Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

GCP INSPECTORATE

GCP INSPECTIONS METRICS REPORT

METRICS PERIOD: 1st April 2017 to 31st March 2018

DATE OF ISSUE: 4th May 2020

MHRA
Inspection & Standards Division,
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Canary Wharf,
London,
E14 4PU

1. INTRODUCTION

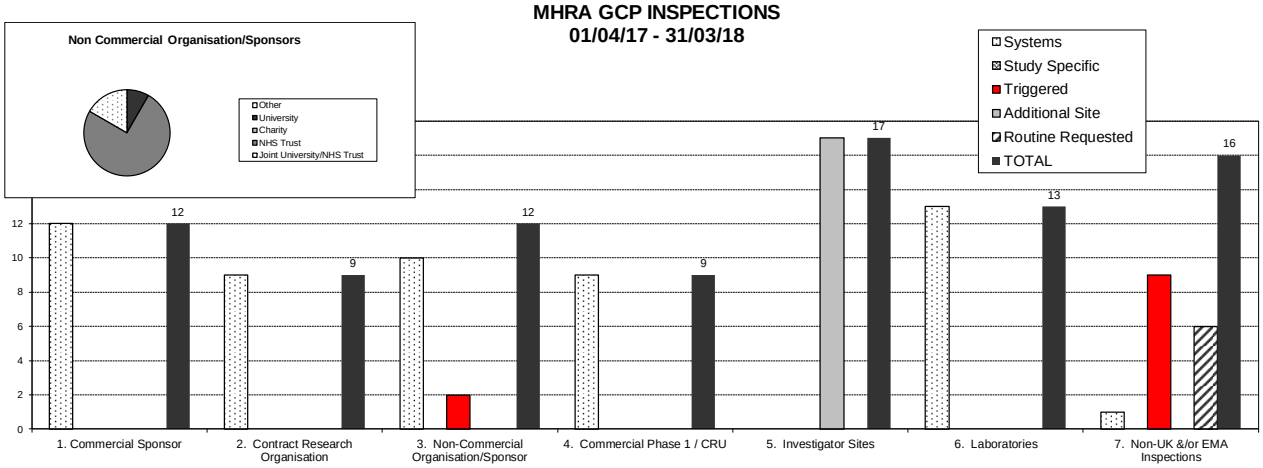
This report covers the metrics period 1st April 2017 to 31st March 2018.

2. GCP INSPECTIONS UNDERTAKEN

During the Metrics Period a total of 88 GCP Inspections were undertaken by the MHRA GCP Inspectorate. The types of inspections are presented below.

The number of UK inspections of non-commercial organisations was 12, of commercial sponsors was 12, of Contract Research Organisations (CROs) was 9, of investigator sites there were 17 and finally there were 9 phase 1 unit inspections. GCP inspections of UK laboratory facilities conducting clinical trial sample analysis are generally conducted by the MHRA Laboratories Inspectorate and there were 13 inspections. The number of non-UK inspections conducted by MHRA GCP inspectorate was 16. Of these 16 there were 6 bioequivalence (BE) which were all triggered and 9 European Medicines Agency (EMA) requested inspections. One of the EMA inspections was actually of an investigator site in the UK conducted by UK/EU inspectors and not part of the UK statutory program so it has been included here. One of the inspections was a biosimilar inspection. These 9 EMA inspections related to 4 EMA marketing authorisation procedures, 2 of which were triggered and 2 were routine. The final inspection of the 16 was a non-UK inspection (a provider of eSystems for clinical trials) where the organisation opted to host the inspection outside of the UK, but this was part of the UK risk based domestic inspection programme and whilst in the figure below is counted as a non-UK inspection, it is included in the CRO metrics in section 3.2, therefore the CRO metrics is based on a total of 10.

Triggered inspections are carried out because of information received by the GCP Inspectorate, for example in response to a serious breach report, or as part of a centralised or national Marketing Authorisation Application. Of the inspections, 11 triggered inspections were undertaken of different types of organisations. There were 2 UK triggered inspections of non-commercial organisations and 9 triggered non-UK BE/EMA inspections.



3. INSPECTION REPORTS AND FINDINGS

Reports relating only to the inspections carried out and completed 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. There are also occasions where there are two separate visits to the same organisation to complete the inspection. Where an inspection was conducted before 1st April 2018 and the other inspections (e.g. associated investigator site or further visit) were conducted after 1st April 2018 (e.g. sponsor site then the investigator site(s)) the findings from the inspections

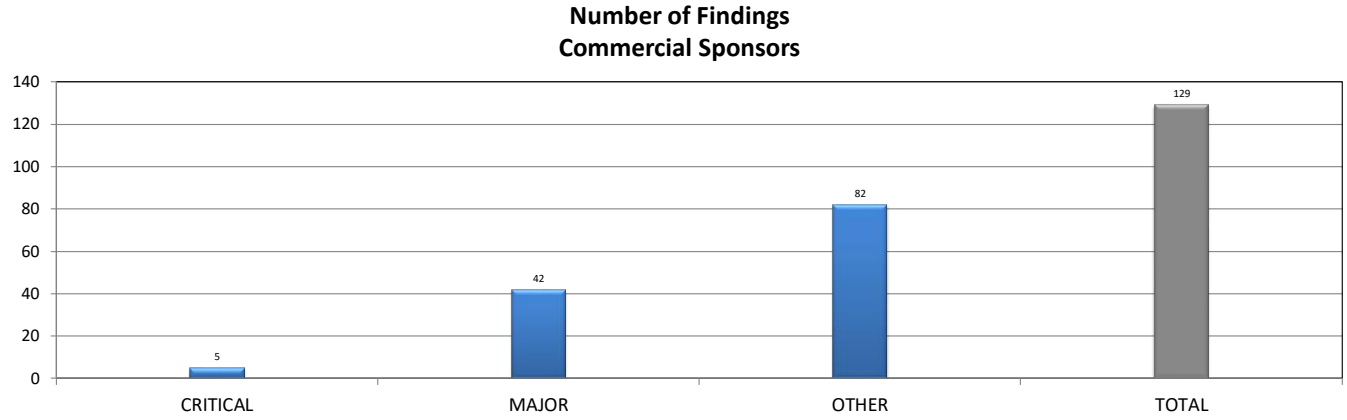
conducted/completed after 1st April 2018 will not be included in this metrics report, as these were inspections conducted/completed during the 2018-2019 Metrics Period.

Two organisations were inspected twice during the year - a Phase 1 unit and a Laboratory. There were 2 investigator site inspections conducted in the reporting period as associated sites of a sponsor inspection was undertaken in the previous reporting period of 2016-2017.

Metrics from inspections requested by the CHMP and coordinated by the EMA are produced by the EMA. Findings from inspections of GCP laboratories and UK triggered BE inspections are reported by the GCP/GLP Inspectorate. The findings are those that were contained in the inspection reports and do not consider any inspection responses but may do so in the explanatory text for critical findings. The metrics data entry had an independent sample Quality Control (QC) check.

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

A total of 12 commercial sponsors were inspected and all have been reported. All these inspections were systems inspections. Of the 12 inspections, 3 (25.0%) had at least one critical finding and all (100 %) had at least one major and/or critical finding. The total number of findings and findings per inspection are represented on the figures below.



Number of Findings Per Inspection (Commercial Sponsors)

	Mean	Median	Mode	Maximum	n
Critical	0.4	0.0	0.0	3	12
Major	3.5	3.5	2.0	7	12
Other	6.8	6.5	10.0	12	12

There were 5 critical findings from 3 organisations.

Critical Finding 1

A pharmaceutical company had a critical finding for **Pharmacovigilance**. This concerned breaches of UK Statutory Instrument 2004/1031 (as amended), Regulations 11 and 22 and 2011/C 172/01: Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use ('CT-3'). This was comprised of the following main observations:

- New versions of Refence Safety Information (RSI) were being uploaded to the pharmacovigilance database and implemented for expectedness assessment prior to regulatory approval.

- SUSARs were being reassessed for expectedness after follow-up information was received and were potentially being downgraded based on the updated unapproved RSI.

- It was not defined anywhere in the Quality Management System what the RSI was and how it was maintained and implemented.

- There was evidence of late reporting of SUSARs across all studies reviewed, one factor for this was the company considered day zero of the reporting timeline to be re-set if new information was received regardless of whether an initial report had been submitted

The company was required to undertake an impact review of all trials for the previous 3 years to identify underreported and inappropriately downgraded SUSARs.

Critical Findings 2, 3 and 4

A pharmaceutical company had 3 critical findings identified during their inspection.

The first critical finding was for **Pharmacovigilance**. This concerned breaches of UK Statutory Instrument 2004/1031 (as amended), Regulation 24 and 2011/C 172/01: Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use ('CT-3'). There were a number of issues identified below that contributed to the underreporting of SUSARs and prevented the inspectors from being able to completely assess if all SUSARs had been reported to the appropriate National Competent Authorities.

- The company did not have systems to effectively oversee the reporting of SAEs from sites. The spreadsheet database used by the PV department for SAEs was inadequate as there were numerous examples of essential fields such as relatedness, date of site awareness and RSI version used for the expectedness assessment not being populated. There was no SOP or formal guidance document associated with the use of the spreadsheet and so there was no consistence in its use.

- When the RSI section of the spreadsheet had been populated there were numerous examples of an Investigator Brochure (IB) containing the RSI being used that had been rejected and therefore not approved by the MHRA.

- When the date of site awareness was populated in the spreadsheet there were numerous examples of late SAE reporting from investigator sites to the sponsor including some over 50 days late, but no further action had been taken by the sponsor to rectify the issue. The formula used to calculate the time taken by sites for reporting to the sponsor in the spreadsheet was also not working correctly in all rows of the spreadsheet resulting inaccurate assessment of whether the case was reported late.

- There were numerous examples of the investigators reporting causality as not assessable or not reported for unexpected events, but these events had not been assessed and considered to be reported as SUSARs by the sponsor, as a result unreported SUSARs were identified.

A second critical finding was given for providing **False and Misleading Information** to the MHRA; a breach of UK Statutory Instrument 2004/1031 (as amended), Regulation 50. Following recent EU Member State inspections, the company was required to commission a number of independent audits to demonstrate that appropriate corrective and preventative actions had been undertaken. A report of an audit of the pharmacovigilance systems had been submitted to regulatory authorities. This report stated that a new validated pharmacovigilance database and updated SOPs were place and in use for all new SAEs. It also stated that a back log of SAEs was being entered into the database. The inspection

revealed that there was no working database and no updated SOPs. On questioning by the inspectors, the company admitted that the audit report was inaccurate.

A third critical finding was given for **Data Integrity**, a breach of UK Statutory Instrument 2004/1031 (as amended) Regulation 28 and Schedule 1, Part 2, (9). The following issues were identified.

- The number of fatal cases listed in a product IB was inconsistent with a Clinical Study Report (CSR), as the CSR for the single study had a higher number of fatalities than the IB containing data from 12 studies of the same product. It was not possible to confirm that the IB data was reliable.

- There was evidence of hard coding of both the outcome and severity of SAEs performed by the statistics department staff in a DSUR, but there was no documentation supporting the hard coding in particular to confirm that the changes made to SAE severity had been approved by the reporting investigator.

- The database for a study was unlocked and could be edited despite the CSR having been submitted to the Regulatory Authority. The data management department were not aware that the data extraction that they provided to the statistics department was used for the creation of the CSR. The database audit trail was provided post inspection and did not show any evidence of post CSR data changes.

Critical Finding 5

A pharmaceutical company was given a critical finding for **Pharmacovigilance** related to breaches of UK Statutory Instrument 2004/1031 (as amended), Regulations Part 4, 28, 31A (2) to (6); Part 5, 32 (9), 33 (1) and (3) and 34 and Schedule 1, Part 2, (4) and (9). Additionally, there were breaches of 2011/C 172/01: Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use ('CT-3'). There was a clear lack of understanding of the requirement in relation to CT-1, CT-3 and the 'Clinical Trials Facilitation Group' CTFG Q&A guidance and the organisation was required to review these documents and provide corrective and preventative actions (CAPA) including an impact assessment of the extent of incorrect and potential under-reporting of SUSARs across all relevant trials, especially for those SAEs where relatedness has not been separated out for IMP, device and procedure. Examples of issues identified included the following:

- There was a lack of understanding about how expectedness should be assessed for a combined IMP and device product for serious adverse events (SAEs) considered related to the investigational medical product (IMP) and it was clear that numerous SAEs had not been assessed for relatedness and expectedness correctly for the IMP. Therefore, there was significant potential for under-reporting of numerous SUSARs. For example:

- There was no individual assessment documented of whether an SAE was related to the IMP, the device or the procedure by the investigator, only one overall relatedness assessment. The IB listed expected adverse events (AEs) for the IMP, device and procedure, but it did not list expected SAEs for the IMP, device and procedure.

- When performing the expectedness assessment, if the term appeared anywhere in the IB (e.g. tables of non-related AEs (not SAEs), or term was similar to that in the IB) it was considered expected, even if this was a listing of AEs regardless of relatedness. In addition, some SAEs were assessed as expected based on medical judgement even when there was no term listed in the IB. Therefore, there was not a specific RSI section identified and being used.

- There was no evidence of sponsor review or oversight of SAEs or their associated narratives in the trial master file (TMF) for any of the trials, as this was all documented via email

correspondence, none of which were located in the TMF or able to be provided during the inspection.

- The version and exact section of the IB to be used as the RSI was not defined or documented. Therefore, it could not be verified or ensured that the IB in place at the event onset would be used to make expectedness assessments.

- There was no formal company causality and expectedness assessment performed by the sponsor until the end of the trial; this assessment was performed at the point of clinical study report (CSR) compilation.

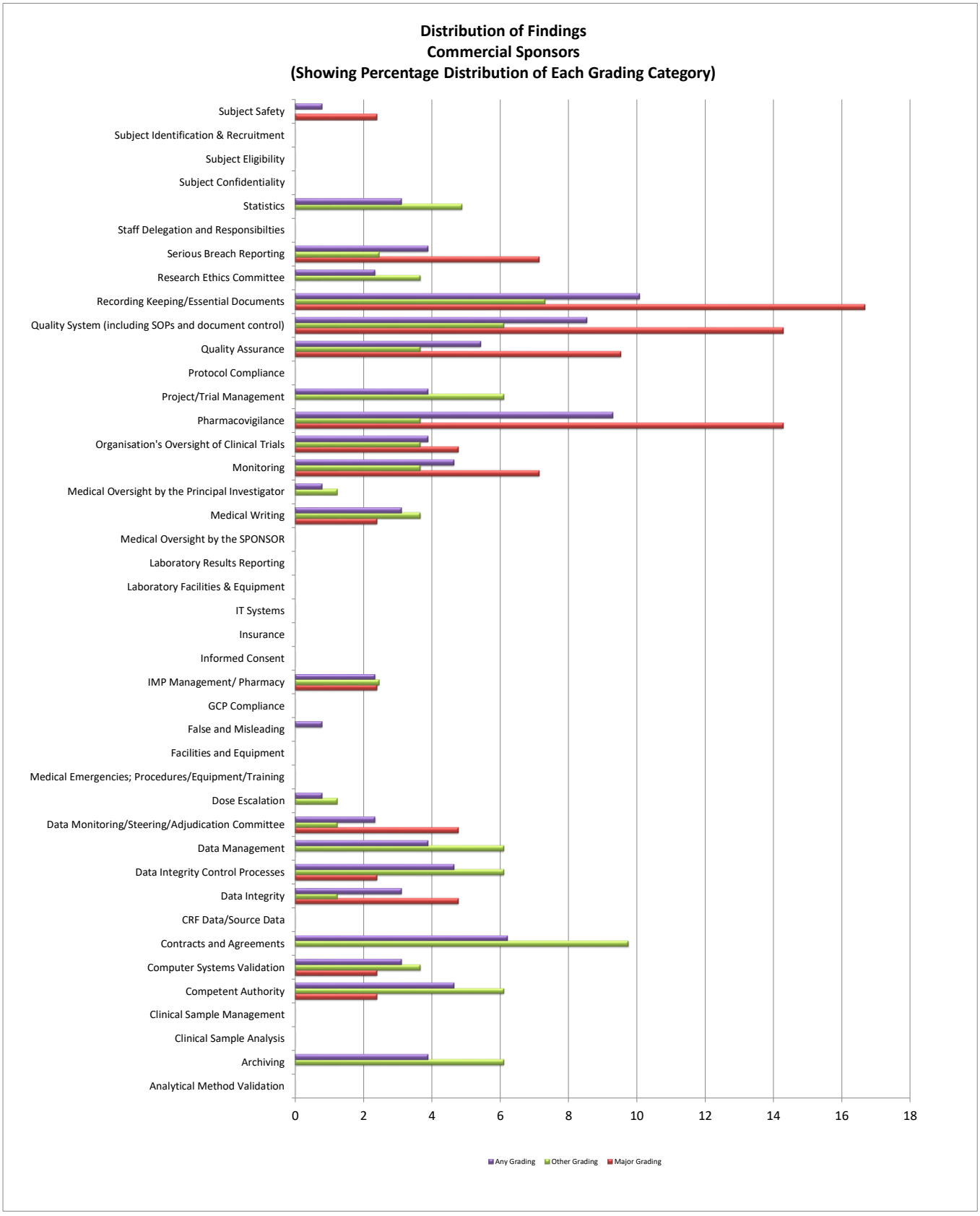
- The TMF was not adequately defined to ensure all relevant documentation for an SAE case could be located.

- The SOP relating to managements of SAEs lacked details about relevant EU/UK legislations and was not in line with current EU expectations which could lead to underreporting of SUSARs.

- It was not possible to identify the RSI that was being used for the drug safety update report (DSUR) line listings that were reviewed during the inspection.

Summary of Findings for Commercial Sponsors

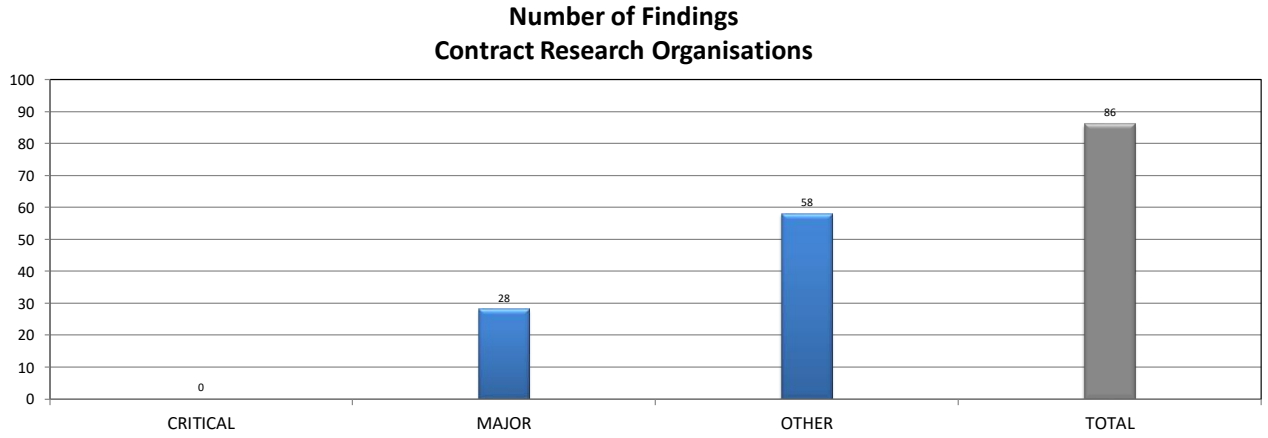
The figure on the following page shows the distribution of Major, Other and any grade of inspection findings. This identifies the areas where GCP inspectors have been making observations of non-compliance with GCP.


Distribution of Findings
Commercial Sponsors
(Showing Percentage Distribution of Each Grading Category)
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 (including SOPs and document control)
Quality Assurance
Protocol Compliance
Project/Trial Management
Pharmacovigilance
Organisation's Oversight of Clinical Trials
Monitoring
Medical Oversight by the Principal Investigator
Medical Writing
Medical Oversight by the SPONSOR
Laboratory Results Reporting
Laboratory Facilities & Equipment
IT Systems
Insurance
Informed Consent
IMP Management/ Pharmacy
GCP Compliance
False and Misleading
Facilities and Equipment
Medical Emergencies; Procedures/Equipment/Training
Dose Escalation
Data Monitoring/Steering/Adjudication Committee
Data Management
Data Integrity Control Processes
Data Integrity
CRF Data/Source Data
Contracts and Agreements
Computer Systems Validation
Competent Authority
Clinical Sample Management
Clinical Sample Analysis
Archiving
Analytical Method Validation
0
2
4
6
8
10
12
14
16
18
Any Grading
Other Grading
Major Grading

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

A total of 10 Contract Research Organisations were inspected and all inspections have been reported. All 10 were systems inspections. It should be noted that vendors of electronic systems and niche providers of services used in clinical trials (aside from clinical conduct of a trial) are and have always been included in this category.

Of the 10 inspections, 0 (0.0 %) had critical findings and 8 (80.0%) had at least one major finding. The total number of findings and the findings per inspection are represented on the figures below.



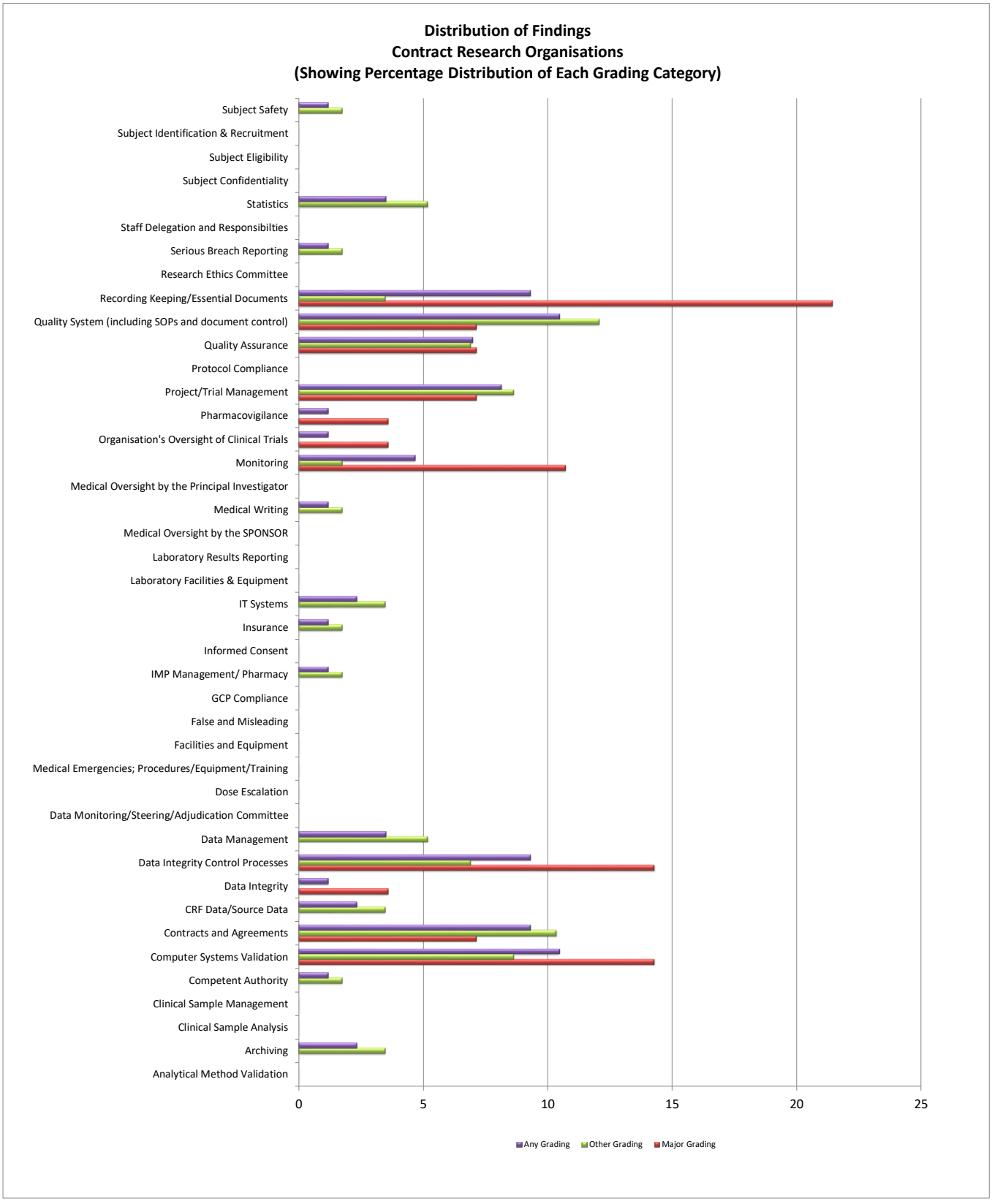
Number of Findings Per Inspection (Contract Research Organisations)

	Mean	Median	Mode	Maximum	n
Critical	0.0	0.0	0.0	0	10
Major	2.8	2.5	1.0	6	10
Other	5.8	6.0	8.0	9	10

There were no critical findings identified.

Summary of Findings from Contract Research Organisations

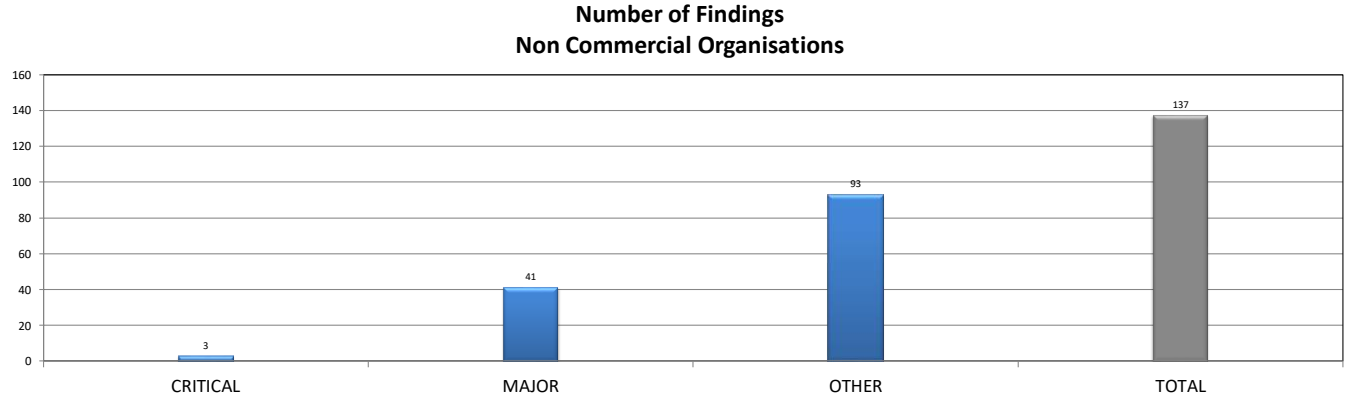
The figure on the following page shows the distribution of Major, Other and any grade of inspection findings. This identifies the areas where GCP inspectors have been making observations of non-compliance with GCP.


Distribution of Findings
Contract Research Organisations
(Showing Percentage Distribution of Each Grading Category)
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 (including SOPs and document control)
Quality Assurance
Protocol Compliance
Project/Trial Management
Pharmacovigilance
Organisation's Oversight of Clinical Trials
Monitoring
Medical Oversight by the Principal Investigator
Medical Writing
Medical Oversight by the SPONSOR
Laboratory Results Reporting
Laboratory Facilities & Equipment
IT Systems
Insurance
Informed Consent
IMP Management/ Pharmacy
GCP Compliance
False and Misleading
Facilities and Equipment
Medical Emergencies; Procedures/Equipment/Training
Dose Escalation
Data Monitoring/Steering/Adjudication Committee
Data Management
Data Integrity Control Processes
Data Integrity
CRF Data/Source Data
Contracts and Agreements
Computer Systems Validation
Competent Authority
Clinical Sample Management
Clinical Sample Analysis
Archiving
Analytical Method Validation
0
5
10
15
20
25
Any Grading
Other Grading
Major Grading

3.3 Non-Commercial Organisations (Routine Systems and Triggered)

A total of 12 non-commercial organisations were inspected. Of the 12, 1 was of a university, 9 were of NHS Trusts/Health Boards and 2 were of a joint inspection of an NHS Trust/Health Board and University. Three of the non-commercial organisations were clinical trial units (CTU), which are inspected in their own right although part of a larger organisation that may also have systems inspections. All have been reported. Two of the inspections were triggered inspections.

Of the 12 inspections, 3 (25.0%) had at least one critical finding and 12 (100.0%) had at least one major and/or critical finding. The number of findings and findings per inspection are represented on the figures below.



Number of Findings Per Inspection (Non-Commercial Organisations)

	Mean	Median	Mode	Maximum	n
Critical	0.3	0.0	0.0	1	12
Major	3.4	3.0	3.0	6	12
Other	7.8	5.5	4.0	17	12

There were 3 critical finding identified from 3 organisations.

Critical Finding 1

A critical finding was identified at a triggered inspection of an NHS Hospital Trust relating to **Investigational Medicinal Products** involving breaches of UK Statutory Instrument 2004/1031 (as amended), Regulations 28, 29, Schedule 1, Part 2, (4) and (9).

A Serious Breach (SB) was received concerning a mix up in administration of IMP between two patients enrolled in a placebo-controlled trial which was placed on a temporary halt pending investigation. It was stated that the root cause was that nurses had followed normal clinical practice which was for medication to be allowed to be given from one patient's medication supply to another patient. As this was a double-blind trial, the sharing of medication could result in the incorrect treatment being received. At the inspection, the serious breach CAPA was reviewed and as the root cause brought the acceptability of standard clinical practice into question a Care Quality Commission inspector also attended the inspection.

As per the SB it was initially identified that a patient erroneously received medication that was destined for another patient potentially due to their initials being the same and both patients being on the same ward at the same time. This could be verified as the electronic medicines administration records

identified who had administered medication and when. Six other potential IMP accountability deviations were identified, but it was not possible to identify if IMP had been taken from one trial patient and given to another trial patient in error due to the following confounding issues.

- The prescribing electronic systems within and without the Intensive Care Unit (ICU) which were used to record administration of IMP did not record the kit number allocation when IMP was administered to patients and this administration was not recorded on any trial specific source documents either.
- Patients were not flagged up in the prescribing systems as trials patients initially.
- One of the systems was brought into use in the ICU part way through the trial.
- The two electronic prescribing systems do not share information, so medications need to be manually updated into the system when discharged from ICU to the ward and back again.
- Ward nurses followed normal procedure for clinical medication for IMP so if IMP was dropped/spilt/lost, this wouldn't be documented.
- It was alleged that it was 'common' for a patient to be given a medicine labelled for another patient. It couldn't be verified that this was this case, however, the Trust policy didn't forbid them from doing so. It was discussed that if this did happen there should be a record in the source that this had occurred. The PI and RN were not aware of this practice.
- There was a change in storage conditions once patients were dispensed IMP from ambient at the patient's bedside to refrigerated. This change resulted in an increase in the number of discrepancies.
- Daily checks on IMP were only brought in part way through the trial and prior to that it was performed at the end of the dosing period, so it was impossible to say when and if discrepancies occurred.
- Checks on administration of IMP in the live system for 3 patients was made, but it was not possible to verify if IMP had been shared with other trials patients as the kit numbers were not recorded in the administration charts.

On review of the issues with the MHRA GCP inspectorate, it was decided that although mix up of medication could not be identified for all patients reviewed, it could not be confirmed for other patients which kit numbers of IMP they received during the trial once they were on the wards as the kit numbers were not recorded in the electronic drug charts when more than one patient was being treated at the same time. Therefore, it was not possible to verify that the patients received the correct IMP, i.e. which patients got which IMP and when, which merited a critical finding.

Critical Finding 2

A critical finding was assigned during a joint NHS Trust/University inspection for **Clinical Trial Authorisation** involving breaches of UK Statutory Instrument 2004/1031 (as amended), Regulation 12 as 2 trials had been conducted without MHRA authorisation.

A committee within the Trust had given permission to an investigator to treat patients with a medicine outside of its licensed indication. The sponsor's research oversight team was given the impression that this was being done on a per patient basis with the possibility that of one of the patients could be used as a case study in the future.

On investigation, it was discovered that the actual intention was to treat 50 subjects and collect efficacy data to assess if the treatment was as effective as the published literature suggested, and then consider changing standard clinical practice to make it an option for all patients in the trust. At the time of the inspection 20 patients had been treated. The committee felt this could be considered an audit of patient treatment rather than a clinical trial. However, whilst there was no formalised protocol a Medical assessor at the MHRA Clinical Trials Unit reviewed the summary of research provided to the Committee and the data collection forms and confirmed it was a clinical trial of IMP. An additional completed study was identified by the same investigator at the same site that also met the criteria for a clinical trial. This trail was completed with 20 patients and the data had been presented to the Committee.

For both trials, there was no MHRA, Ethics, Research and Development/HRA or sponsor approvals, and there was no Trial Master File. The patients did consent to taking treatment but did not consent to their data being collected for research and analysed.

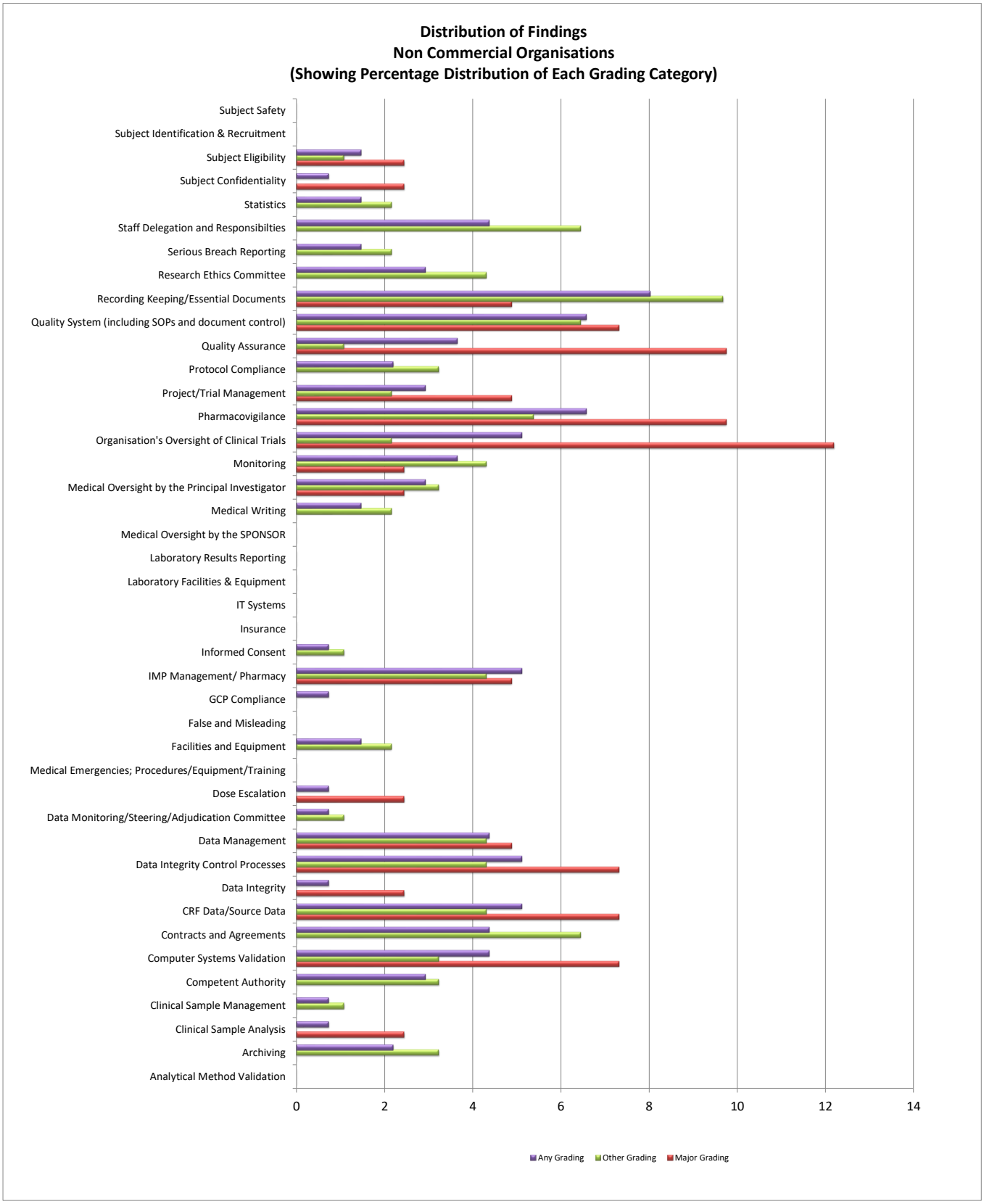
Critical Finding 3

An NHS Trust was given a critical finding for **GCP Compliance** following a triggered inspection. This related to breaches of Statutory Instrument 2004 No. 1031 (as amended), Regulations 28 and 29, Schedule 1 Part 2 (2), (4) and (9) The Rules Governing Medicinal Products in the European Union, Guidance Documents Applying to Clinical Trials Guidance on Investigational Medicinal Products (IMPs) and 'Non-Investigational Medicinal Products (NIMPs), March 2011

There were a significant number of major GCP non-compliances in the inspected trial which was reviewed in relation to the overdosing of a trial subject who subsequently died following errors in preparation of the IMP for the trial in the Aseptic Unit. The overdose was of 900mg IMP over 4.5 days instead of the prescribed 400mg over 10 days. It was identified that a similar error had occurred in 2013 which was not effectively remediated (there was no impact on subject safety on this previous occasion). In the view of the inspectors, these errors were caused by a failure in Trust systems to ensure compliance with the Clinical Trials Regulations. Major findings were identified in the areas of IMP Management, Training, Quality Systems and Source Data. These major findings and the impact on subject safety collectively contributed to this critical finding for GCP Compliance.

Summary of Findings from Non-Commercial Organisations

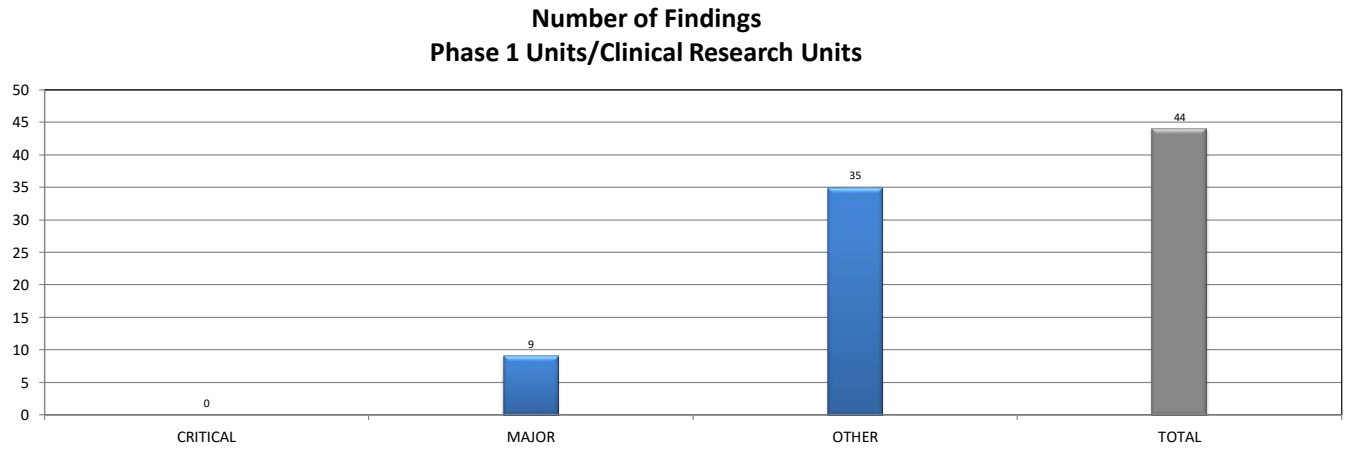
The figure on the following page shows the distribution of Major, Other and any grade of inspection findings. This identifies the areas where GCP inspectors have been making observations of non-compliance with GCP.


Distribution of Findings
Non Commercial Organisations
(Showing Percentage Distribution of Each Grading Category)
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 (including SOPs and document control)
Quality Assurance
Protocol Compliance
Project/Trial Management
Pharmacovigilance
Organisation's Oversight of Clinical Trials
Monitoring
Medical Oversight by the Principal Investigator
Medical Writing
Medical Oversight by the SPONSOR
Laboratory Results Reporting
Laboratory Facilities & Equipment
IT Systems
Insurance
Informed Consent
IMP Management/ Pharmacy
GCP Compliance
False and Misleading
Facilities and Equipment
Medical Emergencies; Procedures/Equipment/Training
Dose Escalation
Data Monitoring/Steering/Adjudication Committee
Data Management
Data Integrity Control Processes
Data Integrity
CRF Data/Source Data
Contracts and Agreements
Computer Systems Validation
Competent Authority
Clinical Sample Management
Clinical Sample Analysis
Archiving
Analytical Method Validation
0
2
4
6
8
10
12
14
Any Grading
Other Grading
Major Grading

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

A total of 9 inspections were done of Commercial Phase 1 Units/Clinical Research Units, 2 inspections were of the same organisation that had one report. Eight of the inspections were routine inspections for the MHRA voluntary phase 1 accreditation scheme and 1 was a systems inspection. None of the inspections were triggered. Note that findings reported here relate to GCP only and not those related to the accreditation scheme.

Of the 8 reported inspections, none (0%) had a critical finding and 4 (50.0%) had at least one major finding. For 2 of the inspections, there were no GCP findings and had no formal report, a letter was used instead. One of these was an office-based inspection and the other was a follow up one day inspection following the main accreditation inspection the previous year. The number of findings and findings per inspection are represented on the figures below.



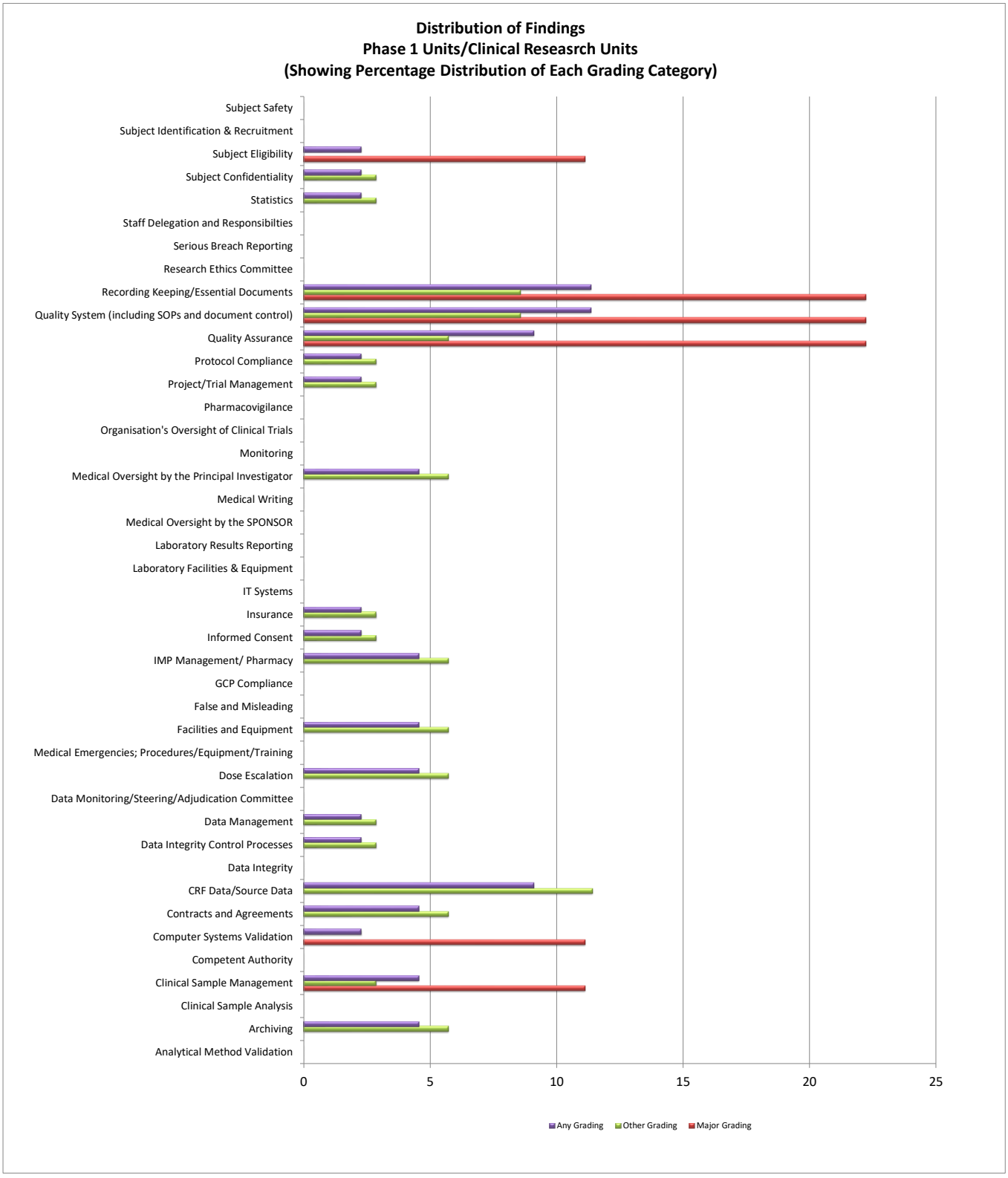
Number of Findings Per Inspection (Phase 1 Units/Clinical Research Units)

	Mean	Median	Mode	Maximum	n
Critical	0.0	0.0	0.0	0	8
Major	1.1	0.5	0.0	4	8
Other	4.4	4.5	0.0	10	8

There were no critical findings.

Summary of Findings for Phase 1 Units/Clinical Research Units)

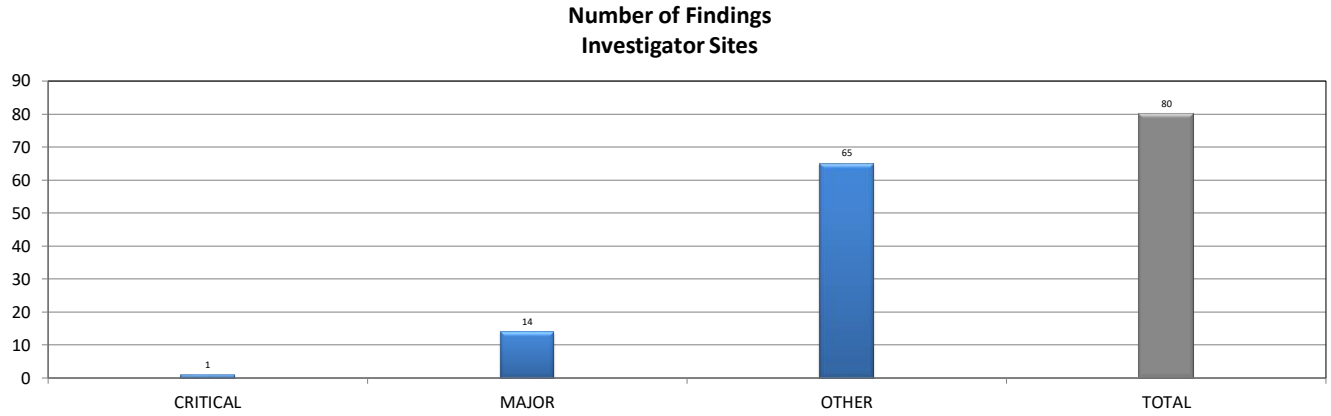
The figure on the following page shows the distribution of Major, Other and any grade of inspection findings. This identifies the areas where GCP inspectors have been making observations of non-compliance with GCP.


Distribution of Findings
Phase 1 Units/Clinical Reseasrch Units
(Showing Percentage Distribution of Each Grading Category)
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 (including SOPs and document control)
Quality Assurance
Protocol Compliance
Project/Trial Management
Pharmacovigilance
Organisation's Oversight of Clinical Trials
Monitoring
Medical Oversight by the Principal Investigator
Medical Writing
Medical Oversight by the SPONSOR
Laboratory Results Reporting
Laboratory Facilities & Equipment
IT Systems
Insurance
Informed Consent
IMP Management/ Pharmacy
GCP Compliance
False and Misleading
Facilities and Equipment
Medical Emergencies; Procedures/Equipment/Training
Dose Escalation
Data Monitoring/Steering/Adjudication Committee
Data Management
Data Integrity Control Processes
Data Integrity
CRF Data/Source Data
Contracts and Agreements
Computer Systems Validation
Competent Authority
Clinical Sample Management
Clinical Sample Analysis
Archiving
Analytical Method Validation
0
5
10
15
20
25
Any Grading
Other Grading
Major Grading

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

A total of 17 investigator sites in the UK were inspected and all were as an associated site with a sponsor/CRO/non-commercial/CTU inspection.

Of the 17 inspections, 1 (5.9%) had a critical finding and 11 (64.7%) 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.



Number of Findings Per Inspection (Investigator Sites)

	Mean	Median	Mode	Maximum	n
Critical	0.1	0.0	0.0	1	17
Major	0.8	1.0	1.0	3	17
Other	3.8	4.0	4.0	6	17

There was 1 critical finding for 1 investigator site.

Critical Finding 1

An investigator site inspection undertaken as an associated site for a commercial sponsor organisation inspection resulted in a critical finding for **Data Integrity**, a breach of UK Statutory Instrument 2004/1031 (as amended), Regulation 28, Schedule 1, Part 2, (9)

The VAS scores that were used as part of the exploratory endpoint for the trial could not be reconstructed. The scores were supposed to be generated by the patient using the tablet device after they had logged in with, a paper back up available if the device was not functioning. In most cases both the paper and the device had been populated. In these cases, there were significant differences between the scores. For example, the score had been entered as 36 on the device but was written as 60 in the paper and when the marking was actually measured it was 62. This has resulted in there being 3 different scores for the same data point with no documentation explaining why multiples were generated or which ones were the true source. There was no time recorded on the paper form and therefore it was not possible to determine which entry was generated first. Most of the paper sheets also had not been signed by the patient (80% by the investigator) and so it was not possible to verify who had completed them. Of the 60 examples checked by the inspectors one match was found between the device and paper entries when the patient had entered 100 (maximum) on both.

The audit trail of the tablet only captured the results once all 3 VAS assessments at the visit had been completed. The patient could change their score at any point until the finish button was pressed on the final confirmation screen. Any changes before this were not recorded in the Audit Trail.

The tablet also displayed numerical value of the point at which the patient was marking their score and can be changed, therefore potentially biasing the scaled assessment.

The final scores used to measure the primary outcome were calculated from the raw data by the sponsors statistics department and these scores were not given to the site when the data was returned to them.

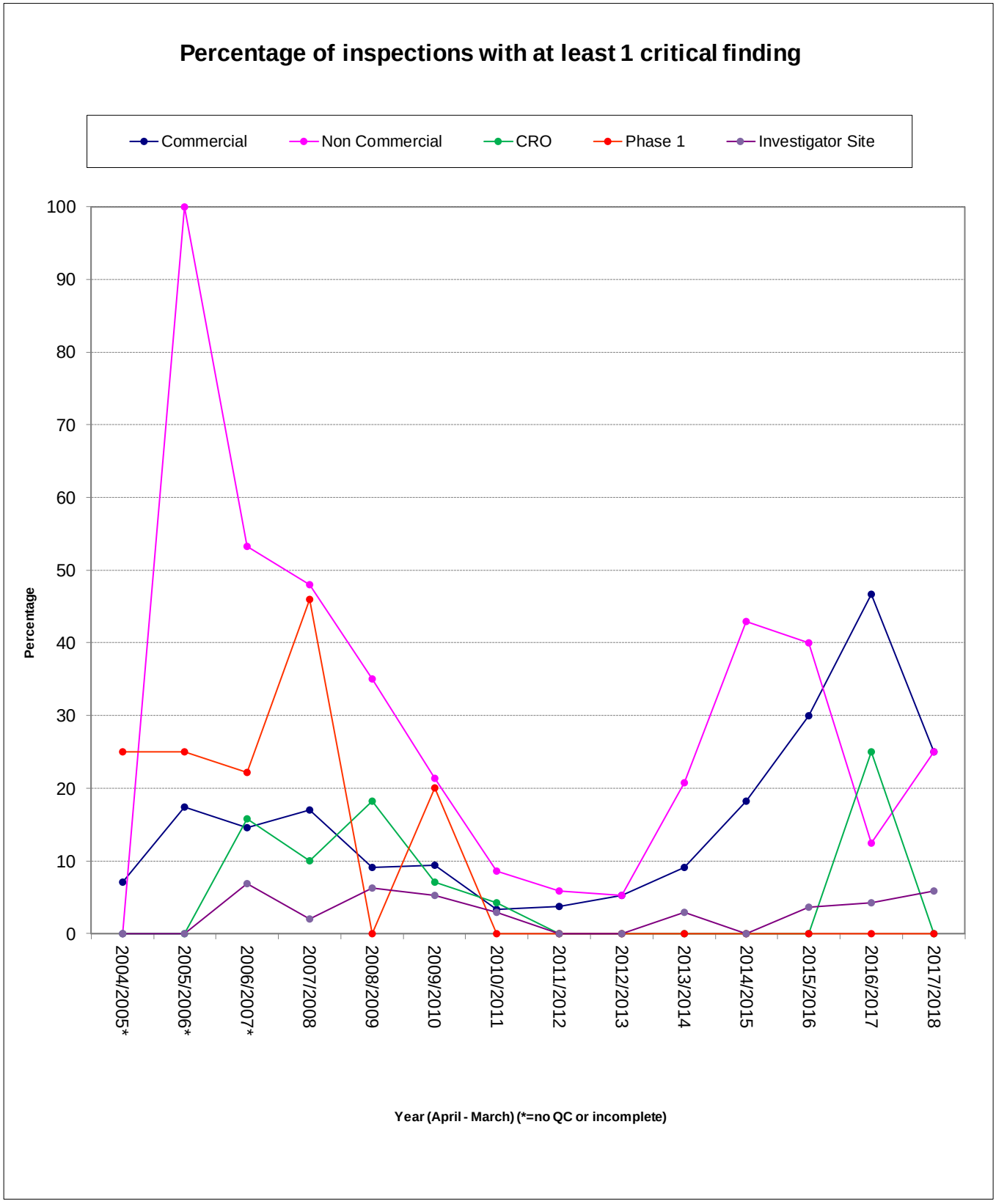
Summary of Findings for Investigator Sites

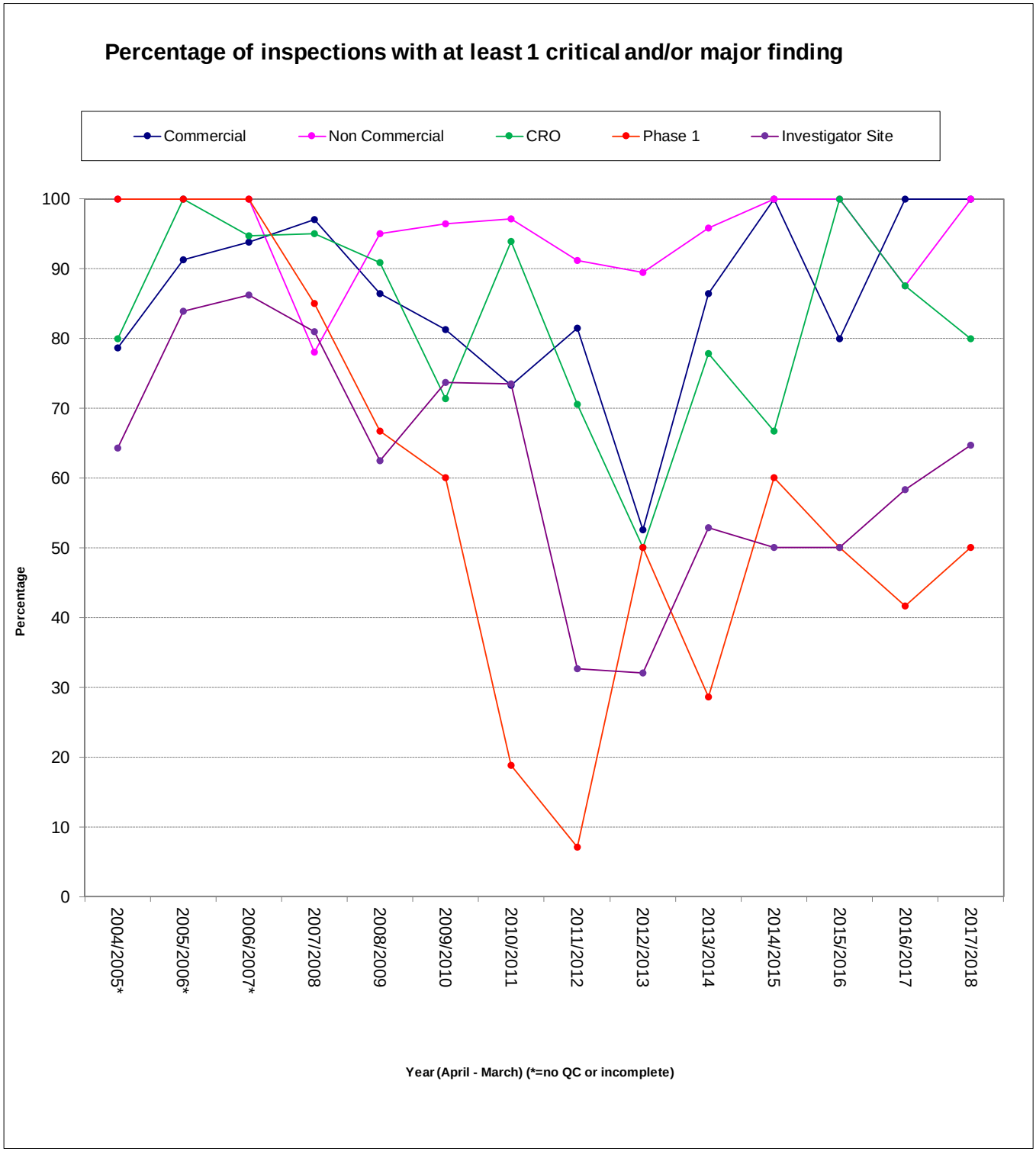
The figure on the following page shows the distribution of Major, Other and any grade of inspection findings. This identifies the areas where GCP inspectors have been making observations of non-compliance with GCP.


Distribution of Findings
Investigator Sites
(Showing Percentage Distribution of Each Grading Category)
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 (including SOPs and document control)
Quality Assurance
Protocol Compliance
Project/Trial Management
Pharmacovigilance
Organisation's Oversight of Clinical Trials
Monitoring
Medical Oversight by the Principal Investigator
Medical Writing
Medical Oversight by the SPONSOR
Laboratory Results Reporting
Laboratory Facilities & Equipment
IT Systems
Insurance
Informed Consent
IMP Management/ Pharmacy
GCP Compliance
False and Misleading
Facilities and Equipment
Medical Emergencies; Procedures/Equipment/Training
Dose Escalation
Data Monitoring/Steering/Adjudication Committee
Data Management
Data Integrity Control Processes
Data Integrity
CRF Data/Source Data
Contracts and Agreements
Computer Systems Validation
Competent Authority
Clinical Sample Management
Clinical Sample Analysis
Archiving
Analytical Method Validation
0
10
20
30
40
50
60
Any Grading
Other Grading
Major Grading

3.6 Inspection Finding Trends Since Statutory GCP Inspections Implementation

The following figures show the date from previous metrics reports and earlier unpublished data to illustrate the changes in the number of findings for different organisations. This shows a general improvement following the introduction of statutory GCP inspections, however, for some types of organisations, recent years have shown general increase in the severity of inspection findings. For this year, there was downward movement for commercial sponsors and CROs. The trend upwards for investigator sites appears to be a result of the impact of increased use of electronic health records and other sponsor provided electronic source data/CRF systems.


Percentage of inspections with at least 1 critical finding
Commercial
Non Commercial
CRO
Phase 1
Investigator Site
Percentage
100
90
80
70
60
50
40
30
20
10
0
2004/2005*
2005/2006*
2006/2007*
2007/2008
2008/2009
2009/2010
2010/2011
2011/2012
2012/2013
2013/2014
2014/2015
2015/2016
2016/2017
2017/2018
Year (April - March) (*=no QC or incomplete)


Percentage of inspections with at least 1 critical and/or major finding
Commercial
Non Commercial
CRO
Phase 1
Investigator Site
Percentage
100
90
80
70
60
50
40
30
20
10
0
2004/2005*
2005/2006*
2006/2007*
2007/2008
2008/2009
2009/2010
2010/2011
2011/2012
2012/2013
2013/2014
2014/2015
2015/2016
2016/2017
2017/2018
Year (April - March) (*=no QC or incomplete)