Safeguarding public health

MHRA

GCP INSPECTORATE

GCP INSPECTIONS METRICS REPORT

METRICS PERIOD: 1st April 2007 to 31st March 2008

DATE OF ISSUE: 22nd October 2009*

MHRA
Central Region Medicines Inspectorate
2 Falcon Way, Shire Park
Welwyn Garden City
Herts AL7 1TW
Telephone: 01707 299130 Fax: 01707 376649

MHRA
2a Hunter House, 57 Goodramgate
York, YO1 1FX
Telephone: 01904 610556 Fax: 01904 625430

Head Office:
Inspection & Standards Division,
Market Towers, 1 Nine Elms Lane,
Vauxhall, London, SW8 5NQ
Tel: 020 7084 2606 Fax: 020 7084 3519

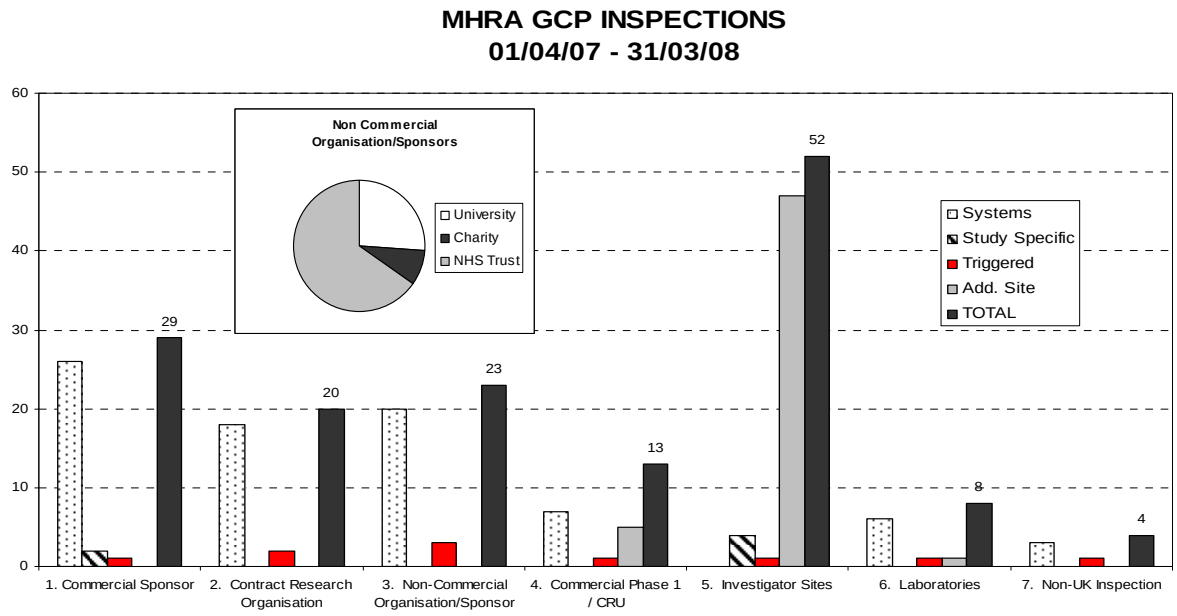
***To correct typo in section 3.2 of Version 24th June 2009 [(20%) to (10%)]**

1. INTRODUCTION

This is the first report of GCP Inspection Metrics since the introduction of Statutory GCP Inspection on 1st May 2004, however, some metrics have been presented at MHRA GCP Inspection seminars in the past. It is the intention of the GCP Inspectorate to issue annual metric reports. This report covers the metrics period 1st April 2007 to 31st March 2008.

2. GCP INSPECTIONS UNDERTAKEN

During the Metrics Period a total of 149 GCP Inspections were undertaken by the MHRA GCP Inspectorate. The types of inspections are below. For the 23 non-commercial sponsor inspections, 6 were of Universities, 15 were of NHS Trusts and 2 were of charitable organisations. The predominant type of inspection was that of investigator sites, due to them being associated with inspections of other commercial sponsors and contract research organisations. Triggered inspections were carried out as a result of information received by the GCP Inspectorate, for example a serious breach report, and several of these were undertaken.



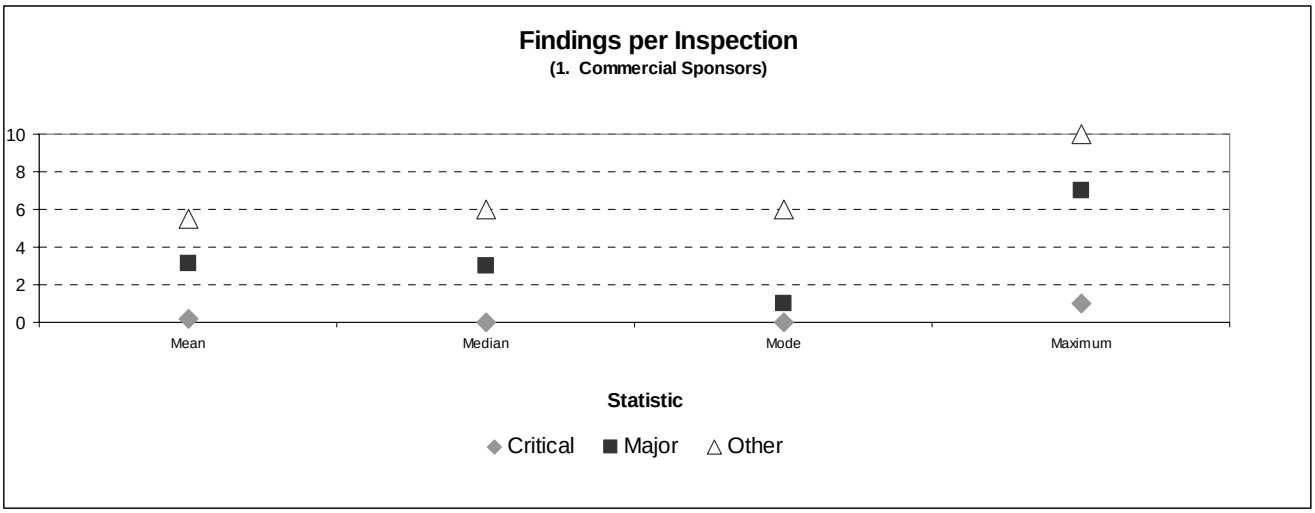
3. INSPECTION REPORTS AND FINDINGS

Reports relating only to the inspections carried out in the Metrics Period were reviewed and it is important to note that multiple inspections can reported in one GCP Inspection Report, for example, a commercial sponsor GCP Inspection Report may consist of the sponsor inspection and associated investigator site inspections. Where an inspection was conducted before 1st April 2007 and the other associated inspections were conducted after 1st April 2007 (e.g. sponsor site then the investigator site(s)) the findings from the inspections conducted after 1st April 2007 (e.g. investigator site(s)) will be included in this metrics report, as these were inspections conducted during this Metrics Period. The findings reported in this document cover UK site inspections only. The presentation of inspection findings are from all inspections conducted during the Metrics Period and that have been formally issued in a GCP Inspection Report. The metrics data entry had an independent QC check.

3.1 Commercial Sponsors (Routine Systems & Study Specific and Triggered)

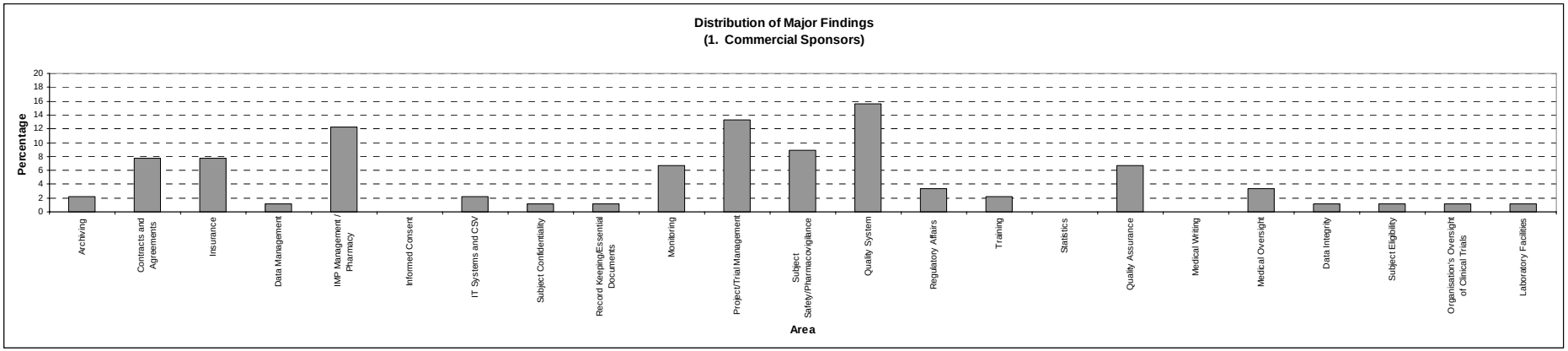
A total of 29 commercial sponsors were inspected and 29 have been reported.

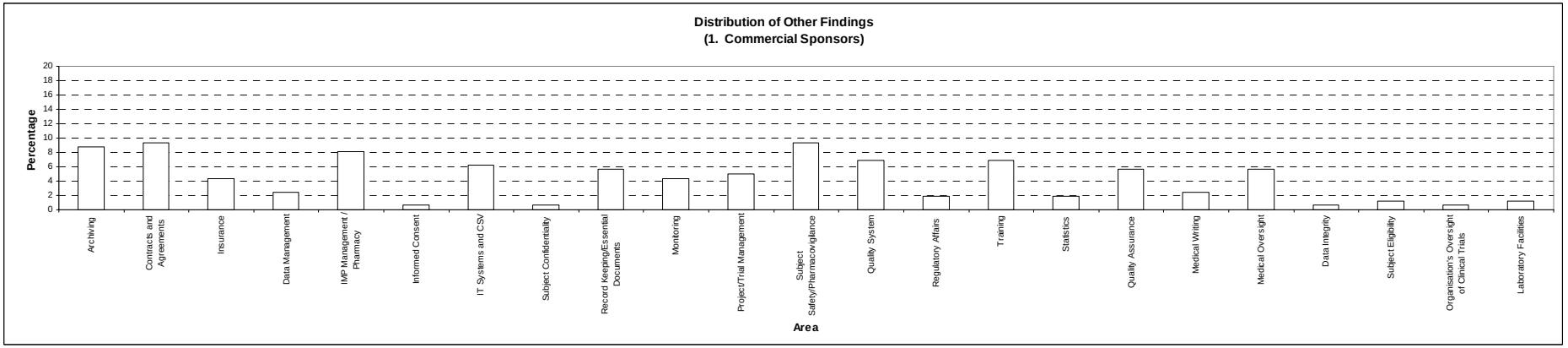
Of the 29 inspections, 5 (17%) had at least one critical finding and 28 (97%) had at least one major and/or critical finding. The number of findings per inspection is represented on the figure below.

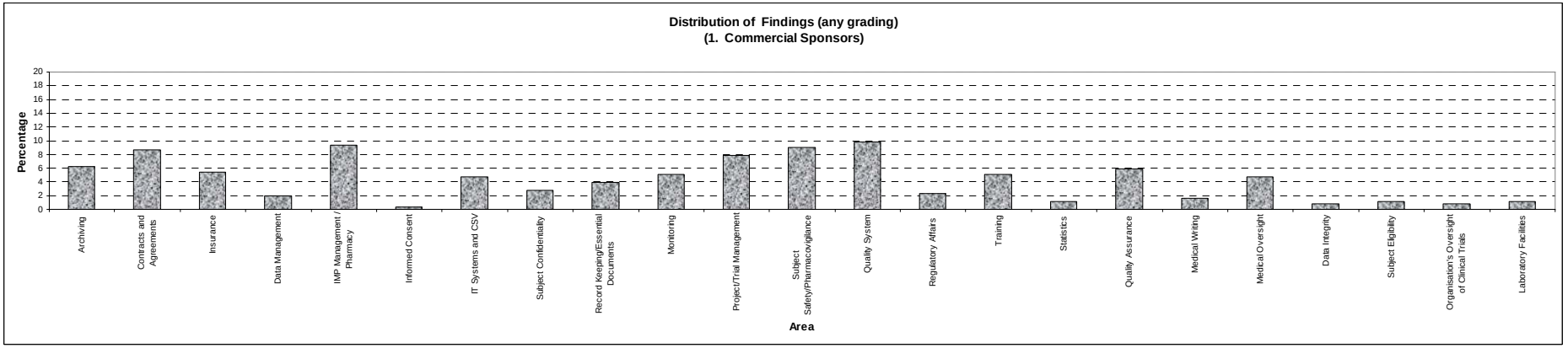


There were 5 critical findings from 5 separate organisations concerning breaches of subject confidentiality. This related to documentation identifying trial subjects being located at the sponsor site without explicit trial subject consent.

The figures on the following page show the distribution of Major, Other and any grade of inspection findings. This identifies the areas where GCP inspectors have been making observations of non-compliance with GCP.


Distribution of Major Findings
(1. Commercial Sponsors)
Percentage
0
2
4
6
8
10
12
14
16
18
20
Archiving
Contracts and Agreements
Insurance
Data Management
IMP Management / Pharmacy
Informed Consent
IT Systems and CSV
Subject Confidentiality
Record Keeping/Essential Documents
Monitoring
Project/Trial Management
Subject Safety/Pharmacovigilance
Quality System
Regulatory Affairs
Training
Statistics
Quality Assurance
Medical Writing
Medical Oversight
Data Integrity
Subject Eligibility
Organisation's Oversight of Clinical Trials
Laboratory Facilities
Area

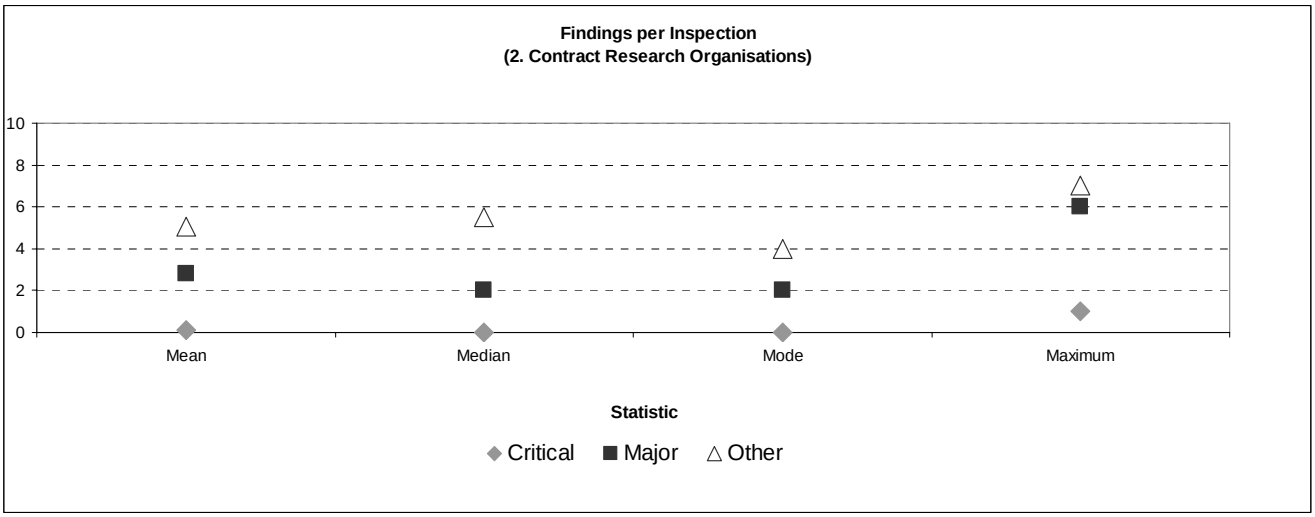

Distribution of Other Findings
(1. Commercial Sponsors)
Percentage
0
2
4
6
8
10
12
14
16
18
20
Archiving
Contracts and Agreements
Insurance
Data Management
IMP Management / Pharmacy
Informed Consent
IT Systems and CSV
Subject Confidentiality
Record Keeping/Essential Documents
Monitoring
Project/Trial Management
Subject Safety/Pharmacovigilance
Quality System
Regulatory Affairs
Training
Statistics
Quality Assurance
Medical Writing
Medical Oversight
Data Integrity
Subject Eligibility
Organisation's Oversight of Clinical Trials
Laboratory Facilities
Area


Distribution of Findings (any grading)
(1. Commercial Sponsors)
Percentage
0
2
4
6
8
10
12
14
16
18
20
Archiving
Contracts and Agreements
Insurance
Data Management
IMP Management / Pharmacy
Informed Consent
IT Systems and CSV
Subject Confidentiality
Record Keeping/Essential Documents
Monitoring
Project/Trial Management
Subject Safety/Pharmacovigilance
Quality System
Regulatory Affairs
Training
Statistics
Quality Assurance
Medical Writing
Medical Oversight
Data Integrity
Subject Eligibility
Organisation's Oversight of Clinical Trials
Laboratory Facilities
Area

3.2 Contract Research Organisations (CRO) (Routine Systems and Triggered)

A total of 20 Contract Research Organisations were inspected and 20 have been reported.

Of the 20 inspections, 2 (10%) had at least one critical finding and 19 (95%) had at least one major and/or critical finding. The number of findings per inspection is represented on the figure below.

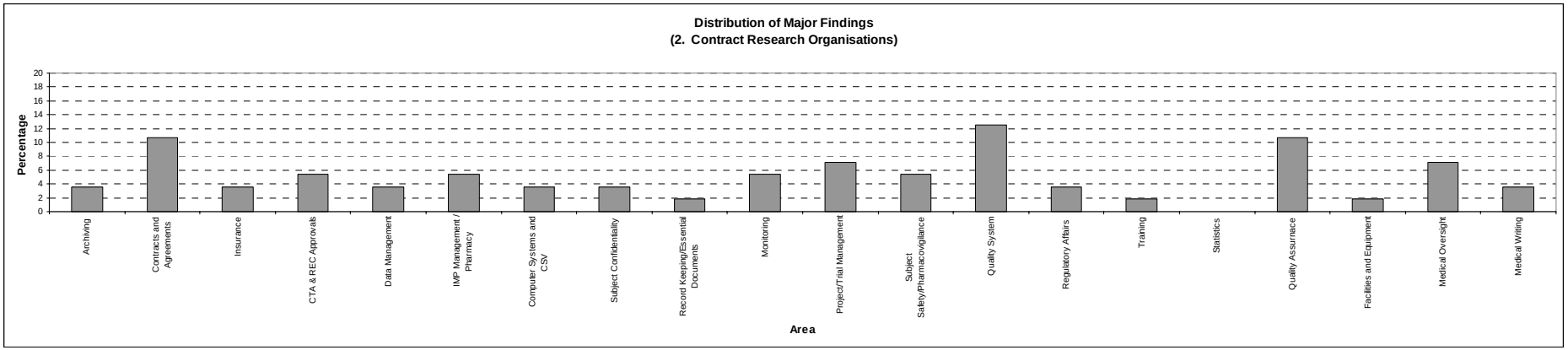


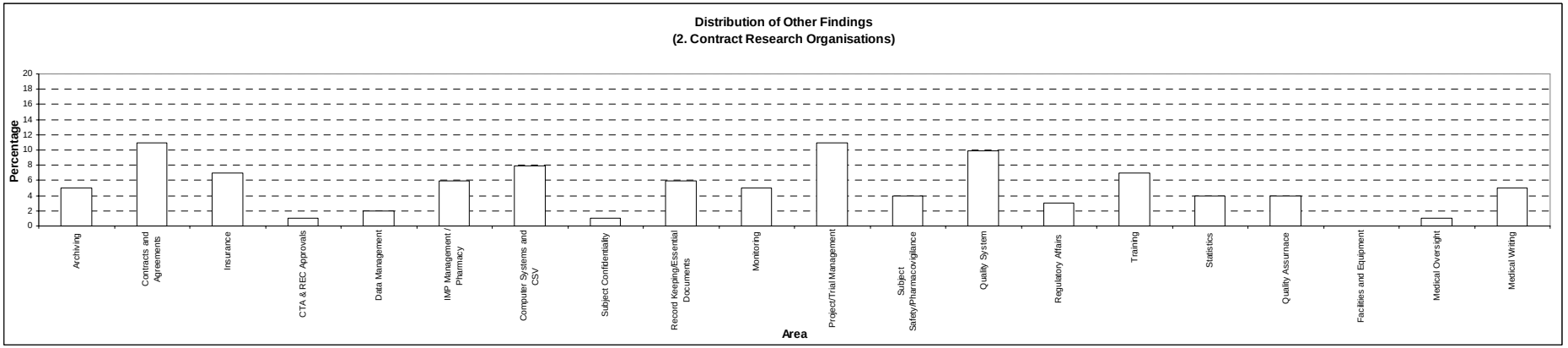
There were 2 critical findings from 2 CRO organisations of this type:

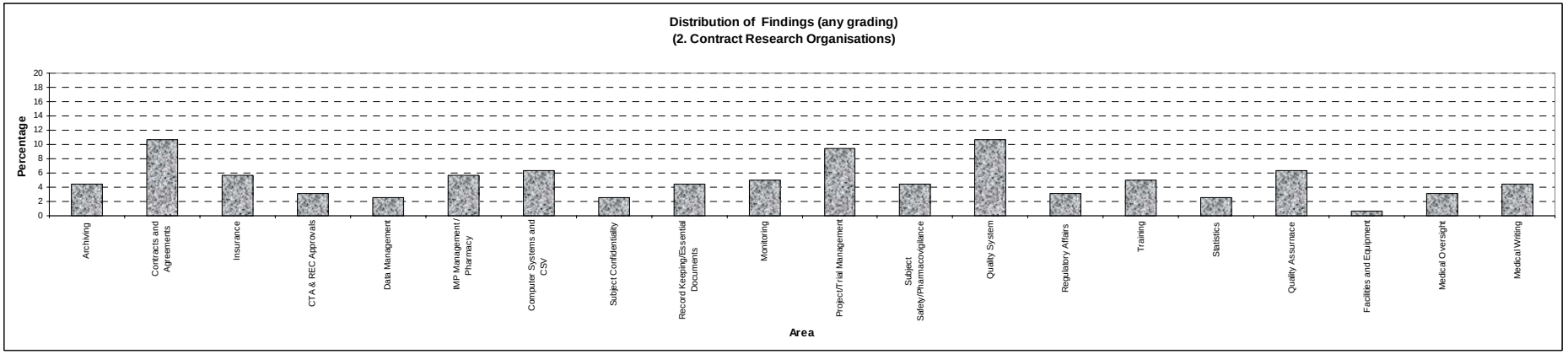
- There was one critical finding from one organisation for subject confidentiality, as documentation that identified trial subjects was at the CRO without explicit subject consent.

- There was one critical finding from one organisation concerning CTA/REC approvals, where the organisation had failed to respond to conditions on the MHRA approval letter regarding provision of stability data of the IMP, therefore the approval was not valid.

The figures on the following page show the distribution of Major, Other and any grade of inspection findings. This identifies the areas where GCP inspectors have been making observations of non-compliance with GCP.


Distribution of Major Findings
(2. Contract Research Organisations)
Percentage
0
2
4
6
8
10
12
14
16
18
20
Archiving
Contracts and Agreements
Insurance
CTA & REC Approvals
Data Management
IMP Management / Pharmacy
Computer Systems and CSV
Subject Confidentiality
Record Keeping/Essential Documents
Monitoring
Project/Trial Management
Subject Safety/Pharmacovigilance
Quality System
Regulatory Affairs
Training
Statistics
Quality Assurance
Facilities and Equipment
Medical Oversight
Medical Writing
Area

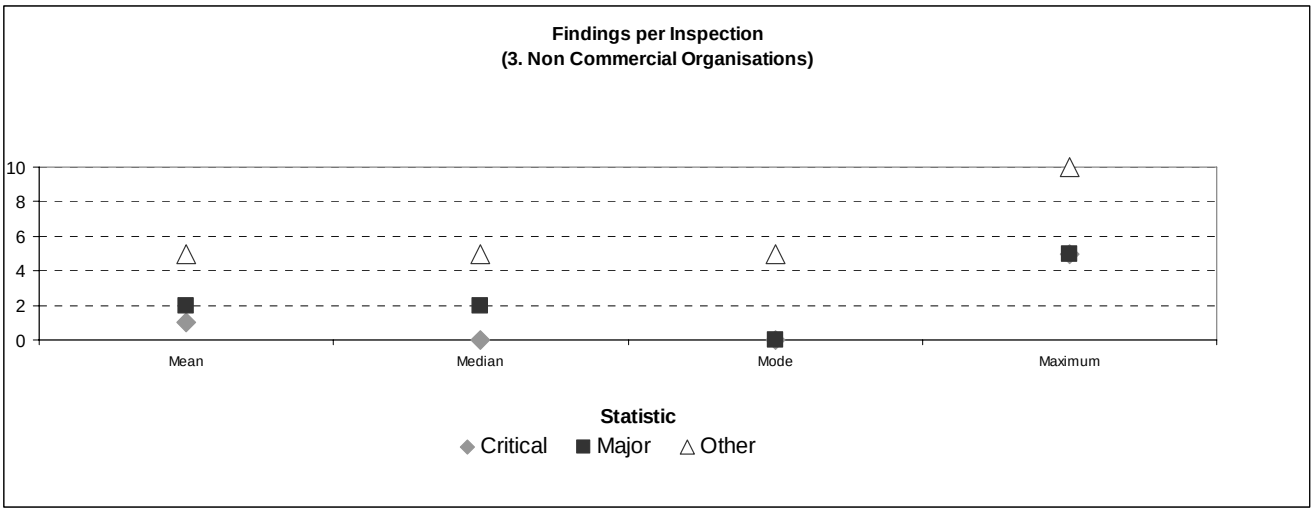

Distribution of Other Findings
(2. Contract Research Organisations)
Percentage
0
2
4
6
8
10
12
14
16
18
20
Archiving
Contracts and Agreements
Insurance
CTA & REC Approvals
Data Management
IMP Management / Pharmacy
Computer Systems and CSV
Subject Confidentiality
Record Keeping/Essential Documents
Monitoring
Project/Trial Management
Subject Safety/Pharmacovigilance
Quality System
Regulatory Affairs
Training
Statistics
Quality Assurance
Facilities and Equipment
Medical Oversight
Medical Writing
Area


Distribution of Findings (any grading)
(2. Contract Research Organisations)
Percentage
0
2
4
6
8
10
12
14
16
18
20
Archiving
Contracts and Agreements
Insurance
CTA & REC Approvals
Data Management
IMP Management/ Pharmacy
Computer Systems and CSV
Subject Confidentiality
Record Keeping/Essential Documents
Monitoring
Project/Trial Management
Subject Safety/Pharmacovigilance
Quality System
Regulatory Affairs
Training
Statistics
Quality Assurance
Facilities and Equipment
Medical Oversight
Medical Writing
Area

3.3 Non Commercial Organisations (Routine Systems and Triggered)

A total of 23 Non Commercial Organisations were inspected. Fifteen were NHS Trusts, 6 were Universities and 2 were Charities. All have been reported.

Of the 23 inspections, 11 (48%) had at least one critical finding and 18 (78%) had at least one major and/or critical finding. The number of findings per inspection is represented on the figure below.



A total of 24 critical findings were identified from 11 organisations inspected. Two organisations (a Trust and a University) had 5 critical findings each, the remaining 9 organisations had 1 or 2 critical findings including one where a critical finding was identified for another (non inspected) non-commercial sponsor during the inspection of the hosting non-commercial sponsor.

A common critical finding consisted of IMP management/pharmacy and a total of 7critical findings were given to 7 organisations for this. Typically one or more of the following observations were made.

- Evidence that formal procedure/systems were not in place or weak:
- Regulatory Green Light, in particular for multicentre trials, but own trials also affected.
- Lack of/inadequate QP Certification.
- Importation and Manufacturing IMP without the appropriate Licence from Competent Authority
- Systems to ensure pharmacy involvement/knowledge of trials being undertaken to ensure legislation met, input into CTA submission and review/receipt of protocol amendments to ensure accurate information about IMP is supplied to MHRA/REC.
- Use of expired/recalled/non GMP manufactured IMP
- Poor/ineffective blinding system
- Poor accountability of IMP
- Lack of agreements with IMP suppliers
- Uncontrolled site to site transfer

A further common critical finding was for an organisation's oversight of clinical trials, and a total of 6 critical findings were given to 6 organisations for this. Typically one or more of the following observations were made.

- Lack of systems to appropriate identify trials that fall under the legislation
- Poorly documented/incorrect sponsorship/Legal Representative arrangements

- Lack of R&D approval
- Failure of R&D systems to ensure awareness of all clinical trials
- Approval & oversight of subcontractors
- Failure to obtain MHRA and REC approvals at all and also for substantial amendments, including one trial conducted that had received a grounds for non-acceptance letter from the MHRA.
- Failure to address remarks/conditions on the CTA issued by MHRA
- Failure to issue End of Trial notifications.
- Little or no oversight of pharmacovigilance requirements when delegated to the principal investigator
- Ensuring staff were trained in GCP/Legislation
- Failure to report serious breaches of trial protocol/GCP to MHRA.

A critical finding was given to one organisation for trial conduct as there was failure to adequately document the trial activities, making it impossible to verify subjects screened, consented and randomized; data recording was poor, there was failure to retain the necessary essential documents and failure to comply with legislative pharmacovigilance requirements.

Do to extensive non-compliance, illustrated by numerous critical & major findings and breaches of legislation, a critical finding for failure to comply with Protocol/GCP compliance was given to 2 organisations.

Breaches of subject confidentiality were given as a critical finding to 2 sponsor organisations, in these cases, Universities, as they had received information that identified subjects without explicit consent from the trial subjects.

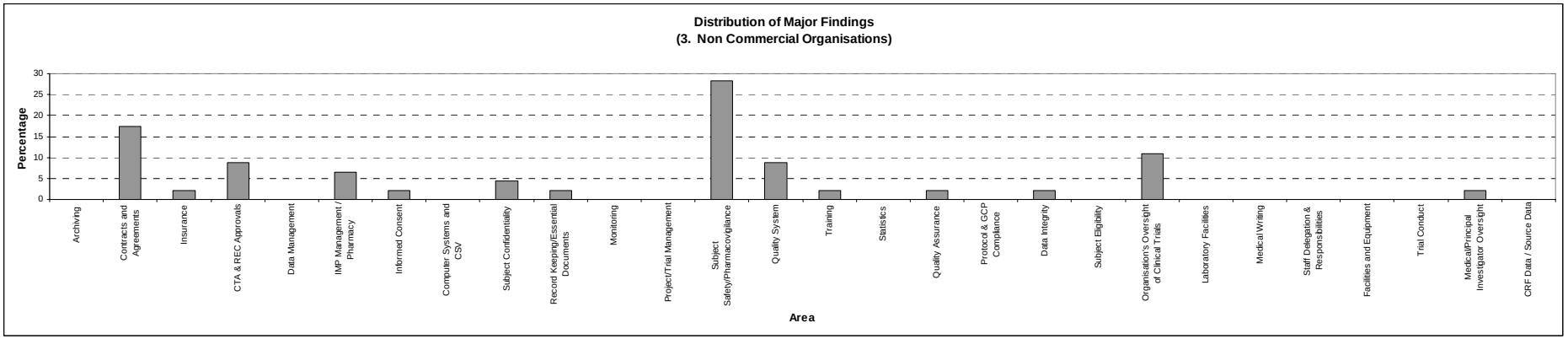
Whilst subject safety/pharmacovigilance was often a major finding at non-commercial inspections (see next section), there were two organisations that were given a critical finding for this. These had one or more of the following observations.

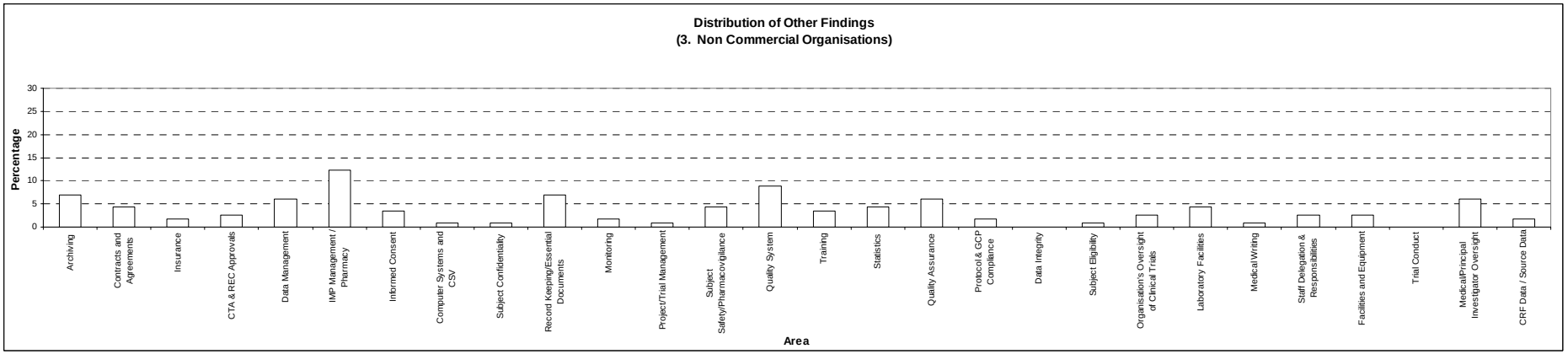
- Lack of/ineffective systems to comply with part 5 of the legislation
- Failure to report SUSARS
- Incorrect/outdated reference document for expectedness assessment
- Failure to submit Annual Safety Reports
- Robust documentation, data basing and follow up of SAEs

A critical finding was issued for training at one organisation for complete ignorance of legislative requirements/GCP whilst conducting a trial in the UK.

A critical finding was given specifically for CTA/REC approval to 3 organisations that were conducting trials without necessary approvals.

The figures on the following page show the distribution of Major, Other and any grade of inspection findings. This identifies the areas where GCP inspectors have been making observations of non-compliance with GCP.


Distribution of Major Findings
(3. Non Commercial Organisations)
Percentage
0
5
10
15
20
25
30
Archiving
Contracts and Agreements
Insurance
CTA & REC Approvals
Data Management
IMP Management / Pharmacy
Informed Consent
Computer Systems and CSV
Subject Confidentiality
Record Keeping/Essential Documents
Monitoring
Project/Trial Management
Subject Safety/Pharmacovigilance
Quality System
Training
Statistics
Quality Assurance
Protocol & GCP Compliance
Data Integrity
Subject Eligibility
Organisation's Oversight of Clinical Trials
Laboratory Facilities
Medical Writing
Staff Delegation & Responsibilities
Facilities and Equipment
Trial Conduct
Medical/Principal Investigator Oversight
CRF Data / Source Data
Area


Distribution of Other Findings
(3. Non Commercial Organisations)
Percentage
0
5
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25
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Archiving
Contracts and Agreements
Insurance
CTA & REC Approvals
Data Management
IMP Management / Pharmacy
Informed Consent
Computer Systems and CSV
Subject Confidentiality
Record Keeping/Essential Documents
Monitoring
Project/Trial Management
Subject Safety/Pharmacovigilance
Quality System
Training
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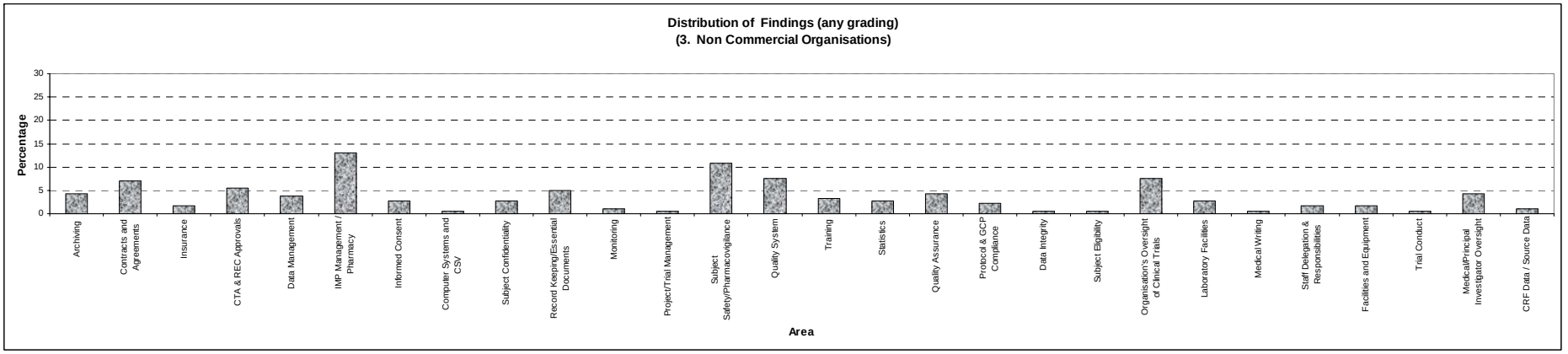
Quality Assurance
Protocol & GCP Compliance
Data Integrity
Subject Eligibility
Organisation's Oversight of Clinical Trials
Laboratory Facilities
Medical Writing
Staff Delegation & Responsibilities
Facilities and Equipment
Trial Conduct
Medical/Principal Investigator Oversight
CRF Data / Source Data
Area


Distribution of Findings (any grading)
(3. Non Commercial Organisations)
Percentage
0
5
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25
30
Archiving
Contracts and Agreements
Insurance
CTA & REC Approvals
Data Management
IMP Management / Pharmacy
Informed Consent
Computer Systems and CSV
Subject Confidentiality
Record Keeping/Essential Documents
Monitoring
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Subject Safety/Pharmacovigilance
Quality System
Training
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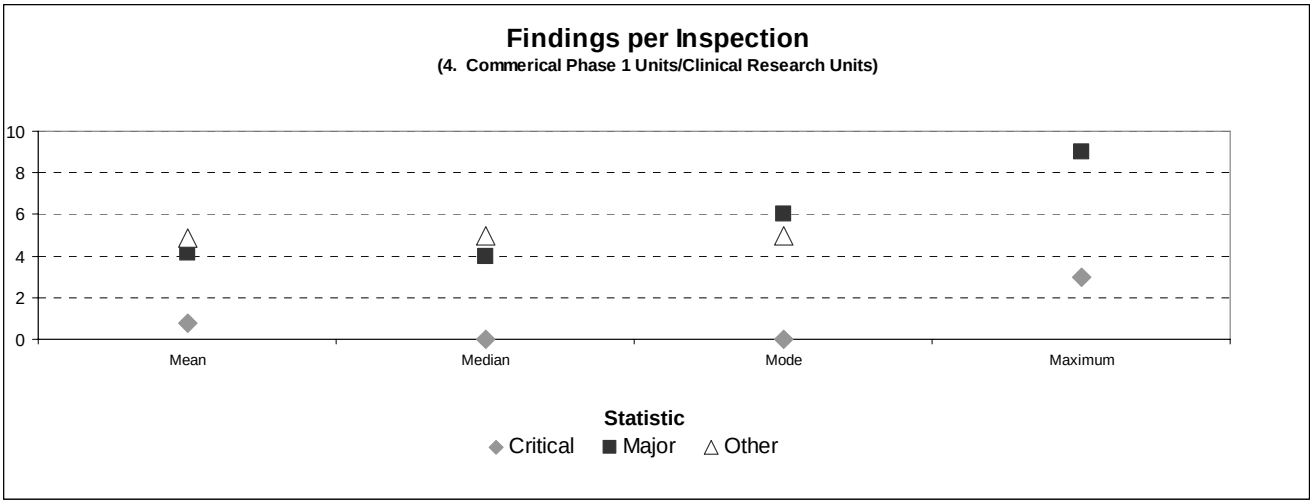
Quality Assurance
Protocol & GCP Compliance
Data Integrity
Subject Eligibility
Organisation's Oversight of Clinical Trials
Laboratory Facilities
Medical Writing
Staff Delegation & Responsibilities
Facilities and Equipment
Trial Conduct
Medical/Principal Investigator Oversight
CRF Data / Source Data
Area

3.4 Commercial Phase 1 Units/Clinical Research Units

A total of 13 Commercial Phase 1 Units/Clinical Research Units were inspected and 8 have been reported as individual inspections, whereas 5 were an associated investigator site inspection and reported in the sponsor/CRO main inspection. All of the 8 inspections with their independent report have been reported.

Of the 13 inspections, 6 (46%) had at least one critical finding and 11 (85%) had at least one major and/or critical finding. The number of findings per inspection is represented on the figure below. It should be noted that this group contains well known commercial units with extensive experience of trials, including FIH trials, as well as other commercial units undertaking low risk topical IMP/ OTC trials and whilst their main business was clinical research, it was not of clinical trials of IMP which fall under the legislation.



A total of 10 critical findings were reported from 4 organisations:

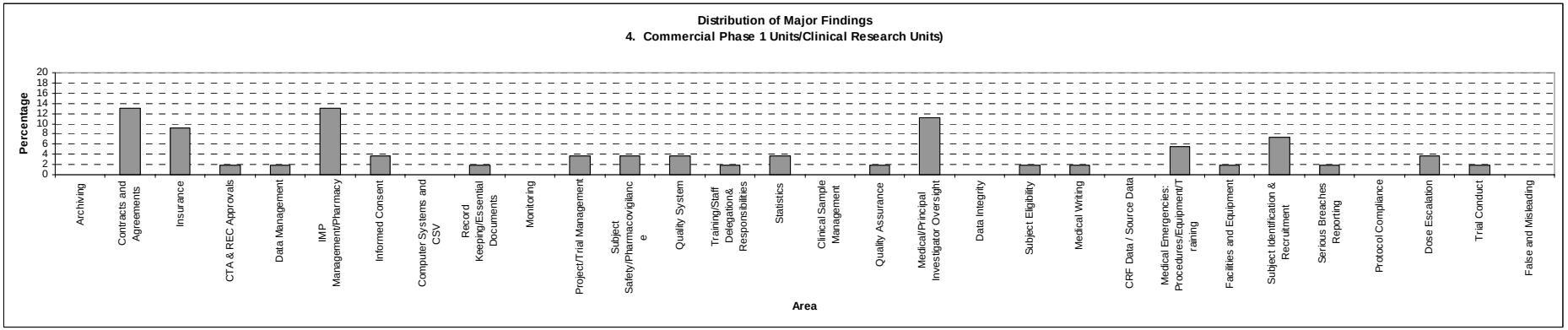
The total critical findings were influenced by one non-compliant organisation involved in low risk trials, which were given a total of 6 critical findings when inspected once as a triggered inspection and twice as an investigator site. Three of these critical findings (at all three inspections) were for data integrity as the trial data were unreliable. In addition, this organisation had a fourth critical finding for subject consent from the triggered inspection, as consent forms for minors were signed by inappropriate individuals, there were unexplained amendments to consent forms and there appeared to be re-recruitment of the same individuals under different names. Also this organisation had a fifth critical finding for subject identification and recruitment at the triggered inspection as the inspectors were unable to verify subjects existed as insufficient documentary ID or other evidence was present. Finally, the organisation had a sixth, critical finding for false and misleading information when inspected as an investigator site, as data supplied to the sponsor (and subsequently to MHRA/REC) contained false and misleading information.

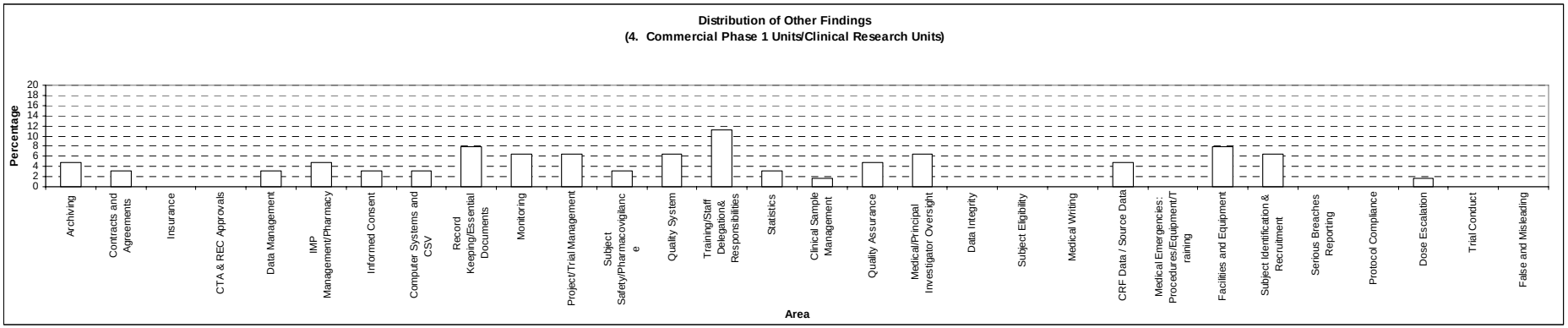
Another organisation, was given one critical finding for quality systems as they had no effective quality system implemented. They were given a second critical finding for data management, as there was a complete lack of systems and missing records for clinical trial data handling.

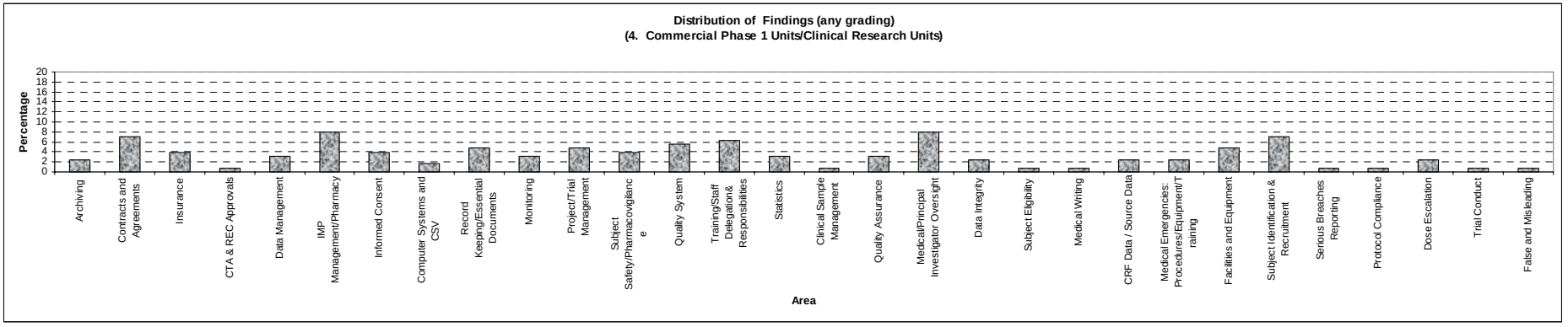
An organisation was given one critical finding for subject safety/pharmacovigilance, as they failed to comply with MHRA CTA approval condition relating to ALS medical cover on site post dose, putting subject safety at risk.

Another critical finding for subject safety/pharmacovigilance for another organisation was that subjects had not been subject to telemetry monitoring immediately post dosing as per the requirements of protocol, putting subject safety at risk.

The figures on the following page show the distribution of Major, Other and any grade of inspection findings. This identifies the areas where GCP inspectors have been making observations of non-compliance with GCP.


Distribution of Major Findings
4. Commercial Phase 1 Units/Clinical Research Units)
Percentage
0
2
4
6
8
10
12
14
16
18
20
Archiving
Contracts and Agreements
Insurance
CTA & REC Approvals
Data Management
IMP Management/Pharmacy
Informed Consent
Computer Systems and CSV
Record Keeping/Essential Documents
Monitoring
Project/Trial Management
Subject Safety/Pharmacovigilance
Quality System
Training/Staff Delegation& Responsibilities
Statistics
Clinical Sample Management
Quality Assurance
Medical/Principal Investigator Oversight
Data Integrity
Subject Eligibility
Medical Writing
CRF Data / Source Data
Medical Emergencies: Procedures/Equipment/Training
Facilities and Equipment
Subject Identification & Recruitment
Serious Breaches Reporting
Protocol Compliance
Dose Escalation
Trial Conduct
False and Misleading
Area

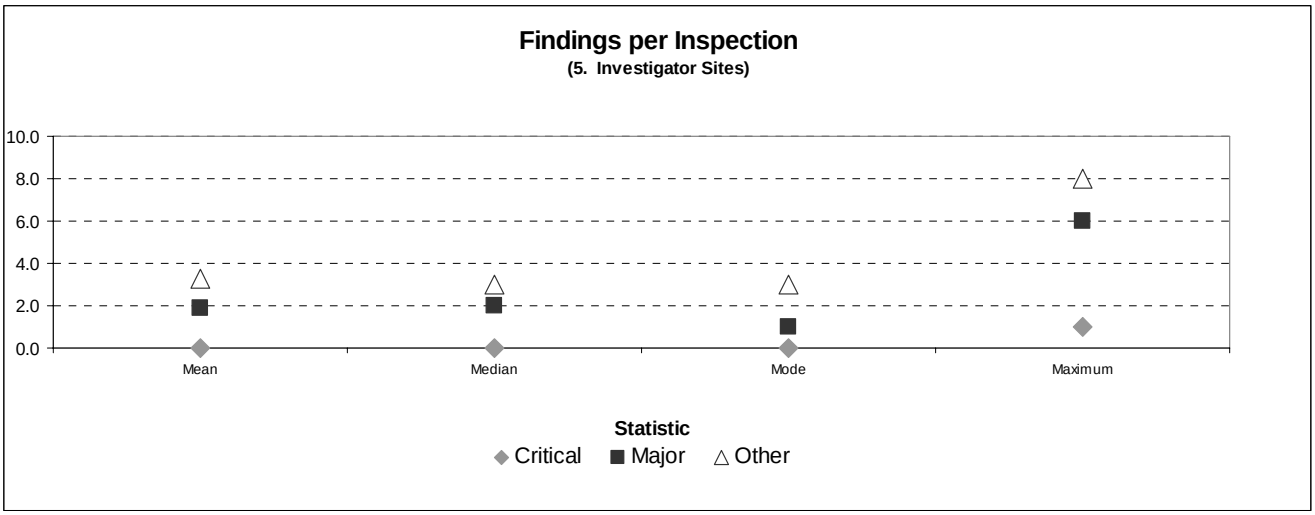

Distribution of Other Findings
(4. Commercial Phase 1 Units/Clinical Research Units)
Percentage
0
2
4
6
8
10
12
14
16
18
20
Archiving
Contracts and Agreements
Insurance
CTA & REC Approvals
Data Management
IMP Management/Pharmacy
Informed Consent
Computer Systems and CSV
Record Keeping/Essential Documents
Monitoring
Project/Trial Management
Subject Safety/Pharmacovigilance
Quality System
Training/Staff Delegation& Responsibilities
Statistics
Clinical Sample Management
Quality Assurance
Medical/Principal Investigator Oversight
Data Integrity
Subject Eligibility
Medical Writing
CRF Data / Source Data
Medical Emergencies: Procedures/Equipment/Training
Facilities and Equipment
Subject Identification & Recruitment
Serious Breaches Reporting
Protocol Compliance
Dose Escalation
Trial Conduct
False and Misleading
Area


Distribution of Findings (any grading)
(4. Commercial Phase 1 Units/Clinical Research Units)
Percentage
0
2
4
6
8
10
12
14
16
18
20
Archiving
Contracts and Agreements
Insurance
CTA & REC Approvals
Data Management
IMP Management/Pharmacy
Informed Consent
Computer Systems and CSV
Record Keeping/Essential Documents
Monitoring
Project/Trial Management
Subject Safety/Pharmacovigilance
Quality System
Training/Staff Delegation& Responsibilities
Statistics
Clinical Sample Management
Quality Assurance
Medical/Principal Investigator Oversight
Data Integrity
Subject Eligibility
Medical Writing
CRF Data / Source Data
Medical Emergencies: Procedures/Equipment/Training
Facilities and Equipment
Subject Identification & Recruitment
Serious Breaches Reporting
Protocol Compliance
Dose Escalation
Trial Conduct
False and Misleading
Area

3.5 Investigator Sites (as part of Commercial/Non-commercial/CRO Routine Systems & Study Specific and Triggered)

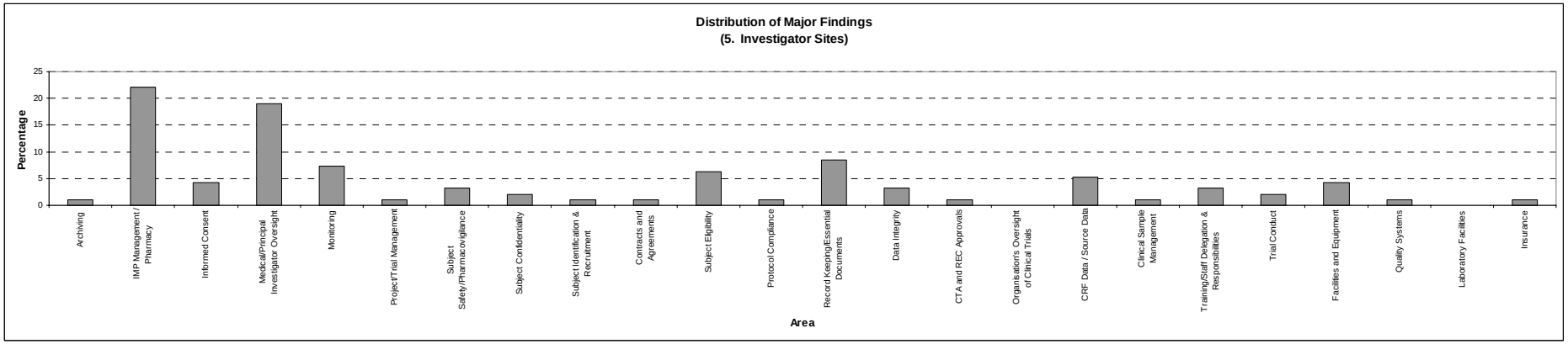
A total of 52 investigator sites in the UK were inspected.

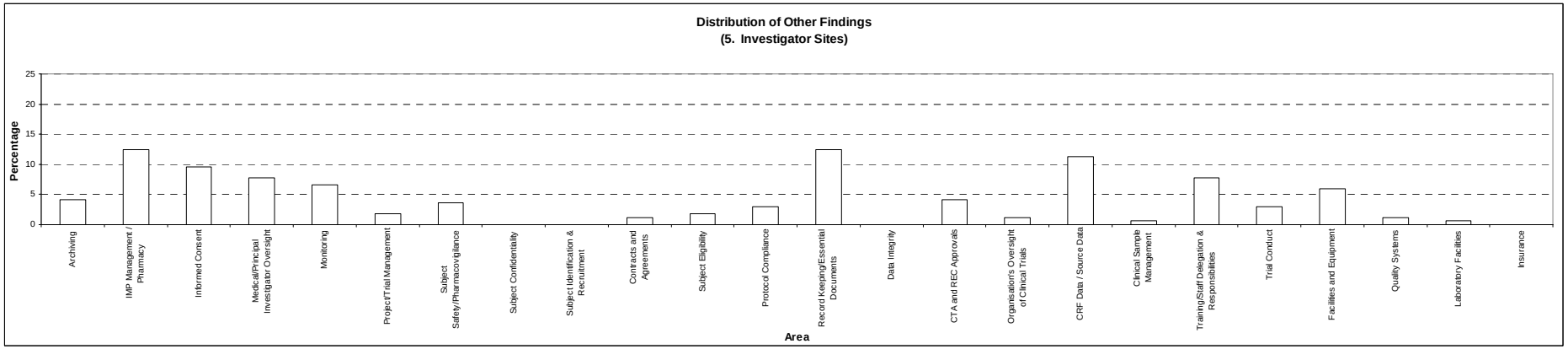
Of the 52 inspections, 1 (2%) had at least one critical finding and 42 (82%) had at least one major and/or critical finding. The number of findings per inspection is represented on the figure below. It should be noted that as associated sites, the emphasis of the inspection was on how the investigator site had been overseen by the sponsor/contracted CRO and thus most, but not all, the findings were for these organisations' systems rather than the hosting site.

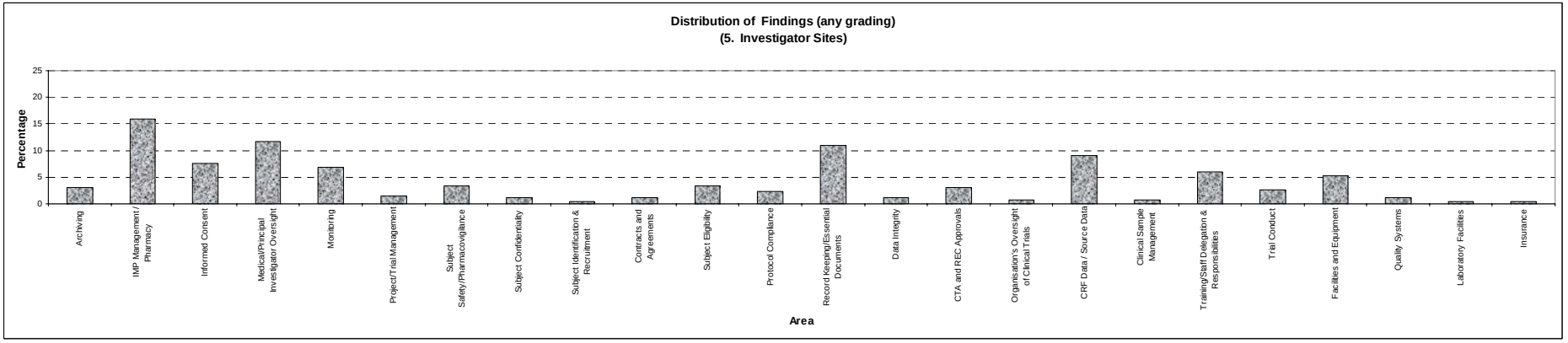


On investigator site was given a critical finding for subject confidentiality, as the documentation they had forwarded to the CRO managing the trial contained information to identify the subject, this was undertaken without explicit subject consent.

The figures on the following page show the distribution of Major, Other and any grade of inspection findings. This identifies the areas where GCP inspectors have been making observations of non-compliance with GCP.


Distribution of Major Findings
(5. Investigator Sites)
Percentage
0
5
10
15
20
25
Archiving
IMP Management / Pharmacy
Informed Consent
Medical/Principal Investigator Oversight
Monitoring
Project/Trial Management
Subject Safety/Pharmacovigilance
Subject Confidentiality
Subject Identification & Recruitment
Contracts and Agreements
Subject Eligibility
Protocol Compliance
Record Keeping/Essential Documents
Data Integrity
CTA and REC Approvals
Organisation's Oversight of Clinical Trials
CRF Data / Source Data
Clinical Sample Management
Training/Staff Delegation & Responsibilities
Trial Conduct
Facilities and Equipment
Quality Systems
Laboratory Facilities
Insurance
Area


Distribution of Other Findings
(5. Investigator Sites)
Percentage
0
5
10
15
20
25
Archiving
IMP Management / Pharmacy
Informed Consent
Medical/Principal Investigator Oversight
Monitoring
Project/Trial Management
Subject Safety/Pharmacovigilance
Subject Confidentiality
Subject Identification & Recruitment
Contracts and Agreements
Subject Eligibility
Protocol Compliance
Record Keeping/Essential Documents
Data Integrity
CTA and REC Approvals
Organisation's Oversight of Clinical Trials
CRF Data / Source Data
Clinical Sample Management
Training/Staff Delegation & Responsibilities
Trial Conduct
Facilities and Equipment
Quality Systems
Laboratory Facilities
Insurance
Area


Distribution of Findings (any grading)
(5. Investigator Sites)
Percentage
0
5
10
15
20
25
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