Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

GCP INSPECTORATE

GCP INSPECTIONS METRICS REPORT

METRICS PERIOD: 1st April 2015 to 31st March 2016

DATE OF ISSUE: 21st July 2017

MHRA
I, E&S/Library
National Institute for Biological Standards and Control - A Centre of the MHRA
Blanche Lane, South Mimms, Potters Bar
Hertfordshire, EN6 3QG

MHRA
Inspections, Enforcement and Standards
Block 14, First Floor, 14F A06/07
FERA (The Food and Environment Research Agency)
Sand Hutton, YORK, YO41 1LZ

MHRA Head Office:
Inspection & Standards Division,
151 Buckingham Palace Road,
Victoria, London, SW1W 9SZ

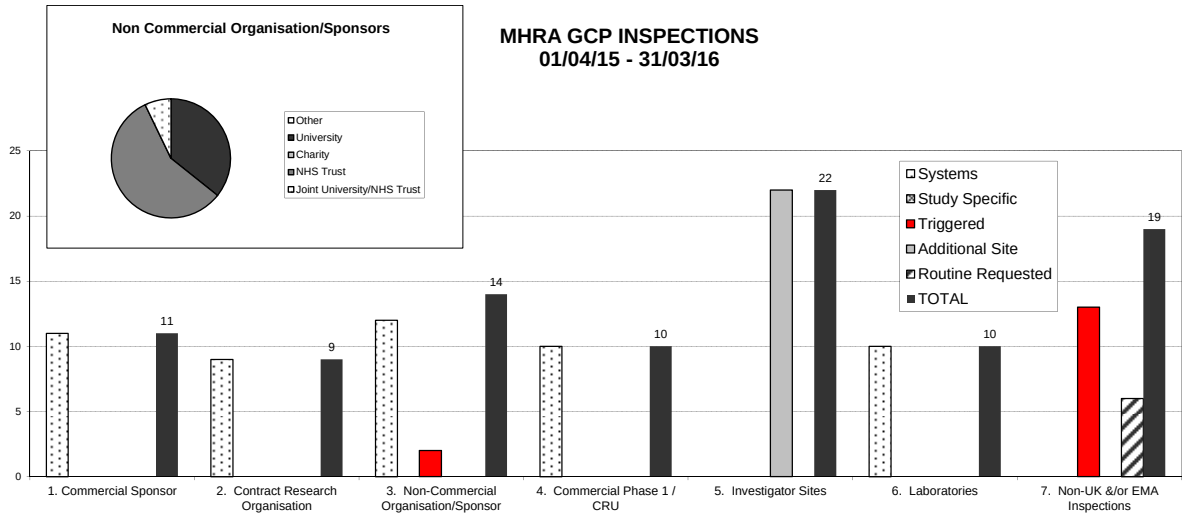
1. INTRODUCTION

This report covers the metrics period 1st April 2015 to 31st March 2016.

2. GCP INSPECTIONS UNDERTAKEN

During the Metrics Period a total of 102 GCP Inspections were undertaken by the MHRA GCP Inspectorate. The types of inspections are presented below.

The number of inspections of non-commercial organisations was 19, of commercial sponsors was 13, of Contract Research Organisations (CROs) was 8, of investigator sites there were 29 and finally there were 10 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 8 inspections. The number of non-UK and European Medicines Agency (EMA) inspections was 15, 7 of which were EMA inspections, the remaining 8 were non EMA foreign bioequivalence inspections. Triggered inspections were carried out as a result of information received by the GCP Inspectorate, for example in response to a serious breach report, and triggered inspections were undertaken of different organisations. Of the 22 triggered inspections, 2 were for commercial sponsors, 2 for CROs, 5 were for non-commercial organisations, 2 were for phase 1 units, 1 was for an investigator site and 10 were non-UK/EMA inspections, with 7 triggered by the EMA Committee for Medicinal Products for Human Use (CHMP) with 3 triggered by MHRA.



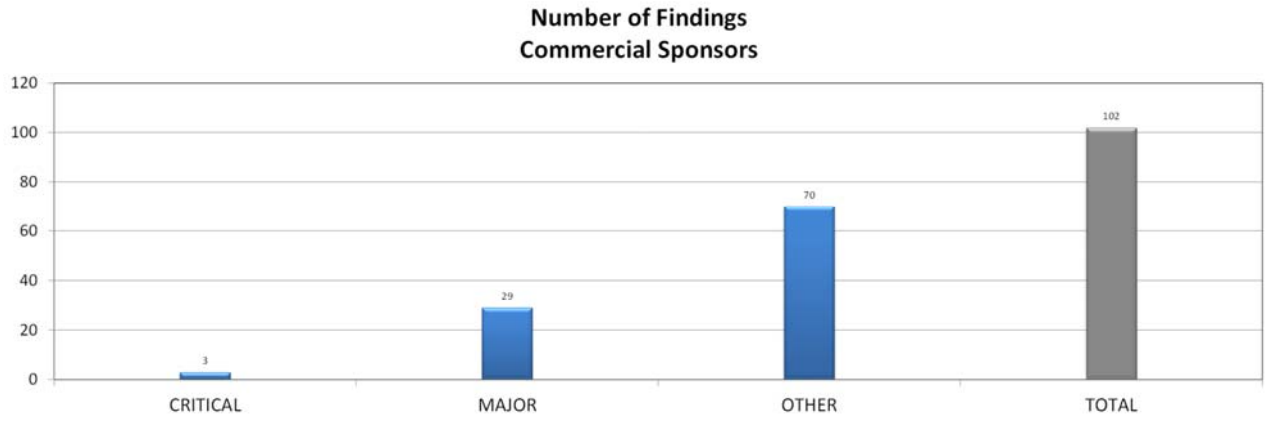
3. INSPECTION REPORTS AND FINDINGS

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 in order to complete the inspection. Where an inspection was conducted before 1st April 2016 and the other inspections (e.g. associated investigator site or further visit) were conducted after 1st April 2016 (e.g. sponsor site then the investigator site(s)) the findings from the inspections conducted/completed after 1st April 2016 will not be included in this metrics report, as these were inspections conducted/completed during the 2016-2017 Metrics Period. There were 3 inspections where two visits were necessary and the second visit was after 1st April 2016, these were 2 commercial sponsors and 1 triggered investigator site inspection. The inspections prior to 1st April 2016 are included in the text and figures in section 2 above, but the findings will be in the 2016-2017 metrics

report and not included in this one. Note however, that the last metrics report (2014-2015), a commercial sponsor organisation had their metrics reported although their second follow up inspection took place in April 2015, this inspection is included in the figures above, but not in the findings below. Therefore the number of inspections for findings to be reported is reduced by 3 for commercial sponsors to 10 and by 1 for investigator site inspection to 28. The findings reported in this document cover UK site inspections only. Metrics from inspections requested by the European Medicines Agency (EMA) are produced by the EMA. The findings are those that were contained in the inspection reports and do not take into account any inspection responses, apart from in the explanatory text for critical findings. The metrics data entry had an independent sample Quality Control (QC) check.

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

A total of 10 commercial sponsors were inspected and all have been reported. Of these inspections, 9 were systems inspections and 1 was triggered. Of the 10 inspections, 3 (30.0%) had at least one critical finding and 8 (80.0%) 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	0.3	0.0	0.0	1	10
Major	2.9	2.5	3.0	8	10
Other	7.0	7.5	6.0	11	10

There were 3 critical findings from 3 organisations.

Critical Finding 1

At the previous GCP inspection in 2013 there was a critical finding for data integrity relating to the use of electronic patient diaries (EPDs) for trial subjects to record details of IMP administration, any bleeding episodes, and responses to treatment. There were changes to subject-reported data that had been requested by investigator site staff and accepted in the study databases that were not supported by

adequate source data [refer to Metrics Report 2013-2014 for detail]. This was a critical finding due to the number of records affected and the direct link between subject-reported data and key study endpoints. In addition, there was a lack of evidence of appropriate testing of EPDs prior to release. This follow up inspection revealed that many of these same issues continued and the critical finding for data integrity remained as the data were unreliable. The observations included the following:

- From the associated investigator site inspection there were 562 data queries raised with the associated generation of data clarification forms (DCFs) for the patient reported data in 3 trials. The majority of all of these requested changes were accepted by the sponsor, despite instances where there was insufficient source data to support the changes. The changes and associated protocol deviations had not been discussed in the clinical study report for one of the trials and deviations had not been reported contrary to the monitoring plan requirements.
- There was insufficient documentation of User Acceptance Testing (UAT) for the EPD as there was no documentation to confirm that the UAT plan steps had been followed, the plan was not approved and it was not possible to determine who had performed all of the UAT.
- Reviews of edited EPD data on a monthly basis (required by study-specific plans as part of sponsor oversight) had not been taking place.
- CAPA commitments from the previous inspection relating to written procedures covering the data query process had not been adequately fulfilled: specific QC and approval steps had not been incorporated and there had been delays in implementation.
- There was a failure to detect and monitor user assignments to the database that contained patient reported data, for example, inappropriate staff had been given Principal Investigator user rights.
- IMP dosing calculation errors at investigator sites were not detected either during monitoring at site or by the data cleaning processes performed in preparation for the interim database lock and an inaccurate interim report had been sent to EMA as a result. Although corrective actions had been performed, no preventative actions had been implemented in the quality system.

Critical Finding 2

A critical finding for data integrity was given for 2 reasons.

Firstly, ineligible subjects were included in the per protocol analysis for 2 trials. This was not in accordance with the definition of the per protocol analysis set defined in ICH E9 'Statistical Principles for Clinical Trials' which includes the absence of any major protocol violations including the violation of entry criteria. This was also related to the issue that processes used to determine how a deviation would be classed as major/minor were not defined anywhere, i.e., the categorisation of an eligibility criterion violation as major, to lead to exclusion of the PP population had not been defined. For example, for 1 of the trials, the Clinical Study Report (CSR) had 44 subjects identified as not meeting the inclusion/exclusion criteria, however of these only 9 were identified as major protocol deviations and excluded from the PP population. This was also not consistent with the protocol deviations list for the trial which stated that 30 subjects failed the eligibility criteria, of which 7 were classified as major. For a further trial, it was identified that out of 13 subjects who had a deviation to the inclusion/exclusion criteria, only two were classified as major and removed from the per protocol analysis set.

Secondly, the audit trail from the Interactive Response Technology (IRT) systems for both trials was not made available during the inspection and when it was provided, there was no time stamp of the actions taken by users. The IRT validation documentation had no evidence that the secondary endpoints scores that were calculated by the IRT system had been validated.

Critical Finding 3

A critical finding was given for essential documents as the Trial Master File (TMF) presented as a hybrid paper and electronic TMF to the inspectors did not meet the requirements of the legislation; i.e., being the basis of the inspection, readily available, directly accessible and complete. As a result the quality of the TMF generally impeded inspectors from assessing GCP and legislative compliance. There was a

particular issue with product and trial level documents. The TMF issues were seen systematically across all trials selected.

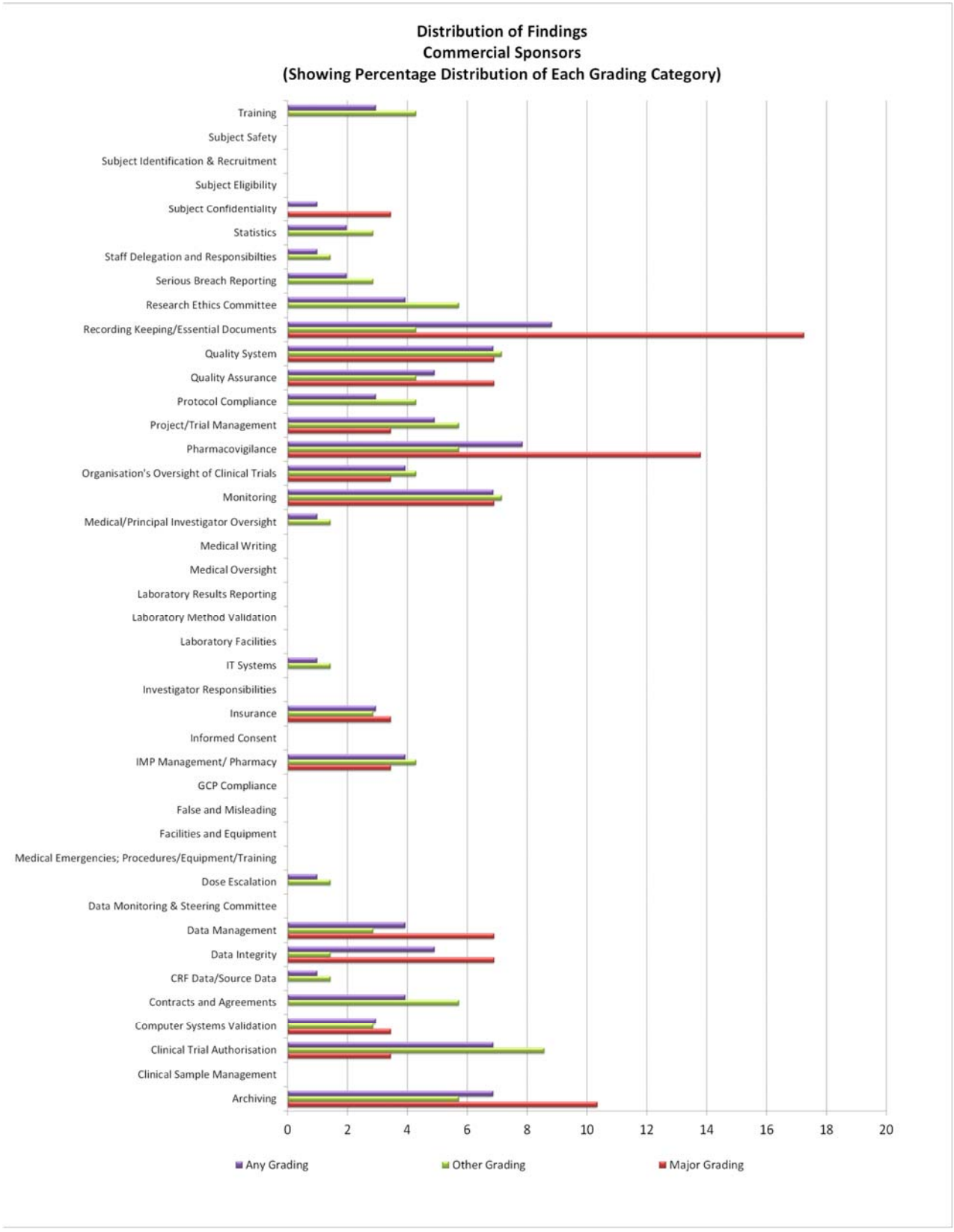
In addition a major finding had been raised at the previous inspection for essential documents due to TMF deficiencies. The preventative measures taken were not sufficient in addressing the fundamental causes of the previous inspection finding or for preventing repeat and escalating non-compliance with the legislation.

Issues identified included:

- The TMF was not defined (i.e., no quality system record to confirm all the systems that held TMF records, e.g. regulatory document system)
- TMFs provided for inspection were incomplete (missing records)
- There was a lack of Quality Control (QC) process of the TMFs
- The DIA TMF Reference model had been implemented (although with modifications) via a table of contents for each trial to identify the location of TMF essential documents in defined sections, however the structure of the actual TMF electronic folders had not been changed to reflect the model.
- The TMF table of contents was found to be unreliable as the location of documents was not accurate.
- The document date was in the file name and the date in the system was either the upload date or finalisation date. For this reason it was not possible to order documents in document date order.
- The was a lack of integration with other TMF systems i.e. there were no links or placeholders directing the inspectors to the relevant repository or system for the relevant documents and data.
- It was not possible to set the TMF to archive status to prevent further changes.
- Documents were not consistently held in the TMF.
- Previous versions of documents were not present.
- There was extensive duplication of scanned documents.
- There was evidence that the uploading of documents was not being undertaken in a timely manner
- If a document was not “finalised”, the inspectors could not view it.

For the other systems that contained essential documents, there had not been adequate consideration of the requirements, for example, how direct access by inspectors would be granted, or how archiving of clinical trial information would be considered

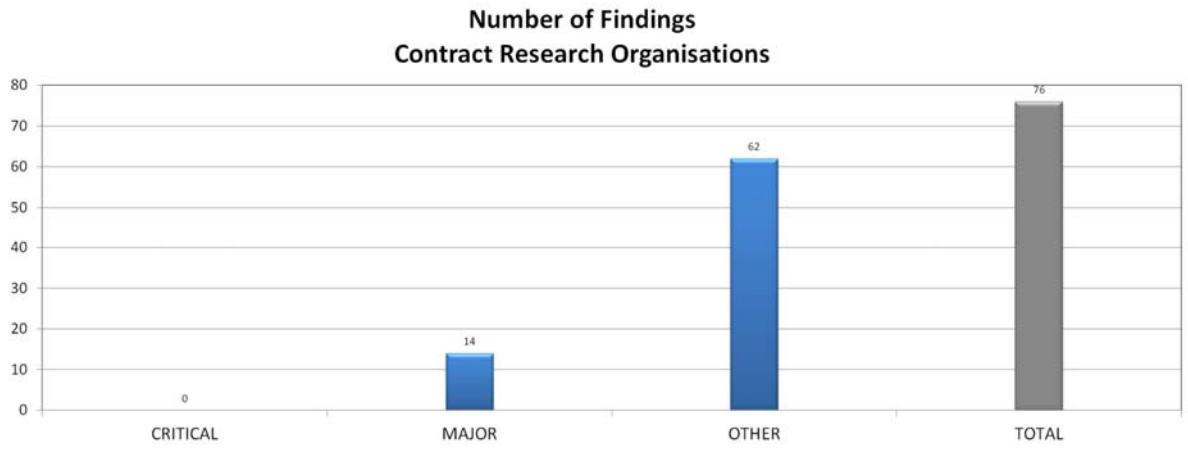
The figure on the following page shows the distribution of Major, Other and any grade of inspection findings. This identifies the areas where GCP inspectors have been making observations of non-compliance with GCP.


Distribution of Findings
Commercial Sponsors
(Showing Percentage Distribution of Each Grading Category)
Training
Subject Safety
Subject Identification & Recruitment
Subject Eligibility
Subject Confidentiality
Statistics
Staff Delegation and Responsibilties
Serious Breach Reporting
Research Ethics Committee
Recording Keeping/Essential Documents
Quality System
Quality Assurance
Protocol Compliance
Project/Trial Management
Pharmacovigilance
Organisation's Oversight of Clinical Trials
Monitoring
Medical/Principal Investigator Oversight
Medical Writing
Medical Oversight
Laboratory Results Reporting
Laboratory Method Validation
Laboratory Facilities
IT Systems
Investigator Responsibilities
Insurance
Informed Consent
IMP Management/ Pharmacy
GCP Compliance
False and Misleading
Facilities and Equipment
Medical Emergencies; Procedures/Equipment/Training
Dose Escalation
Data Monitoring & Steering Committee
Data Management
Data Integrity
CRF Data/Source Data
Contracts and Agreements
Computer Systems Validation
Clinical Trial Authorisation
Clinical Sample Management
Archiving
0
2
4
6
8
10
12
14
16
18
20
Any Grading
Other Grading
Major Grading

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

A total of 8 Contract Research Organisations were inspected and all have been reported. Six were systems inspections and 2 were triggered inspections.

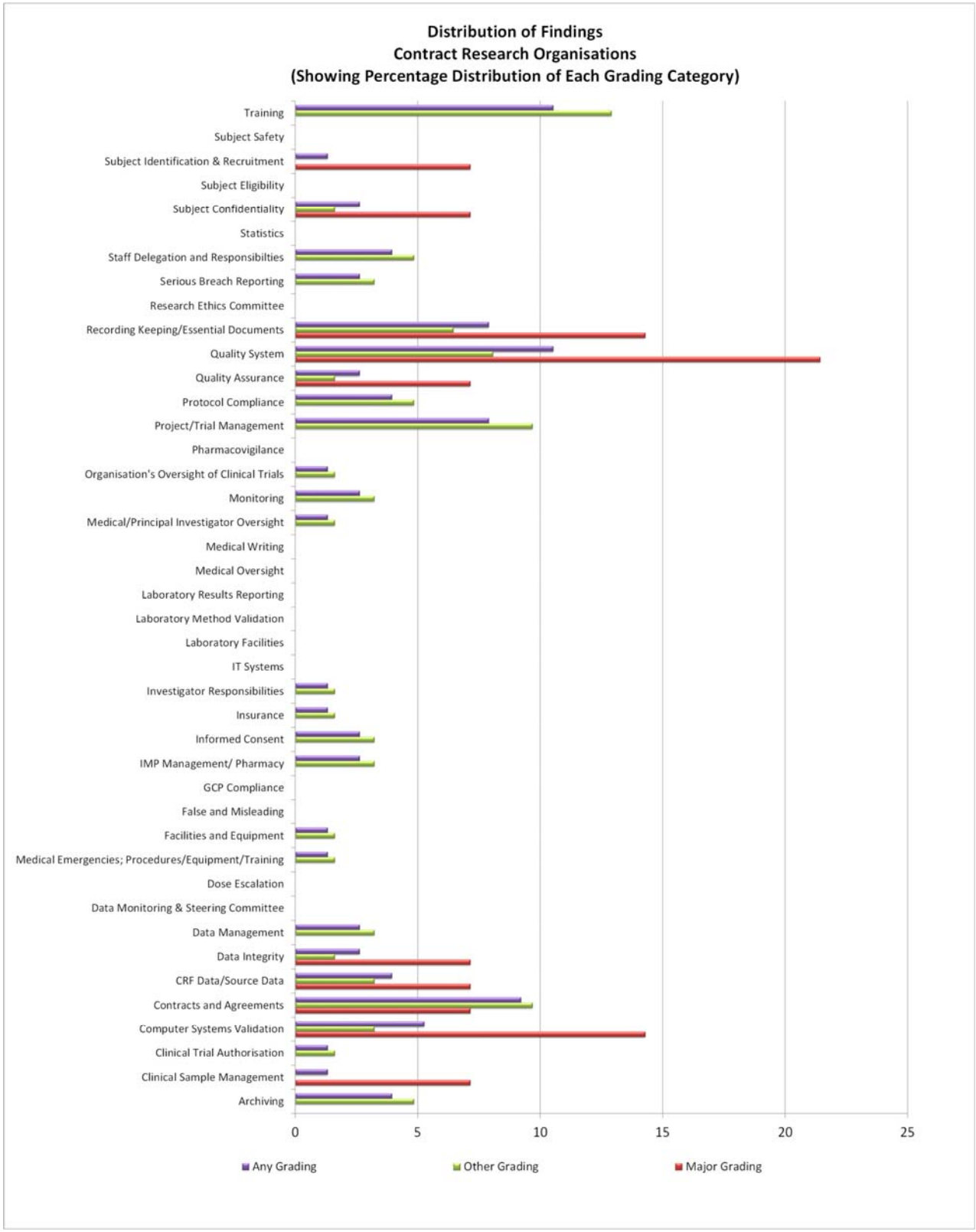
Of the 8 inspections, none had any critical findings and 8 (100.0%) had at least one major finding. The total number of findings and findings per inspection are represented on the figures below.



Number of Findings Per Inspection (Contract Research Organisations)

	Mean	Median	Mode	Maximum	n
Critical	0.0	0.0	0.0	0	8
Major	1.8	2.0	2.0	3	8
Other	7.8	7.0	6.0	12	8

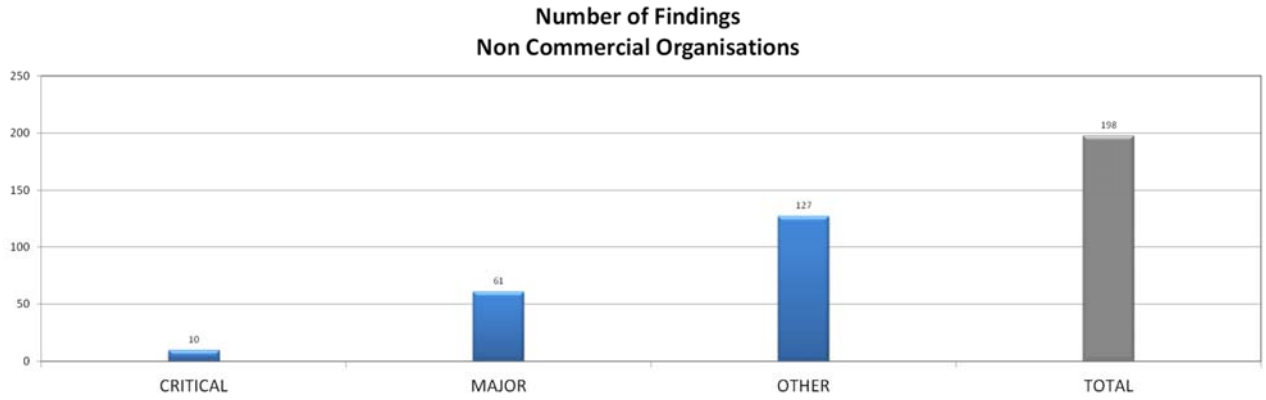
The figure on the following page shows the distribution of Major, Other and any grade of inspection findings. This identifies the areas where GCP inspectors have been making observations of non-compliance with GCP.


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

3.3 Non-Commercial Organisations (Routine Systems and Triggered)

A total of 20 non-commercial organisations were inspected, however one of these was a combined inspection of 2 NHS Trusts that worked very closely together and has been counted as a single inspection in section 2 above, hence 19 was reported there; but their findings have been reported separately, giving a total of 20 inspections for metrics presented here. Of the 20, 9 were of universities, 8 were of NHS trusts (including the joint trust inspection counted as 2), 1 inspection of a charity and 2 were a joint inspection of a NHS trust and university. Four of the non-commercial organisations were university clinical trial units (CTU), which are inspected in their own right and 1 university inspection was a joint inspection with their CTU. All have been reported. Five of the inspections were triggered inspections.

Of the 20 inspections, 8 (40.0%) had at least one critical finding and 20 (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	0.5	0.0	0.0	2	20
Major	3.1	3.0	1.0	6	20
Other	6.4	6.5	5.0	13	20

There were 10 critical findings identified from 8 different organisations. Two NHS trusts had 1 critical finding each (Findings 1 and 2), a university had 2 critical findings (Findings 3 and 4), a university and its CTU had 1 critical finding (Finding 5), one university had a critical finding (Finding 6), two university CTUs had a critical finding each (Findings 7 and 8) and a joint university and NHS trust had 2 critical findings (Findings 9 and 10).

Critical Finding 1

A critical finding was given for Principal investigator oversight. Two trials sponsored by the NHS trust had issues that demonstrated a lack of oversight of the trial conduct by the principal investigators.

- The contract between the NHS Trust sponsor and the Chief Investigator (CI)/Principal Investigator (PI) for a site had expired. Whilst this was being resolved, the trial recruitment was halted, but

notifications were not made to MHRA or Research Ethics Committee (REC). The CI/PI left the NHS trust and had moved to a university some distance away from the sponsor, whilst he was still acting as CI/PI, but with no contract. As a result the NHS indemnity would therefore have been invalid for the CI/PI during this period. A sub-investigator conducted the trial, but there was no evidence seen during the inspection of any formal oversight of this by the absent CI/PI.

- The review of inclusion/exclusion and eligibility decision was not documented in the patient notes, but completed in the Case Report Form (CRF) by the research nurse after randomisation. It was not evident in the trial documentation for all subjects in this trial that the eligibility decision was made by an appropriately qualified medical doctor, therefore there was a lack of the principal investigator's oversight of the conduct of the trial.

Critical Finding 2

A critical finding was given for pharmacovigilance as there was significant potential for Suspected Unexpected Serious Adverse Reactions (SUSARs) to go unreported through a number of failing processes that included:

- The Reference Safety Information (RSI) for all studies using Summary of Product Characteristics (SmPCs) was being updated without an amendment being sent to the MHRA or any assessment of new expected terms being carried out.
- A trial was being run under different sponsors in different countries across Europe with a group in Italy coordinating the study across Europe. There was no contract between the Trust and this group and no process for Serious Adverse Events (SAEs) in other countries to be sent to the Trust. This created the possibility for UK relevant SUSARs to go unidentified and not be reported to the MHRA. The study was active in UK, Belgium, Ireland and Italy.
- A number of Serious Adverse Reactions (SARs) on the trial had been misclassified as the PI stated that the event was possibly or probably related to the Investigations Medicinal Product (IMP), but then classifying them as SAEs. This error was not identified by the CI and data manager during their review. There was no evidence that these events had been assessed against the RSI to determine if they were SUSARs. This may have been done by the group in Italy, but the Trust was not sure at the time of the inspection and there was no agreement in place to cover it.
- All SAEs for another trial were reviewed by the CI, but the SAE form only had space for one causality assessment done by the PI. There was evidence of the CI's assessment differing to that of the PIs and only the CIs assessment being recorded on the final version of the form. There was no evidence provided of the PI agreeing to the CIs changes.
- There were no processes in place to ensure Investigator Brochures (IBs) that contain the RSI were reviewed on an annual basis and the Trust were unaware of this requirement.

Critical Findings 3 & 4

A critical finding was given for essential documents because the TMF, both sponsor and investigator files had been lost for a trial that was selected for inspection and therefore unavailable as the basis for the inspection. As a result there were no CRFs available or the ability to identify patients and therefore the source data that supports the publication of the trial results. The trial could not be reconstructed. A further trial also had documents missing from the TMF.

A second critical finding was given for sponsor oversight. There was a lack of a formal quality system to effectively cover the requirements of sponsorship as a result there were no processes within the organisation to cover key sponsor responsibilities such as:-

- Decision on sponsorship
- Protocol and amendments review and approval
- Urgent safety measures

- Serious breaches
- TMF and archiving
- Monitoring
- Pharmacovigilance requirements
- Vendor selection
- Training
- Data Management

The sponsor failed to oversee the protocol amendments of a trial and let the pharmaceutical company (the funder) undertake this role. There was a lack of formal delegation of sponsor responsibilities to the chief investigator with lack of direction and oversight by the sponsor.

The lack of oversight contributed to GCP non-compliance identified in the trials reviewed.

Critical Finding 5

Since 2008, the university had sponsored three clinical trials and co-sponsored two. In 2013, the need for formal processes to cover granting sponsorship and oversight of Clinical Trials of Investigational Medicinal Products (CTIMPs) was identified. However, in light of three trials being sponsored since 2013, whilst there had been a recent formation of the joint Quality Assurance (QA) office, there was no action to implement processes. This resulted in a critical finding for sponsor oversight.

There had been, until very recently, no formal process in place for granting sponsorship of CTIMPs so it was not possible to identify who was authorised to grant approval of sponsorship within the University, under what circumstances and when approval would be granted. As a result, there was no documented approval of sponsorship by the university for 4 out of 5 trials prior to the trials commencing. The sponsor had difficulties in identifying whether they actually were the sponsor of a trial, for one trial they were not aware that they were a co-sponsor. Whilst a the new process had recently been implemented, there were still process deficiencies identified, for example, risk assessment, assessment of whether the trial was a CTIMP (or contacting the MHRA if unsure) and how it would be ensured that only Type A trials would be sponsored (as per stated university policy).

There was a lack of documentation to demonstrate oversight by the sponsor of the trials, for example, the sponsor only had a co-sponsorship agreement for 1 trial and for a further trial the sponsor responsibility for reporting results to the MHRA had not been undertaken.

Until recently, there was no formal process to delegate sponsor functions to the chief investigator. Where such a document existed for recent trials, as part of a delegation log, annexed to a co-sponsorship agreement, all the sponsor functions were not adequately covered, e.g., CTA application, Regulatory Green Light (RGL) process, IMP Management and handling and serious breach reporting. There were also examples where tasks had been formally delegated after they had been performed (e.g. CTA and REC submissions.).

Critical Finding 6

This inspection was triggered from serious breach reports and required the inspection of 8 investigator sites and the sponsor site. There was particular focus on the sponsor's oversight of the management of IMP.

A critical finding was given for sponsor oversight. The majority of sponsor oversight was performed as remote activities. However, these were not adequately defined or documented, therefore resulting in the serious breaches notified to the MHRA.

For example:

- There was no consistency in the process for investigator site identification, selection and initiation activities conducted for the UK investigator sites. For example the SOPs in place were not followed, uncontrolled forms used with inconsistency in content for different sites, failure to ask appropriate information to assess the site's ability to conduct the trial, no risk assessment to determine on-site or remote initiation visit required and no documented assessment of each site's suitability and the decision to accept the site by the sponsor.
- The responsibility for assessing the suitability of drug storage in both trials was delegated to the sites in the site clinical trial agreement. Therefore, there was no sponsor review/assessment and agreement of the suitability of the IMP storage arrangements where the IMP was held outside pharmacy for any of the UK sites.
- During the conduct of both trials, there was no ongoing oversight of changes at the trial sites (such as any changes to IMP storage or staff delegation, unless this led to a change in the access to the trial database by the site for data entry).
- There was no requirement for UK sites to provide self-monitoring reports (this was only required by non-UK sites), delegation logs or for sites to notify the sponsor of any changes in IMP management or storage occurring at the site.
- Whilst there were copies of drug accountability records in the sponsor site files of TMF, there was only a stamp of when these had been received by the sponsor, there was no documentation of what the clinical trial unit (CTU) actually did with them (e.g. any review or assessment, by whom or when and whether any actions were required and followed up or whether they were just filed).
- The sponsor failed to adapt their oversight process for the storage and management of IMP in light of the three serious breaches that occurred in 2 trials. In addition there were two additional outstanding missing IMP investigations at 2 sites which had not been closed and a root cause analysis and CAPA had not been considered at a sponsor level as a result of these systemic issues at the time of the inspection.

As a result of the above issues, following the inspection, the sponsor undertook a review of IMP storage across all trial sites which resulted in a further two trial sites being identified as having drug unaccounted for, that has potentially been dosed to non-trial patients.

Critical Finding 7

A critical finding was given for data integrity at a university CTU. This was because systems and processes examined during the inspection of the trial and the observations made cast doubt on the reliability of the data contained in the database for this trial and consequently the reliability of the trial results. Similar processes were used for other trials. The key issues identified were:

- Inability to adequately confirm that the database changes to the data had all been authorised by the investigator prior to the change being made. This was due to the process of resolving queries by email.
- Changes made to the database prior to investigator approval and inappropriate use of "self-evident corrections".
- Lack of Quality Control (QC) of data entry from paper CRFs, ineffective audit trials within the database and the paper trials of data amendments retained at the investigator site.
- Loss of control of the source data by the investigator in the database (Investigator entered some source data into the database) and complete absence of key source data at the site (no trial diaries were retained upon advice of the CTU) relating the endpoint of the trial.
- Inconsistencies between the data at site on paper CRF/Worksheet and the database and whether data were complete (e.g. adverse events reported).
- The database was initially used for data management staff to enter paper CRF data, but access was given to investigators to enter data themselves with no thought given to the implications of this. Therefore there were concerns regarding the validation status of the database build and whether the "eCRF functionality" was fit for purpose. Note that the validation of this database was not specifically assessed, but another trial database showed validation deficiencies and it was clear that the eCRF functionality for database had not been adequately validated for GCP requirements.

- Lack of effective trial monitoring.

Critical Finding 8

Multiple areas of non-compliance were seen regarding pharmacovigilance activities and a critical finding was given for pharmacovigilance. Firstly there were issues with RSI:

- Trial teams were found to be unaware that substantial amendments need to be approved by the MHRA and REC in relation to RSI changes prior to implementation.
- There was evidence of new RSI versions implemented without MHRA and REC approval. Changes to the SmPC versions were not submitted to the MHRA as substantial amendments prior to implementation. Neither was the impact on the patient information sheet assessed.
- The SmPCs were being used for both trial IMPs, whereas it was the IB that had been submitted to the MHRA in the initial clinical trial authorisation application.
- RSI was not clearly defined for a trial as there was insufficient assessment to determine whether the RSI was suitable for the trial population.
- The versions of the SmPCs used for expectedness assessments were not recorded to enable reconstruction of the RSI version used to assess expectedness at the time of the event.

Other issues in the pharmacovigilance requirements included the following,

- An example was seen of a SUSAR relating to the miscarriage of the pregnancy of partner of a male trial participant that was not reported to the MHRA
- Events missing from the Development Safety Update Report (DSUR
- There were issues seen with the inadequate completion of SAE reports in two of the trials reviewed. These issues had not been detected by the trial manager reviewing the SAEs.
- There were multiple errors in the SAE listings for the selected trials provided to the inspectors prior to the inspection. There had been no QC checks on the data provided. Further inaccuracies were seen in the between the safety information contained in the trial database versus the SAE report forms.
- The safety reporting procedures were inadequate in that they were not sufficiently detailed to cover the CTU process, where the CTU were responsible for PV, for example, submitting substantial amendments for RSI changes, compiling a DSUR, tracking SAEs.
- Significant variation was seen in the various SAE templates being used for CTU trials, which resulted in not all assessment criteria being captured for all trials. For example, not capturing expectedness assessments to be documented or containing different relatedness criteria.

Critical Finding 9 & 10

One critical finding was given for subject eligibility because in one trial reviewed, six eligibility violations, out of eighty patients meeting exclusion criteria (concerning the prohibited use of opioids), but enrolled in the study by the CI as waivers, these were identified retrospectively by the sponsor, who was not made aware at the time, following the completion of the trial. In another trial a Body Mass Index (BMI) of 29.98 was s rounded up to 30 to allow the subject onto the study. The sponsor's processes failed to ensure the eligibility violations were identified, assessed and escalated in a timely manner. At the time of Inspection a 100% QC of eligibility had not been performed and no preventative actions had been identified to rectify and prevent this issue reoccurring and ensure all incidences of ineligible patients had been identified.

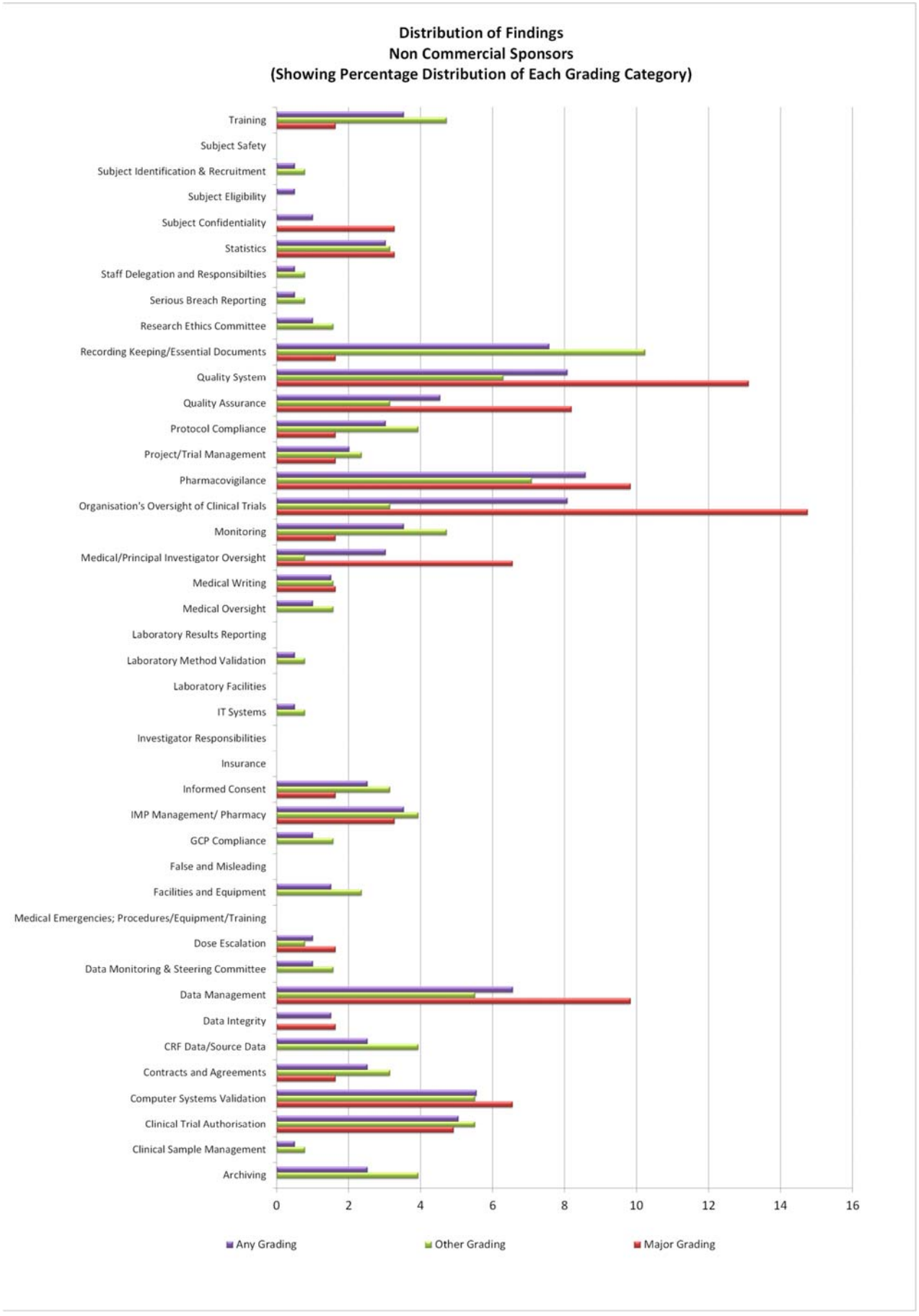
A further critical finding was given for data integrity. One trial examined had numerous issues that meant there was a concern about the reliability of the trial data to be used in a publication. Source Data Verification (SDV) by the inspectors of three patients identified a numerous inaccuracies within a trial database resultant from unclear data entry guidelines, database field issues and untimely entry/correction of source data. None of the patients reviewed had a completely accurate data set in the

database. There had been no on-site monitoring by the sponsor. Additionally, the source documentation for IMP administration was unreliable.

- The database contained 12 numbered entries in the fields, but the source data showed 14 numbered entries so it was not clear how staff entering the data could identify the correct data point.
- Data had been "interpreted" from the source and entered differently in the database for which, there were no agreed data entry rules for doing so. It was stated that this would be more clearly defined in the Statistical Analysis Plan; this plan, however, had not been approved.
- Examples were seen where the source document care plan (which contained some of the source data) had been amended and/or retrospectively completed a significant period of time after the subjects participation in the trial had ended for several trial patients
- Examples of data in the care plan was not consistent with other source data within the patient's notes.
- Examples where the incorrect CRF/care plan version had been used.
- There were a significant number of discrepancies between the un-blinded randomisation data (i.e. the allocation of placebo or active medication to each patient), the informed consent form and the patient database effectively meaning that it was not possible to determine which patient had been randomised to which drug.
- One patient had been dosed twice.

There were also discrepancies identified between source data and the database on another trial, though the extent was not as great.

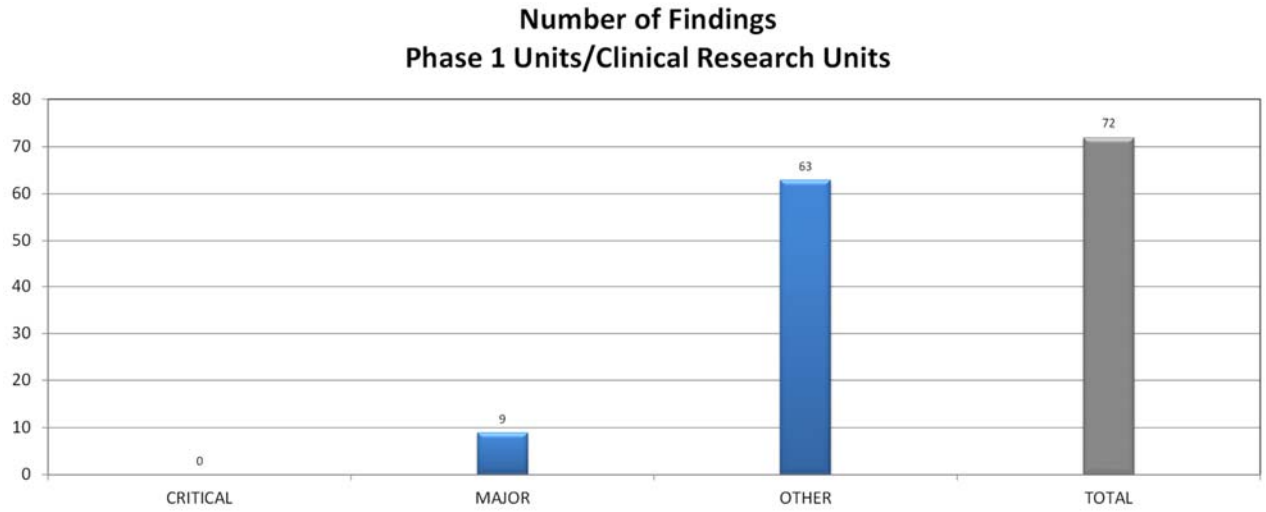
The figure on the following page shows the distribution of Major, Other and any grade of inspection findings. This identifies the areas where GCP inspectors have been making observations of non-compliance with GCP.


Distribution of Findings
Non Commercial Sponsors
(Showing Percentage Distribution of Each Grading Category)
Training
Subject Safety
Subject Identification & Recruitment
Subject Eligibility
Subject Confidentiality
Statistics
Staff Delegation and Responsibilties
Serious Breach Reporting
Research Ethics Committee
Recording Keeping/Essential Documents
Quality System
Quality Assurance
Protocol Compliance
Project/Trial Management
Pharmacovigilance
Organisation's Oversight of Clinical Trials
Monitoring
Medical/Principal Investigator Oversight
Medical Writing
Medical Oversight
Laboratory Results Reporting
Laboratory Method Validation
Laboratory Facilities
IT Systems
Investigator Responsibilities
Insurance
Informed Consent
IMP Management/ Pharmacy
GCP Compliance
False and Misleading
Facilities and Equipment
Medical Emergencies; Procedures/Equipment/Training
Dose Escalation
Data Monitoring & Steering Committee
Data Management
Data Integrity
CRF Data/Source Data
Contracts and Agreements
Computer Systems Validation
Clinical Trial Authorisation
Clinical Sample Management
Archiving
0
2
4
6
8
10
12
14
16
Any Grading
Other Grading
Major Grading

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

A total of 10 inspections were done of Commercial Phase 1 Units/Clinical Research Units. Eight of the inspections were routine inspections for the MHRA voluntary phase 1 accreditation scheme and 2 inspections were triggered. Note that findings reported here relate to GCP and not those related to the accreditation scheme.

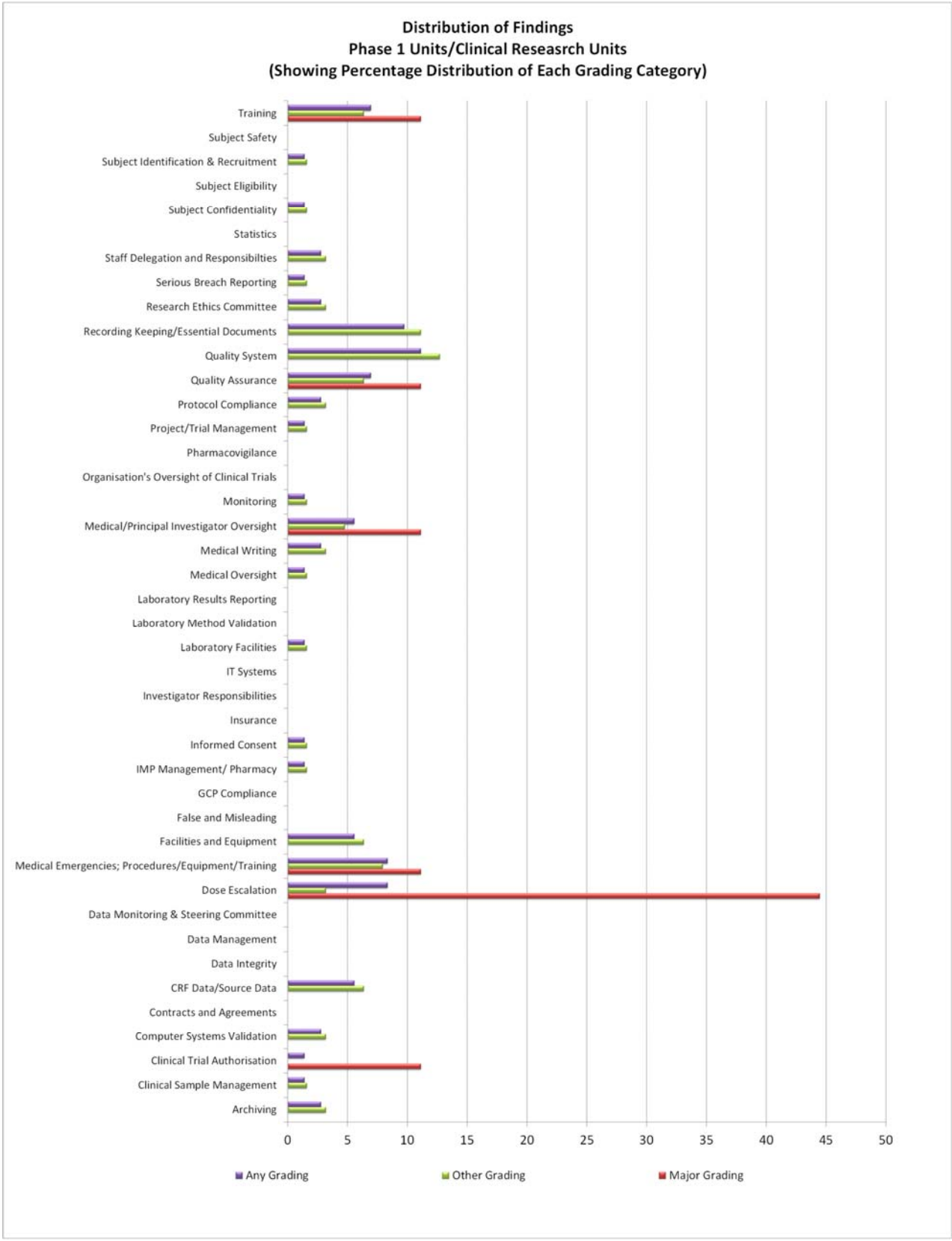
Of the 10 reported inspections, none had a critical finding and 5 (50.0%) had at least one major finding. The number of findings and findings per inspection are represented on the figures below.



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

	Mean	Median	Mode	Maximum	n
Critical	0.0	0.0	0.0	0	10
Major	0.9	0.5	0.0	3	10
Other	6.3	5.5	8.0	13	10

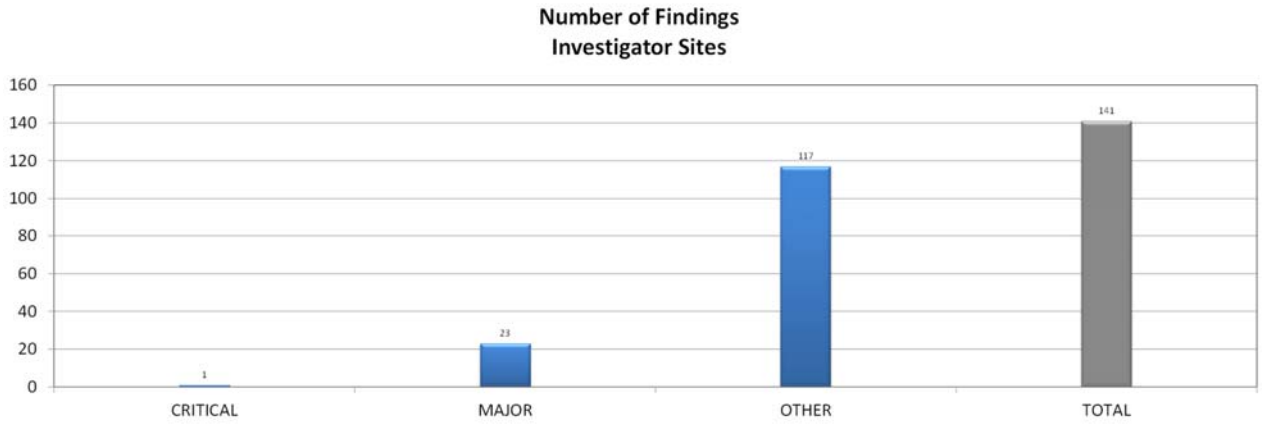
The figure on the following page shows the distribution of Major, Other and any grade of inspection findings. This identifies the areas where GCP inspectors have been making observations of non-compliance with GCP.


Distribution of Findings
Phase 1 Units/Clinical Reseasrch Units
(Showing Percentage Distribution of Each Grading Category)
Training
Subject Safety
Subject Identification & Recruitment
Subject Eligibility
Subject Confidentiality
Statistics
Staff Delegation and Responsibilties
Serious Breach Reporting
Research Ethics Committee
Recording Keeping/Essential Documents
Quality System
Quality Assurance
Protocol Compliance
Project/Trial Management
Pharmacovigilance
Organisation's Oversight of Clinical Trials
Monitoring
Medical/Principal Investigator Oversight
Medical Writing
Medical Oversight
Laboratory Results Reporting
Laboratory Method Validation
Laboratory Facilities
IT Systems
Investigator Responsibilities
Insurance
Informed Consent
IMP Management/ Pharmacy
GCP Compliance
False and Misleading
Facilities and Equipment
Medical Emergencies; Procedures/Equipment/Training
Dose Escalation
Data Monitoring & Steering Committee
Data Management
Data Integrity
CRF Data/Source Data
Contracts and Agreements
Computer Systems Validation
Clinical Trial Authorisation
Clinical Sample Management
Archiving
0
5
10
15
20
25
30
35
40
45
50
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 28 investigator sites in the UK were inspected, all were as an associated site with a sponsor/CRO/non-commercial/CTU inspection.

Of the 28 inspections, 1 (3.6%) had a critical finding and 14 (50.0%) 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	0.0	0.0	0.0	1	28
Major	0.8	0.5	0.0	4	28
Other	4.2	4.0	5.0	9	28

There was 1 critical finding given for IMP management at an investigator site. This was an associated site for the inspection that had Critical Finding 6 in section 3.3.

The lack of IMP management and accountability at the site resulted in the 'highly likely' possibility that two vials of trial IMP were administered to a non-trial subject, presenting with a cardiac arrest, who therefore was not eligible and had not consented to the trial. The patient subsequently died, however it was not considered to be related to the IMP or dosing error. A number of systematic failures were identified with regards to IMP management at this site. There was inadequate documentation of the investigation into the issue, root cause and the outcome by both the sponsor and the site, despite the sponsor being aware of a similar incident resulting in a serious breach at another site for another trial. Issues identified included:

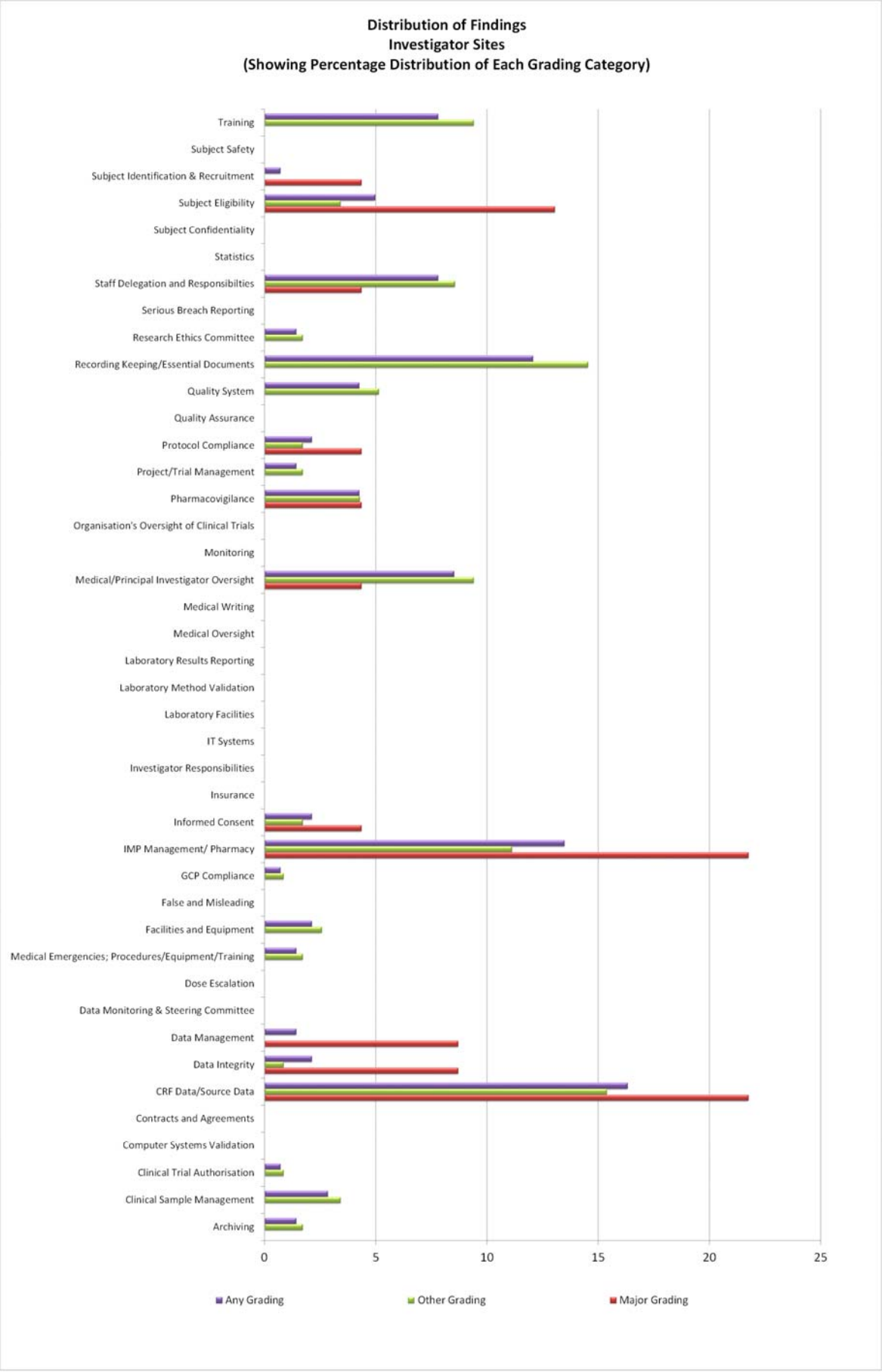
- A for-cause audit by the sponsor concluded that there were no areas for concern, despite not being able to account for the missing IMP.
- The investigations conducted by the PI had not been documented at the time of the inspection. There was no independent investigation into the incident within the trust and the initial incident report in the incident reporting system had not been escalated to Research and Development department, as they were not on the report distribution list.

- Witness statements were not obtained from all staff involved in the incident, for example no statement had been obtained from sub-investigators.
- At the time of the inspection, the remaining four vials of the IMP had not been located. It was acknowledged that the missing four vials were located post inspection; however, these had not been located in earlier investigations conducted by the site and sponsor.

There was a lack of oversight of IMP stored in the emergency department. For example:

- A risk assessment of IMP stored outside of pharmacy had not been performed and a process for performing a risk assessment had only recently been implemented.
- The trial IMP was transferred to several different locations within the emergency department. There was no documentation available to document the transfer of IMP and the suitability of storage areas prior to transfer.
- There were no checks performed of the IMP cupboard to ensure that there had been no unauthorised use of IMP between subject randomisations.

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)
Training
Subject Safety
Subject Identification & Recruitment
Subject Eligibility
Subject Confidentiality
Statistics
Staff Delegation and Responsibilties
Serious Breach Reporting
Research Ethics Committee
Recording Keeping/Essential Documents
Quality System
Quality Assurance
Protocol Compliance
Project/Trial Management
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IMP Management/ Pharmacy
GCP Compliance
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Data Monitoring & Steering Committee
Data Management
Data Integrity
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Contracts and Agreements
Computer Systems Validation
Clinical Trial Authorisation
Clinical Sample Management
Archiving
0
5
10
15
20
25
Any Grading
Other Grading
Major Grading