# GCP INSPECTORATE

# GCP INSPECTIONS METRICS REPORT

**METRICS PERIOD: 1st April 2012 to 31st March 2013**

**DATE OF ISSUE: 24th April 2014**


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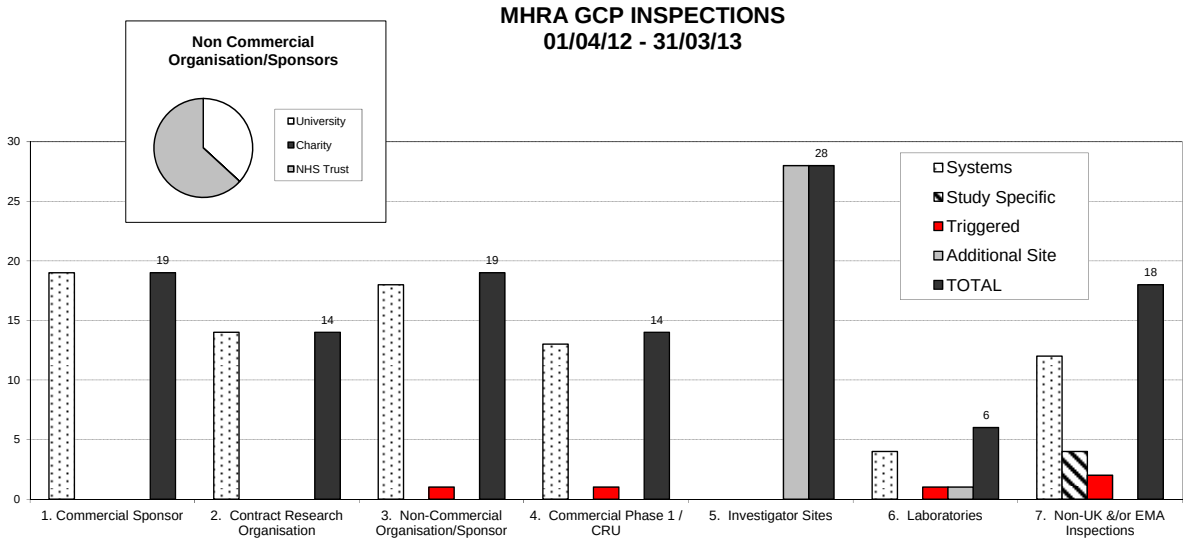
## 1. INTRODUCTION

This report covers the metrics period 1st April 2012 to 31st March 2013.

## 2. GCP INSPECTIONS UNDERTAKEN

During the Metrics Period a total of 113 GCP Inspections were undertaken by the MHRA GCP Inspectorate. The types of inspections are presented below. For the 19 non-commercial sponsor inspections, 7 were of Universities and 12 were of NHS Trusts. The number of inspections of commercial sponsors was 19, of Contract Research Organisations (CROs) was 14, of investigator sites there were 28 and finally there were 14 phase 1 unit inspections. The GCP inspection of UK laboratory facilities conducting clinical trial sample analysis is conducted by the MHRA GLP Inspectorate and there were 6 inspections, however, 1 of these was done by the MHRA GCP inspectorate as an associated site. The number of non-UK and EMA inspections was 18. 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 triggered inspections were undertaken of different organisations. For triggered inspections, 1 was a non-commercial sponsor, 1 was of a phase 1 unit, 1 was of a laboratory and 2 were non-UK/EMA inspections.

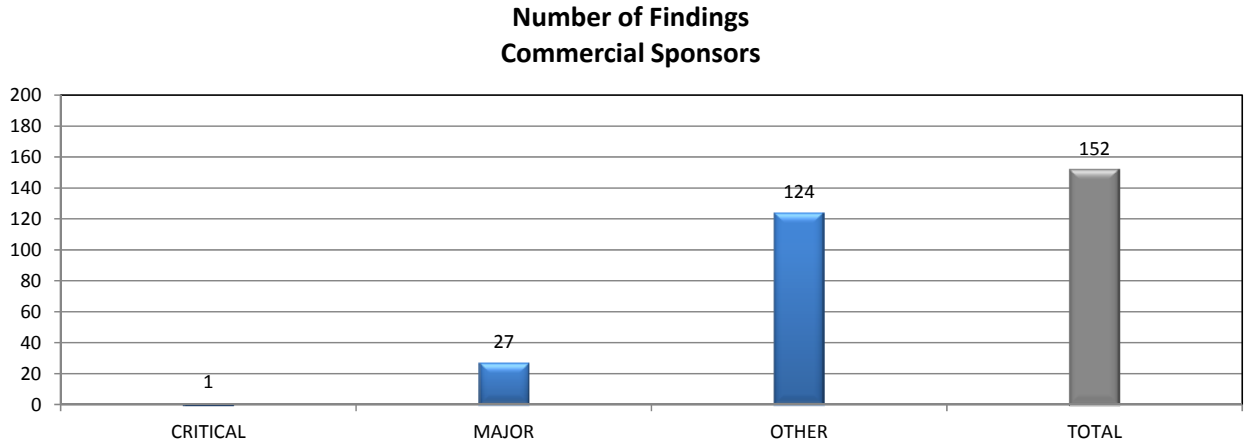


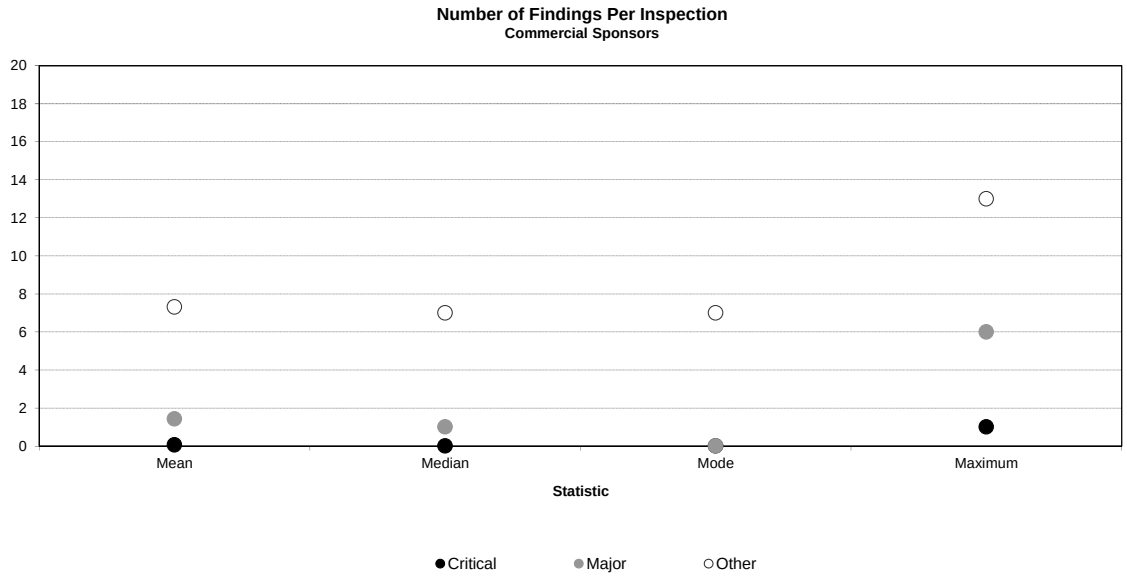

## 3. INSPECTION REPORTS AND FINDINGS

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 2012 and the other associated inspections were conducted after 1st April 2012 (e.g. sponsor site then the investigator site(s)) the findings from the inspections conducted after 1st April 2012 (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 19 commercial sponsors were inspected and all have been reported. Of the 19 inspections, only 1 (5.3%) had at least one critical finding and 10 (52.6%) had at least one major and/or critical finding. The total number of findings and findings per inspection are represented on the figures below.



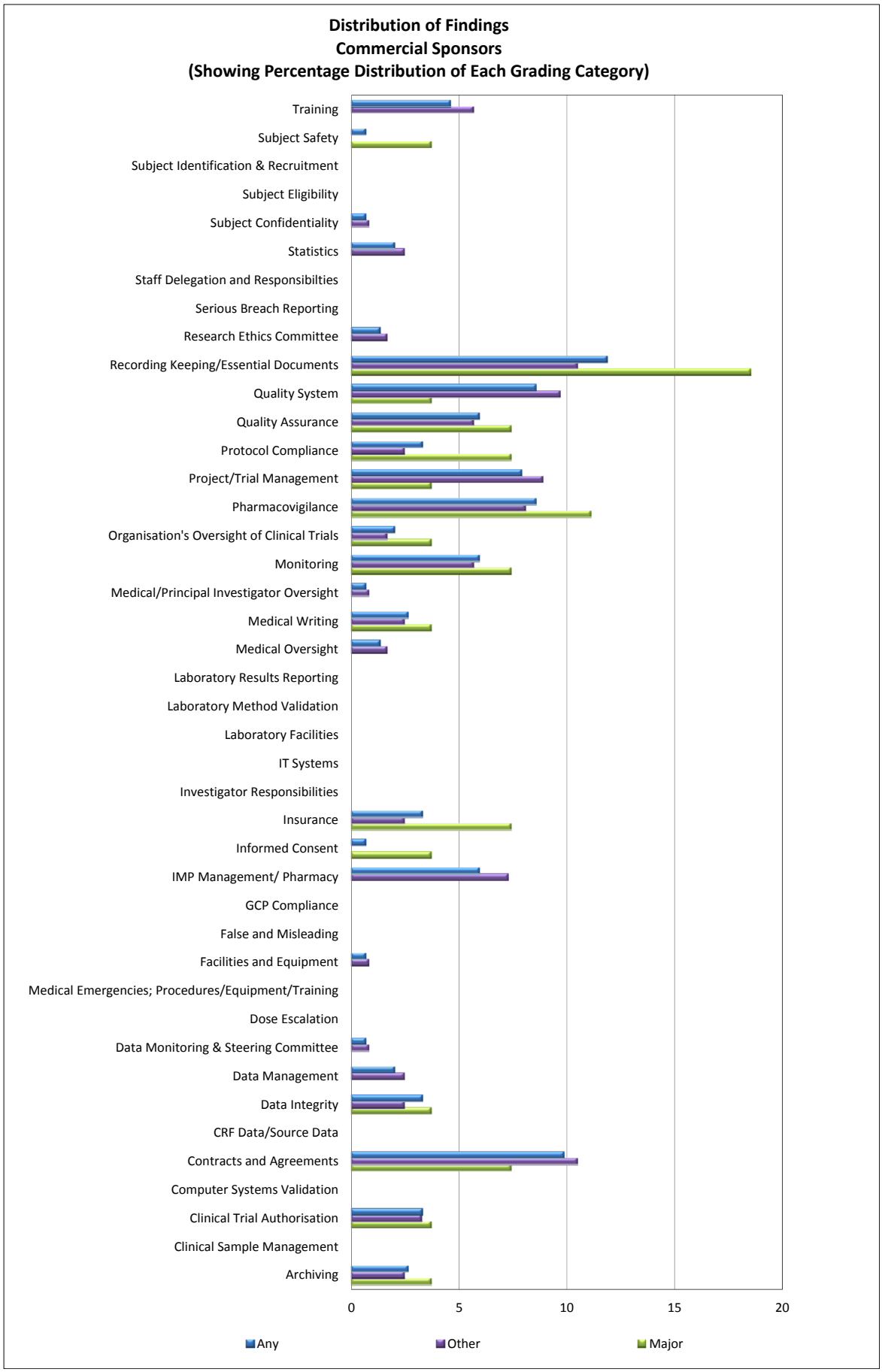

There was 1 critical finding from 1 organisation.

The critical finding was in relation to data integrity. Out of 17 trials sponsored by the organisation that had been described as double-blind, the blind had been potentially or actually compromised in 9 trials (53%). Issues that affected the integrity of the double-blind included placebos that were not adequately matched to the test products, unmatched primary packaging, treatment codes printed on labels, protocol procedures for maintaining the blind not being followed, and delegation of duties between blinded and unblinded staff not being clearly defined. Additionally, a range of deficiencies in trial management and quality assurance for one trial added to concerns regarding the conduct of this trial and the reliability of data.

The main issues that were identified included:

- The recruitment target was not reached due to the IMP expiring after approximately three quarters of patients were recruited.
- Majority of patients were excluded from the per protocol population due to “treatment non-compliance”.
- The trial steering committee referred to in the protocol that was to be responsible for ensuring quality assurance and quality control was not convened.
- There was no process for deviations picked up during monitoring to be passed on to the statistician and the author of the study report. As a result deviations recorded in monitoring visit reports were not reflected in the study report.
- There was a lack of understanding by the investigators of the definition of an adverse event. As a result, adverse events that had been recorded in the patient diaries had not been transferred to the case report forms.
- It was unclear how the analysis populations were determined and whether this was done in a blinded fashion.
- There were statements in the study report that were incorrect and other documents indicated that results were not being correctly interpreted (e.g. an email stated “I have put a positive tone into my interpretations of the findings…”)

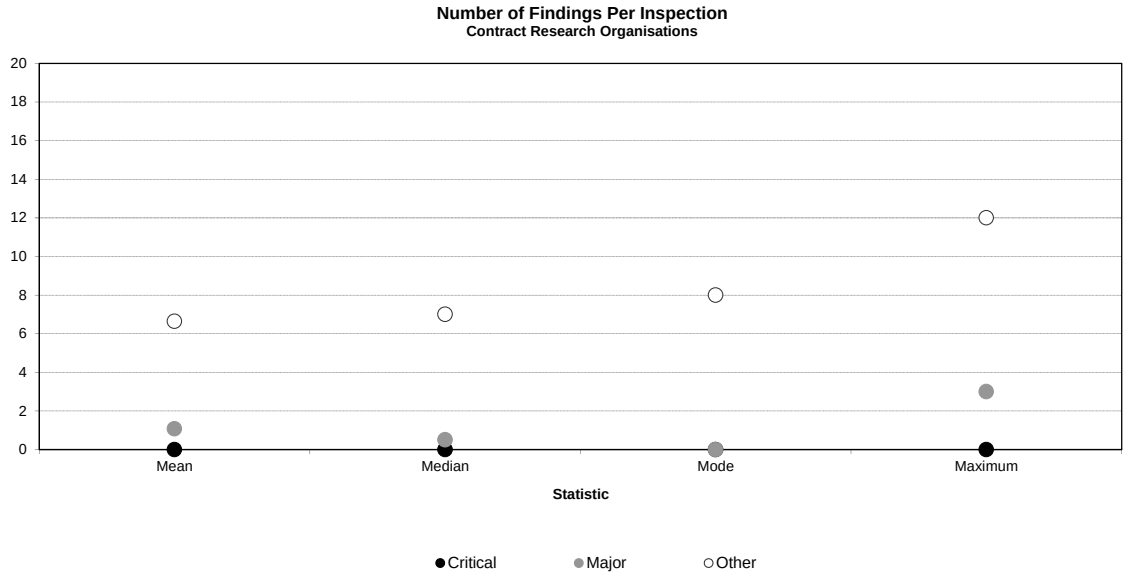
The figure on the following page shows the distribution of Major, Other and any grade of inspection findings. This identifies the areas where GCP inspectors have been making observations of non-compliance with GCP.


Distribution of Findings
Commercial Sponsors
(Showing Percentage Distribution of Each Grading Category)
Training
Subject Safety
Subject Identification & Recruitment
Subject Eligibility
Subject Confidentiality
Statistics
Staff Delegation and Responsibilties
Serious Breach Reporting
Research Ethics Committee
Recording Keeping/Essential Documents
Quality System
Quality Assurance
Protocol Compliance
Project/Trial Management
Pharmacovigilance
Organisation's Oversight of Clinical Trials
Monitoring
Medical/Principal Investigator Oversight
Medical Writing
Medical Oversight
Laboratory Results Reporting
Laboratory Method Validation
Laboratory Facilities
IT Systems
Investigator Responsibilities
Insurance
Informed Consent
IMP Management/ Pharmacy
GCP Compliance
False and Misleading
Facilities and Equipment
Medical Emergencies; Procedures/Equipment/Training
Dose Escalation
Data Monitoring & Steering Committee
Data Management
Data Integrity
CRF Data/Source Data
Contracts and Agreements
Computer Systems Validation
Clinical Trial Authorisation
Clinical Sample Management
Archiving
0
5
10
15
20
Any
Other
Major

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

A total of 14 Contract Research Organisations were inspected and all have been reported.

Of the 14 inspections, none had any critical findings and 7 (50.0%) had at least one major finding. The total number of findings and findings per inspection are represented on the figures below.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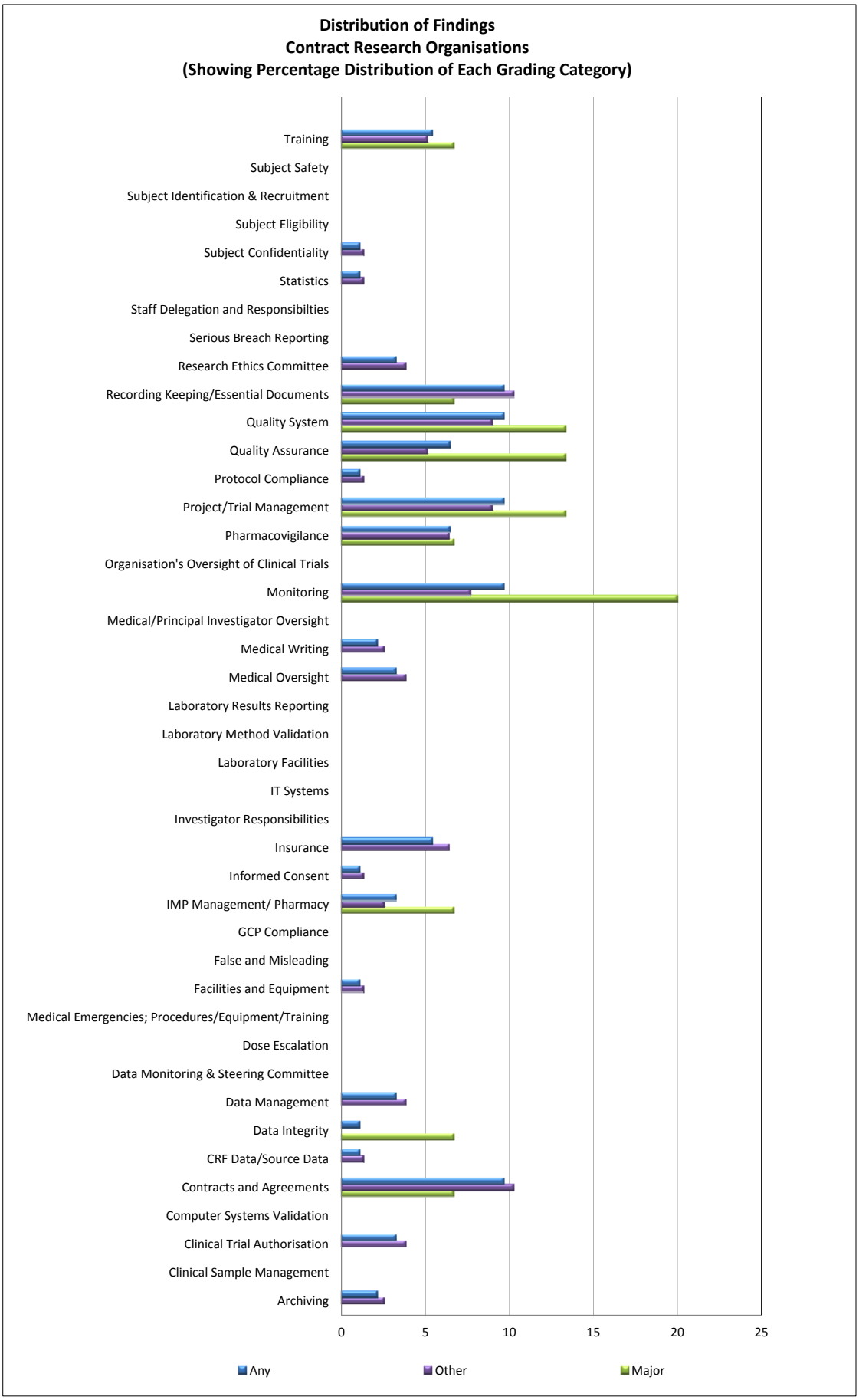
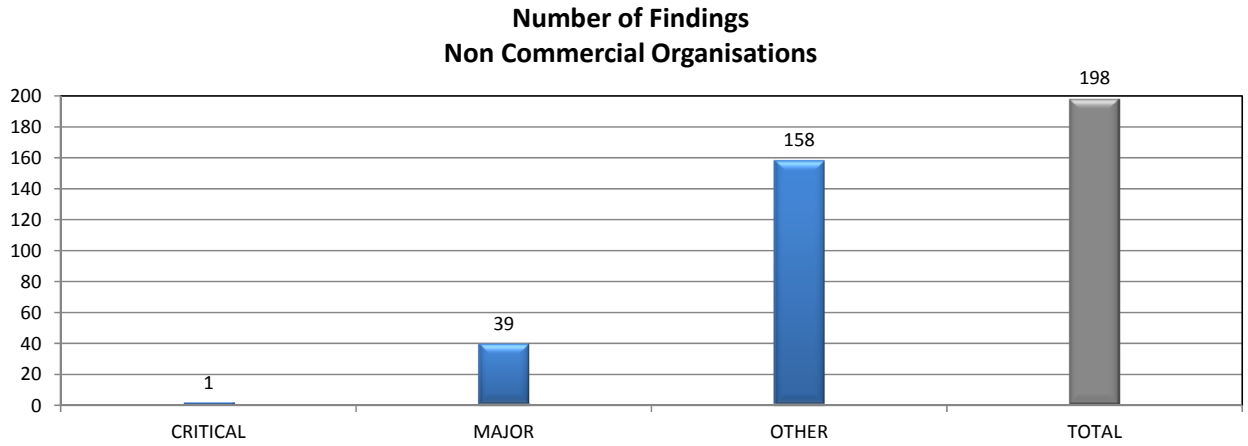
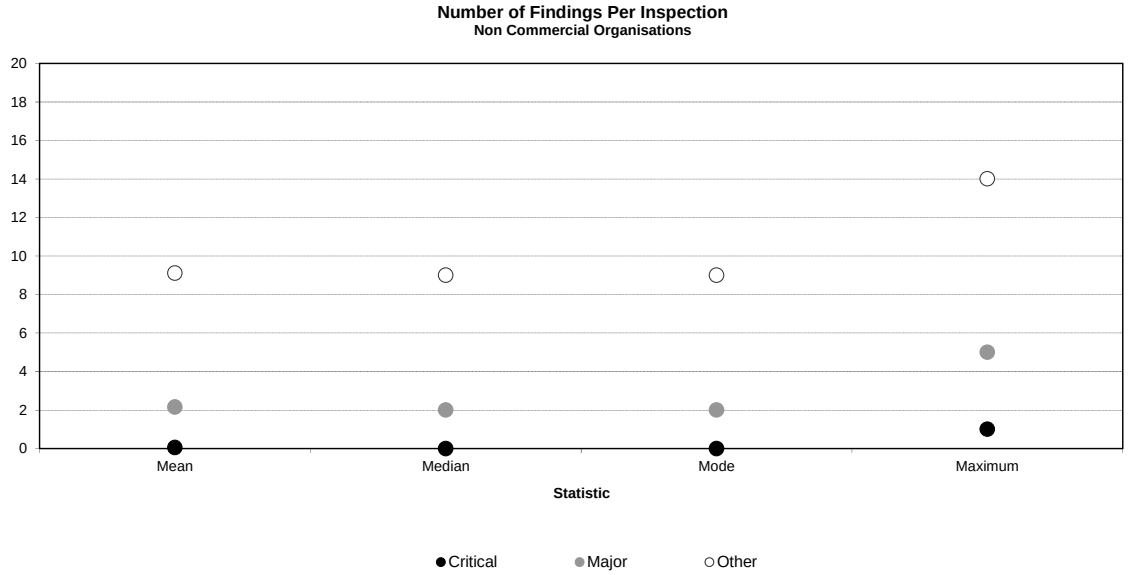

Distribution of Findings
Contract Research Organisations
(Showing Percentage Distribution of Each Grading Category)
Training
Subject Safety
Subject Identification & Recruitment
Subject Eligibility
Subject Confidentiality
Statistics
Staff Delegation and Responsibilties
Serious Breach Reporting
Research Ethics Committee
Recording Keeping/Essential Documents
Quality System
Quality Assurance
Protocol Compliance
Project/Trial Management
Pharmacovigilance
Organisation's Oversight of Clinical Trials
Monitoring
Medical/Principal Investigator Oversight
Medical Writing
Medical Oversight
Laboratory Results Reporting
Laboratory Method Validation
Laboratory Facilities
IT Systems
Investigator Responsibilities
Insurance
Informed Consent
IMP Management/ Pharmacy
GCP Compliance
False and Misleading
Facilities and Equipment
Medical Emergencies; Procedures/Equipment/Training
Dose Escalation
Data Monitoring & Steering Committee
Data Management
Data Integrity
CRF Data/Source Data
Contracts and Agreements
Computer Systems Validation
Clinical Trial Authorisation
Clinical Sample Management
Archiving
0
5
10
15
20
25
Any
Other
Major

## 3.3 Non Commercial Organisations (Routine Systems and Triggered)

A total of 19 Non Commercial Organisations were inspected, of these, 13 were NHS Trusts and 6 were Universities. All have been reported.

Of the19 inspections, 1 (5.3%) had at least one critical finding and 17 (89.5%) had at least one major and/or critical finding. The number of findings and findings per inspection are represented on the figures below.




There was 1 critical finding identified from 1 organisation (NHS Trust) following a triggered inspection.

The critical finding was given for GCP Compliance. There were a number of findings that were in breach of GCP and the Regulations, which are outlined as 4 major findings for Authorisations, Data Integrity, Record Keeping/Essential Documents and Subject Safety. These findings were graded in this manner, rather than 4 critical findings, as it was recognised that a number of these issues were outside the control of the Trust, and that a number of new procedures had been put in place to prevent these issues recurring.

- Two trials were assessed as meeting the definition of a CTIMP; however neither trial had MHRA approval. One of these trials was queried with the MHRA by the Trust previously and MHRA confirmed that a Clinical Trial Authorisation (CTA) was required, however the study had already commenced at the time of the enquiry but the trial was neither halted nor was approval sought. The PI continued to conduct the trial without approval despite being informed of the requirement by the Trust.

- Although Research Ethics Committee (REC) approval was sought for both studies, the approvals were invalid as the REC that provided the favourable opinion was not recognised as a CTIMPs REC. The REC approval for one trial was further invalidated as it referred to the Trust as the trial site and the trial was not conducted there. The other study was also further invalidated as a REC condition had not been adhered to.

- One of trials commenced prior to REC approval and as there was no MHRA approval this was contrary to the conditions of sponsorship of the Trust.

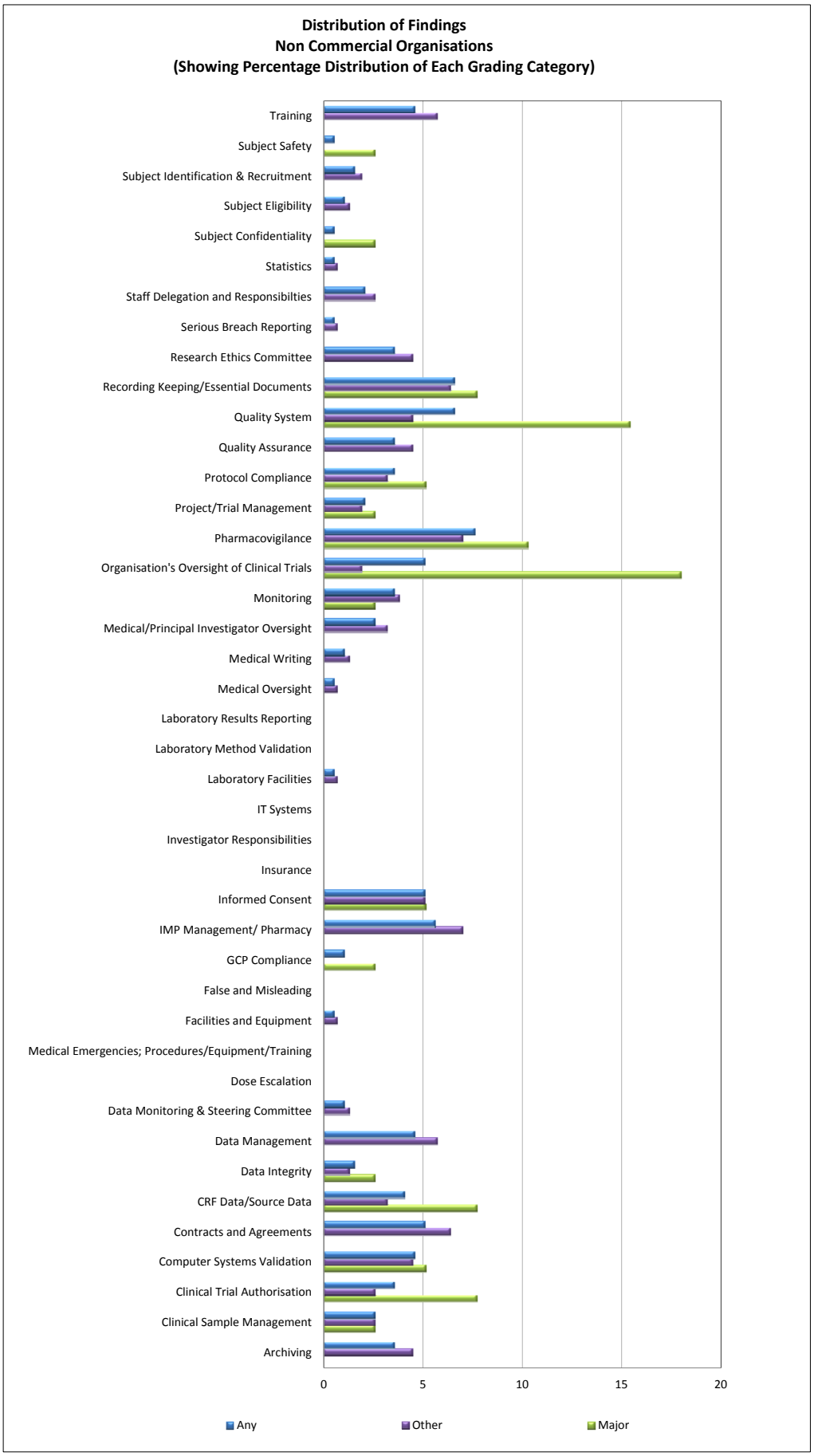
- One study was classified as an ATIMP trial, and as such would have been required to include long term follow-up of patients for safety events. If the trial had been approved by MHRA, then a 2-year safety follow-up would have been expected as part of the protocol. This had not been undertaken for the trial patients.

- There was no trial master file for either study reviewed during the inspection; therefore it was not possible to reconstruct either trial. Key documentation was missing, for example:

    - Signed consent forms for each patient
    - Patient notes; source documentation,
    - Data relating to the trial (for example records of ultrasounds, questionnaires, screening procedures)
    - Any records of IMP manufacture, shipping, receipt, QP certification, labelling etc.
    - Safety records, i.e. SUSAR reports, Annual Safety Reports
    - Statistical records (randomisation, analysis etc.)
    - Investigators brochure.

- The results in the publication were questionable as there was no data to verify them against.

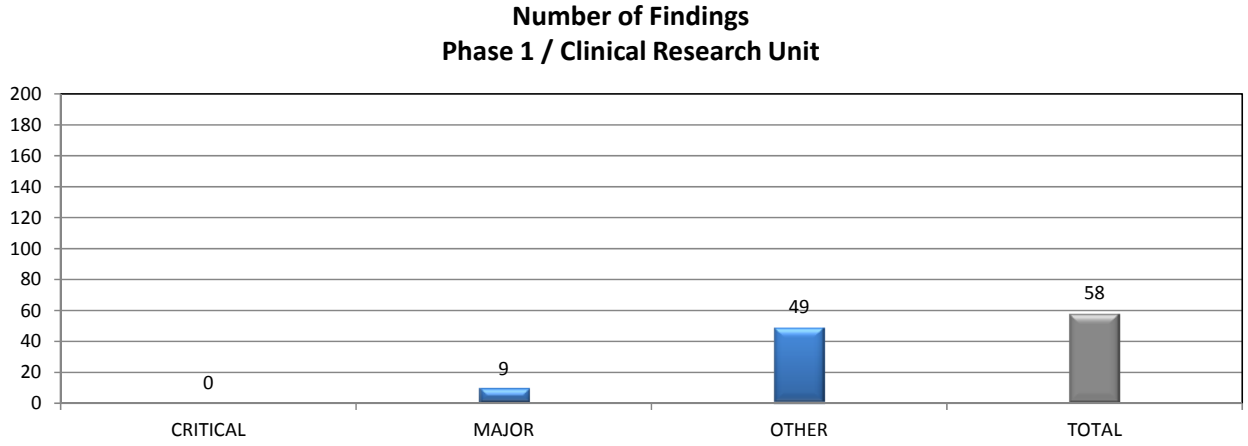
The figure on the following page shows the distribution of Major, Other and any grade of inspection findings. This identifies the areas where GCP inspectors have been making observations of non-compliance with GCP.

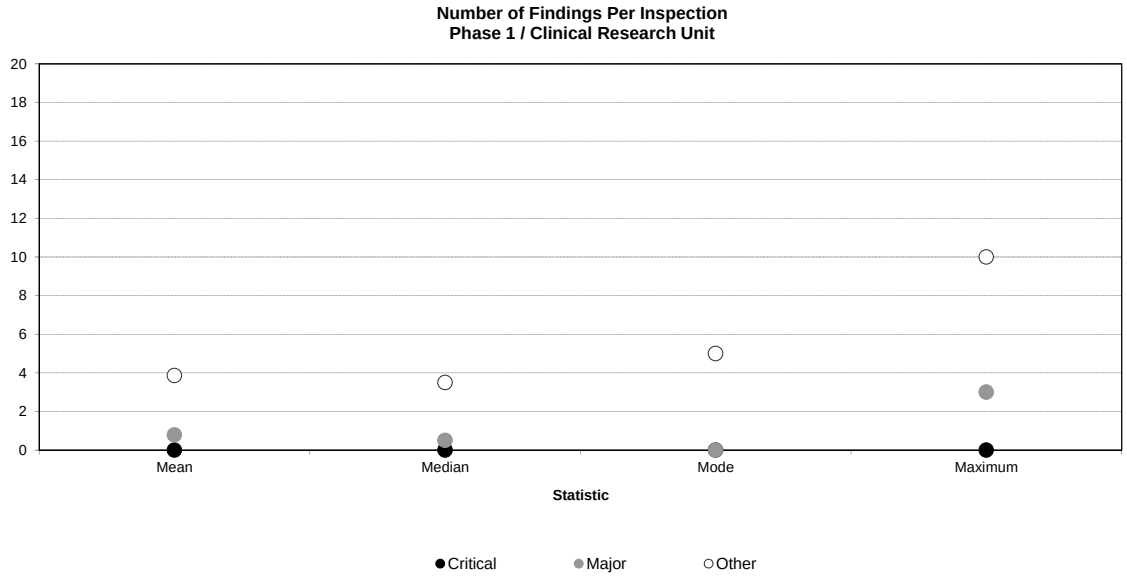

Distribution of Findings
Non Commercial Organisations
(Showing Percentage Distribution of Each Grading Category)
Training
Subject Safety
Subject Identification & Recruitment
Subject Eligibility
Subject Confidentiality
Statistics
Staff Delegation and Responsibilties
Serious Breach Reporting
Research Ethics Committee
Recording Keeping/Essential Documents
Quality System
Quality Assurance
Protocol Compliance
Project/Trial Management
Pharmacovigilance
Organisation's Oversight of Clinical Trials
Monitoring
Medical/Principal Investigator Oversight
Medical Writing
Medical Oversight
Laboratory Results Reporting
Laboratory Method Validation
Laboratory Facilities
IT Systems
Investigator Responsibilities
Insurance
Informed Consent
IMP Management/ Pharmacy
GCP Compliance
False and Misleading
Facilities and Equipment
Medical Emergencies; Procedures/Equipment/Training
Dose Escalation
Data Monitoring & Steering Committee
Data Management
Data Integrity
CRF Data/Source Data
Contracts and Agreements
Computer Systems Validation
Clinical Trial Authorisation
Clinical Sample Management
Archiving
0
5
10
15
20
Any
Other
Major

## 3.4 Commercial Phase 1 Units/Clinical Research Units (Routine Systems and Triggered)

A total of 14 inspections were done of Commercial Phase 1 Units/Clinical Research Units. All but 2 were also inspections for the MHRA voluntary phase 1 accreditation scheme. One of the inspections was a triggered inspection.

Of the 14 reported inspections, none had a critical finding and 7 (50.0%) had at least one major finding. The number of findings and findings per inspection are represented on the figures below.

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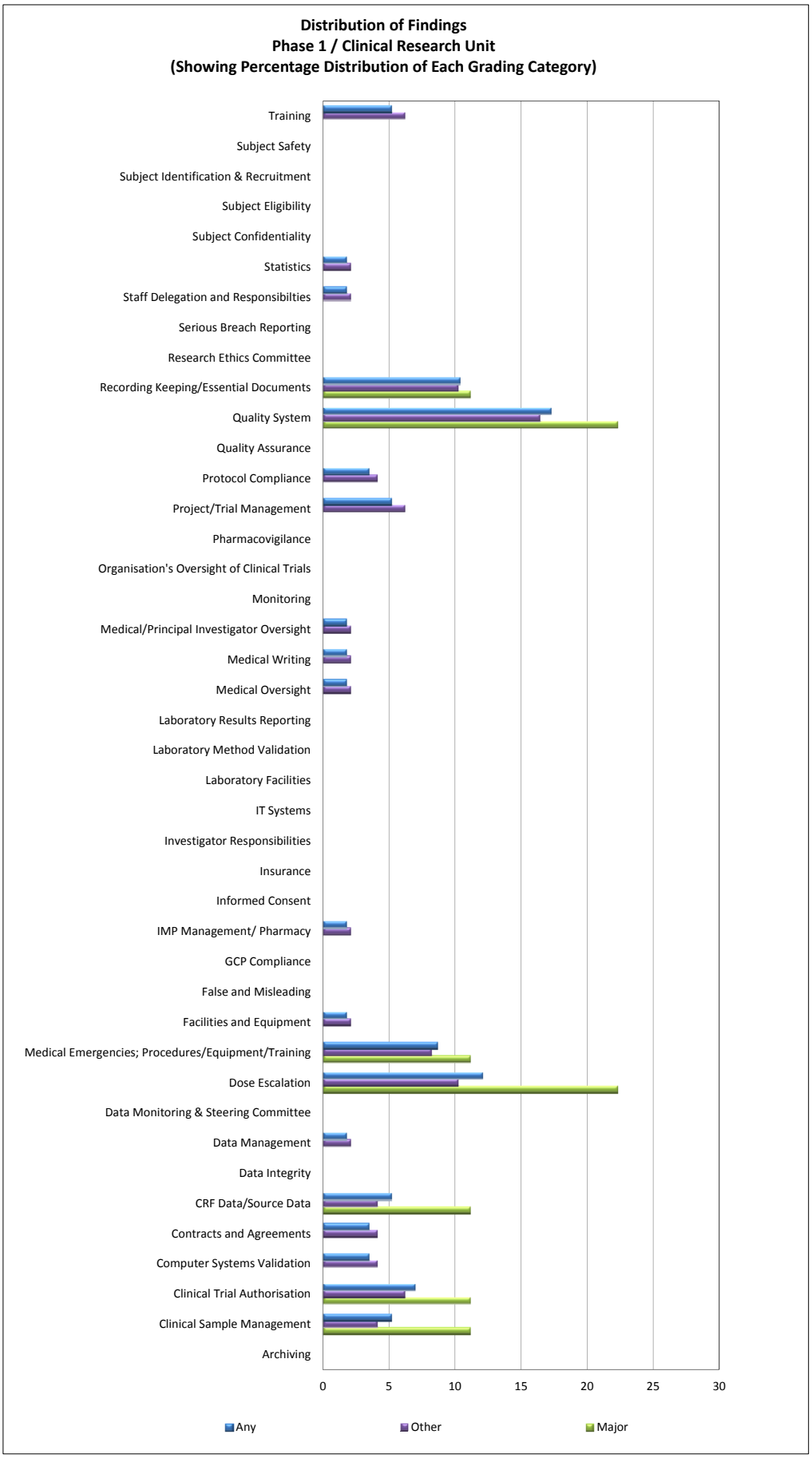
Distribution of Findings
Phase 1 / Clinical Research Unit
(Showing Percentage Distribution of Each Grading Category)
Training
Subject Safety
Subject Identification & Recruitment
Subject Eligibility
Subject Confidentiality
Statistics
Staff Delegation and Responsibilties
Serious Breach Reporting
Research Ethics Committee
Recording Keeping/Essential Documents
Quality System
Quality Assurance
Protocol Compliance
Project/Trial Management
Pharmacovigilance
Organisation's Oversight of Clinical Trials
Monitoring
Medical/Principal Investigator Oversight
Medical Writing
Medical Oversight
Laboratory Results Reporting
Laboratory Method Validation
Laboratory Facilities
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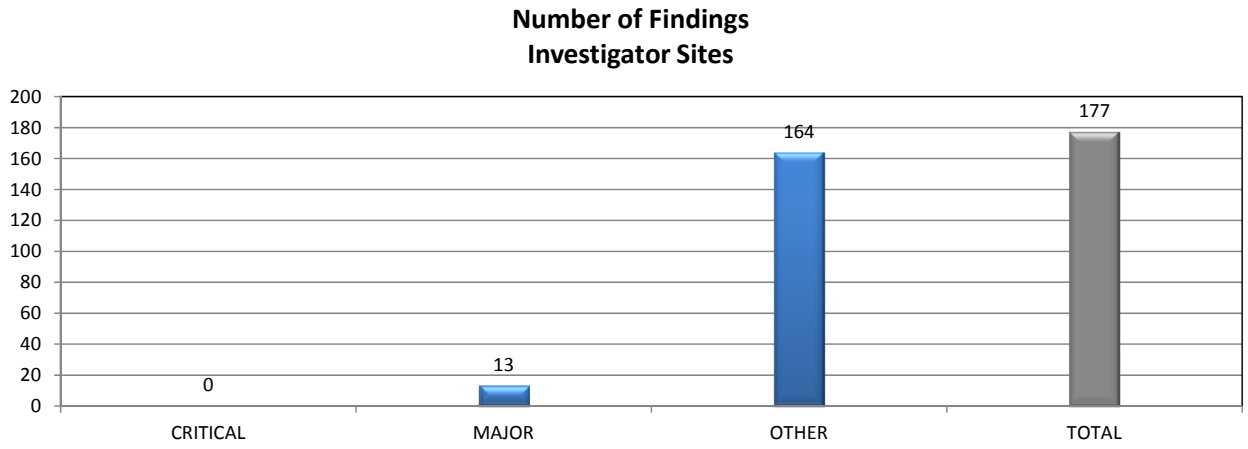
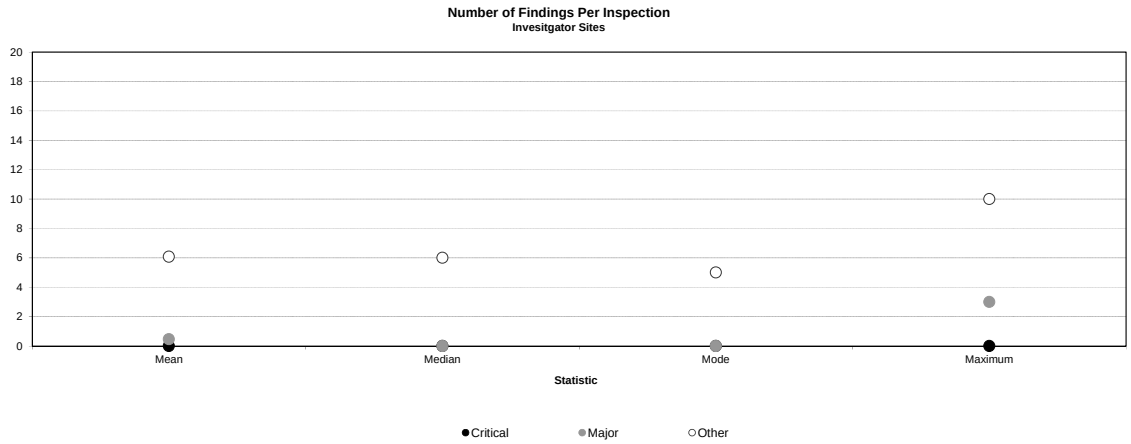
Data Monitoring & Steering Committee
Data Management
Data Integrity
CRF Data/Source Data
Contracts and Agreements
Computer Systems Validation
Clinical Trial Authorisation
Clinical Sample Management
Archiving
0
5
10
15
20
25
30
Any
Other
Major

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

A total of 28 investigator sites in the UK were inspected, all were as an associated site with a sponsor inspection.

Of the 28 inspections, none had a critical finding and 9 (32.1%) had at least one major finding. The number of findings and findings per inspection are represented on the figures 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.

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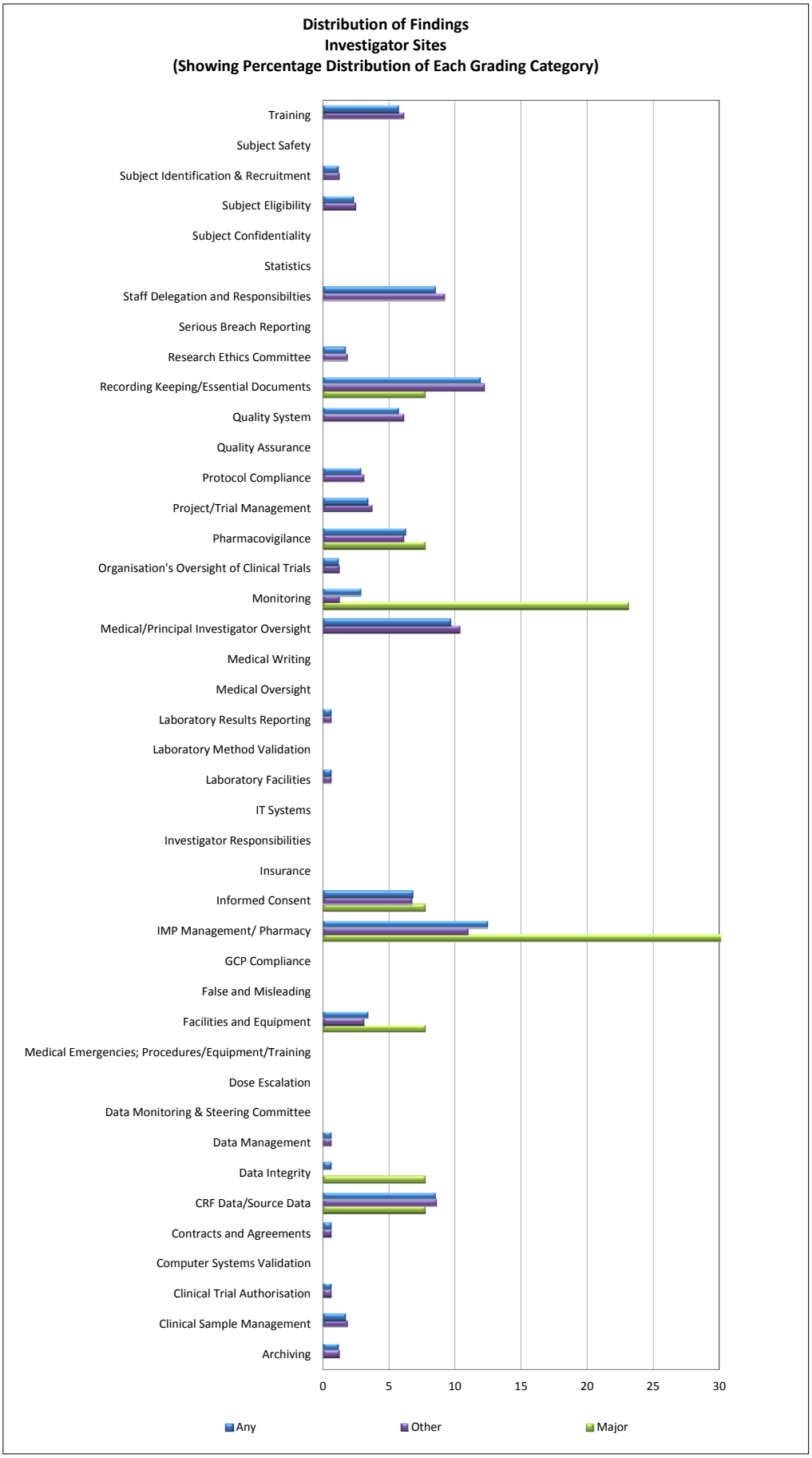
Distribution of Findings
Investigator Sites
(Showing Percentage Distribution of Each Grading Category)
Training
Subject Safety
Subject Identification & Recruitment
Subject Eligibility
Subject Confidentiality
Statistics
Staff Delegation and Responsibilties
Serious Breach Reporting
Research Ethics Committee
Recording Keeping/Essential Documents
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Medical Emergencies; Procedures/Equipment/Training
Dose Escalation
Data Monitoring & Steering Committee
Data Management
Data Integrity
CRF Data/Source Data
Contracts and Agreements
Computer Systems Validation
Clinical Trial Authorisation
Clinical Sample Management
Archiving
0
5
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20
25
30
Any
Other
Major