Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

GCP INSPECTORATE

GCP INSPECTIONS METRICS REPORT

METRICS PERIOD: 1st April 2014 to 31st March 2015

DATE OF ISSUE: 11th April 2016

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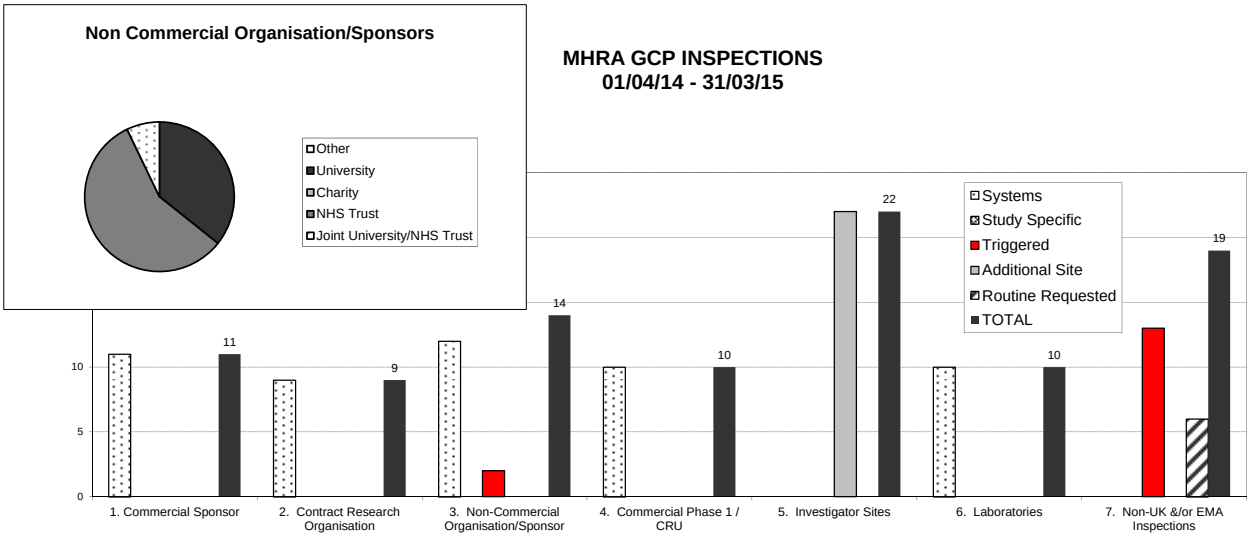
1. INTRODUCTION

This report covers the metrics period 1st April 2014 to 31st March 2015.

2. GCP INSPECTIONS UNDERTAKEN

During the Metrics Period a total of 95 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 14, of commercial sponsors was 11, of Contract Research Organisations (CROs) was 9, of investigator sites there were 22 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 10 inspections. The number of non-UK and European Medicines Agency (EMA) inspections was 19. 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 15 triggered inspections, 2 were for non-commercial co-sponsors, and 13 were non-UK/EMA inspections, with 11 triggered by the EMA Committee for Medicinal Products for Human Use (CHMP) with 2 triggered by MHRA.

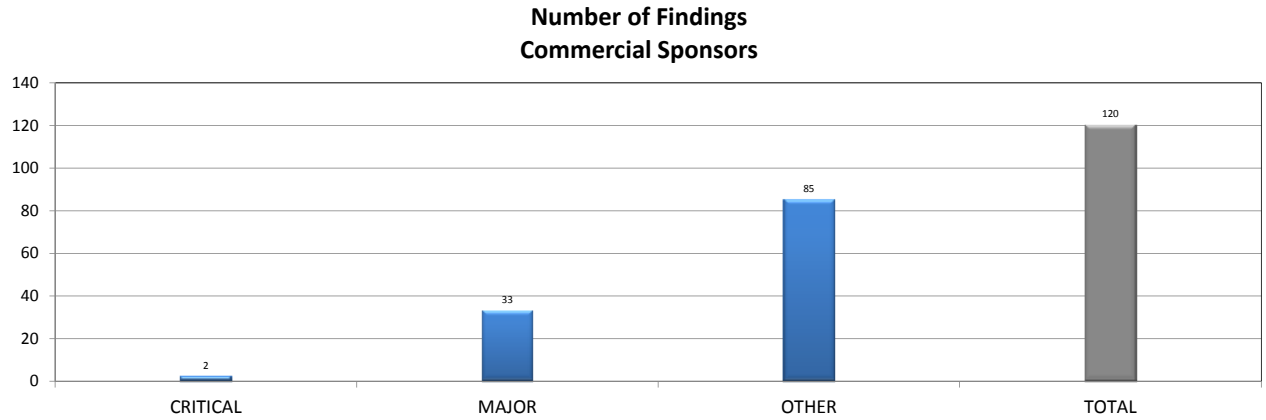


3. INSPECTION REPORTS AND FINDINGS

Reports relating only to the inspections carried out in the Metrics Period were reviewed. It is important to note that multiple inspections can be reported in one GCP Inspection Report, for example, a commercial sponsor GCP Inspection Report may consist of the sponsor inspection and associated investigator site inspections. Where an inspection was conducted before 1st April 2014 and the other associated inspections were conducted after 1st April 2014 (e.g. sponsor site then the investigator site(s)) the findings from the inspections conducted after 1st April 2014 (e.g. investigator site(s)) will be included in this metrics report, as these were inspections conducted during this Metrics Period. The findings reported in this document cover UK site inspections only. Metrics from inspections requested by the European Medicines Agency (EMA) are produced by the EMA. The findings are those that were contained in the inspection reports and do not take into account any inspection responses, apart from in the explanatory text for critical findings. The metrics data entry had an independent sample Quality Control (QC) check.

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

A total of 11 commercial sponsors were inspected and all have been reported. Of the 11 inspections, 2 (18.2%) had at least one critical finding and 11 (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	0.2	0.0	0.0	1	11
Major	3.0	1.0	1.0	13	11
Other	7.7	7.0	7.0	13	11

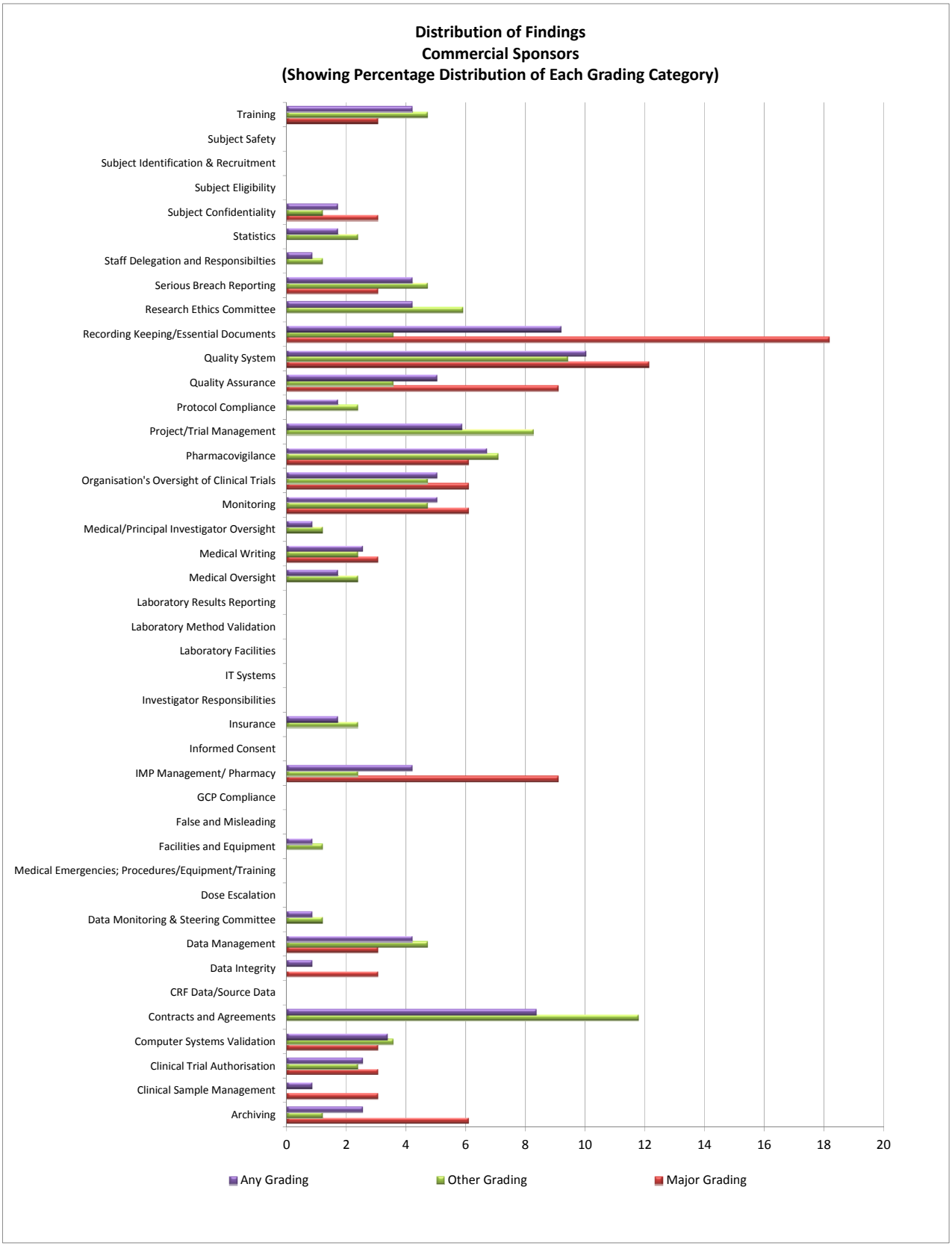
There were 2 critical findings from 2 organisations.

These were for 2 different large global pharmaceutical companies and an initial verbal critical finding was given to the companies concerning the failure of the organisations Trial Master File (TMF) to be the basis for inspection, readily available, directly accessible and complete as per the requirements of Statutory Instrument 2004/1031 Regulation 31A. MHRA GCP inspectorate had updated the definition of critical finding to include failures for the provision of the TMF because it obstructs the inspectors carrying out their statutory duty in assessing the compliance of the trials with the legislation. It should be noted that previously other organisations have had similar issues, but were not at that time graded as critical.

An initial inspection showed that the presentation of the selected trial TMFs overall was grossly inadequate. The TMF was not readily available or accessible and there was some evidence of it being incomplete. Essentially, there was a failure to have a single TMF within the company, because lots of different electronic systems based on drug/function hierarchy were pulled together to be called the TMF, but there was no single system that was designed to be the eTMF with the appropriate functionality. Ability of inspectors to access documents for review and the TMF itself being complete was severely hampered as a result. Following the verbal critical finding at the closing meeting, the companies were both given the opportunity to present the full TMF for some trials at a subsequent inspection a few months later in order for the inspectors to assess the compliance of the trials.

The TMFs were presented for inspection in paper format at one organisation and primarily electronic format at the other. The companies demonstrated that a single TMF for a trial could be provided, by collating all the documents from the different systems into one place; however, provision of the TMF in this way for this subsequent inspection was not something that could be undertaken in a short period of time and took considerable effort. Therefore, the critical finding remained, because the TMF could not be regarded as being "readily available" until the planned eTMF system, as a preventative action, is implemented. The companies were required at the inspection closure to provide quarterly summary updates to the Lead Inspectors of the progress of the development of the eTMF project and the implementation of the new system. This is required to include details of its use following deployment, for example migration of ongoing trials and use for new trials. This will enable a further inspection to be scheduled at an appropriate time to assess the new eTMF for compliance with the legislation.

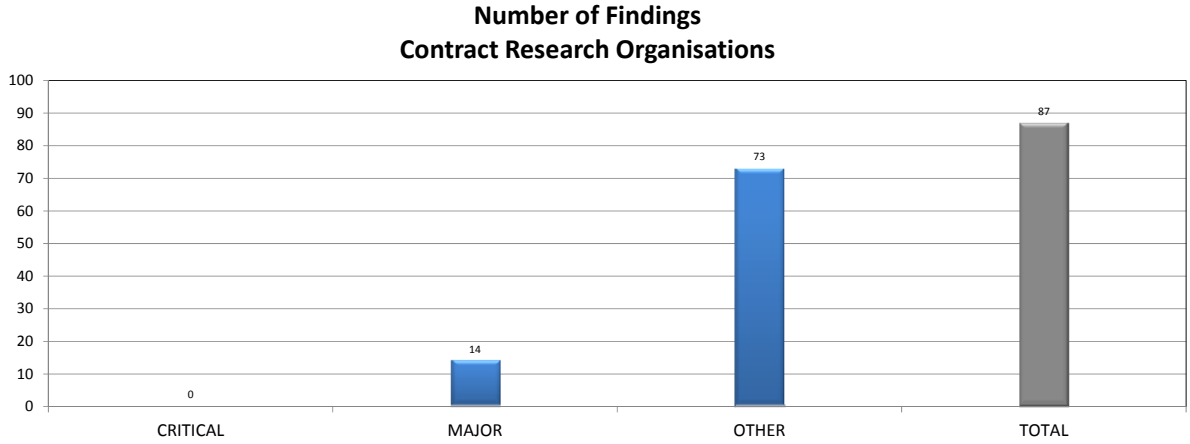
The figure on the following page shows the distribution of Major, Other and any grade of inspection findings. This identifies the areas where GCP inspectors have been making observations of non-compliance with GCP.


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 9 Contract Research Organisations were inspected and all have been reported. All were systems inspections.

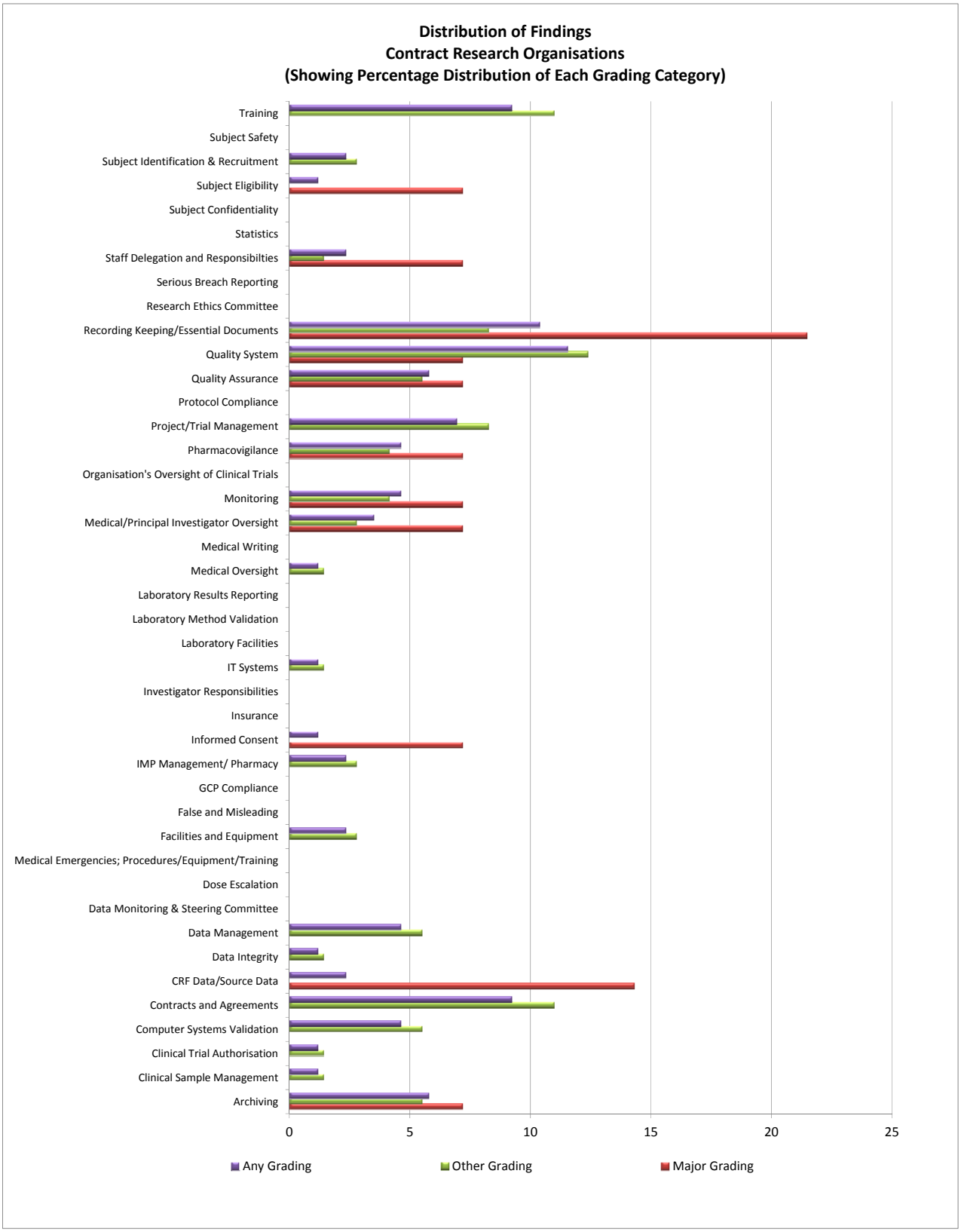
Of the 9 inspections, none had any critical findings and 6 (66.7%) had at least one major finding. The total number of findings and findings per inspection are represented on the figures below.



Number of Findings Per Inspection (Contract Research Organisations)

	Mean	Median	Mode	Maximum	n
Critical	0.0	0.0	0.0	0	9
Major	1.6	1.0	0.0	6	9
Other	8.1	8.0	5.0	11	9

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
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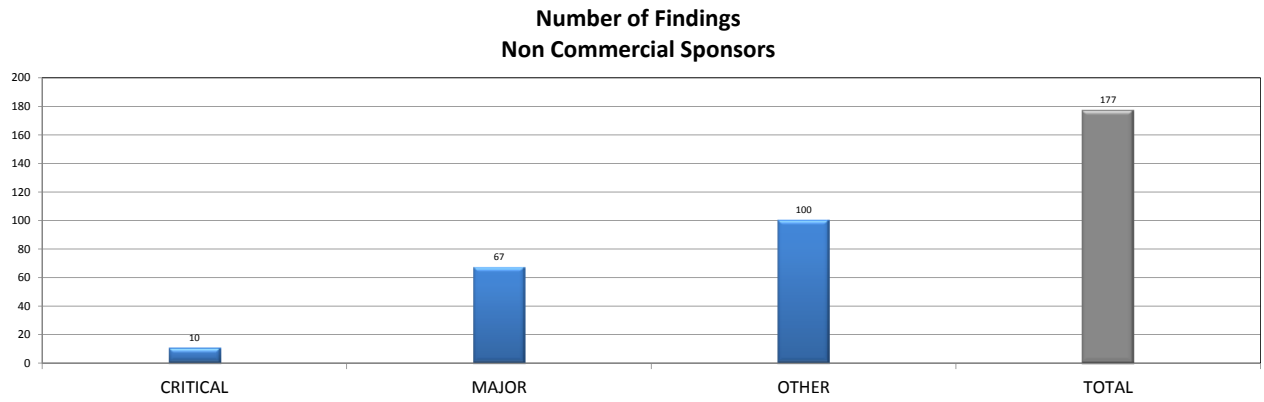
Insurance
Informed Consent
IMP Management/ Pharmacy
GCP Compliance
False and Misleading
Facilities and Equipment
Medical Emergencies; Procedures/Equipment/Training
Dose Escalation
Data Monitoring & Steering Committee
Data Management
Data Integrity
CRF Data/Source Data
Contracts and Agreements
Computer 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 14 non-commercial organisations were inspected, 5 were of universities, 8 were of NHS Trusts and 1 was a joint inspection of a NHS Trust and university. Some of the non-commercial organisations were clinical trial units, which are inspected in their own right. All have been reported.

Of the 14 inspections, 6 (42.9%) had at least one critical finding and 14 (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	0.7	0.0	0.0	3	14
Major	4.8	4.5	1.0	10	14
Other	7.1	7.5	5.0	15	14

There were 10 critical findings identified from 6 different organisations. Two NHS Trusts had 1 critical finding each (critical findings 1 and 2), a further 2 Trusts had 2 critical findings each (findings 3 & 4 and 5 & 6) and one of these Trust inspections was a triggered inspection. A university had 1 critical finding (Finding 7) and a Joint university and Trust inspection had 3 critical findings (Findings 8, 9 and 10).

Critical Finding 1

A critical finding was found in a trial conducted by an NHS Trust. It should be noted that this trial was the only one not supported by the CTU and the PI was inexperienced in conducting CTIMPs. The other trials, ran in the CTU, did not have significant non-compliance.

The critical finding was for data integrity due to not being possible to determine which patient received which investigational medicinal product (IMP) and issues with failure to maintain the trial blinding using a masked assessor for pain assessment (trial endpoint).

The trial protocol required that half the subjects receive eye drops (IMP 1) alone and the other half receive eye drops plus a further sub-conjunctival injection (IMP 2) prior to a further non-IMP injection that both treatment groups receive. The medical notes contained an entry on the date of the IMP administration; however each entry, for all subjects reviewed by the inspector and later confirmed for all

trial subjects, these source documents stated that they received both drops and a further sub-conjunctival injection regardless of what was stated on the randomisation. Therefore it was impossible to verify whether all patients received both IMPs, or were dosed as per protocol. This in turn impacts on the integrity of the trial data, and the interpretation of the results.

The drug accountability logs were temporarily misplaced, but when found; they did match the randomisation list. Although the accountability logs appeared correct, a number of patients (on some days up to 10) were dosed on the same day. Therefore the documentation demonstrated that a number of batches of IMP were dispensed to the treating physician for that day, but it was not possible to determine with certainty which subjects received which IMPs.

The protocol also required that the pain assessment scores were handled by a 'masked assessor' who was not aware which treatment arm the subjects were randomised to. This was also not verifiable. The masked assessments being primarily carried out by staff who were also delegated responsibilities in relation to drug accountability, and the drug accountability logs unmasked the trial. There were entries into the medical notes on the IMP administration page by the same staff, where the IMP was listed. There were no written instructions/procedures to ensure that the masked assessors were not either present in theatre, or remained masked throughout the trial. For the first seven subjects in the trial, it was not recorded who performed the masked assessments, therefore it was not possible to verify if this was carried out by a masked assessor. Part of the CRF to be completed by a masked physician was completed by the same physician completing the CRF concerning administration of the IMP therefore if the CRF is to be believed then the assessing physician was also unmasked for these patients

Critical Finding 2

Similar issues were found in a trial at another NHS Trust as a critical finding was given as the data integrity of the trial could not be assured, due to issues with drug accountability and blinding. This was for an old trial and one that the sponsor has had issues with dating back to the previous inspection in 2011. The sponsor agreed verbally to halt the trial and not use the data.

The trial was a double blind study, with four treatment arms. There was no drug accountability for the majority (approximately 73%) of patients, therefore it was not possible to reconstruct which patient received which treatment and when. Randomisation was managed via individual envelopes, which contained the treatment allocation – either A, B, C or D. When a patient was enrolled, the envelope was opened by an unblinded member of staff; the allocated IMP was drawn up and checked by a second unblinded person. This step was not documented, either in the patients' notes, or on an accountability form.

Following an MHRA GCP inspection in 2011, a per-patient form was produced that recorded the treatment, who drew up the IMP, who checked it and when. This form was then stored with the randomisation envelope, and the envelope was resealed and stored with the CRF. The inspector reviewed all the trial CRFs (approx. 185) and it was apparent that the majority of the CRFs did not contain the randomisation envelope, and therefore for these patients it was not possible to reconstruct which study treatment they received. It should also be noted that the presence of the randomisation envelope did not always result in true verification of the administration of the IMP. For example not all the envelopes contained a note that stated what the patient had received (as per the process post 2011). As the majority of the envelopes were sealed, in order to protect the blind the inspector did not open those that were still sealed. It is not known what has happened to the missing randomisation envelopes and missing accountability forms.

In addition to the accountability issues there were a number of concerns in relation to maintaining the blind of the trial. These were that the randomisation list was created by a statistician, but then given to the CI, who then generated the randomisation envelopes, therefore negating the blind. For one patient, the new CI prepared the IMP, as there was no other unblinded member of staff available. Therefore he accessed the entire randomisation list and the unblinded pharmacy file and newly created (2014)

unblinded accountability log. Finally, a number of CRFs included the randomisation allocation (A, B, C or D) therefore unblinding anyone who accesses the CRF and inputs the data into the database.

Critical Findings 3 and 4

A NHS Trust did not have robust procedures and management in place to ensure oversight of 2 sponsored clinical trials and as result a further critical finding arose as they didn't oversee the shipment of IMPs to the hospital. The two trials had the same Chief Investigator (CI).

The inspection demonstrated that the Trust had not been, and at the time of the inspection was still not in a position to be sponsoring CTIMPS. This was due to:

- Poor R&D leadership and management. For example, the current research directorial responsibilities are under the very broad role of the Director of Nursing, but the post holder informed the inspectors that he was unaware of this for several months. The Director of Nursing post holder had asked the Chief Investigator (CI) of the trial in response to CI's request for a sponsorship letter, what are the expectations on the Trust in terms of sponsoring the study, which demonstrated that the Director of Nursing had no knowledge of the standard to which CTIMPs are required to be conducted and thus be in a position to make the decision on sponsorship alone. Additionally, verbal information provided by staff to the inspectors and previous documentary evidence showed that the Trust was not in a position to sponsor CTIMPs. Much of the concern documented about sponsorship centred on triggering a MHRA inspection, Trust reputation and cost, but not patient safety, results reliability and compliance with the regulations.
- Lack of effective resourcing of R&D. During a 12 month period, the Trust failed to provide a suitable level of RG resource whilst the RG Manager was on maternity leave. A member of CLRN was only able to do this for just 1 day per week compared to the 5 days of the permanent member of staff. There was no documentation that could be provided to indicate how this provision had been formalised and the responsibilities that had been assigned to this person with respect to the oversight of the sponsored CTIMP that commenced during this period.
- Relationship with another NHS Foundation Trust as part of the CQC "buddying" not formalised in terms of services provided to the Trust for R&D Governance.
- Lack of or failure to follow existing procedures that were in place, for sponsorship approval and oversight of trials.
- Poorly functioning R&D Committee in terms of oversight of sponsored trials.
- Poor risk assessment processes.
- Failure to provide clear delegation of sponsor's duties and functions to the Chief Investigator. It was stated that these were covered to a certain extent in the SOPs, this was inadequate, particularly as there was no evidence that the CI had received training in the SOPs. Additionally, the Trust by its own admission confirmed that the SOPs do not cover the additional responsibilities of sponsorship and this was confirmed by a partial review by the inspector.

It should be noted that the Trust at the time of the inspection was under special measures by the Care Quality Commission (CQC). The extent of the deficiencies identified in this GCP inspection merited a critical finding because without appropriate sponsor oversight, serious breaches of the legislation with potential harm to trial subjects or the trial results have a significant potential to occur. In fact, non-compliance, as major findings, were found in the trial that was currently ongoing within the Trust.

A second critical finding was given for IMP. There was a shipment of the trial IMPs (both products), addressed to the CI at the clinic (as per the delivery address stated in the contract with pharmaceutical company and the delivery note), as such the IMP was NOT received by the pharmacy (in order to implement quarantine prior to Regulatory Green Light). This shipment was prior to MHRA approval for the trial, which was a breach of Regulation 13. These issues resulted from the failure of the pharmaceutical company to adequately determine the control of the IMP prior to shipping under quarantine (i.e. there was no clinical trial authorisation in place) and also the failure of the sponsor to

oversee the entire process of sourcing, delivery, labelling and Regulatory Green Light of IMP for sponsored trials effectively.

The contract with the pharmaceutical company clearly stated that the Sponsor was responsible for final labelling, which was done under the Regulation 37 exemption, thus no final QP Certification was required for the IMP. There was the QP Certification for the batch which stated, "I hereby certify that this batch complies with the requirements of Article 13.3 of Directive 2001/20/EC. The batch of product has been manufactured, including packaging and quality control in full compliance with the GMP requirements of the local Regulatory Authority and according to valid Manufacturing Descriptions and Quality Specifications for investigational drug products." The QP could not certify against Article 13.3 and thus Article 9(2) of the directive was because there was no evidence that they had received a copy of the request for a clinical trial authorisation, and the MHRA approval letter (although not sufficient on its own) was not sent until afterwards.

Critical Findings 5 and 6

A number of significant issues and concerns were identified in relation to the levels of oversight of the sponsor, a NHS Hospitals Foundation Trust, concerning the conduct of a trial that resulted in a critical finding for organisation's (sponsor) oversight of clinical trials. This was graded as a critical finding as there were several underlying systematic issues:

- There was no evidence of sponsor oversight of safety reporting in the trial, resulting in a critical finding for pharmacovigilance (see below).
- The sponsor had not ensured that the trial protocol had been submitted to the MHRA for review and approval as a substantial amendment prior to its implementation.
- There was no formal delegation of the sponsor functions to the Chief Investigator for the trial.
- The Trust quality system for sponsoring clinical trials of IMP was wholly inadequate for several reasons:
    - SOPs had not been followed by the R&D team.
    - Half of the SOPs had only recently been issued, and the other half were in draft format.
    - There were areas identified where there were no formal procedures in place to cover all aspects of sponsorship to ensure adequate delivery of sponsor oversight responsibilities. For example:
        - Processes and requirements for sponsorship/co-sponsorship decisions and conduct of risk assessments for Trust sponsored clinical trials.
        - R&D approval processes for IMP clinical trials.
        - Production of key clinical trial documentation such as clinical protocols, protocol amendments, Patient Information Sheets (PIS), Informed Consent Forms (ICF) and Development Safety Update Reports (DSURs).
        - For assessment and selection of vendors for Trust sponsored IMP clinical trials including arrangements for establishing formal contracts. A Major finding was raised during the inspection in relation to Contracts and Agreements as there were examples where no contracts were in place with three vendors.
        - Study set up, approvals (including oversight of regulatory and REC approvals and study progress).
        - Sponsor oversight of substantiality decisions with regards to amendments to IMP clinical trial protocols and Clinical Trial Authorisations (CTA).
        - Clinical trial monitoring.

For the trial reviewed, a number of deficiencies were identified in relation to safety reporting resulting in a second critical finding for pharmacovigilance:

- Serious Adverse events identified during the conduct of the trial were not reported to the sponsor within 24 hours, as required.
- No distinction had been made between causality and expectedness assessments for all SAEs occurring in the trial.
- The seriousness and causality assessment requirements in the protocol for the study were incorrect. As a result, there was significant potential that the assessment of these adverse events that had already been undertaken would be incorrect and may lead to the identification of unreported Suspected Unexpected Serious Adverse Reactions (SUSARs).
- There was no mechanism to track the reporting of SAEs to the sponsor, the pharmaceutical company supplying the IMP, MHRA and the REC. As a result there was a lack of evidence to show that all SAEs had been forwarded appropriately.
- No DSURs had been prepared and submitted to the MHRA during the trial.
- The safety reporting SOP in place within the Trust was inadequate, for example:
    - It did not include any detail relating to the process to be followed for reporting SUSARs.
    - The most up to date version of the SmPC was to be used as the reference safety information for expectedness assessments of safety events occurring in IMP clinical trials using licensed IMP, this should always be the RSI approved by the MHRA.
    - It did not include any provision for control of unblinding.
    - It was inconsistent with the trial protocol terminology for causality/relatedness assessments and the study SAE forms.
    - It indicated that SUSARs would be reported to the MHRA via the eSUSAR portal; however, no staff members at the Trust had a registered account in the portal for this activity.
- The trial protocol was deficient in that:
    - Information relating to potential side effects of study medication was inconsistent with the relevant SmPC. In addition, there was no documented justification for the differences identified.
    - There were exclusions for particular patient populations listed in the protocol appendix that were not listed in the inclusion/exclusion criteria.
    - The unblinding mechanism for the study described in the protocol was inappropriate as this allowed the Chief Investigator to reveal subject treatment allocations following SAEs or SARs irrespective of whether this was needed as a medical emergency to manage the clinical symptoms.
    - The definitions for causality of safety events in the protocol were incorrect and could lead to incorrect assignments during the assessment of safety cases. For example, the causality assessment section of the protocol stated that ‘likely’ events would be those that were detailed in the side effect profile of the study drug and ‘since they will be unexpected’ they will also be termed SUSARs.

The outcome of the inspection was the Trust was not in a position to undertake sponsorship of CTIMPs.

Critical Finding 7

There were a number of major issues identified that, taken together resulted in a significant lack of organisational oversight and resulted in a critical finding for sponsor oversight at a university.

- It was unclear who the sponsor representative was for CTIMPs, as this varied between finance, the college, the chief investigator, the CTU and Research Development and innovation.
- There were no staff involved in the sponsorship decision and sponsor oversight functions with sufficient experience in GCP and applicable legislation for CTIMPs.

- The sponsorship decision had not taken into account relevant GCP risks associated with the trial, only risk to the university reputation and finance.
- The sponsorship decision was not robust, as there was no formal process in place at the time of sponsorship, and the process that was implemented did not cover the aspects of sponsorship needed (e.g. how the decision was undertaken and by whom, revoking sponsorship in event of non-compliance, what would be sponsored, delegation of responsibilities, expectations of GCP and SOP training to all relevant staff,
- There was no formal delegation of sponsor responsibilities in 2 trials.
- There was no sponsor oversight of the activities delegated.
- The activities actually delegated to the CTU were not as described in the document completed for one of the trials.

The outcome of the inspection was that the university was not in a position to undertake sponsorship of CTIMPs until adequate corrective and preventative actions had been implemented.

Critical Findings 8, 9 and 10

The MHRA selected a trial conducted at and overseen by the joint NHS Trust/university organisation. A pre-inspection review was conducted by the organisations and a serious breach report was submitted.

a) Only the first part of the trial had been conducted (the trial consisted of four parts) which meant that the trial objectives and endpoints could not be delivered as they required data from each part.
b) Patients had been dosed incorrectly, by following local clinical practice rather than the trial protocol.
c) Limited data had been recorded about the dose given which meant that it was not possible to determine what dose was administered to each patient at each visit.

The organisations were requested by the inspector to retrieve the trial master file and the laptop associated with the imaging data from the trial team and to hold them securely until the inspection commenced. The medical records were also requested to be retrieved and held except where upcoming appointments had been made.

Prior to the inspection, the inspector was notified that both the CI and PI were suspended from any research activities until notified otherwise. None of the staff involved in the trial had any previous clinical trial experience although they had some experience of general clinical research.

The data from the trial had been presented at one meeting, after the team had determined that there were issues with the data. The data had also been provided by the PI to an intercalated BSc student whose dissertation he was supervising. The dissertation was marked by the CI. The organisations have already stated that the data will not be permitted to be used for the PI's MD thesis.

It should be noted that four other trials were reviewed during this inspection, but the quality of the data and trial management was significantly better.

Following the inspection, **3** critical findings were given relating to Subject Safety, Data Integrity and Medical / Investigator Oversight.

There were issues with protocol compliance such that the safety of subjects could be impacted and a critical finding was given.

The first issue related to overdosing of the IMP:

- The MHRA approved protocol stated the required treatment of one lesion on a patient, but the Principal Investigator (PI), due to slow recruitment, decided to inject multiple lesions with IMP to reach the desired number of treated lesions. This was submitted as a substantial amendment twice

to the REC but there was no evidence of successful submission of this amendment on either occasion to the MHRA. The REC did not respond to first submission suggesting that they also did not receive it and rejected the repeat submission. Retrospective dosing worksheets, compiled by the research nurse, indicated that multiple lesions were dosed and a review of the dosing data by the CI prior to the inspection indicated that IMP doses five times greater than those described in the protocol were given.

- One patient was enrolled 3 times into the trial, and pharmacy dispensing records showed that medication had been dispensed for each patient number (1 dose as subject 10, 5 doses as subject 22 and 6 doses as subject 9 on a different arm of the study). As described below it was not possible to demonstrate from the medical records that the majority of doses had actually been administered. It was therefore not possible to confirm whether this patient had received this additional medication.
- Two patients restarted treatment after a break so were exposed to additional doses of IMP, but restarting of treatment in the event of a break was not described in the protocol.

The second issue related to inadequate follow up of a trial patient when the patient announced that she was pregnant. The patient was withdrawn from the trial and a pregnancy notification form was completed and submitted by the CI to the sponsor, but this was missing the expected due date. There was no subsequent follow up associated with the birth of the child and the trial team had failed to determine the outcome either via the patient or via other healthcare professionals associated with her care e.g. GP. The CI had been told by the PI that the patient had not received any trial medication whereas she had actually received a dose following notification to the trial team that she was pregnant. It was confirmed post inspection that mother and child had suffered no adverse effects associated with this dose and that both were well.

There were several issues noted that made the integrity of the clinical trial data questionable and a critical finding was given.

- Only the first part of the trial had been conducted (the trial consisted of four parts) which meant that the trial objectives and endpoints could not be delivered as they required data from each part.
- The protocol was not followed and the patients were dosed with IMP following standard clinical practice.
- The standard of completion of the medical notes was very poor, and in the absence of a CRF other than a cover page, meant that significant events could not be reconstructed from the medical records, such as:

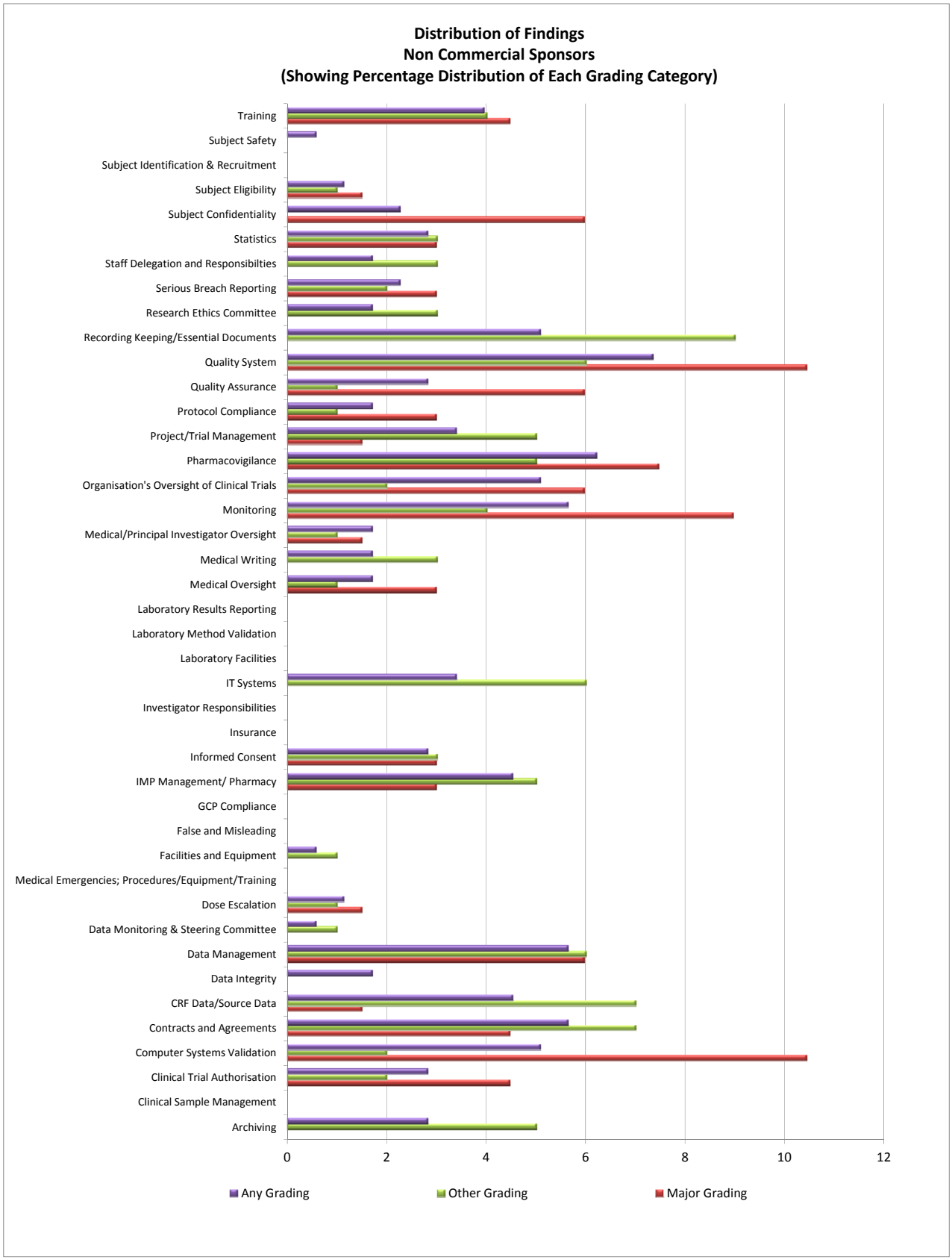
    - Provision of the patient information sheet.
    - Eligibility decision (there was no evidence of this for any patient) as described above.
    - Entire clinic visits other than the date and clinic name.
    - Dosing (until late in the trial when and dosing sheets started to be used by the research nurse).
    - End of trial.

- It was not possible to demonstrate from the medical records that the majority of IMP doses had actually been administered or the IMP amount dosed, only that they had been ordered via the prescription from the pharmacy department. This was despite at least two methods of recording this being available, a trial specific log book and space on the prescription form.
- One patient had been enrolled and dosed three times into the trial, and the documentation showed inconsistent names.
- There were a significant number of examples of questionnaires where it could not be determined when they had been completed; therefore they could not be related to a particular trial visit or treatment cycle.
- A patient signed her consent form in advance of her appointment. When the discrepancy between that date and the PI's dates was queried during a monitoring visit the PI amended their date to be consistent, but this was a day when no clinic was scheduled and there was no evidence to support the patient attending the hospital within her medical notes.

There was insufficient documentation to support the CIs involvement in the trial; it was therefore impossible to demonstrate the discharge of his responsibilities as the CI. The PI did not discharge his duties in an appropriate manner during the set up and conduct of the trial including making decisions which fundamentally affected the outcome of the trial, and a critical finding was given for medical/investigator oversight, for example:

- 58% of patients were ineligible as they did not meet all of the inclusion criteria and there was no documentation within the medical record or trial master file to support the assessment of patient eligibility by a physician (all patients were recruited by the PI).
- The protocol stated that patients would be followed up for the trial for two years following the last dose, but entries in the notes and discussions with the study team demonstrated that they were only being followed up for three months.
- There was a significant breakdown in communication between the CI and PI as described in interview sessions, for example, the PI did not try to contact the CI regarding a patient's pregnancy, the CI was not involved in the monitoring visits and told the Inspector that he felt that he had been excluded by the PI, the nurse was told not to speak to the CI about the trial and that if she had any issues or problems then she was to tell the PI. Also, as there were no meeting minutes or documentation of communication other than occasional emails it was not possible to demonstrate the interaction between members of the trial team.
- The trial protocol was poorly written and the approved version contained large sections of the central protocol template which had not been removed or sections completed as required during discussion with the CI, the inspector was told that the PI had written the protocol, that the CIs input had been mainly grammatical.

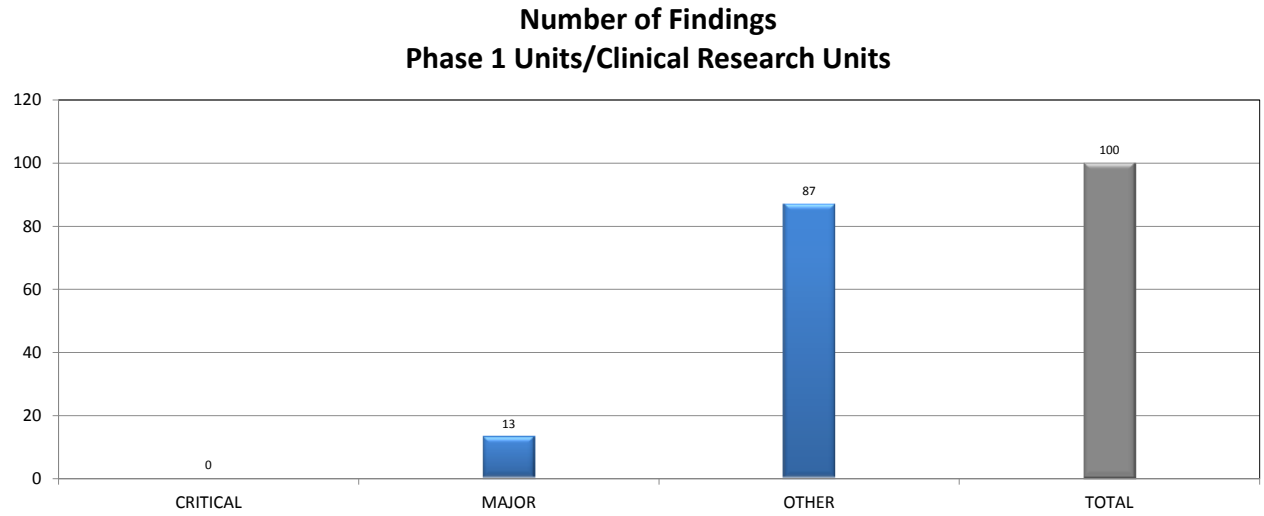
The figure on the following page shows the distribution of Major, Other and any grade of inspection findings. This identifies the areas where GCP inspectors have been making observations of non-compliance with GCP.


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
Any Grading
Other Grading
Major Grading

3.4 Commercial 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. All but 1 was also routine inspections for the MHRA voluntary phase 1 accreditation scheme. Note that findings relate to GCP and not those related to the accreditation scheme.

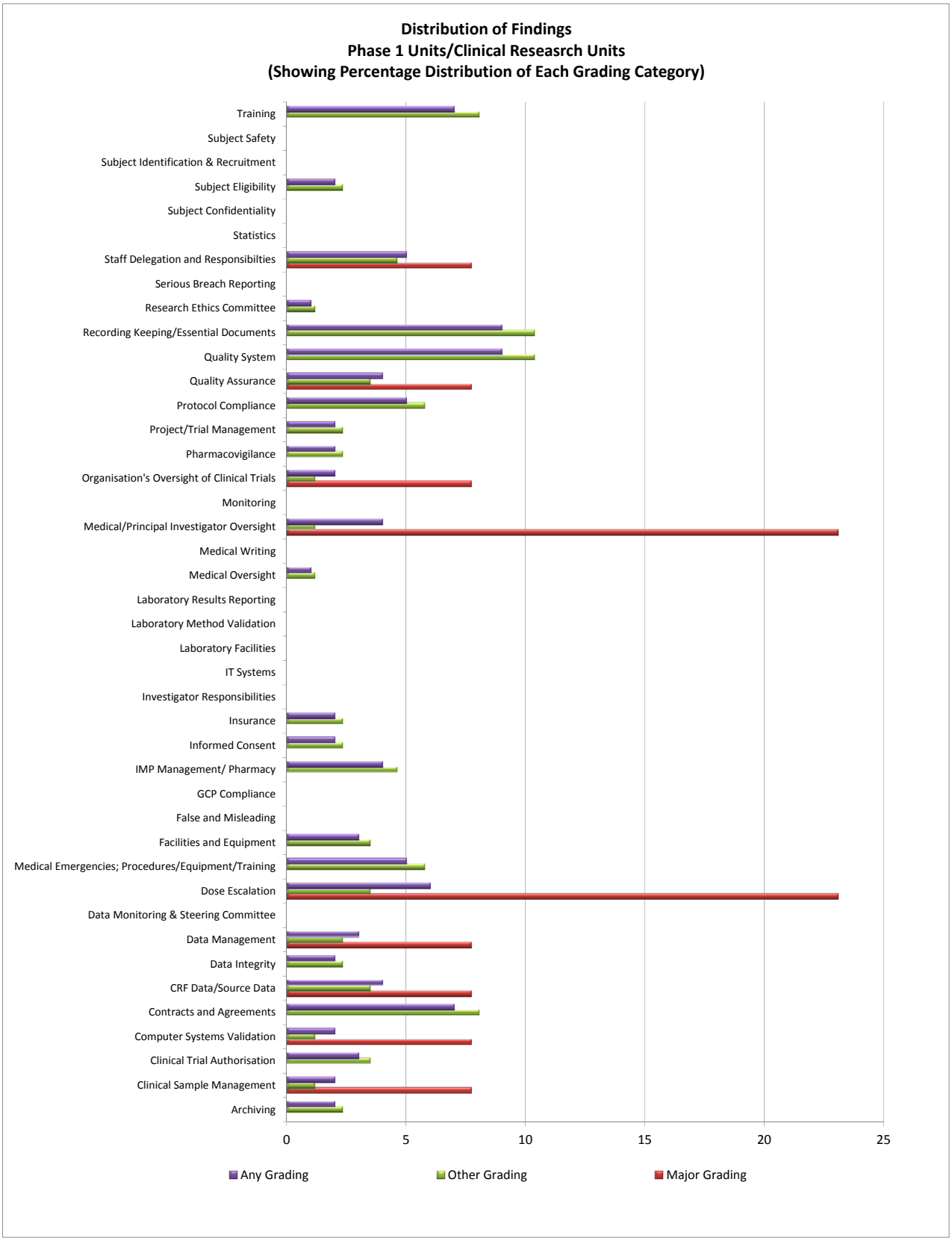
Of the 10 reported inspections, none had a critical finding and 6 (60.0%) had at least one major finding. The number of findings and findings per inspection are represented on the figures below.



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	1.3	1.0	0.0	4	10
Other	8.7	8.5	6.0	14	10

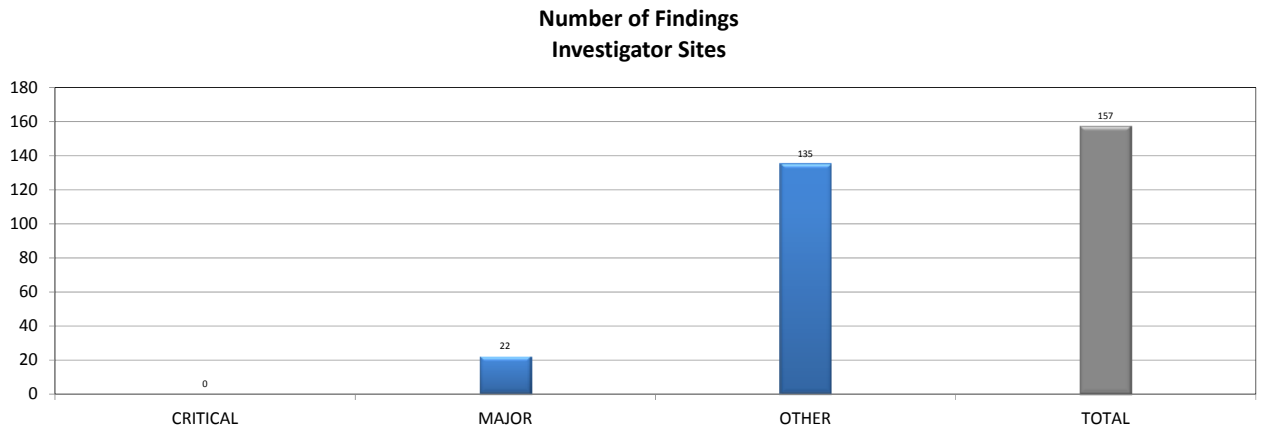
The figure on the following page shows the distribution of Major, Other and any grade of inspection findings. This identifies the areas where GCP inspectors have been making observations of non-compliance with GCP.


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
Any Grading
Other Grading
Major Grading

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

A total of 22 investigator sites in the UK were inspected, all were as an associated site with a sponsor/CRO inspection.

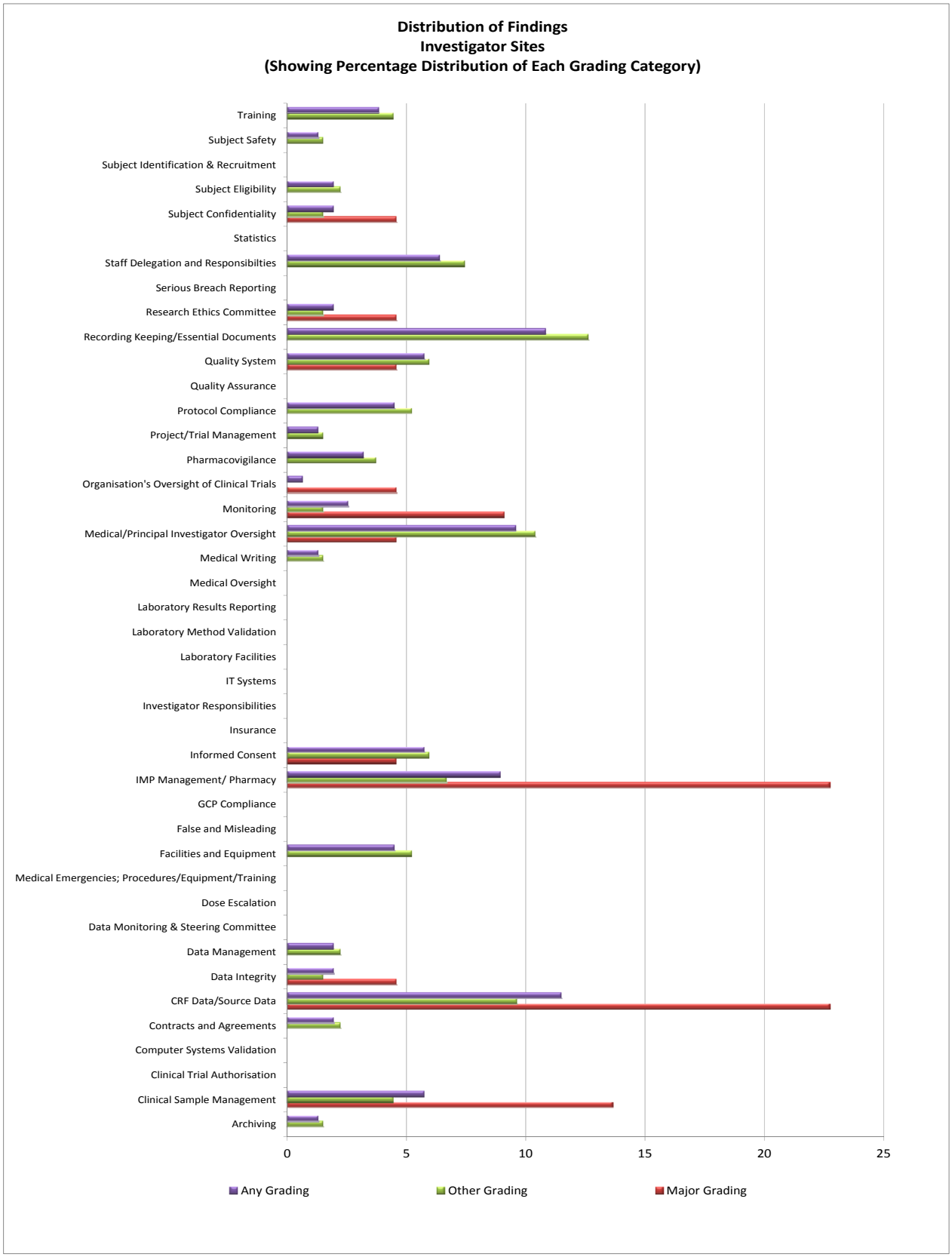
Of the 22 inspections, none had a critical finding and 11 (50.0%) had at least one major finding. The number of findings and findings per inspection are represented on the figures below. It should be noted that as associated sites, the emphasis of the inspection was on how the investigator site had been 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	0	22
Major	1.0	0.5	0.0	4	22
Other	6.1	6.0	6.0	11	22

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
Pharmacovigilance
Organisation's Oversight of Clinical Trials
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Clinical Sample Management
Archiving
0
5
10
15
20
25
Any Grading
Other Grading
Major Grading