GCP INSPECTORATE

GCP INSPECTIONS METRICS REPORT

METRICS PERIOD: 1st April 2010 to 31st March 2011

DATE OF ISSUE: 14th March 2014

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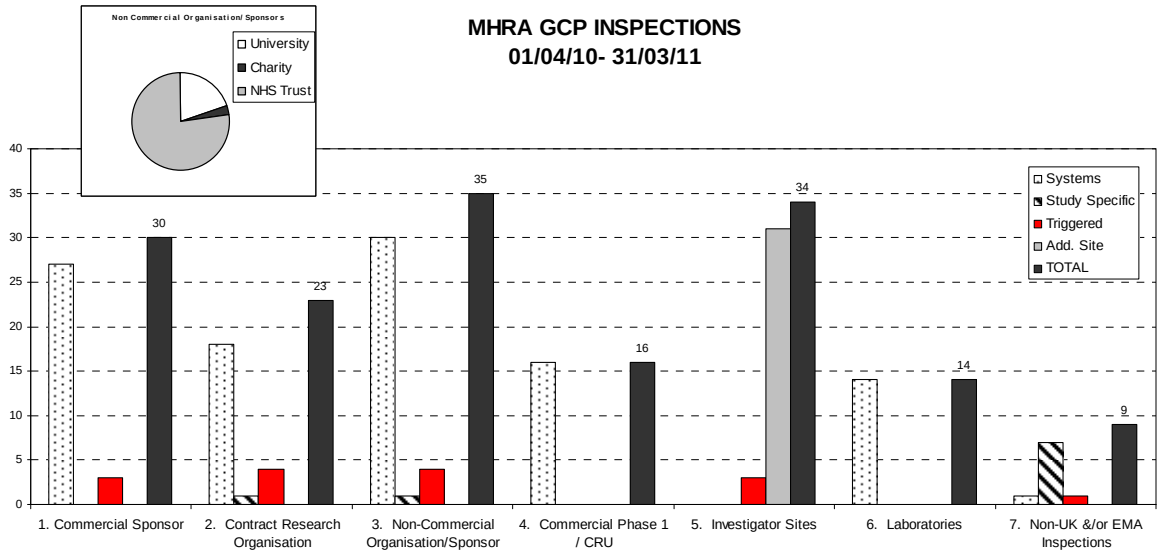
1. INTRODUCTION

This report covers the metrics period 1st April 2010 to 31st March 2011.

2. GCP INSPECTIONS UNDERTAKEN

During the Metrics Period a total of 161 GCP Inspections were undertaken by the MHRA GCP Inspectorate. The types of inspections are presented below. For the 35 non-commercial sponsor inspections, 7 were of Universities, 27 were of NHS Trusts and 1 was of a charitable organisation. The number of inspections of commercial sponsors, non-commercial sponsors and investigator sites were similar. Triggered inspections were carried out as a result of information received by the GCP Inspectorate, for example in response to a serious breach report, and a number of these were undertaken in 5 different types of organisation.



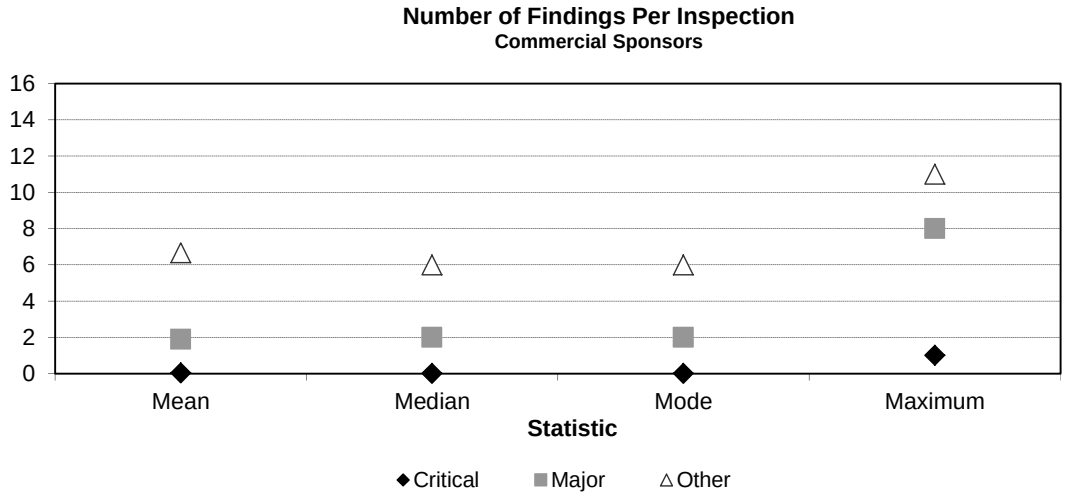
3. INSPECTION REPORTS AND FINDINGS

Reports relating only to the inspections carried out in the Metrics Period were reviewed. It is important to note that multiple inspections can be 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 2010 and the other associated inspections were conducted after 1st April 2010 (e.g. sponsor site then the investigator site(s)) the findings from the inspections conducted after 1st April 2010 (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. Metrics from inspections requested by the European Medicines Agency (EMA) are produced by the EMA. The findings are those that were contained in the inspection reports and do not take into account any inspection responses, apart from in the explanatory text for critical findings. The metrics data entry had an independent sample QC check.

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

A total of 30 commercial sponsors were inspected and all have been reported.

Of the 30 inspections, only 1 (3.3%) had at least one critical finding and the majority 22 (73.3%) but not all had at least one major and/or critical finding. The number of findings per inspection is represented on the figure below.



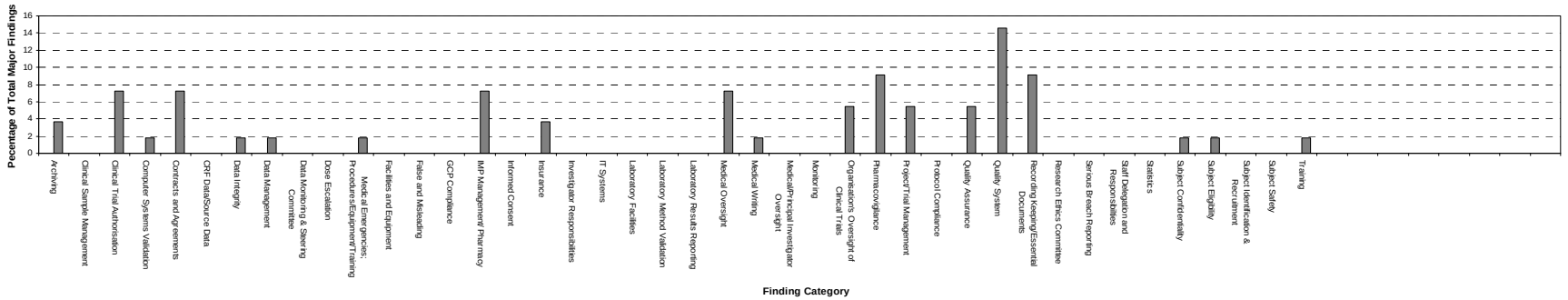
There was 1 critical finding from 1 organisation.

The first finding relating to subject confidentiality* and concerned a sponsor organisation that had SAE reports and drug accountability logs in the TMF that had trial subject names written on them. The organisation also did not have a formal procedure for the management of such information if it was inadvertently received.

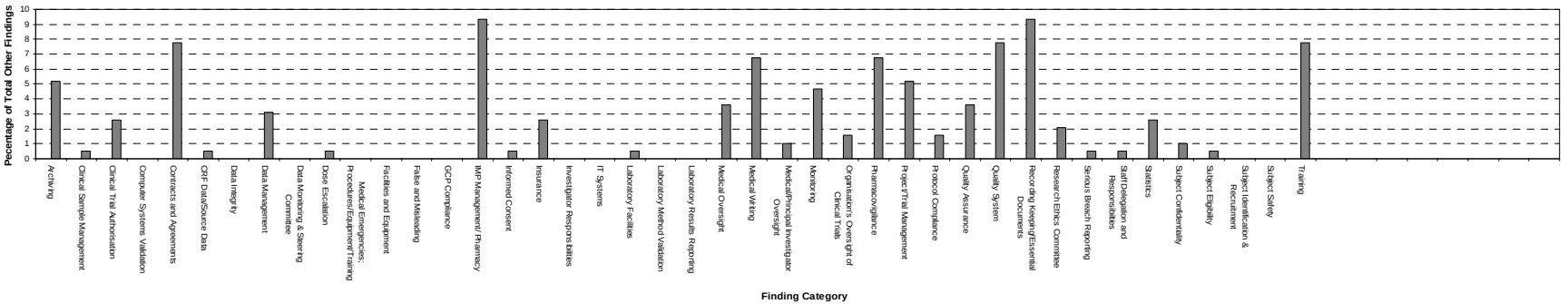
The figures on the following page show the distribution of Major, Other and any grade of inspection findings. This identifies the areas where GCP inspectors have been making observations of non-compliance with GCP.

* MHRA GCP inspectorate had a definition for critical findings that included subject confidentiality. As a result there were many critical findings awarded for breaches involving a single incidence. The wording has since been revised. Only significant breaches of confidentiality in a systemic way would now be graded as critical.

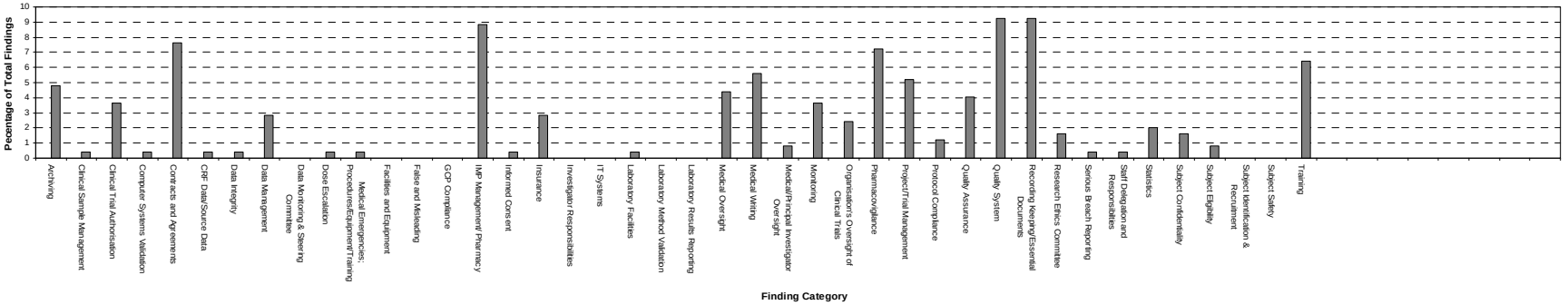
Distribution of Major Findings
1. Commercial Sponsors



Distribution of Other Findings
1. Commercial Sponsors



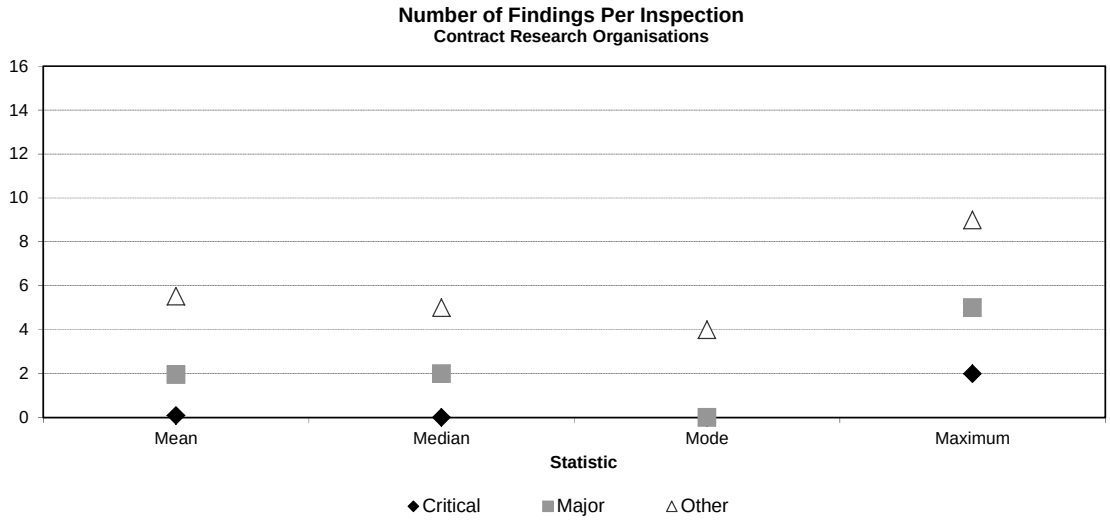
Distribution of All Findings (of any grading)
1. Commercial Sponsors



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

A total of 23 Contract Research Organisations were inspected and all have been reported.

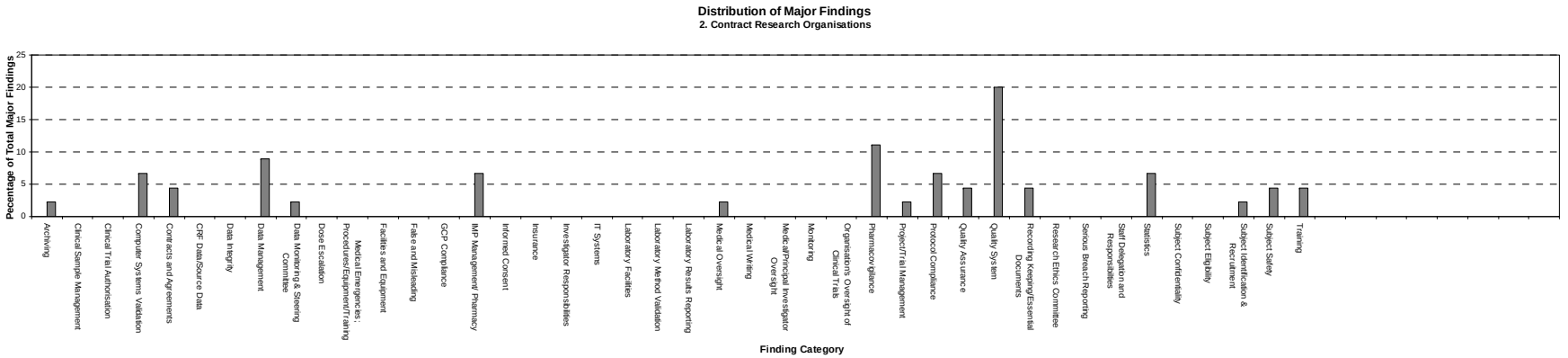
Of the 23 inspections, 1 (4.3%) had at least one critical finding and 17 (73.9%) had at least one major and/or critical finding. The number of findings per inspection is represented on the figure below.



There were 2 critical findings from 1 CRO organisation. The first critical finding was for subject confidentiality*, because the organisation had transferred source data documentation, for example, assessment forms, consent forms and logs, containing trial subject names to the trial sponsor. The second critical finding related to the manufacturing operations relating to IMP without an appropriate licence.

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.

* MHRA GCP inspectorate had a definition for critical findings that included subject confidentiality. As a result there were many critical findings awarded for breaches involving a single incidence. The wording has since been revised. Only significant breaches of confidentiality in a systemic way would now be graded as critical.


Distribution of Major Findings
2. Contract Research Organisations
Pecentage of Total Major Findings
0
5
10
15
20
25
Archiving
Clinical Sample Management
Clinical Trial Authorisation
Computer Systems Validation
Contracts and Agreements
CRF Data/Source Data
Data Integrity
Data Management
Data Monitoring & Steering Committee
Dose Escalation
Medical Emergencies; Procedures/Equipment/Training
Facilities and Equipment
False and Misleading
GCP Compliance
IMP Management/ Pharmacy
Informed Consent
Insurance
Investigator Responsibilities
IT Systems
Laboratory Facilities
Laboratory Method Validation
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Medical Oversight
Medical Writing
Medical/Principal Investigator Oversight
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Project/Trial Management
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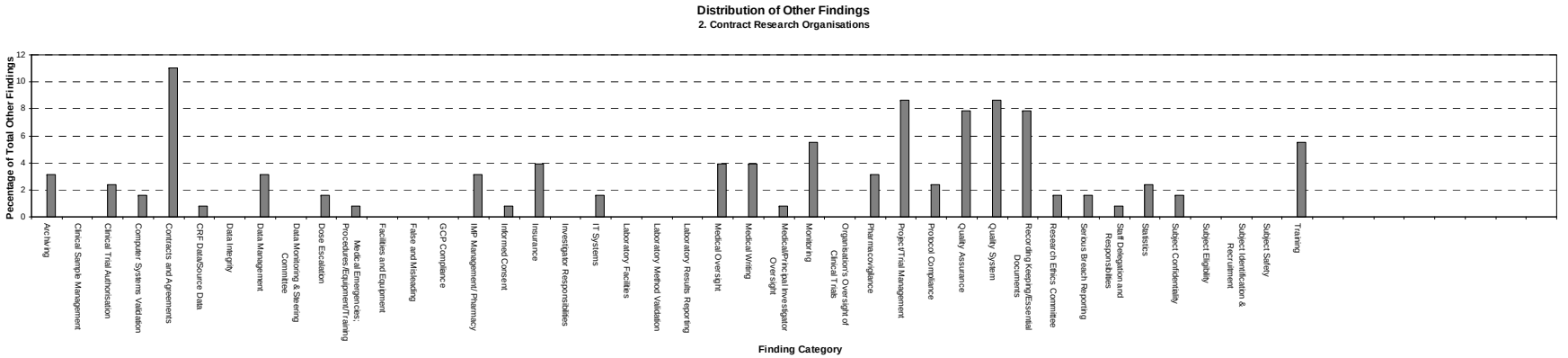
Quality Assurance
Quality System
Recording Keeping/Essential Documents
Research Ethics Committee
Serious Breach Reporting
Staff Delegation and Responsibilities
Statistics
Subject Confidentiality
Subject Eligibility
Subject Identification & Recruitment
Subject Safety
Training
Finding Category


Distribution of Other Findings
2. Contract Research Organisations
Pecentage of Total Other Findings
0
2
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6
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10
12
Archiving
Clinical Sample Management
Clinical Trial Authorisation
Computer Systems Validation
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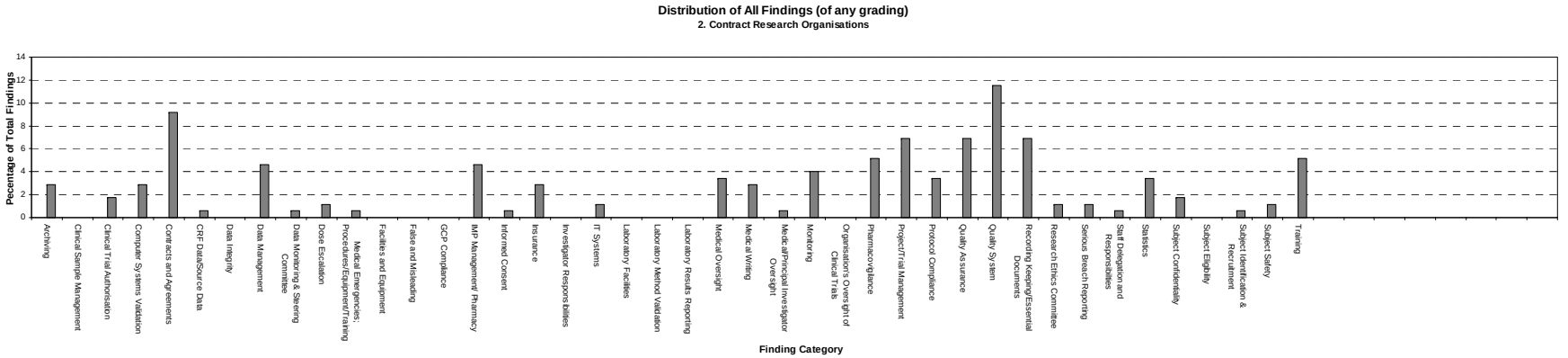
Distribution of All Findings (of any grading)
2. Contract Research Organisations
Pecentage of Total Findings
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2
4
6
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12
14
Archiving
Clinical Sample Management
Clinical Trial Authorisation
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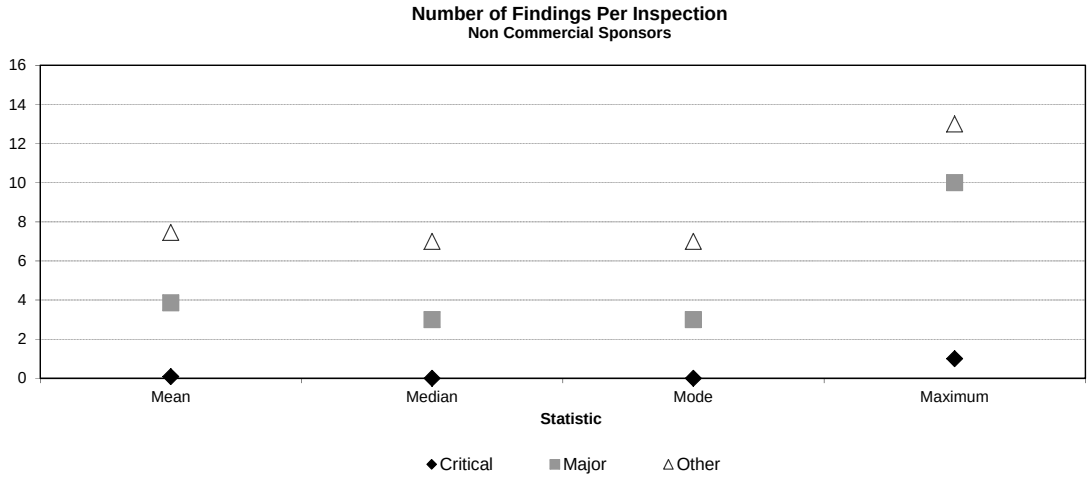
3.3 Non Commercial Organisations (Routine Systems and Triggered)

A total of 35 Non Commercial Organisations were inspected. Twenty-seven were NHS Trusts, 7 were Universities and 1 was a Charitable organisation. All have been reported.

Of the 35 inspections, 3 (8.6%) had at least one critical finding and 34 (97.1%) had at least one major and/or critical finding. The number of findings per inspection is represented on the figure below.



A total of 3 critical findings were identified from 3 organisations inspected. Two NHS Trusts had 1 critical finding each and one university had 1 critical finding.

For the university, there was one critical finding given at a second follow up inspection following previous critical findings that had been referred to the MHRA Inspection Action Group. This critical finding was assigned to the organisation's oversight of clinical trials and consisted of the following components:

- Failure to follow new R&D approval procedures which required that an initiation training visit was conducted prior to initial R&D approval and that subsequent amendments required R&D approval prior to implementation.
- Failure to implement a system to monitor trials that the organisation was sponsoring.
- Not all Chief Investigators had signed the updated document that formally defined and transferred the sponsor's functions to the Chief Investigator and that the Chief Investigator had received GCP and SOP training.
- For one trial rolled over from a DDX, substantial amendments had not received MHRA approval prior to implementation.

For the first Trust, there was one critical finding given at a second follow up inspection following previous critical findings that had been referred to the MHRA Inspection Action Group. This critical finding was assigned to the organisation's oversight of clinical trials and consisted of the following components:

- The new R&D processes had not been fully implemented as per the CAPA plan. In particular this related to risk assessment processes, insurance assessment and updates to all the existing trials into the new processes to ensure compliance (e.g. protocol and trial specific SOP changes).

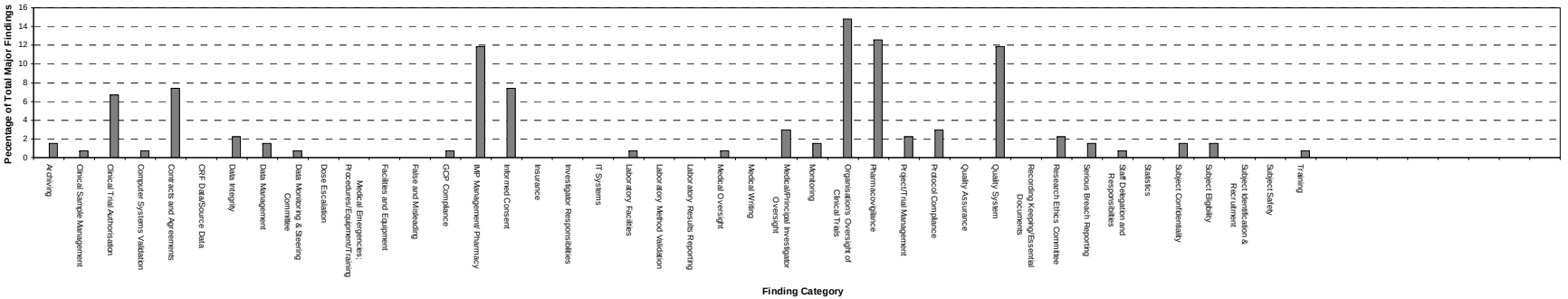
- The were failures to report a temporary halt, end of trial notifications, end of study summary reports and annual safety reports either at all or in a timely manner.

For the second NHS Trust, this was their first GCP systems inspection. A critical finding was assigned for the organisation's oversight of clinical trials due to the extensive number of major findings spanning across various areas because there was clear evidence of the failure of the Trust to have effective systems in place to ensure compliance with regulations and in particular with the principles of GCP. There were 10 major findings citing many aspects of non compliance relating to pharmacovigilance, investigational medicinal products/pharmacy, sponsor oversight of clinical trials, quality systems, contacts and agreements, serious breach reporting, clinical trial authorisation, informed consent, clinical trial data integrity and protocol compliance.

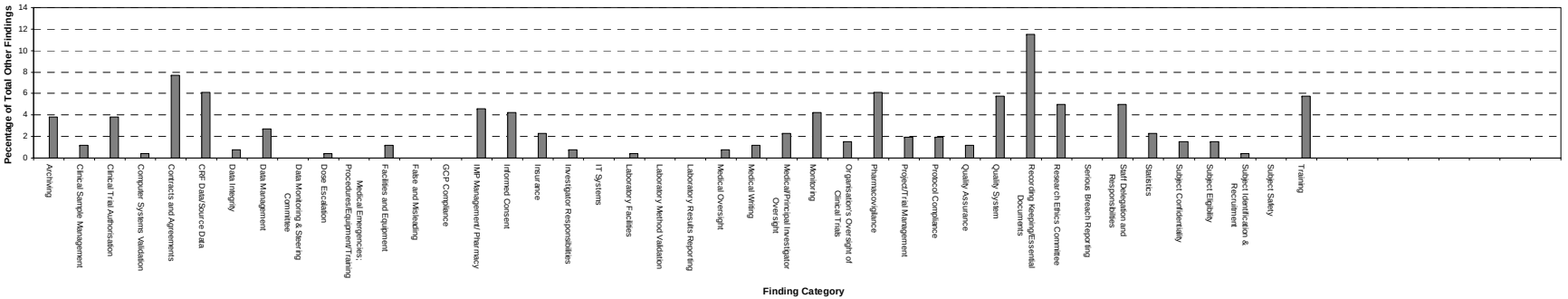
These major findings covered lack of specific systems and processes within the Trust to manage trial aspects. In summary, the issues raised, included, non submission of ASRs, failure to address remarks on MHRA clinical trial authorisation, not gaining MHRA approval for substantial amendments and not submitting end of trial notifications and serious breach reports. Additionally, the control of IMP was a large issue in particular there was a systemic failure to ensure double-blind trials remained blinded. The organisation had not had clear oversight of trials that were being conducted and sponsored and the associated contracts and agreements had deficiencies. For one trial, the informed consent process was poor, including a minor included in a trial without consent of a person with parental responsibility. Finally, for one trial, it was impossible to verify the trial and its conduct due to failure to maintain the necessary essential documents.

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.

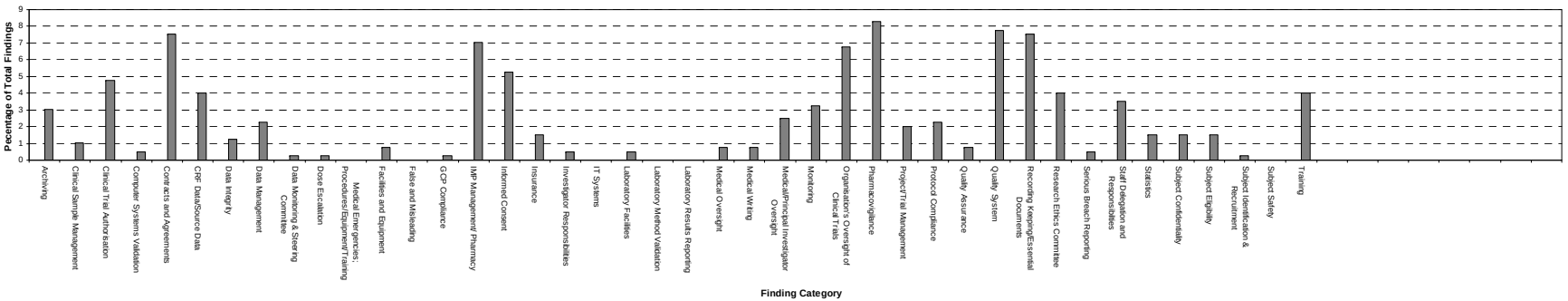
Distribution of Major Findings
3. Non Commercial Sponsors



Distribution of Other Findings
3. Non Commercial Sponsors



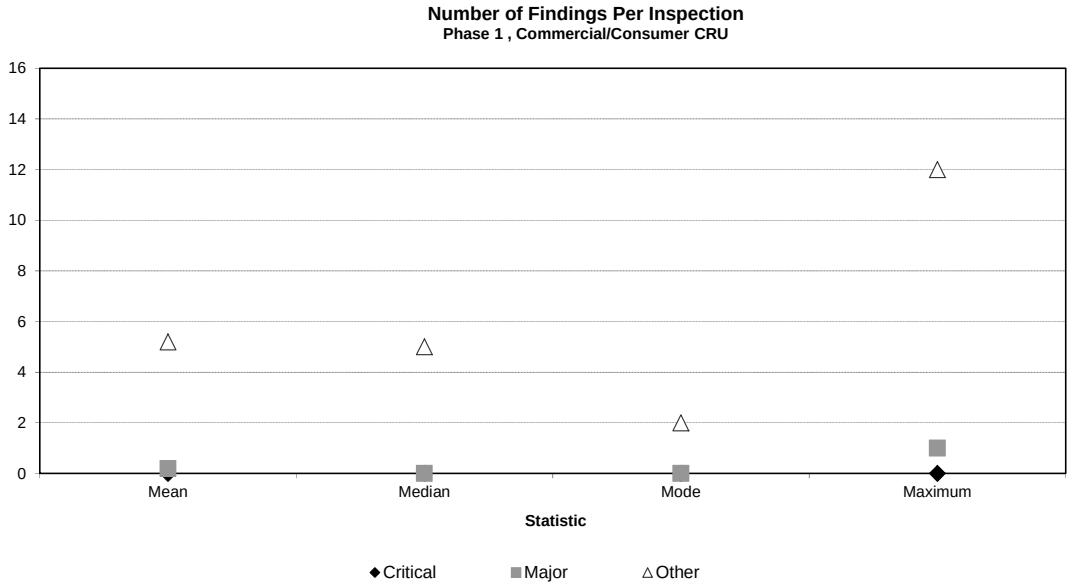
Distribution of All Findings (of any grading)
3. Non Commercial Sponsors



3.4 Commercial Phase 1 Units/Clinical Research Units

A total of 16 inspections were undertaken of Commercial Phase 1 Units/Clinical Research Units. The majority (14) were also inspections for the MHRA voluntary phase 1 accreditation scheme. All of the inspections have been reported.

Of the 16 reported inspections, none had a critical finding and 3 (18.8%) had at least one major finding. The number of findings per inspection is represented on the figure below.



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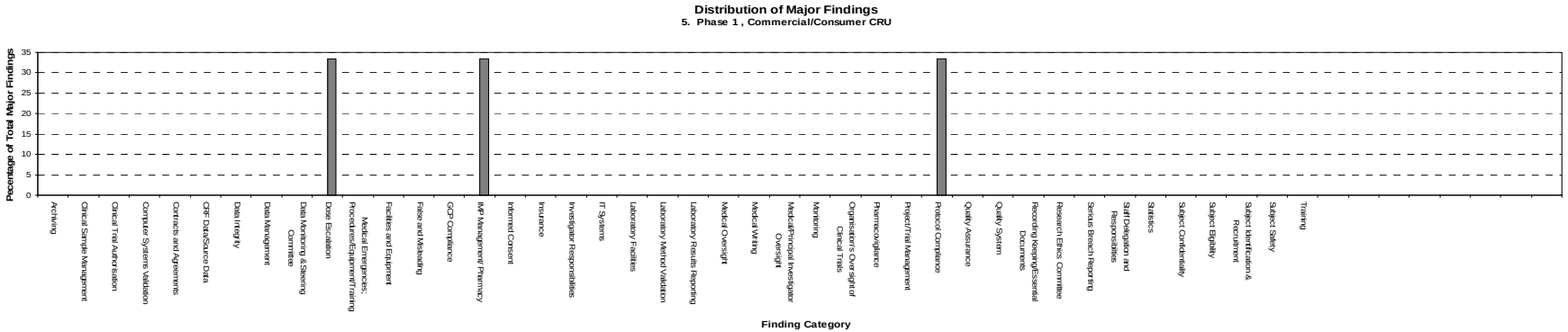
Distribution of Major Findings
5. Phase 1 , Commercial/Consumer CRU
Pecentage of Total Major Findings
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Archiving
Clinical Sample Management
Clinical Trial Authorisation
Computer Systems Validation
Contracts and Agreements
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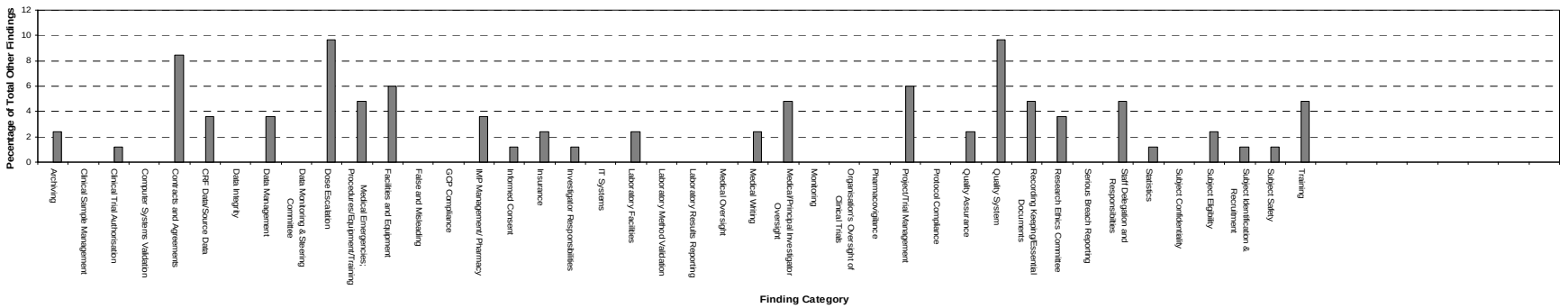
Distribution of Other Findings
5. Phase 1 , Commercial/Consumer CRU
Pecentage of Total Other Findings
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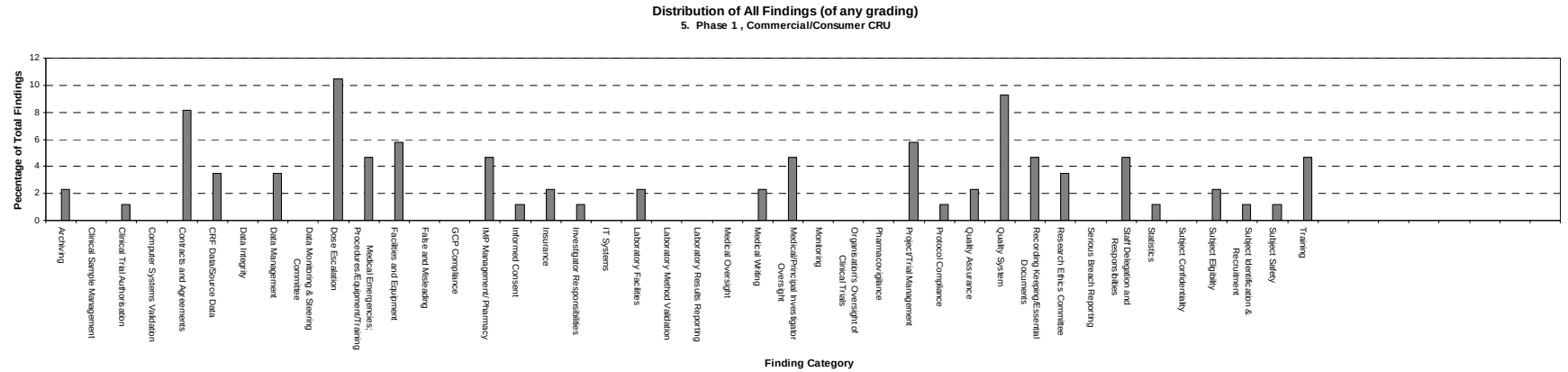
Distribution of All Findings (of any grading)
5. Phase 1 , Commercial/Consumer CRU
Pecentage of Total Findings
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Archiving
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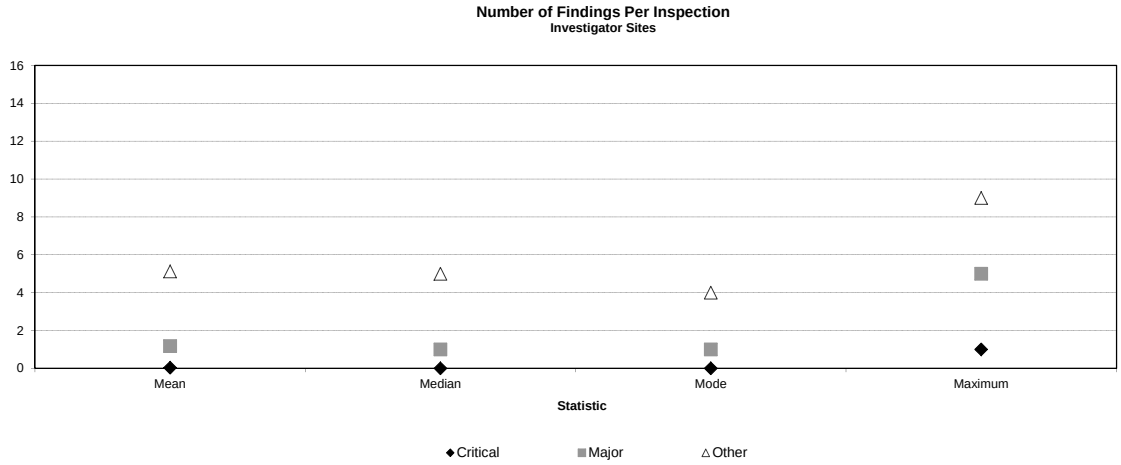
Subject Safety
Training
Finding Category

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

A total of 34 investigator sites in the UK were inspected, all were as an associated site with a sponsor inspection, but 3 were triggered inspections, 2 of which were part of the same inspection report and one of these sites had a critical finding as described below.

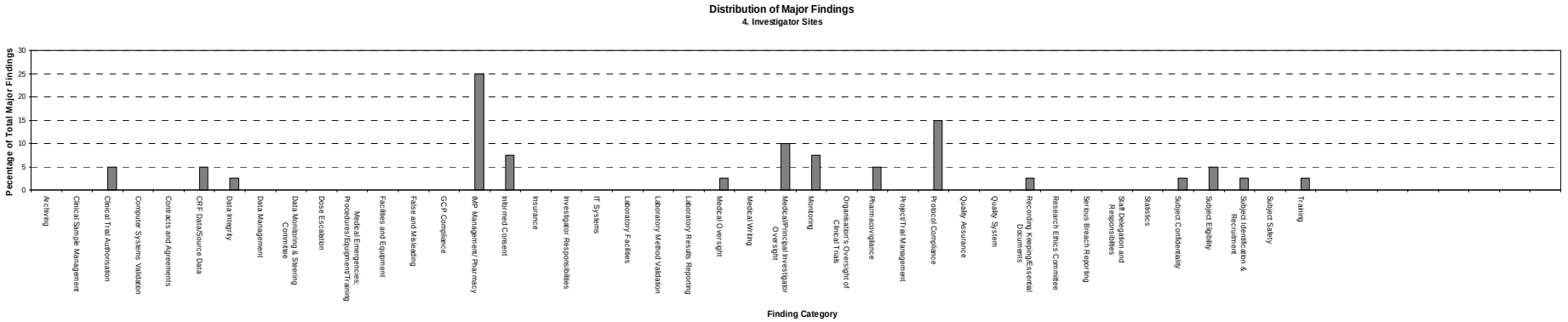
Of the 34 inspections, 1 (2.9%) had at least one critical finding and 25 (73.5%) had at least one major and/or critical finding. The number of findings per inspection is represented on the figure below. It should be noted that as associated sites, the emphasis of the inspection was on how the investigator site had been overseen by the sponsor/contracted CRO.



There was 1 critical finding from 1 investigator site.

This related to the poor packaging and labeling presentation of the IMP and provision of IMP of strengths higher than required being given to trial subjects. As a result of this, a patient mistakenly took an overdose of IMP and died. Whilst this critical finding was identified at the investigator site, the trial sponsor who was responsible for the packaging and labeling of the IMP for the trial had identified that there was a potential issue via pharmacovigilance signals. . However the sponsor failed to take prompt action and as a result of this a UK patient died. Subsequently, an inspection was triggered of the sponsor organisation. This was conducted in a third country and as such the sponsor accepted this inspection on a voluntary basis.

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. Investigator Sites
Pecentage of Total Major Findings
0
5
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15
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25
30
Archiving
Clinical Sample Management
Clinical Trial Authorisation
Computer Systems Validation
Contracts and Agreements
CRF Data/Source Data
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Subject Eligibility
Subject Identification & Recruitment
Subject Safety
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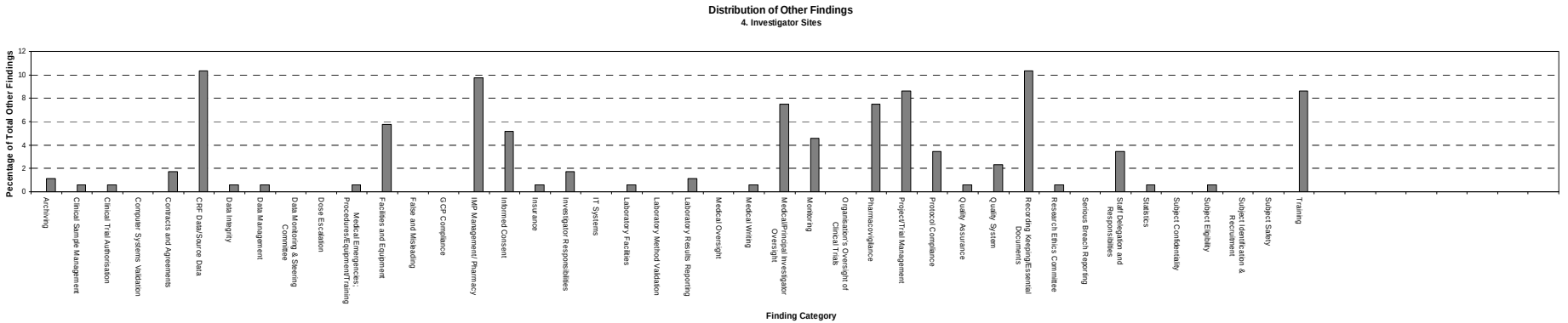
Finding Category


Distribution of Other Findings
4. Investigator Sites
Pecentage of Total Other Findings
0
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Archiving
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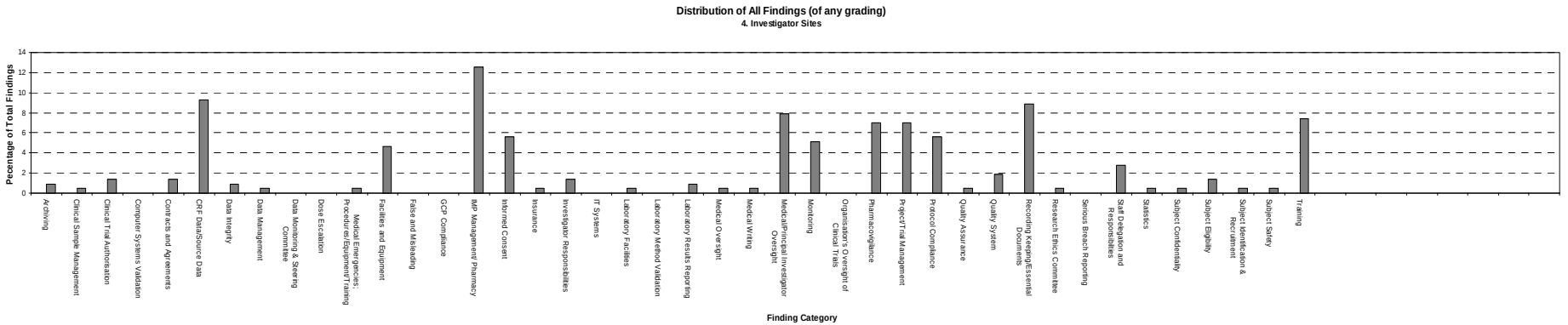
Distribution of All Findings (of any grading)
4. Investigator Sites
Pecentage of Total Findings
0
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