace quality

Work smarter – not harder

Evaluating Source Data Verification as a Quality control measure in clinical trials

- Therapeutic Innovation & Regulatory Science 2014. Vol 48(6) 671-681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SDV Corrections
Other Corrections
Auto-Queries

Risk based quality management

- Purpose of good quality within Clinical Research: Collection of data to generate information to support decision making.
- The quality of collected data should be of sufficient quality to allow a correct basis for decision making.

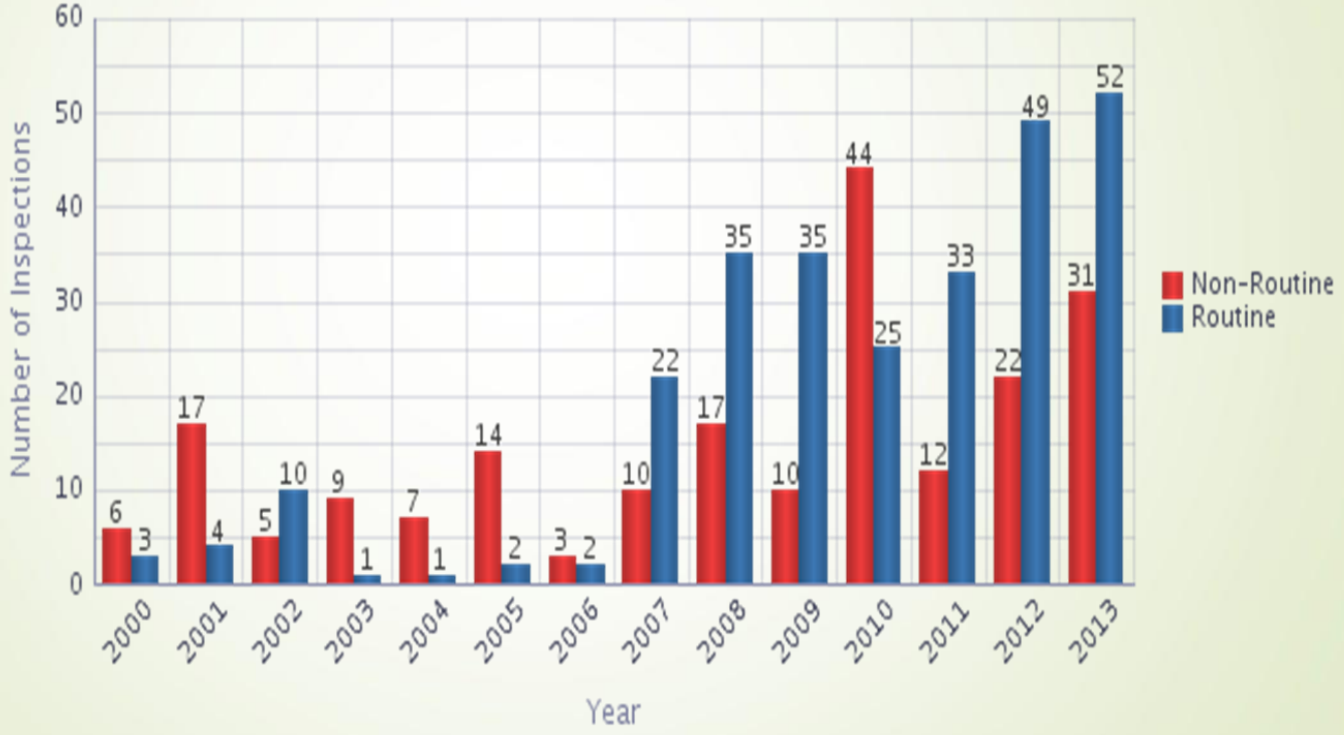
Risk based quality management

- What is acceptable quality?
  - The rights, safety and integrity is not compromised in any way so it does affect the patient
  - The decision would be the same if the data quality was perfect

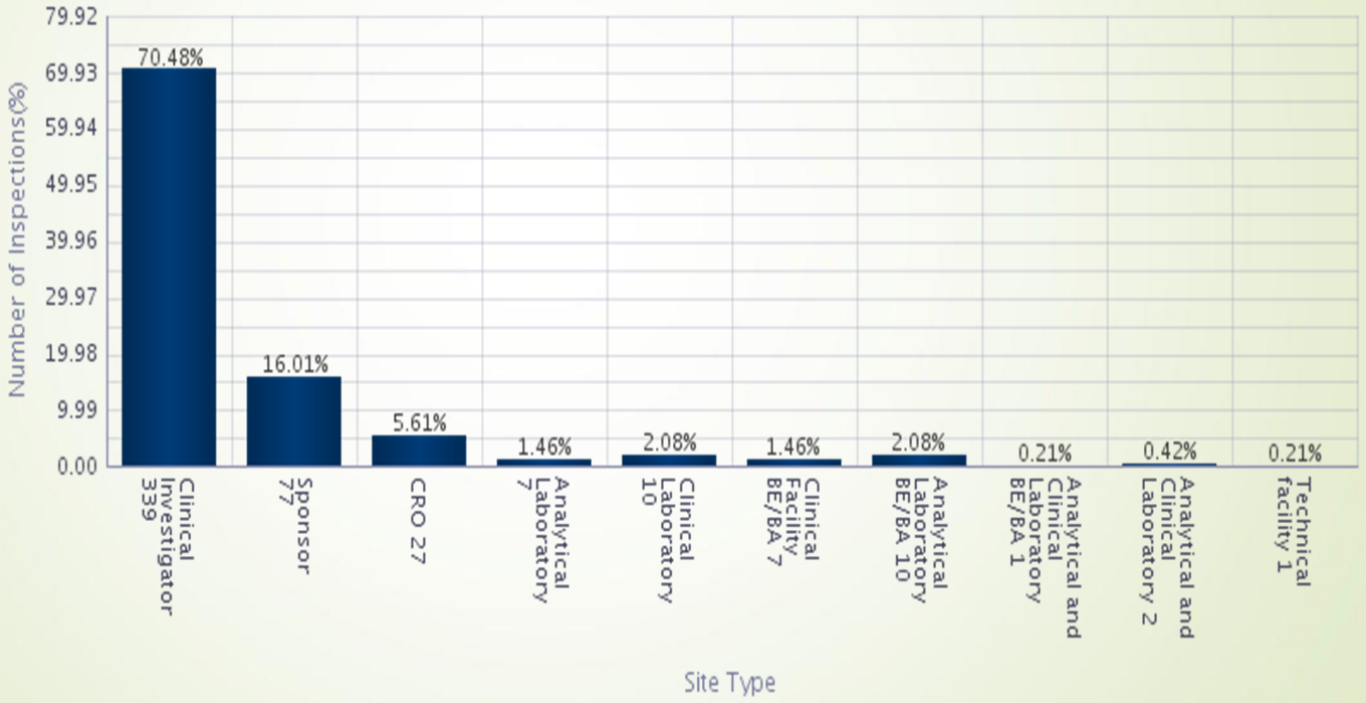
Remember:

- Quality must be build into the process from the start.
- The protocol and monitoring manual are two important documents in order to ensure quality of the clinical trial already from the planning phase.
- Quality can not be achieved by auditing or inspection afterwards.

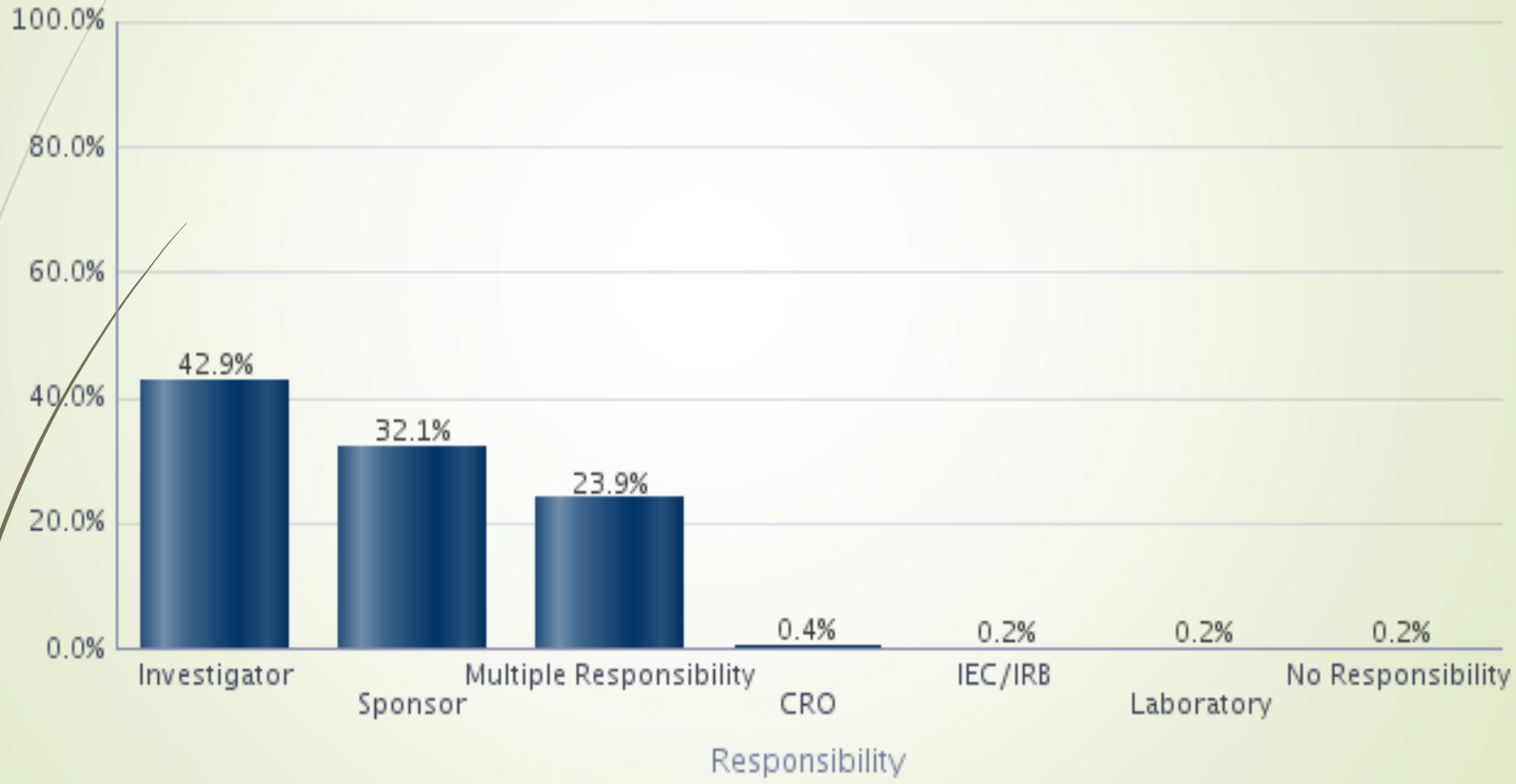
Number of EMA conducted inspections by type of inspection and year, 2000-2013



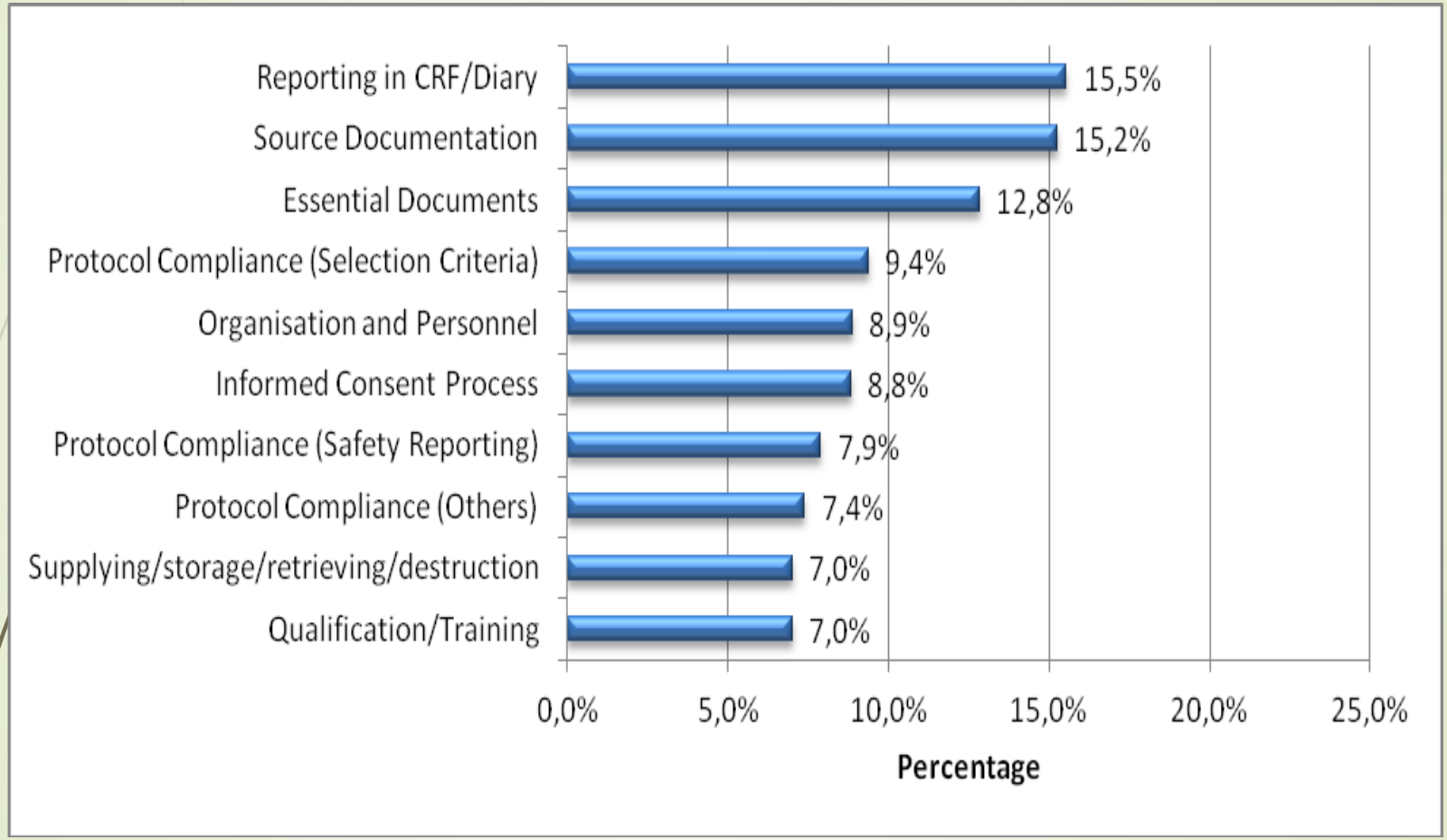
Number of EMA conducted inspections by type of inspection site, 2000-2013



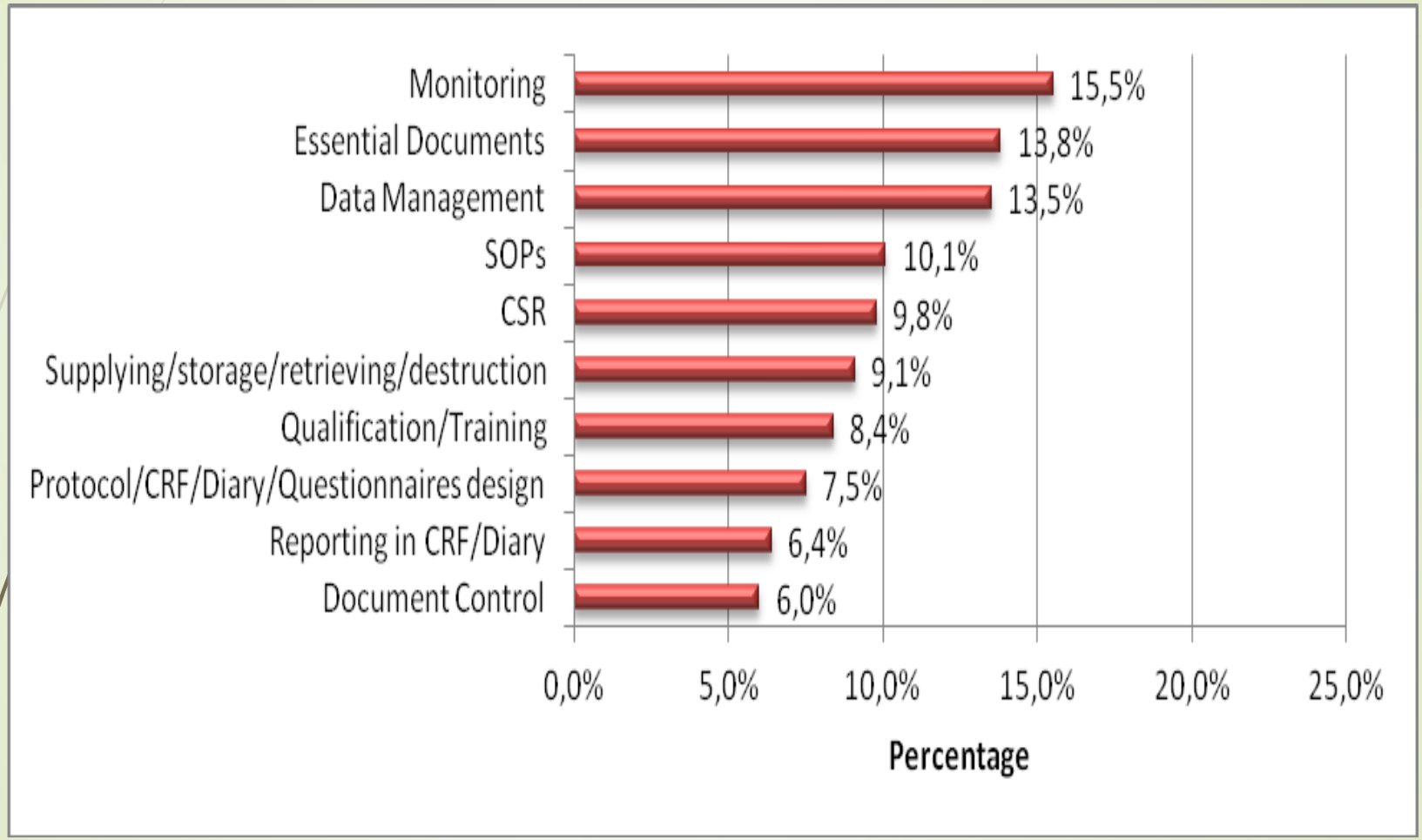
Responsibility of the findings related to the investigator site



Investigator responsibility by category of the total findings



Sponsor responsibility by category of total findings



Ranking of the top 10 critical GCP findings

Finding Sub Category Name	N	% *	% **
Monitoring	49	9.2%	0.9%
Data Management	48	9.0%	0.8%
CSR	47	8.8%	0.8%
Protocol Compliance (Selection Criteria)	33	6.2%	0.6%
Source Documentation	32	6.0%	0.6%
Protocol Compliance (Assessment of Efficacy)	23	4.3%	0.4%
Protocol/CRF/Diary/ Questionnaires design	21	3.9%	0.4%
IMP Accountability	20	3.8%	0.4%
Protocol Compliance (Safety Reporting)	19	3.6%	0.3%
Prescription/Administration /Compliance	18	3.4%	0.3%
Reporting in CRF/Diary	18	3.4%	0.3%
Total	328	61.6%	5.8%
Grand Total	532	100%	9.4%

Common findings

Legal and administrative documents

Contacts with regulatory authority and ethics committee (IEC/IRB):

- Change of investigator not reported
- Annual safety report not submitted
- Protocol amendments not submitted (non-approved version or unsigned version used)

Informed consent procedure

- Informed consent has been obtained after the start of the trial
- The wrong version has been used
- Trial staff have dated the form on behalf of the patient
- Informed consent has been taken by non-trial staff
- Amended informed consents have been introduced late
- A copy of ICF has not been given to participant

Common findings

Organisation and personnel

- Delegation log incomplete
- The tasks assigned are not in accordance with the actual conduct of the trial
- Previous experience in clinical trials is not mentioned
- No records of GCP/study specific training for the trial staff is available

IMP handling

- IMP handling is incorrect
- IMP accountability is incomplete; delivered and returned IMP do not match
- IMP inventory is missing
- IMP is incorrectly stored
- The IMP storage area is not secure
- The temperature log is missing or not followed-up
- Breaking of the treatment code can only be done via the sponsor

Common findings

Adverse Event reporting

- The time lines for reporting Serious Adverse Events (SAE) have not been complied with
- The SAE reports are incomplete e.g. date missing
- SAE follow-up reports are missing

Essential documents

- Essential documents incomplete
- The lists and logs are incomplete
- They contain irrelevant information or are missing required information
- Organisation and content of the investigator file difficult to assess
- Archiving facilities not appropriate and retention period not decided

Case Report Form (CRF)

- Not always accurately filled in
- Many corrections done
- Not filled in in a timely manner

Common findings

Conduct of the trial

- Deviations from the protocol
- Patients who do not fulfil the eligibility criteria have been included in the trial
- Patient visits are outside the window defined in the protocol
- The sponsor prospectively approves deviations from the protocol
- Amendments not handled correctly
- Protocol amendments have been introduced too early or too late

Source data

- Location of source data unknown
- Location of source data document missing
- Hospital records incomplete
- Not all visits have been recorded
- Confirmation of subject eligibility by investigator missing
- Inconsistencies between source data and data recorded in the CRF

Common findings

Monitoring

- Initiation visit missing or done too early. Sometimes the investigators' meeting replaces the site initiation visit
- The trial is inadequately monitored
- The monitoring plan is not being followed
- Identified issues are not being followed up
- Obvious mistakes have not been identified
- The monitor only conducts source date verification during the visits
- The monitoring reports are inadequate and not informative
- Not all available documentation is being verified by the monitor