Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

GCP INSPECTORATE

GCP INSPECTIONS METRICS REPORT

METRICS PERIOD: 1st April 2018 to 31st March 2019

DATE OF ISSUE: 12th February 2021

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1. INTRODUCTION

This report covers the metrics period of 1st April 2018 to 31st March 2019.

2. GCP INSPECTIONS UNDERTAKEN

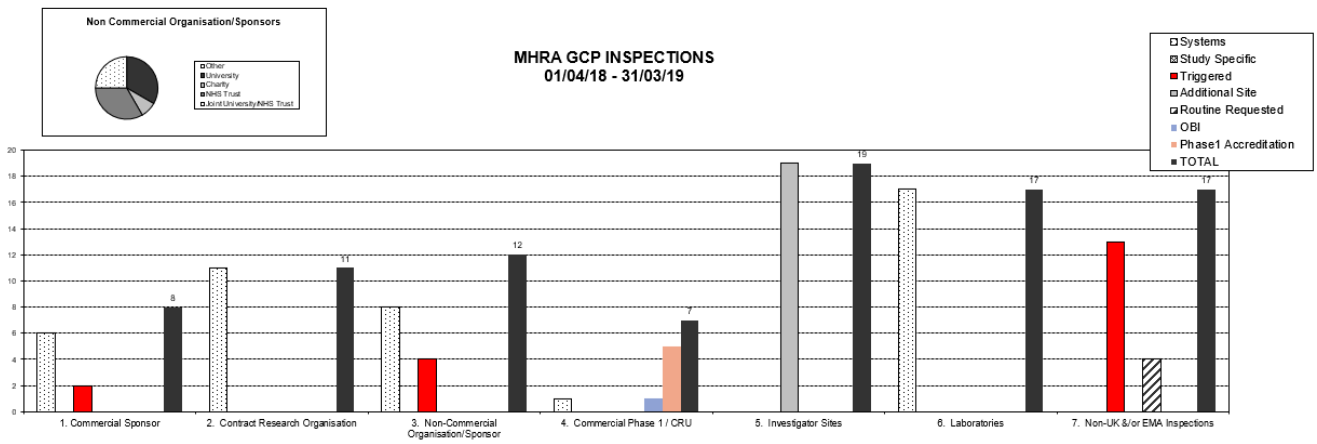
During the metrics period a total of 91 GCP Inspections were undertaken by the MHRA GCP Inspectorate. The types of inspections are presented below.

The number of UK inspections of non-commercial organisations was 12, of commercial sponsors was 8, of Contract Research Organisations (CROs) was 11, of investigator sites there were 19 and finally there were 7 Phase 1 unit inspections. Of these inspections, one was conducted remotely via an Office Based Inspection (OBI) as part of a variation assessment of a Phase I unit.

GCP inspections of UK laboratory facilities conducting clinical trial sample analysis are conducted by the MHRA Laboratories Inspectorate and there were 17 of these inspections. Additionally, there were also 17 non-UK inspections that were conducted by MHRA inspectorate. Of these 17 non-UK inspections, 8 were bioequivalence (BE) inspections carried out by Laboratories inspectors and 7 of these BE inspections were triggered and 1 was a routine inspection. There were also 7 European Medicines Agency (EMA) requested inspections. One of these EMA inspections was of an investigator site located in the UK that was conducted by both UK and other European Union (EU) GCP inspectors. As these inspections were EMA inspections, and not part of the UK statutory program, they have not been included here. A further one of these EMA inspections was of an analytical laboratory and was therefore conducted by MHRA/EU Laboratories inspectors. All 7 of these EMA inspections were related to 3 EMA marketing authorisation procedures, 2 of which were triggered and 1 was routine.

The final 2 inspections of the 17 non-UK inspections were triggered by the MHRA Licensing department following the evaluation of a national variation application for a Marketing Authorisation. These inspections were of two foreign investigator sites located in the USA. As these were UK and not EMA licensing inspections, the metrics for these inspections have been captured within the investigator sites in section 3.5.

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, 19 triggered inspections were undertaken of different types of organisations. There were 2 UK triggered inspections of commercial sponsors, 4 UK triggered inspections of non-commercial organisations and 13 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 and in some cases, follow up inspections were conducted remotely via an Office Based Inspection. Findings from such inspections can also be reported in one GCP Inspection report. Where an inspection was conducted before 1st April 2019 and the other inspections (e.g. associated investigator site or further visit) were conducted after 1st April 2019 (e.g. sponsor site then the investigator site(s)) the findings from the inspections conducted/completed after 1st April 2019 will not be included in this metrics report, as these were inspections conducted/completed during the 2019-2020 metrics period.

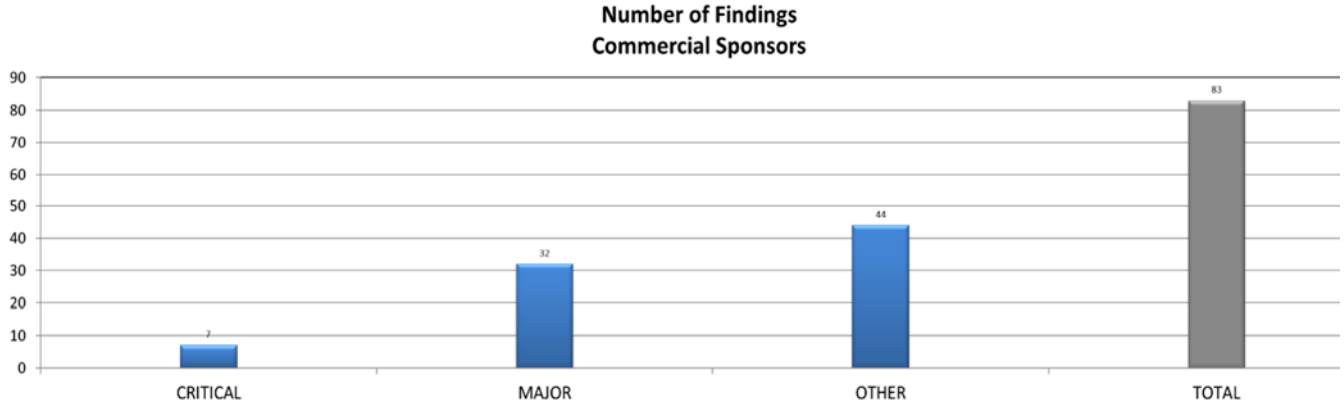
Three organisations were inspected twice during the year, a CRO and two Laboratories.

There were 4 investigator site inspections conducted in the metrics period as associated sites of sponsor and CRO inspections that were undertaken in the previous metrics period of 2017-2018.

Metrics from inspections requested by the EMA Committee for Medicinal Products Human Use (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. Non-UK inspections that do not fall into these 2 categories will have their findings reported in the appropriate organisation type. 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 8 commercial sponsors were inspected, and all have been reported. There were 6 systems inspections and 2 triggered inspections. One of the systems inspections that took place required further document review following the initial inspection which was conducted remotely. Out of the 8 total inspections, 4 (50%) 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	0.9	0.5	0.0	2	8
Major	4.0	4.0	6.0	6	8
Other	5.5	4.5	4.0	10	8

There were 7 critical findings from 4 organisations.

Critical Findings 1 and 2

A pharmaceutical company had 2 critical findings identified during their inspection.

The first critical finding was for **Pharmacovigilance** (PV). This concerned a breach of UK Statutory Instrument 2004/1031 (as amended), Regulations 28 1 & 2, Schedule 1, Part 2, (4) and Regulation 35. There were a number of issues identified that had led to the late or under reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs) and subsequently impacted the integrity of data included in Development Safety Update Reports (DSURs). Examples of issues identified included the following:

- There was no process in place to ensure the Reference Safety Information (RSI) had been approved by the MHRA prior to implementation and use for the expectedness assessment of Serious Adverse Reactions (SARs). As a result, the incorrect version of the RSI was used for expectedness assessments during case evaluation with subsequent under reporting of SUSARs.
- Issues with the accuracy of a tracker developed to track Investigator Brochure (IB) approval dates were identified and did not include the RSI approval dates for comparator products.
- The company's procedures did not require that the RSI used at the onset of an event should be used to evaluate the case throughout the follow up period. This led to the incorrect version of the RSI being used for expectedness assessments during case evaluation with subsequent under-reporting of SUSARs.
- The process for ensuring that the RSI applied to assess expectedness of SARs was consistent with the RSI approved by the MHRA was deficient and led to the under reporting of SUSARs and the subsequent impact on DSURs.
- The version of the RSI used to assess expectedness of SARs was not documented (nor was there any procedural requirement to do so). In addition, the RSI version cited as used for SAR expectedness assessments in response to a document request was populated for the purpose of the inspectors (based on approval dates) and not extracted from a source where this information had been captured contemporaneously; errors were identified with the RSI versions cited.
- Issues were identified with the control of the auto-listings in use. For example, the list of terms used for automated expectedness assessments were not consistent with the RSI submitted and approved by the MHRA Clinical Trials Unit; the lists of terms in the database were compiled using medical concepts and did not take account of the intricacies of the tables in the IB (i.e. events may be expected if SARs, but not if the SAR was life threatening or fatal or of a different severity). An example was identified where a fatal SAR was auto-listed as expected and was not corrected to unexpected by the manual medical review.
- There were numerous examples of deficiencies in the Safety/Pharmacovigilance group Quality Management System (QMS) processes.
- There was no evidence of Serious Adverse Event (SAE) reconciliation outcome resolution for outputs provided for a number of trials. Following the assessment of a number of trials, it was found that the data review plan required SAE reconciliation to be conducted between the clinical

& safety databases twice a year and at database lock. However, ensuring that reconciliation had been performed in advance of DSUR line listing production was not specified anywhere
- Examples were seen of late receipt of serious cases by the company PV department.

A second critical finding was given for **Record Keeping/Essential Documents**. This was given due to breaches of UK Statutory Instrument 2004/1031 (as amended), Regulation 28, (2), Regulation 31A (1), (2), (3), (4) (7) and Schedule 1, Part 2, (4). The Trial Master Files (TMF) selected were incomplete and direct access was not readily provided to all document repositories comprising the TMF. This was found to impede the inspection with the inspection having to be performed primarily with document requests. This was a major finding at the previous inspection of this organisation and was therefore escalated to a critical finding. The primary issues identified included:

- The TMFs presented to inspectors being incomplete or inaccurate, which resulted in an inability to reconstruct the trial or procedural conduct to enable the verification of GCP compliance.
- Several documents being filed outside the core electronic TMF (eTMF). Whilst the TMF master list did state that these were filed across various locations, it did not index exact locations and direct access could not be provided to inspectors.
- A number of “Data” files were classified as non-essential and filed outside the eTMF, this included SAE data listings. Such data files, however, were essential for demonstrating key safety processes and sponsor oversight and thus should have been held in the eTMF.
- Documents could not readily be located due to file naming conventions that had been applied.
- There were several examples of documents/data not being uploaded in a timely manner. alongside evidence of the eTMF having been updated substantially just prior to the inspection.
- The Standard Operating Procedures (SOPs) that were supposed to detail the eTMF best practices for quality management did not define the TMF and how it should contain all trial essential documents. It also did not define all the different systems that make up the TMF.
- Essential documents were not defined in the SOP nor was there any clear policy and process to ensure the accurate completeness of the TMF contemporaneously.
- There were several functionality issues with the eTMF system. For example, the Library view relied on other software (Excel®) to sort and filter documents as per binder levels which was time consuming. The functionality within the system itself should aid inspection and document review, whereas this was a work around. In addition, there was no functionality to identify files not appearing in the binder view.

Critical Findings 3 and 4

A pharmaceutical company had 2 critical findings identified during their inspection.

The first critical finding was for **Clinical Trial Authorisation** (CTA). This concerned breach of UK Statutory Instrument 2004/1031 (as amended), Regulations 28 and 31, Schedule 1, Part 2, (8), (10) and (12). This consisted of the following main observations:

- Another regulatory authority had put the trial on hold, but the sponsor failed to notify to the MHRA in a timely manner of this relevant new information concerning the trial which may have affected the benefit/risk assessment of the trial by the MHRA for the MHRA to give due consideration on whether the trial should continue. The sponsor had informed investigators and the UK CRO but ignored advice from the CRO to inform the MHRA by notification of a temporary halt to MHRA and Research Ethics Committee (REC). Once the MHRA was aware, the sponsor had been instructed verbally and in writing by the MHRA that planned patient dosing should not proceed until a risk assessment had been conducted and provided to the MHRA. Despite clear correspondence from the MHRA stating that it was not acceptable from a safety perspective to continue dosing with the product in the UK trial, a patient was dosed, and the sponsor failed to provide the requested risk assessment to the MHRA beforehand.

- The sponsor/CRO failed to inform the Principal Investigator (PI) of the MHRA instruction to not continue dosing prior to the PI actually dosing the patient. The PI stated that had the MHRA position been known, they may have acted in a different manner.

The second critical finding was for **Protocol Compliance**. These concerned breaches of UK Statutory Instrument 2004/1031 (as amended), Regulations 28, 29 and Schedule 1, Part 2, (8). The primary observations were:

- The trial had not been conducted in accordance with the approved protocol as deliberate protocol waivers had been implemented and a process existed where waivers to eligibility criteria could be granted by the sponsor.
- The sponsor had purposely recruited patients from outside the UK to the trial knowing that the requirements for the long term follow up of the patients set out in the protocol could not be met as patients would be known to leave the UK after a period of 6 months, thereby leaving the care of the principal investigator (PI). The sponsor disregarded the requirements of the protocol and decided that such requirements could be met by transfer of the trial patients to an alternative protocol not approved in the UK. The sponsor did not consider it necessary to substantially amend the approved protocol or inform the MHRA of their intended action. This would have resulted in a significant number of patients reported as lost to follow up when in fact follow up may have been undertaken and the MHRA would not have been made aware of this data.
- It was not determined if patients had been enrolled in a long term follow up trial that was being conducted outside of the UK and the PI was unable to confirm that they were involved in receiving follow up information about the patients.
- The sponsor ignored the advice from the CRO to not recruit the foreign patients.

Critical Findings 5 and 6

A pharmaceutical company had 2 critical findings identified during their inspection.

The first critical finding was for **Pharmacovigilance**. This concerned breaches UK Statutory instrument 2004/1031 (as amended), Schedule 1, Part 2, (4), (8) & Regulation 28. This consisted of the following observations:

- The corrective and preventative actions (CAPA) implemented following a critical finding from a previous inspection was ineffective and did not extend to comparator Investigational Medicinal Products (IMPs) which was not in accordance with the “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) and there was a risk that SARs could be assessed incorrectly which may have impacted SUSAR reporting. As this finding was not remediated the grading remained critical as the use of an unapproved RSI could have led to under reporting of SUSARs which had a significant potential impact on subject safety.
- It was identified from review of the safety database that an updated RSI continued to be implemented prior to MHRA approval and the implemented CAPA which required regulatory approval to be obtained prior to the implementation of an updated RSI had failed.
- There were examples of event terms being considered expected, which were not in accordance with the MHRA approved RSI. There were discrepancies between the expected terms in the MHRA approved RSI and those in the safety database.
- There was a lack of tracking to determine when the last approval for the RSI was obtained. In addition, where the RSI had been submitted for multiple trials, there was a lack of tracking to ensure that this could be implemented at a trial level.
- During the previous inspection, it was identified that the company’s quality system did not place a requirement to identify which version of the RSI was used during case processing. A fix was implemented, but this had not effectively remediated this finding because it was still not possible

to reconstruct the contemporaneous decisions made by case evaluators in order to demonstrate compliance.

The second critical finding was for **Data Integrity Control Processes**. This was due to breaches of UK Statutory Instrument 2004/1031 (as amended), Schedule 1, Part 2, (3), (4), (8) and Regulation 29. The main observations surrounding this finding included:

- The organisation permitted unplanned reviews of unblinded clinical trial data (in double blind trials) for business decision purposes, which had a significant potential to introduce bias into the trial, impacting data integrity. There were several examples where management had requested for unblinded data to be provided to them for double blind clinical trials. However, this request and review was outside of any agreed interim/preliminary analysis described in the protocol, prior to formal completion of the trial. These unplanned reviews of unblinded data were interim analyses, as in most cases the intention was to compare treatment arms with respect to efficacy and safety prior to formal completion of the trial to make internal decision regarding the future of development programmes, resource and planning.
- For some trials, the unblinded data was reviewed before the Statistical Analysis Plan (SAP) was finalised.
- There was a lack of adequate rationale and review of the potential consequences considered and documented for unblinding for unplanned interim analysis.
- Senior management within the organisation were able to authorise their own requests to unblinded data.
- In another trial, there was a lack of contemporaneous documentation of the actions taken following accidental unblinding within the trial to demonstrate how any potential bias was minimised.
- There was no process for ensuring that any inadvertent unblinding or unplanned unblinding was transparently documented in the Clinical Study Report (CSR).

Critical Finding 7

A pharmaceutical company had one critical finding identified during their inspection.

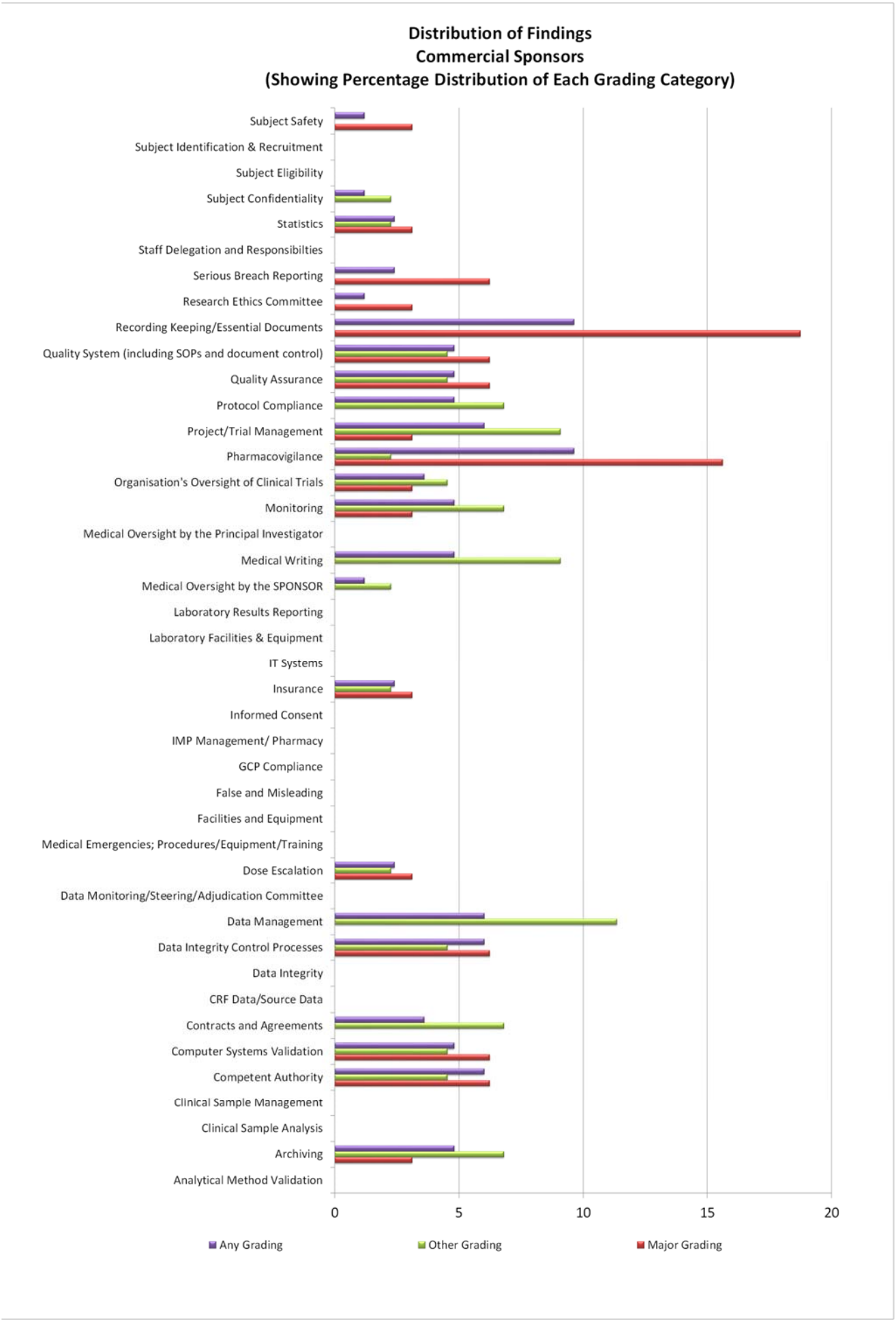
This finding was for **Record Keeping/ Essential Documents** and concerned breaches of UK Statutory Instrument 2004/1031 (as amended), Schedule 1, Part 2 (4) and Regulation 31A (1-3). The following observations were made:

- The TMF did not meet the requirements of Regulation 31A which resulted in inspectors having to request a large number of documents in order to conduct the inspection as well as an additional office-based inspection.
- The TMFs reviewed were incomplete to such an extent that they could not form the basis of inspection and therefore impeded/obstructed inspectors carrying out their duties in verifying compliance within the Regulations.
- There was a failure to define the TMF within the quality system and there were several issues identified with procedures covering the TMF that resulted in the TMFs provided to inspectors being incomplete.
- For some trials, ancillary systems that contained essential trial documents had not been defined to be part of the TMF and were not subject to the same controls as a TMF.
- One trial had a paper TMF defined, yet all documents required to reconstruct trial activities and compliance with the quality system were not filed in this paper TMF but rather kept in alternative electronic systems/locations.
- The paper TMF was used as a document archive rather than a working TMF and trial team members did not have access to the paper TMF, but instead used an electronic “shadow TMF”

during the trial. Upon review, it was found that there were a large number of documents in the "shadow TMF" which were not filed in the paper TMF.
- There were a number of essential documents for a trial retained by vendors which were not defined in the TMF plan or TMF index.
- The TMF index for a trial was at an artefact level and the quality system did not address an overview all the systems holding essential documents.
- There was a lack of effective oversight QC of an eTMF by the sponsor.
- Several issues were identified with the eTMF including examples of missing, misfiled, misnamed and duplicated documents.

Summary of Findings for Commercial Sponsors

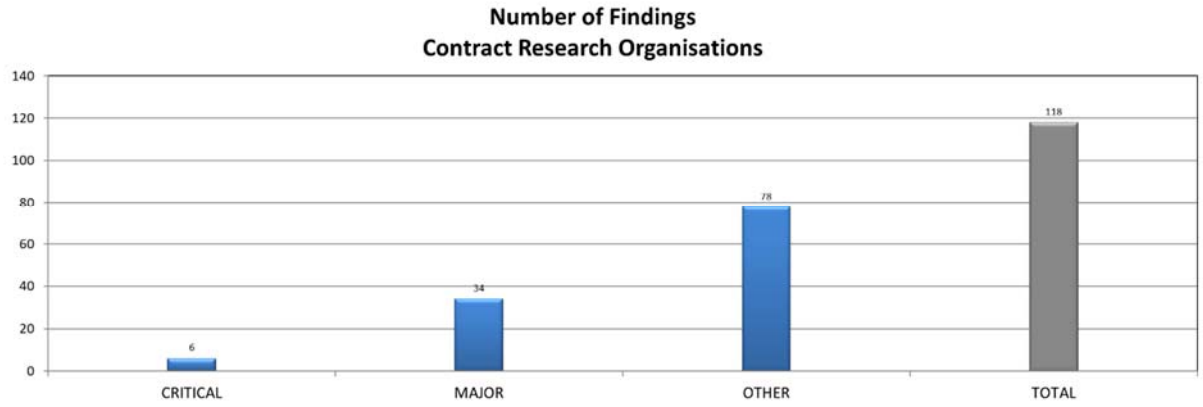
The figure on the following page shows the distribution of Major, Other and any grade of inspection findings. This identifies the areas where GCP inspectors have been making observations of non-compliance with GCP.


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
5
10
15
20
Any Grading
Other Grading
Major Grading

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

A total of 11 Contract Research Organisations were inspected. Two of these 11 inspections were of the same organisation and therefore had one report. Another one of the 11 inspections that took place within the 2018/19 metrics period was not reported due to additional inspection activity conducted during the 2019/20 metrics period. As a result, this inspection will be included in the 2019/20 GCP annual metrics report. Due to these reasons, there was a total of 9 GCP inspection reports from the 11 inspections during the metrics period. All 11 of these inspections 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 9 GCP inspection reports, 4 (40.0 %) had critical findings and 9 (90.0%) 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	0.7	0.0	0.0	2	9
Major	3.8	4.0	4.0	7	9
Other	8.7	8.0	11.0	14	9

There were 6 critical findings from 4 organisations.

Critical Findings 1 and 2

A CRO had two critical findings identified during their inspection.

The first critical finding was for **Clinical Trial Authorisation**. This concerned breaches of UK Statutory Instrument 2004/1031 (as amended), Regulation(s) 3, 28, 29, 49, 50, 51 and Schedule 1, Part 2: (4). The following observations were made:

- The CRO failed to implement adequate procedures to ensure that regulatory requirements concerning the conduct of the medicinal product clinical trial duties and functions delegated by sponsors were appropriately complied with.
- There was a lack of formal procedures to adequately identify clinical trials being conducted in the UK under a CTA issued by the MHRA.
- The dossier of information provided to GCP inspectors had numerous errors and omissions which included examples of trials stated as not being in the UK, despite having a CTA and approved protocol.

- The CRO failed to have any formal procedures in place to ensure that its Interactive Response Technology (IRT) systems deployed into production for UK trials were compliant with the MHRA and the REC approved protocol.
- The IRT system in production was inconsistent with the approved trial protocol. For example, in one trial, the IRT system would have assigned the incorrect dose to patients and had a further inconsistency with the protocol which was described as being there to avoid a programming error. Validation functional testing procedures of dose levels were also inadequate. Whilst no sites were active this IRT system posed a significant risk to patients due to the possibility of site activation imminently and patients being recruited and dosed incorrectly. In another trial, the IRT system was released and the sponsor activated a site prior to regulatory approval. This led to an entire cohort of subjects being enrolled and some receiving IMP.

The second critical finding was for **Patient Safety**. This concerned breaches of UK Statutory Instrument 2004/1031 (as amended), Regulation(s), 3, 28 and Schedule 1, Part 2, (1). This was given due to the organisation's failure to comply with the approved protocol which could have potentially put the safety of UK patients at risk due to the possibility of the incorrect dosing of patients. Such possibilities could have resulted in ineffectiveness or overdose which was an additional safety concern.

Critical Findings 3 and 4

A CRO had two critical findings identified during their inspection.

The first critical finding was given in relation to **Dose Escalation.** This concerned breaches of UK Statutory Instrument 2004/1031 (as amended), Regulation 28, Schedule 1, Part 2, (4), (9) and CT-3 2011/C 172/07. The following observations were made:

- There was a lack of data available to verify that the Dose Escalation Steering Committee (DESC) were provided with all relevant trial data of the decisions taken in one of the trials reviewed.
- There was no procedure in place to ensure that trials where key safety decisions were being made had used robust and accurate data.
- The decisions taken regarding dose escalation in one of the trials could not be reconstructed and verified in order to demonstrate protocol compliance.
- There was a lack of information available to demonstrate what data was reviewed in order to make decisions.
- CRF data listings were not provided to the DESC despite the CRO's medical monitor confirming that such listings were reviewed monthly.
- Dose Limiting Toxicity forms were not completed by an investigator site of the CRO on time nor were they provided back to the site by the Medical Monitors as required by the Safety Monitoring Management plan.
- The DESC process produced by the CRO and the Sponsor was not comprehensive and did not outline what data would be reviewed or when and how this would be provided to the DESC.
- There was an over reliance on the sponsor driving the dose escalation decisions and providing the outcome to the investigators, which was not transparent in the protocol and could not be reconstructed.
- There was no reference within the QMS to ensuring the QC of any data collated to be used in a dose escalation decision meeting
- In one of the trials reviewed, monitoring and data management activities were contracted to the CRO, yet there was no strategy or requirement within the CROs trial plans to ensure that the data provided to the Data Monitoring Committee (DMC) was subjected to QC prior to extraction.

The second critical finding was for **Record Keeping/ Essential Documents**. This was given in relation to breaches of UK Statutory Instrument 2004/1031 (as amended), Regulation 31A (1-3) and Schedule 1, Part 2 (4). The following observations were made:

- The CRO's eTMF provided for review by the inspectors did not contain all the essential documents required to enable the reconstruction of trial events. Additionally, the eTMF failed to demonstrate compliance with the regulations and the CRO's quality system.
- A number of essential documents were retained within different electronic systems which were not defined to be part of the TMF.
- The eTMF provided did not meet the definition of a TMF as per regulation 31A (1-3) and could not form the basis for inspection.
- The TMF content was not defined in the QMS including all systems, locations and documents that comprised the TMF for the selected trials. As a result, there was a lack of control of documents across various sections of the TMF.
- The eTMF system lacked essential functionality to enable inspection of the trials to such an extent that it impeded the review of process documentation (thereby increasing document requests) to be able to verify compliance with regulations.
- There were inconsistencies with naming conventions of documents in the eTMF which made it difficult to identify particular documents/ groups of documents. Additionally, document descriptions were not reflective of the contents and thus documents had to be opened to identify what they were.
- The TMF for a selected trial was incomplete to such an extent that key trial processes could not be reconstructed from the available documentation.
- There were examples of documents not being added to the eTMF in a timely manner.
- The eTMF system audit trial was extremely limited and could not be used for the review of TMF completeness over time.
- There was no clear audit programme in place or periodic review of the eTMF system audit trial to demonstrate oversight and quality assurance of completeness and accuracy of the TMF systems in place.

Critical Finding 5

A CRO had one critical finding identified during their inspection relating to **Trial Management.** This concerned breaches of UK Statutory Instrument 2004/1031 (as amended), Regulation 12, 28, 29 and Schedule 1, Part 2, (4), (9). The following observations were made:

- There was a lack of source data available to verify the exact dose of IMP provided to subjects during home visits.
- Despite one of the main objectives of this trial being the review of the efficacy of the proposed dosing regimen, there was a lack of source data available to verify this aspect from a data integrity perspective.
- There was a lack of processes in place to ensure that adequate and correct dosing instructions were provided to patients.
- It was not possible to verify if trial systems and documents were produced in accordance with the trial protocol as the version used was not always documented and there was a lack of documented QC check to ensure they were generated in accordance with the approved trial protocol.
- Site Initiation Visit (SIV) training slides presented to sites were inaccurate and not consistent with the trial protocol.
- The patient diaries produced for the selected trial by the CRO were not fit for purpose as they did not capture the exact dose and/ or volume administered by/ to the subject at each visit during the maintenance phase.
- There was a lack of change control and risk assessment applied when implementing protocol amendments in a trial.

- It was stated in meeting minutes between the CRO and Sponsor that the lack of source data issue would not be reported in the CSR which would have resulted in a misleading CSR being submitted to Regulatory Authorities and Ethics Committees.

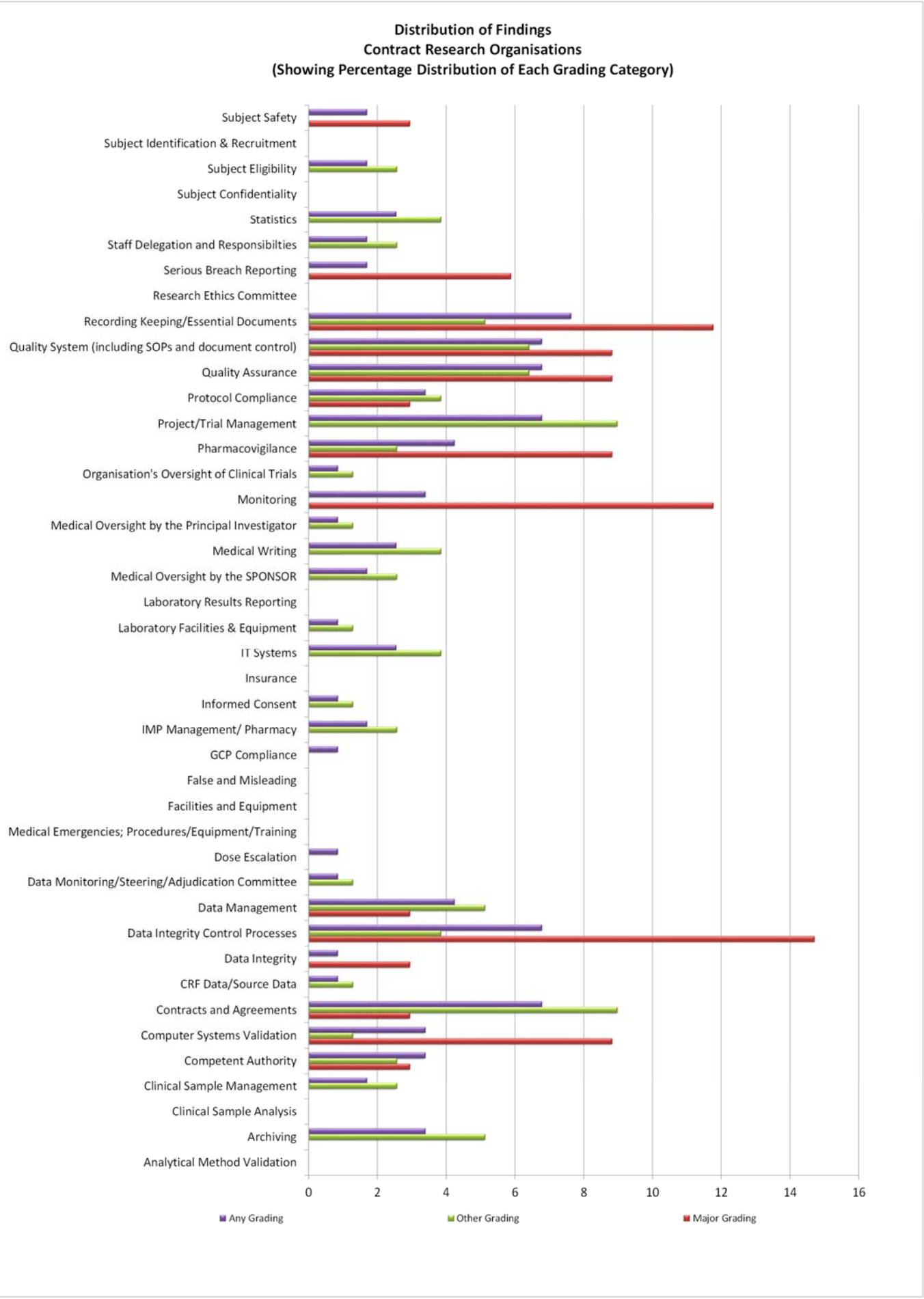
Critical Finding 6

A CRO had a critical finding during their inspection for **GCP compliance**. This was in relation to breaches of UK Statutory Instrument 2004/1031 (as amended), Regulation(s), 2,3, 28, 29, 47,51 and Schedule 1, Part 2, 4, 9 and Schedule 9 and of UK Statutory Instrument 2012/1916 Regulations, 325-327. This consisted of the following observations:

- There was a failure by the CRO to acknowledge the requirement that they must comply with the principles of GCP as per the UK legislation relating to clinical trials of medicinal products. There was no confirmation from the CRO that they will comply with UK legislation for GCP and protocol compliance concerning the duties and functions delegated to them by the sponsor or their role in the conduct of the trial even though the position of the MHRA that compliance was expected had been made clear at the previous inspection. MHRA was concerned about the risk of non-compliance in relation the eCRF and IRT trial specific builds that the CRO performed for trial sponsors. These could be for the eCRF not being compliant with the protocol, potentially resulting in incorrect or missing data or if the IRT system was non-compliant with the trial protocol or functioning correctly, then patients could be randomised and/or dosed incorrectly or there could be unavailability of IMP at site.
- During the inspection, inspectors were unable to investigate fully issues pertaining to a serious breach and the organisation was obstructive in allowing the MHRA to conduct their duties in relation to this matter. The MHRA was notified of functionality issues with the IRT system provided by the CRO that resulted in the overdosing of multiple trial participants. There were also some participants that were inadequately dosed, and several participants experienced Serious Adverse Events and there was one fatality. It could not be confirmed by the sponsor if the death was caused by the IMP overdose, but as a conservative approach, the death had been reported as a SUSAR. The CRO did not provide assurance to inspectors that the issues identified were isolated incidents or that the root causes had been identified and remediated across all trials.

Summary of Findings from Contract Research Organisations

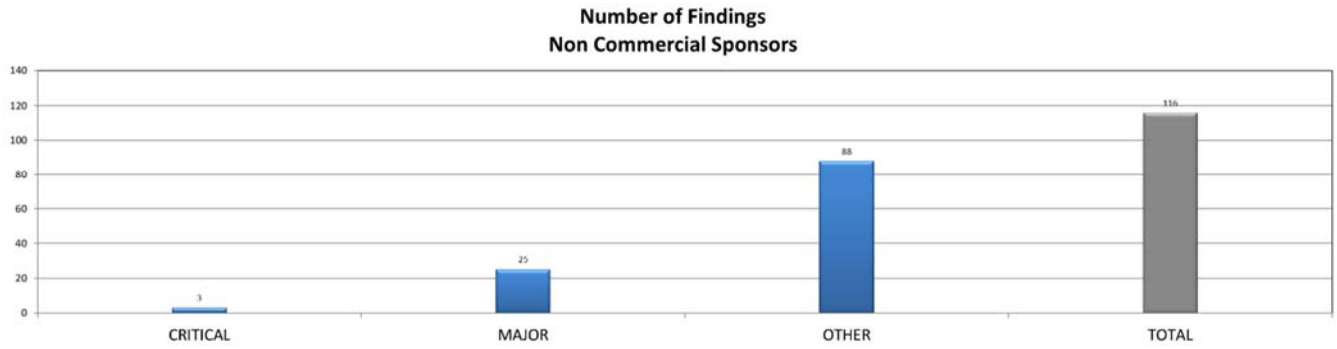
The figure on the following page shows the distribution of Major, Other and any grade of inspection findings. This identifies the areas where GCP inspectors have been making observations of non-compliance with GCP.


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
2
4
6
8
10
12
14
16
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, 4 were of Universities, 6 were of NHS Trusts/Health Boards, one was a joint inspection of an NHS Trust/Health Board and University and one was of a charity organisation. Four 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. Of the 12 organisations inspected, 11 have been reported. One of the inspections was not reported because the inspection revealed there was no basis for non-compliance information that triggered the inspection. Four of the inspections were triggered inspections.

Of the 11 GCP inspection reports, 2 (16.7%) had at least one critical finding and 8 (66.7%) 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	2	11
Major	2.3	2.0	0.0	9	11
Other	8.0	7.0	5.0	17	11

There were 3 critical finding identified from 2 organisations.

Critical Finding 1

A non-commercial CTU organisation had one critical finding identified during their inspection for **Pharmacovigilance**. This concerned breaches of UK Statutory Instrument 2004/1031 (as amended), Regulation 33 and Schedule 1, Part 2, (4). The following observations were made:

- The process for sponsor assessment of IMP causality of SARs, SUSAR reporting and follow up was not robust.
- For SAEs reviewed, the company assessment was changed from the original assessment of "related" to "unrelated", but the rationale for changing the company assessment was not adequately justified and documented.
- There were SAE reports that were received by the organisation where causality was assessed by the clinical coordinator and initially sponsor as "related" and then later changed to sponsor causality as "unrelated". These were not reported as SUSARs when they were classed as "related".
- Whilst a requirement within an SOP allowed the trial coordinator to receive consensus from the investigator and sponsor in cases where there was a difference in the assessment of causality between them, there was no guidance on what basis questions should be asked. This led to the

potential that clinical trial coordinators and investigators could have felt compelled to change their assessment of causality.
- There were cases of follow ups not being performed to ensure resolution of an initial SUSAR event. Additionally, no follow-up reports were submitted to the MHRA.

Critical Finding 2 and 3

A non-commercial sponsor organisation had two critical findings identified during their inspection.

The first critical finding was for **Data Integrity**. This was given due to breaches concerning UK Statutory Instrument 2004/1031 (as amended), Regulations 28, (2), 29, and Schedule 1, Part 2, (3) and (4).The following observations were made:

- In one of the selected trials, there was a lack of robust control of the Master Randomisation List and associated treatment allocation to ensure maintenance of the trial blind and therefore the integrity of the data generated.
- The Master Randomisation List was produced by a blinded co-investigator who was also responsible for collating the data collected and for conducting interim analysis according to the information provided by the sponsor during the inspection.
- The Master Randomisation List and Patient Randomisation List were present in the TMF and could be accessed by anyone that had access to the TMF including blinded trial team members.
- A copy of the Master Randomisation List was accessible by the monitor working on the trial, therefore unblinding them to the treatment allocation of patients they were monitoring.
- The delegation log did not clearly define who could access the randomisation list and other unblinding information related to trial participants and trial team members who could not.
- There was no evidence of statistical input into the randomisation list, how it had been produced or against which version of the protocol and randomisation requirements it had been based upon.
- There was no information or procedure within the TMF that described how allocation of patients would be managed to ensure that allocation was balanced or not required between different groups.
- The Master Randomisation List within the TMF was not version controlled or marked in any way to indicate provenance and approval status.
- Despite IMP stock being quarantined in pharmacy and brought to the attention of both the principal and co-investigators, medication was still dispensed to subjects. During this quarantine period a participant could only receive placebo medication and dispensing should have ceased.
- No Interim analysis had been pre-defined in the previous version of the trial protocol and no statistical analysis Plan was available in the TMF to describe how the data would be analysed and reported.
- There was a risk that subjects may not have been randomised in accordance to the trial protocol and Master Randomisation List.

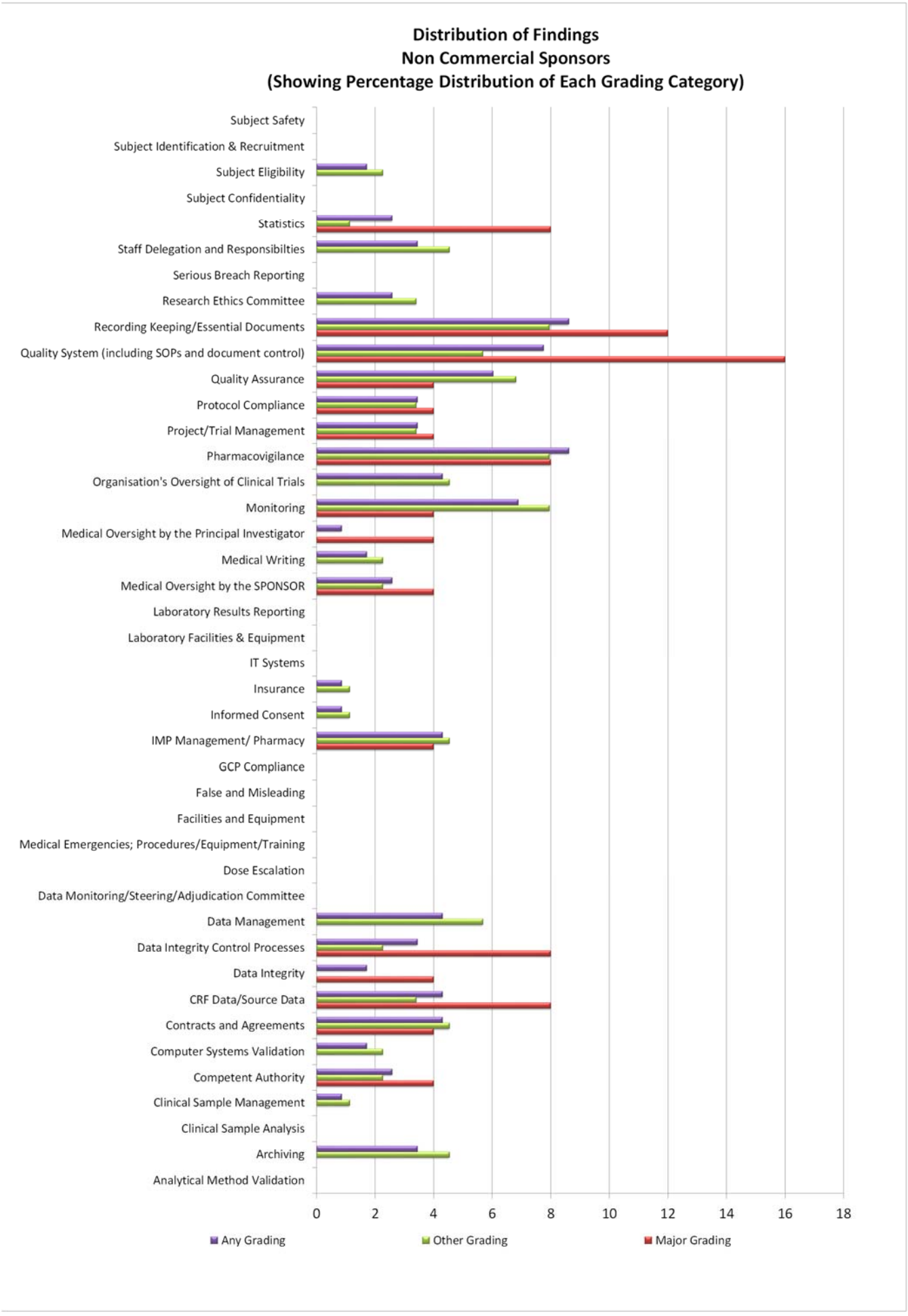
The second critical finding was given in relation to **Organisation's Oversight of Clinical Trials of Investigational Medicinal Products**. This concerned breaches of UK Statutory Instrument 2004/1031 (as amended) Regulations 3, (12), 28 (2), 29 and Schedule 1, Part 2, (4) and (9). This consisted of the following observations:

- There was a lack of appropriate oversight by the sponsor and a lack of suitable systems and processes in place for the effective conduct of trials of investigational medicinal products.
- There were no formal processes for the assessment of a proposed trial and its conduct as part of the decision to sponsor the trial.
- The protocol of a selected trial relied upon interpretation in order to understand the trial design. It consisted of two parts (known as two protocols) and within these parts there were a number of experiments that contained the objectives of the trial. However, the trial design was unclear and therefore difficult to reconstruct (e.g. randomisation process, data management etc).

- The sponsor representative and trial monitor confirmed that they did not understand the trial protocol and found it confusing.
- The Chief Investigator (CI) was inexperienced in running clinical trials however there were no mechanisms in place to ensure that they were properly qualified through experience, training and education or to provide support for their role as CI in order to mitigate this.
- There was no formal delegation of activities by the sponsor to the CI that clearly defined which activities were to be undertaken by the CI on behalf of the sponsor.
- The selected trial included an investigator site, however there were no systems for the oversight of this additional site or appropriate arrangements made for the conduct of the trial.
- There was no process for the sponsor to verify the suitability of vendors selected by the CI prior to their use.
- The sponsor was unaware that result for interim analysis of the selected trial had been published and presented.
- There was insufficient documentation within the trials TMF and associated Research and Innovation files with the participation of the investigator site to ensure that the trial was conducted appropriately.

Summary of Findings from Non-Commercial Organisations

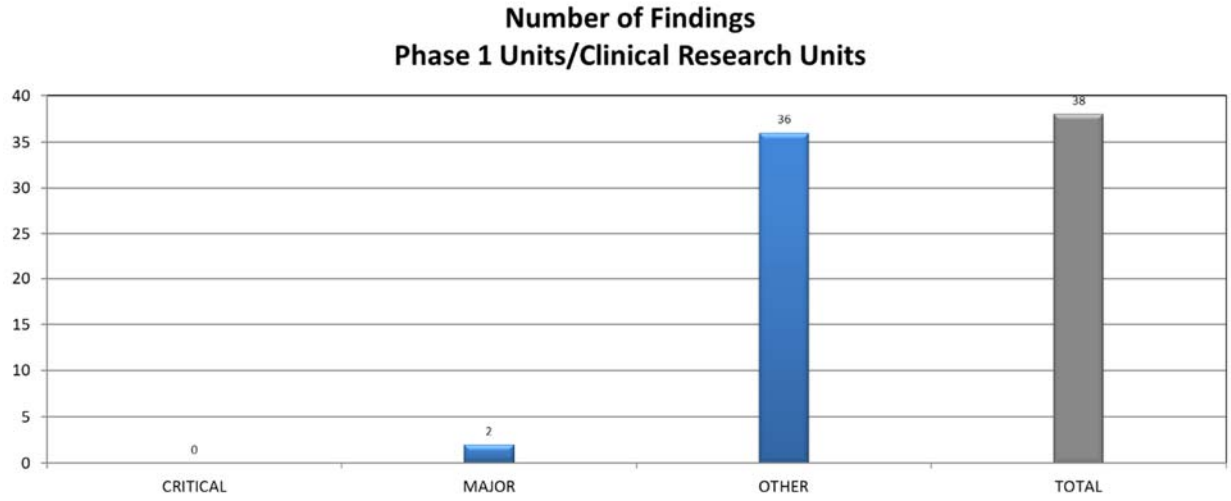
The figure on the following page shows the distribution of Major, Other and any grade of inspection findings. This identifies the areas where GCP inspectors have been making observations of non-compliance with GCP.


Distribution of Findings
Non Commercial 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

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

A total of 7 inspections were done of Commercial Phase 1 Units/Clinical Research Units. Five of the inspections were routine inspections for the MHRA voluntary phase 1 accreditation scheme, 1 was a GCP systems inspection and another was an office-based inspection completed as part of a phase 1 variation assessment. None of the inspections were triggered. Note that findings reported here relate to GCP only and not those related to the phase 1 accreditation scheme.

Of the 7 inspections that took place, 6 were reported. The seventh inspection was not reported as it was part of a variation assessment that was carried out via an Office Based Inspection. Of the 6 reported inspections, none (0%) had a critical finding and 1 (14.3%) had at least one major finding. The number of findings and findings per inspection are represented on the figures below.



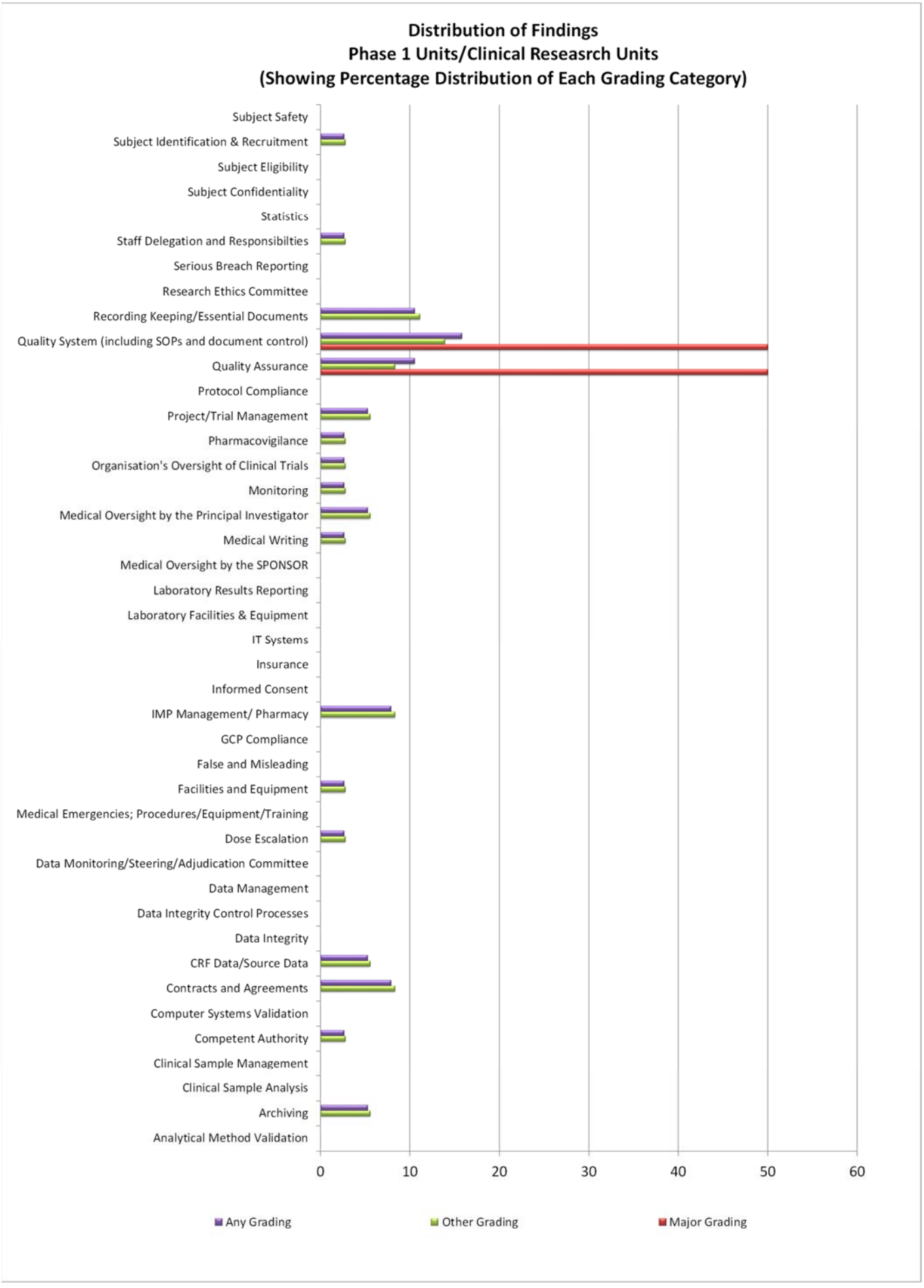
Number of Findings Per Inspection (Phase 1 Units/Clinical Research Units)

	Mean	Median	Mode	Maximum	n
Critical	0.0	0.0	0.0	0	6
Major	0.3	0.0	0.0	2	6
Other	6.0	5.0	4.0	14	6

There were no critical findings.

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

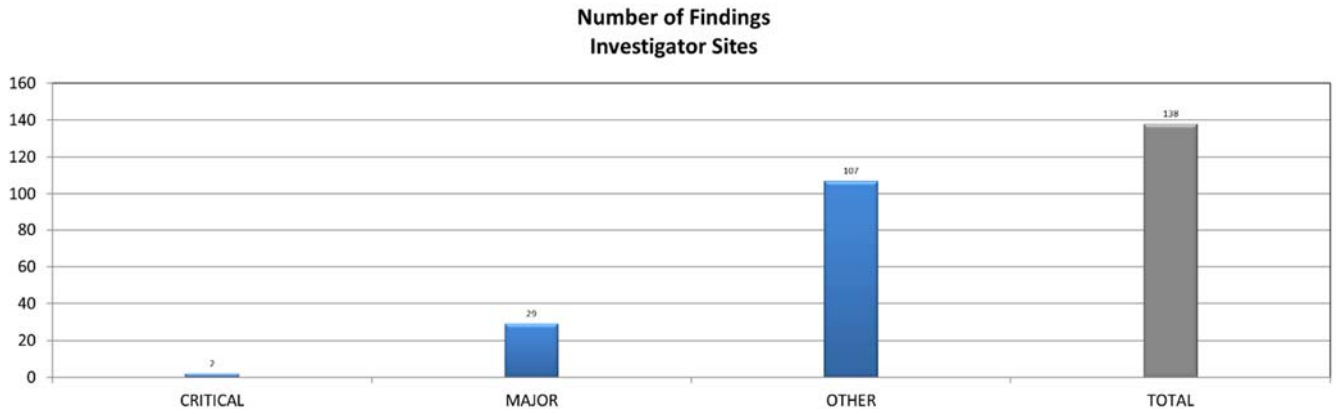
The figure on the following page shows the distribution of Major, Other and any grade of inspection findings. This identifies the areas where GCP inspectors have been making observations of non-compliance with GCP.


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
10
20
30
40
50
60
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 19 investigator sites in the UK were inspected and all were as an associated site with a sponsor/CRO/non-commercial/CTU inspection. It is important to note however that whilst there were 19 investigator site inspections in the UK, the summary of findings is based on 21 inspections. These 2 additional inspections were non-UK GCP investigator site inspections but have been reported here as inspection metrics would not be reported by the MHRA GCP Laboratory Inspectorate or by the EMA.

Of the 21 reported inspections, 1 (4.8%) had a critical finding and 13 (61.9%) 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	2	21
Major	1.4	1.0	0.0	5	21
Other	5.1	6.0	6.0	8	21

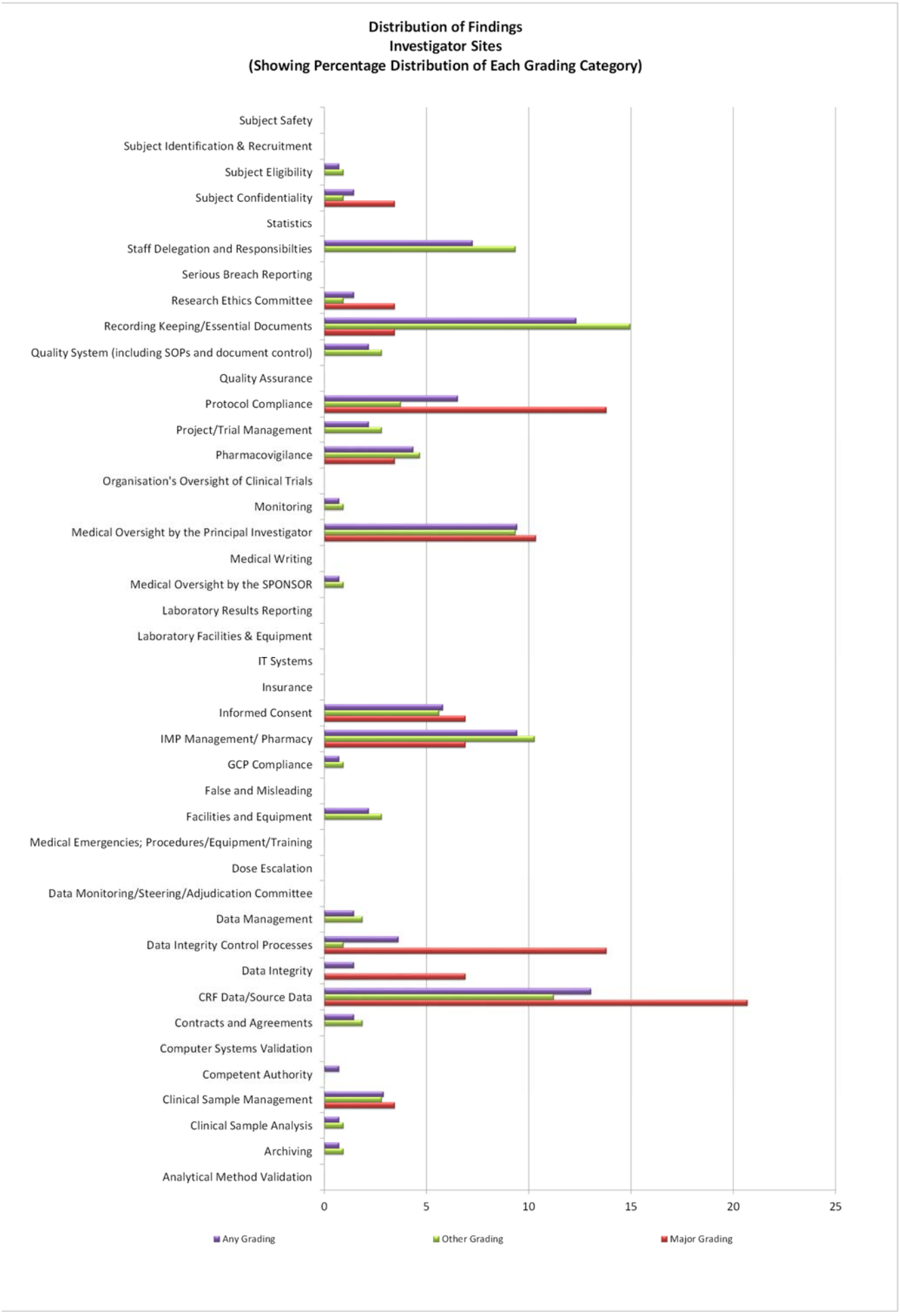
There were 2 critical findings for 1 investigator site.

Critical Findings 1 and 2

An Investigator site had 2 critical findings identified during their inspection. These findings correlate with the critical findings 3 & 4 that have been detailed in the Commercial Sponsors section. As with the commercial sponsor, the two critical findings identified were in relation to **Clinical Trial Authorisation** and **Protocol Compliance**. Under the legislation mentioned, the investigator site and the sponsor are both responsible for protocol compliance and informing the relevant regulatory authorities when new information that may affect the benefit/risk management of a trial has been discovered. As a result of non-compliance with such legislation, these findings were attributed to both the Commercial Sponsor and this Investigator Site.

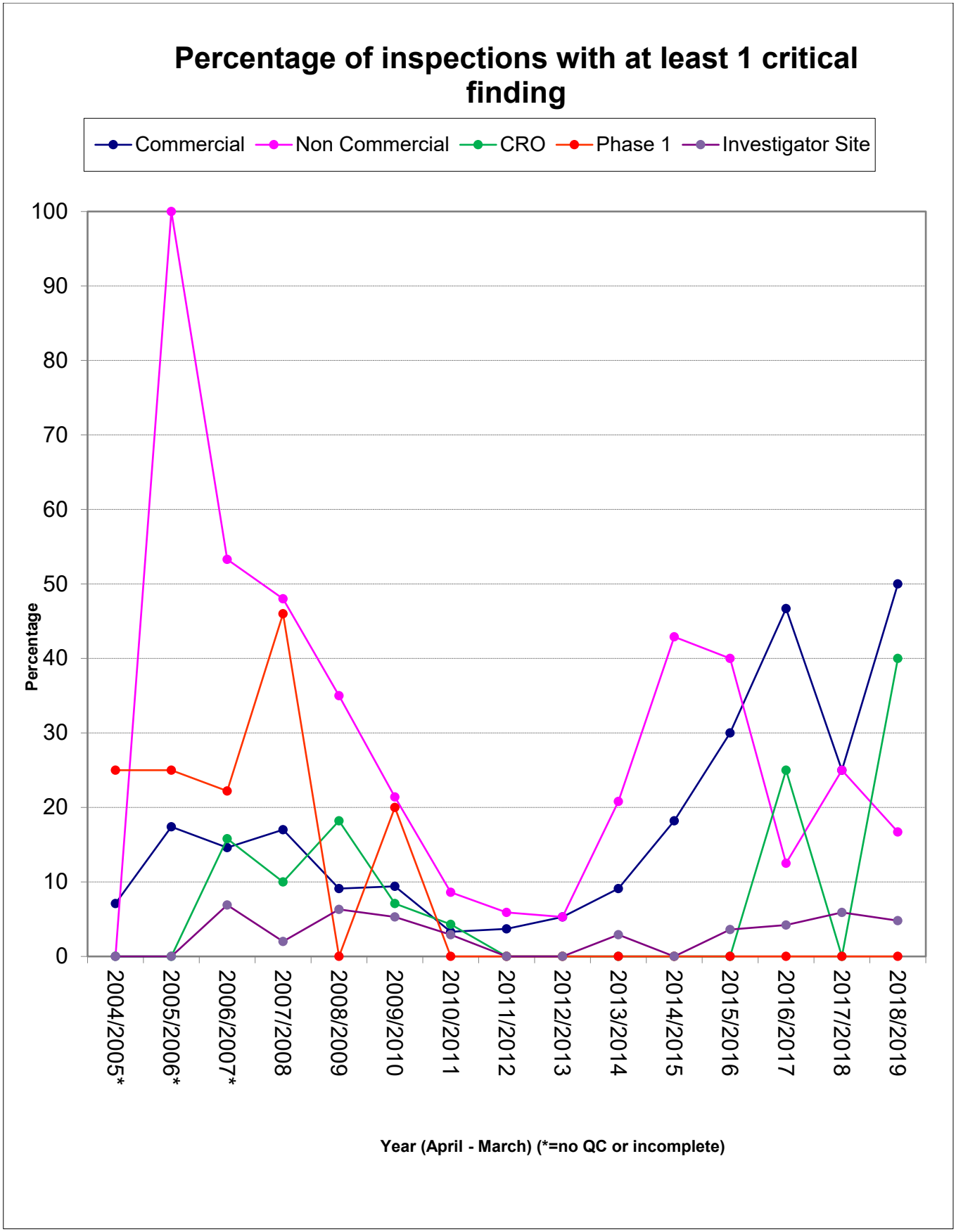
Summary of Findings for Investigator Sites

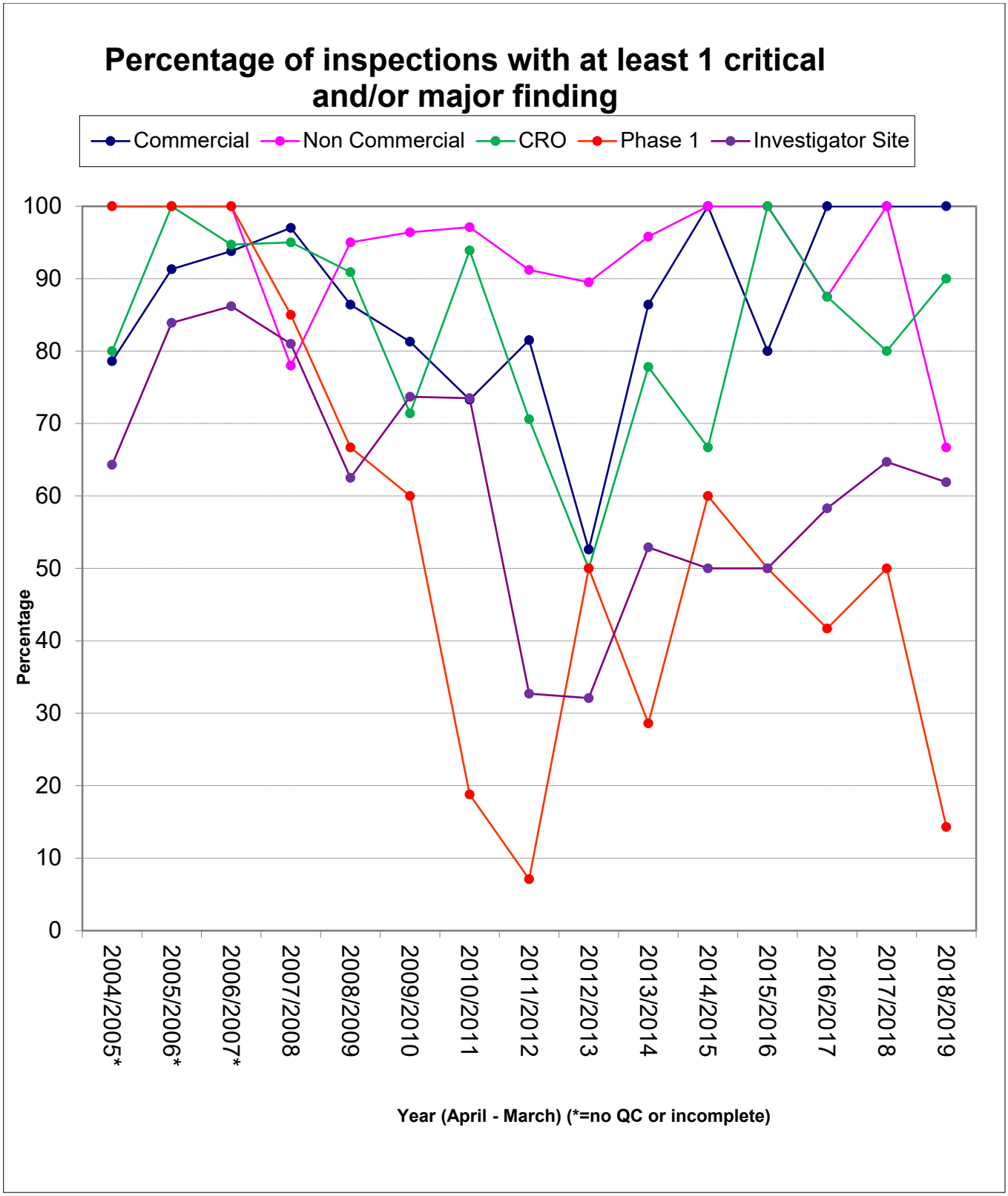
The figure on the following page shows the distribution of Major, Other and any grade of inspection findings. This identifies the areas where GCP inspectors have been making observations of non-compliance with GCP.


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
5
10
15
20
25
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.


Percentage of inspections with at least 1 critical finding
Commercial
Non Commercial
CRO
Phase 1
Investigator Site
100
90
80
70
60
50
40
30
20
10
0
Percentage
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
2018/2019
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
2018/2019
Year (April - March) (*=no QC or incomplete)