Medicines & Healthcare products Regulatory Agency

GCP Inspectorate

GCP Inspections Metrics Report

Metrics Period: 1st April 2019 to 31st March 2020

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Contents

INTRODUCTION 3
GCP INSPECTIONS UNDERTAKEN 4
INSPECTION REPORTS AND FINDINGS 5
Commercial Sponsors (Routine Systems, Study Specific and Triggered) 6
Critical Finding 1 6
Critical Finding 2 7
Critical Finding 3 8
Critical Finding 4 9
Summary of Findings from Commercial Sponsors 10
Contract Research Organisations (CRO) (Routine Systems and Triggered) 11
Critical Finding 1-4 11
Summary of Findings from Contract Research Organisations 15
Non-commercial Organisations (Routine Systems and Triggered) 16
Critical Finding 1-3 16
Critical Finding 4 18
Summary of Findings from Non-commercial Organisations 21
Phase 1 Units/Clinical Research Units (Routine Systems and Triggered) 22
Critical Finding 1 22
Summary of Findings for Phase 1 Units/Clinical Research Units) 24
Investigator Sites - as part of Commercial/ Non-commercial/CTU/CRO (Routine Systems, Study Specific and Triggered) 25
Summary of Findings for Investigator Sites 26
Inspection Finding Trends Since Statutory GCP Inspections Implementation 27

INTRODUCTION

This report covers the metrics period of 1st April 2019 to 31st March 2020.

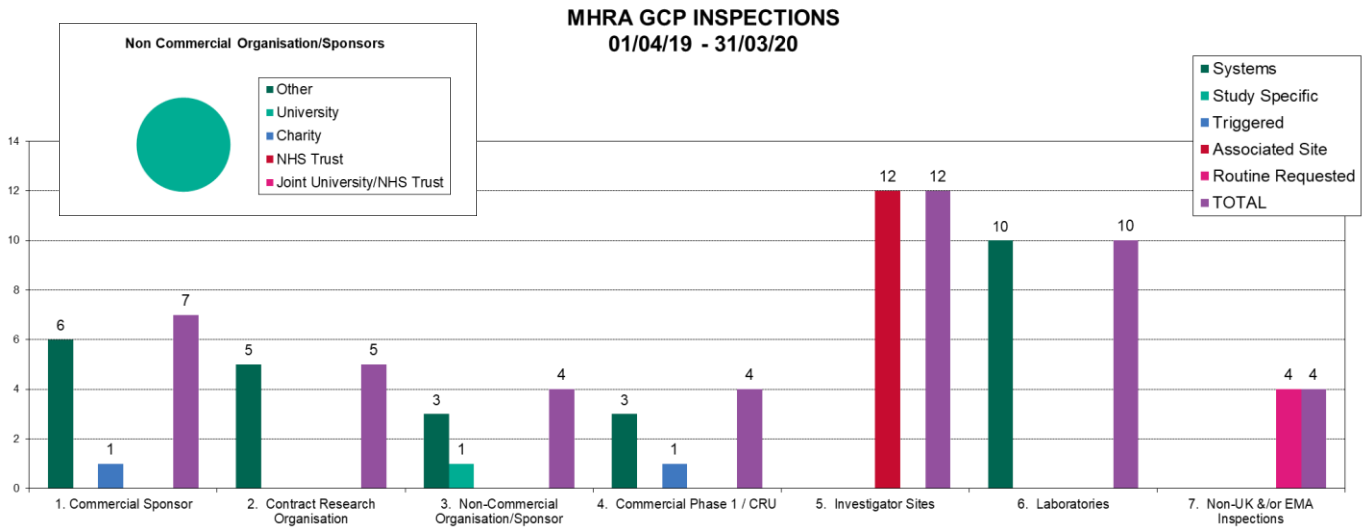
GCP INSPECTIONS UNDERTAKEN

During the metrics period a total of 36 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 four, of commercial sponsors was seven, of Contract Research Organisations (CROs) was five, of investigator sites there were 12 and finally there were four Phase 1 unit inspections.

GCP inspections of UK laboratory facilities conducting clinical trial sample analysis are conducted by the MHRA Laboratories compliance team and there were 10 of these inspections. Additionally, there were also 4 non-UK bioequivalence (BE)inspections conducted by members of the Laboratories compliance team.

Triggered inspections are carried out because of information received by the GCP Inspectorate, for example in response to a serious breach report or an identified concern. Of the inspections conducted, two triggered inspections were undertaken. There was one UK triggered inspection of a commercial sponsor and one of a UK Phase 1 unit.



INSPECTION REPORTS AND FINDINGS

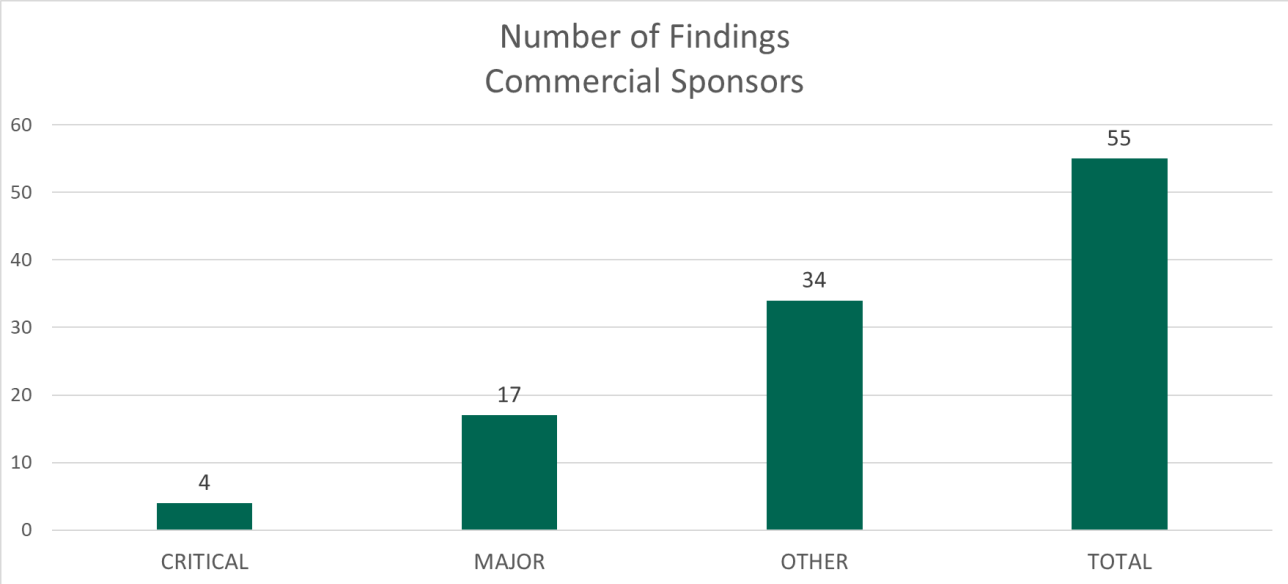
Reports relating only to the inspections carried out and completed in the metrics period were reviewed. It is important to note that multiple inspections can be reported in one GCP Inspection Report, for example, a commercial sponsor GCP Inspection Report may consist of the sponsor inspection and associated 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. Findings from such inspections can also be reported in one GCP Inspection report. Where an inspection was conducted before 1st April 2020 and the other inspections (e.g. associated investigator site or further visit) were conducted after 1st April 2020 (e.g. sponsor site then the investigator site(s)) the findings from the inspections conducted/completed after 1st April 2020 will not be included in this metrics report, as these were inspections conducted/completed during the 2020-2021 metrics period.

There were three 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 2018-2019.

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 MHRA laboratories compliance team. Non-UK inspections that do not fall into these two 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.

Commercial Sponsors (Routine Systems, Study Specific and Triggered)

A total of seven commercial sponsors were inspected, and all have been reported. There were six systems inspections and one triggered inspection. Out of the seven inspections, four (57.1%) had at least one critical finding and all (100.0%) 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 Sponsor)

	Mean	Median	Mode	Maximum	n
Critical	0.6	1.0	1.0	1	7
Major	2.4	2.0	1.0	5	7
Other	4.9	5.0	-	9	7

There were four critical findings from four organisations.

Critical Finding 1

A pharmaceutical company had 1 critical finding 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 24 (3 & 4), 28, 29, 33, 35 and Schedule 1, Part 2 (4,8 & 9). The inspection identified that case processing was not in compliance with UK legislation and guidance documents CT-3 and CT-1 and Clinical Trial

Facilitation Group (CTFG) Q&A Reference Safety Information (RSI), that there was a failure to implement Corrective and Preventative Actions (CAPA) for previous major inspection findings and there were new findings in clinical trial pharmacovigilance. These issues can have a significant impact on the reporting of safety information to regulatory authorities and taken together these constitute a critical finding grading. Examples of issues identified included the following:

- The inspection findings in relation to the major finding for pharmacovigilance from the last MHRA GCP inspection had not been addressed with a robust CAPA in a timely manner and there was evidence that implemented actions had been ineffective.

- The format, implementation and use of the RSI for expectedness assessments for serious Adverse Events (SAEs) and Serious Adverse Reactions (SARs) was not in accordance with CT-3 Guidance and CTFG Q&A RSI (November 2017). Therefore, there was significant potential for under-reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs) due to use of unapproved terms being classed as “expected” events.

- There were more adverse reaction terms considered expected in the safety database used for SAR case assessment than contained in the RSI that had been approved by the MHRA in the Clinical Trial Authorisation (CTA).

- There was no requirement in the quality system to ensure only section 4.8 of the Summary of Product Characteristics (SmPC) was used for expectedness assessments of comparator products (products not owned by the pharmaceutical company).

- Remarks and comments provided on MHRA CTAs approvals regarding the format of RSI that were requested to be addressed in the next substantial amendment had not been addressed. This was not performed at subsequent amendments and there was no formalised process to ensure feedback and requirements in relation to the RSI were addressed at the next RSI or Investigator Brochure (IB) update (until a Grounds for Non-Acceptance was issued).

- A conservative approach was not applied where the investigator’s causality assessment was missing on an SAE report submitted from the investigator site. Instead, the assigned company causality would drive reporting requirements as stated in company operating procedures This resulted in delayed reporting of SUSARs and had the potential for under reporting of SUSARs.

- Inconsistencies between the clinical database and safety database were identified.

Critical Finding 2

The second critical finding was for **Pharmacovigilance** (PV). This concerned a breach of UK Statutory Instrument 2004/1031 (as amended), Regulations 29, 33 and Schedule 1, Part 2 (4 & 9). Parts of the CAPA from two previous inspections for this company were reviewed and continued to be ineffective. The company continued to implement processes which were not

consistent with CTFG RSI Q&A guidance. Examples of issues identified included the following:

- It was identified that the RSI continued to be implemented without ensuring MHRA approval had been received. Whilst other aspects of the previous critical finding had been addressed this aspect had not been effectively remediated.

- The process for RSI implementation was not in accordance with Regulation 29 of UK SI 2004/1031, CT-3 and CT-1. The process implemented by the company determined the effective date of an RSI at the product level and not the trial level. An algorithm was utilised by the company to determine the implementation date of the RSI which was the date of the first EU/EEA CTA approval (for any trial submission) plus 35 days. After this date, the RSI would be effective for all ongoing trials regardless of whether the RSI had been approved as a substantial amendment for any other trials. This resulted in a number of RSIs for selected trials being implemented prior to MHRA approval. There was therefore a risk of under-reporting of SUSARs due to implementation of an RSI prior to approval (and an example of this was noted).

- For the production of the Development Safety Update Report (DSUR), the RSI in effect at the start of the reporting period was used, however, this was not necessarily the RSI approved by all member states at the start of the reporting period as recommended by CTFG. There was also the risk that the RSI used had not been approved by the MHRA at the start of the reporting period.

- A number of events had been reported late as SUSARs due to an incorrect expectedness assessment upon the event becoming Fatal/Life Threatening. This demonstrated that the RSI was not being applied correctly to all cases upon initial receipt.

- Organisations had until 01 January 2019 to comply with CTFG Q&A guidance. However, a review of the company's products and effective dates demonstrated that there were products where life threatening events were still considered expected beyond this date.

- There was significant lack of follow up of pregnancy reports reviewed cases were not followed-up in a timely manner in line with company procedures.

Critical Finding 3

The third critical finding was for **Pharmacovigilance** (PV). This concerned a breach of UK Statutory Instrument 2004/1031 (as amended), Regulations 28, 33, 35 and Schedule 1, Part 2 (4). Examples of issues identified included the following:

- The previous inspection CAPA and resulting process were not robust in ensuring that, for SARs with a suspect drug product of a marketed comparator IMP, the RSI (i.e. SmPC version) used at the event onset was used to evaluate the case throughout the follow-up period. The SmPC was reviewed in a central database and there was no documented check of the version against the MHRA approvals to ensure the correct version was used for these cases. This could have therefore led to the incorrect version of the RSI

being used for expectedness assessments of comparator marketed products using an SmPC as the RSI.

- According to written procedural documents the process in place for release and use of RSI did not ensure that the RSI had been submitted and approved by the MHRA prior to implementation and use for the expectedness assessment of SARs by the Case Processing Team. IBs were released and became effective on day 1 of the DSUR reporting period and released at a product level with no check of trial level clinical trial authorisations to ensure that the RSI had been submitted and approved for use. There was also no process in place for ensuring marketed comparator Investigational Medicinal Products (IMPs) using SmPCs for the RSI had been submitted and approved by the MHRA prior to release. SmPCs were reviewed manually via a central database.

- It was standard practice to assess 'lack of efficacy' events as 'expected', irrelevant of the terms that were listed in the approved RSI.

- Examples were seen of SAEs being grouped as single cases in the safety database without adequate justification. For example, a second event of sepsis had been classified as a follow-up to an initial event of Sepsis and urinary tract infection under Neutropenic Sepsis.

- For SARs with a suspect drug product of a marketed comparator IMP, the version of the RSI (i.e. SmPC version) used to assess the expectedness was not documented. There was no procedural requirement to do so.

- A discrepancy was identified in the reconciliation of trial events which compared safety data reported in the clinical and safety databases.

Critical Finding 4

The fourth critical finding was for **Pharmacovigilance (PV).** This concerned a breach of UK Statutory Instrument 2004/1031 (as amended), Regulations 28, 35 and Schedule 1, Part 2 (4). This finding was graded as Critical as the non-compliance from the previous inspection had not been rectified and unreported SUSARs were still present within the system.

- Unreported SUSARs were still found due to investigator causality of 'unknown' or 'not assessable' and a non-conservative approach taken.

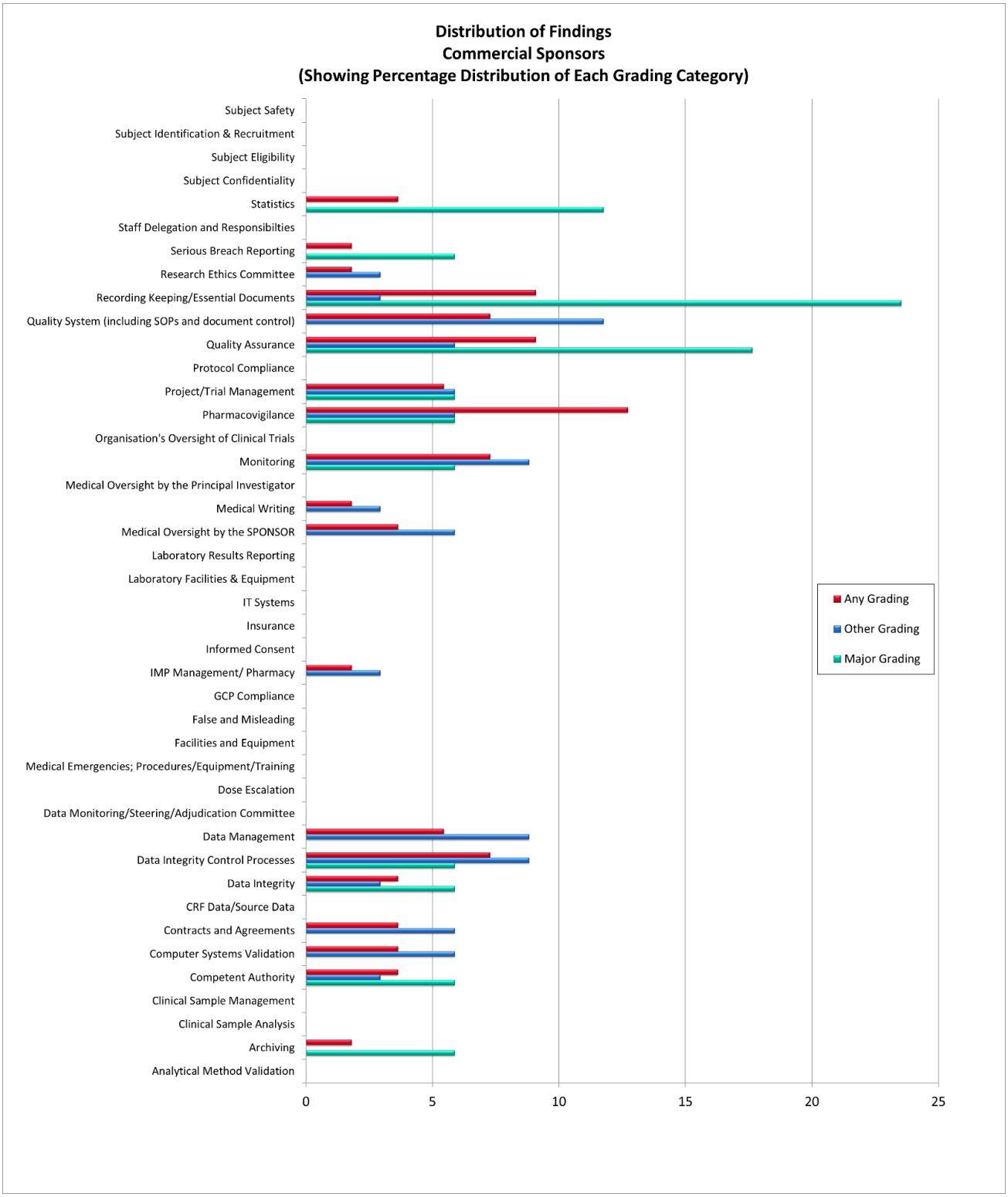
- Unreported SUSARs were still found due to incorrect expectedness assessments against the MHRA approved RSI at the time of event onset (initial and follow-up reports).

- The process for updating, management and implementation of the RSI remained undefined in the Standard Operating Procedures (SOPs)/Quality System.

- A number of discrepancies were identified in the safety database which could have led to underreporting of SUSARs. For example, fatal events being classed as expected and disease progression/lack of efficacy/general health deterioration classed as expected.

Summary of Findings from 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.



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

A total of five Contract Research Organisations were inspected. 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 five GCP inspections, one (20.0%) had critical findings and all (100.0%) 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	0.8	0.0	0.0	4	5
Major	5.0	3.0	2.0	11	5
Other	8.2	9.0	9.0	10	5

There were four critical findings from one organisation.

Critical Finding 1-4

A CRO had four critical findings identified during their inspection.

The first critical finding was for **Data Integrity Control Processes**. This concerned breaches of UK Statutory Instrument 2004/1031 (as amended) Regulation 28 and Schedule 1, Part 2: (4 & 9). The following observations were made:

- The CRO did not document and explain decisions made and processes followed regarding Database lock of the blinded phase of one trial. There were several database locks in this trial and three of which were following the release of unblinded data in the trial. This resulted in the analysis of the blinded phase data being performed after unblinding of the trial had occurred.

- There was insufficient documentation available to demonstrate when database pages were frozen, unfrozen and re-frozen between database locks in order to verify what data had been changed and by whom or when.

- The data extraction used for the analysis, required hard coding of a response to one of the questions which made up part of the primary endpoint yet there was no documentation of when temporary hard coding was removed from the statistical programmes to prevent further changes. There was also insufficient documentation available to verify the level of QC of data which had been hard coded.

- From database records it was not possible to verify if any data changes made to the primary endpoint data has been confirmed by the PI prior to analysis.

- Findings above were of particular concern as CRO data management staff had data edit rights to the trial eCRF and were not delegated this activity by the investigator.

- Several issues were identified regarding audit trails:

    - The audit trail provided from the eCRF system was not in a suitable format to aid review at a system level to identify what data changes were made, by whom and when in order to verify if the changes were authorised.

    - There was a lack of documentation to demonstrate that the eCRF audit trail had been reviewed between database locks by data management or reviewed during the trial to verify what changes were being made in the eCRF by data management staff.

    - The IRT audit trail for the trial could not be provided during the inspection in order to verify the data in the trial which was integrated to the eCRF nor the activities within the IRT system as it had been decommissioned by the vendor. Therefore, the inspector was unable to verify during the inspection the activities performed in IRT.

The second critical finding was for **IMP Management**. This concerned breaches of UK Statutory Instrument 2004/1031 (as amended) Regulations 29, 29A, 30 and Schedule 1, Part 2 (4 & 9). The following observations were made:

- A PI at site informed inspectors that they had raised concerns with regards to the packaging of IMP in blister wallets which were not clearly labelled to state when each dose should be taken or what the strength of each tablet was. Initial stock of IMP contained no labelled inside wallets to indicate when dose should be taken. Whilst the inspected site took steps to protect trial patients from dosing errors by educating the parents/carers of all the trial participants and by halting recruitment at this site, there was no urgent safety measure or potential serious breach submitted by the Sponsor/ CRO to ensure that trial participants did not come to any harm due to the lack of adequate labelling. Furthermore, the PI concerns were not reflected in the monitoring visit reports.

- The patient information leaflet was not updated following update to packaging in light of issue outlined above.

- It was not possible to verify the actual dose administered to subjects in the inspected trial. The trial protocol required doses to be adjusted based on patient's weight as well as other safety related factors. However, the inspector was unable to verify the dose administered to subjects as the following documentation did not contain the actual dose of IMP contained in the kits:

    - The labels supplied with the IMP kits did not state what the actual dose was of the kit supplied.

    - The Interactive Response Technology system emails did not state what dose was supplied with the kit, only the kit the number.

    - The shipment records and consignment reports accompanying the shipments did not state what dose the kits supplied were but did state the batch number.

    - The Certificates of Conformance (CoC) for the respective batches did not specify what the dose was for that batch (each kit could contain more than one strength of the tablet).

- There was a lack of overall accountability of IMP received, dispensed and returned as well as compliance checks to verify if patients took the required amount of medication.

The third critical finding was for **Data Integrity**. This concerned breaches of UK Statutory Instrument 2004/1031 (as amended) Regulation 28 and Schedule 1, Part 2: (4 & 9). The following observations were made:

- There was a concern that primary endpoint data had been queried and reviewed with investigator sites following the unblinding of the trial and review of the unblinded results and copies of source data by the Sponsor. Evidence was seen for one subject where a missing value was changed to an absolute value by the site in response to the query. This query was raised despite the data being source data verified prior to unblinding. Therefore, there was a risk of bias introduced to the trial data as a result of the queries initiated at the request of the sponsor as well as questions raised over the reliability of the trial data due to the changes in data observed following the query. Whilst only the

primary endpoint data was examined during the inspection, the Clinical Study Report (CSR) for the trial would contain all the other endpoints.

- Multiple runs of the statistical analysis had been taking place following and between each database snapshot. The records to demonstrate why these had taken place had not been maintained to allow reconstruction in a timely manner. The inspectees were unable to explain during interview, why the primary endpoint analysis had been repeated several times, even with the same data extract, the p-value of the primary endpoint analysis changed throughout these runs.

- It was found that the audit trial was unreliable as it had not documented accurately the data changes made for primary endpoint data.

The fourth critical finding was for **Protocol Compliance**. This concerned breaches of UK Statutory Instrument 2004/1031 (as amended) Regulations 29, 29A and Schedule 1, Part 2 (4 & 9). The following observations were made:

- There was a lack of robust process in place for ensuring protocol compliance with dose reductions required by the selected trial protocol.

- There was evidence of a participant not receiving the required dose reduction as mandated by the protocol but instead had their dose increased.

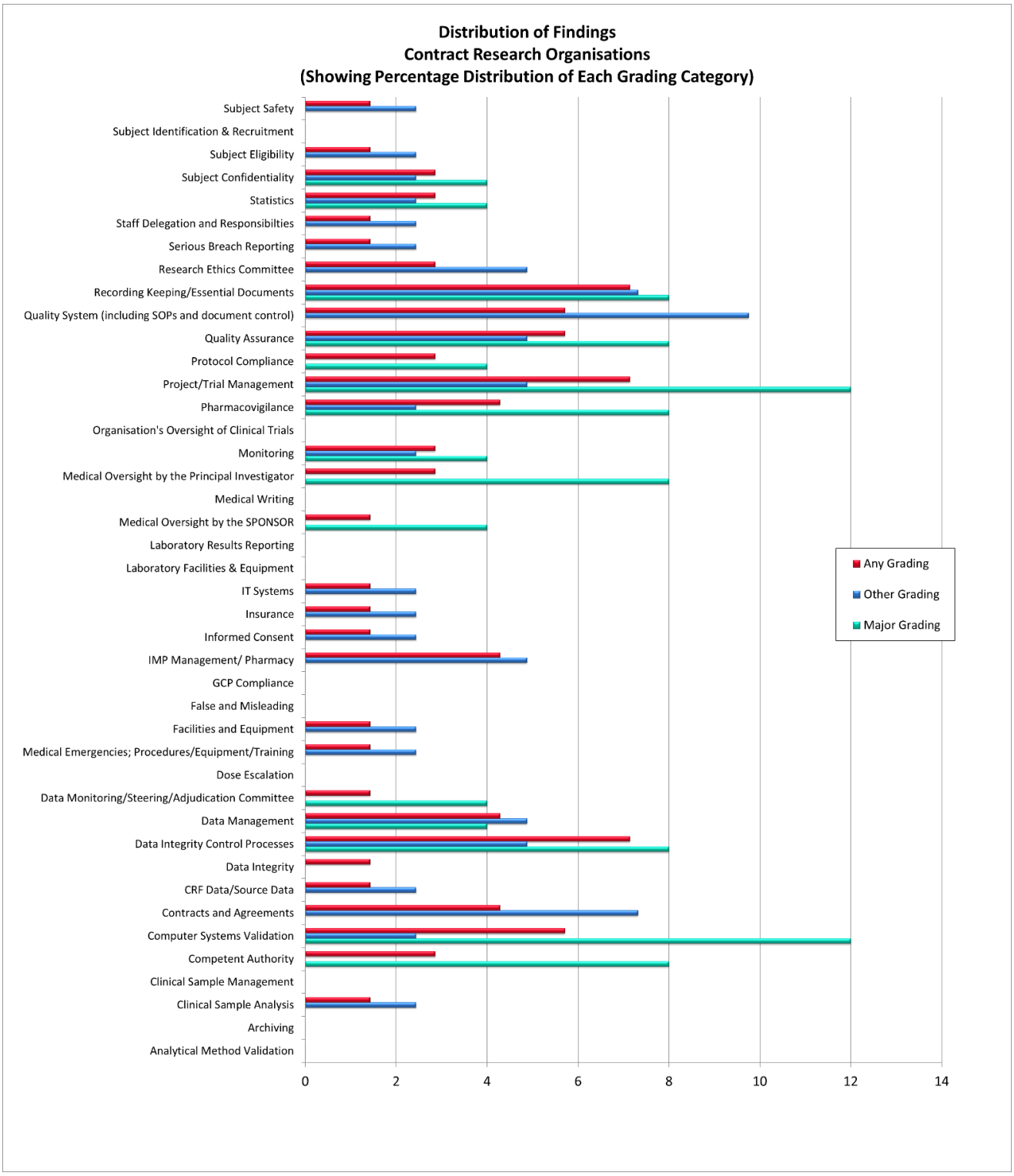
- It was found that there was a delay to action being taken when changes in safety blood measures from baseline (required to inform any dose reduction) could not be calculated due to missing baseline data. The lack of action was unacceptable, as CRO personnel failed to ascertain the impact of a missing baseline value on the safety of the trial patient. This demonstrated a lack of understanding of the trial protocol by the pharmacovigilance representative.

- There were no timelines specified in the Medical Monitoring Plan for actioning an alert received from the Central Laboratory or IRT system by the Pharmacovigilance team. As a result, there was a delay in actioning an alert for a patient who required a dose reduction.

- Several concerns were raised during interview regarding the process and appropriateness of pharmacovigilance staff receiving alerts and performing dose reductions in the IRT system. There was a lack of documented training on the Medical Monitoring Plan by pharmacovigilance representatives. Therefore, it could not be confirmed that the individuals taking these dosing decisions were suitably trained and qualified to perform this task. It is expected that the PI should have oversight of the dose changes in the trial.

Summary of Findings from Contract Research Organisations

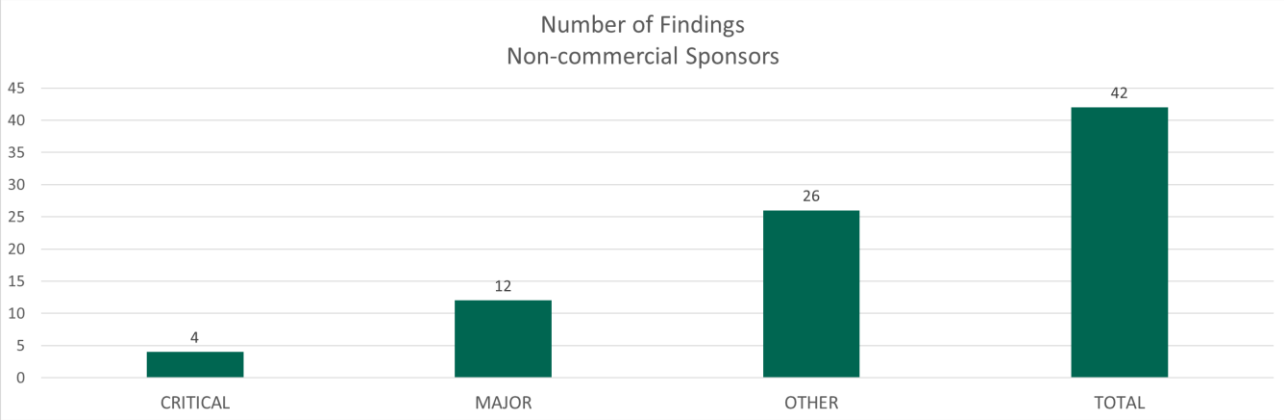
The figure on the following page shows the distribution of Major, Other and any grade of inspection findings. This identifies the areas where GCP inspectors have been making observations of non-compliance with GCP.



Non-commercial Organisations (Routine Systems and Triggered)

A total of four non-commercial organisations were inspected. Of the four, all were of Universities. One of the non-commercial organisations inspections included a trial-specific inspection at a 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 four organisations inspected, three have been reported. One of the inspections was not reported because the inspection was abandoned mid-inspection at the start of the COVID-19 pandemic.

Of the three GCP inspection reports, two (50.0%) had at least one critical finding and two (50.0%) 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	1.3	1.0	-	3	3
Major	4.0	3.0	-	9	3
Other	8.7	10.0	-	11	3

There were four critical findings identified from two organisations.

Critical Finding 1-3

A joint university/trust had three critical findings identified during their inspection.

The first critical finding was for **Clinical Sample Analysis**. This concerned breaches of UK Statutory Instrument 2004/1031 (as amended) Regulation 28 and Schedule 1, Part 2: (2,3,4 & 8). Clinical sample analysis was not conducted according to a suitably validated method based on the requirements of the EMA Method Validation guidance document (the protocol stated that the study would comply with all relevant guidance relating to medicines and clinical studies). Plasma drug concentration was being measured as a secondary objective of the trial. The following observations were made:

- There was no documentation or assessment undertaken by sponsor to demonstrate that the sample analysis method used for the analysis of trial patient samples had been suitably validated to support for the work undertaken.

- Samples from trial participants were also analysed for other levels on request from the Chief Investigator (CI) but this analysis was not included in the study protocol or the patient information sheet therefore permission had not been obtained from the Regulators or informed consent from the patients to whom these samples belonged.

The second critical finding was for **Data Integrity**. This concerned breaches of UK Statutory Instrument 2004/1031 (as amended) Regulation 28, 29 and Schedule 1, Part 2: (2,3 & 4).

- Results of unscheduled sample analyses provided to the CI during the trial CI to the treatment allocations and pharmacokinetic data for these patients. The clinical trial protocol did not permit this unscheduled analysis.

The third critical finding was for **Organisation's Oversight of Clinical Trials of Investigational Medicinal Products**. This concerned breaches of UK Statutory Instrument 2004/1031 (as amended) Regulations 28 and 29.

- Sponsor research governance staff had at least two opportunities to identify significant issues existed with this trial yet failed to take appropriate action including the notification of a serious breach.

- The Chief Investigator (CI) for the inspected trial was a PhD doctor with a pharmacology background rather than a medical doctor despite review by the trial sponsor and site Research Governance function. The Medicines for Human Use Regulations, 2(1) define the CI as: *'In relation to a clinical trial conducted at a single trial site, the investigator for that site'.* An investigator is defined as: *'The authorised health professional responsible for the conduct of that trial at a trial site, and if the trial is conducted by a team of authorised health professionals at a trial site, the investigator is the leader responsible for that team'.* An Authorised Health Professional is defined "*as (a) a doctor, (b) a dentist, (c) a nurse, or (d) a pharmacist."*

- Review of the sponsor trial master file for another selected trial demonstrated insufficient oversight of the conduct of the overall trial and lack of freedom to act leading to an inability to perform the functions of a sponsor effectively and appropriately. The trial was primarily run and coordinated outside of the UK by another non-EU sponsor. Delegation of sponsor activities between the two entities existed, but this delegation did not ensure

that UK sponsor had sufficient awareness, control and oversight of activities conducted on their behalf. As sponsor of the trial, it is expected that sponsor have oversight of trial steering committee decision making, centralised monitoring decision making, pharmacovigilance activities, data management activities and of the overall trial conduct including provision of documentation and information supporting trial activities such as review and approval of the trial database etc. There was insufficient documentation present within the sponsor trial master file to demonstrate appropriate oversight of the UK investigator sites because the majority of the supporting records were maintained by the non-EU sponsor. The UK sponsor file only contained documentation relating to the regulatory approval of each site and contractual arrangements. All other documentation relating to, for example, recruitment of trial participants, monitoring etc. was held by the non-EU sponsor. It was therefore not possible to determine how the UK sponsor had appropriate oversight of trial activities undertaken by UK sites.

Critical Finding 4

A trial-specific inspection at a CTU identified one critical finding during their inspection.

The critical finding was for **Pharmacovigilance**. This concerned breaches of UK Statutory Instrument 2004/1031 (as amended) Regulations 29, 33 and Schedule 1, Part 2: (4 & 9). Numerous issues were identified with the processing of SAEs including determination and reporting of SUSARs to the MHRA and Research Ethics Committee (REC) in the inspected trial. A previous major finding for Pharmacovigilance (for the CTU) required an impact assessment to be performed which returned no under reporting of SUSARs. However, during this inspection three unreported SUSARs were identified which had not been detected by the impact assessment performed.

- During the inspection it was identified that the RSI for a trial was not used in accordance with CT-1, CT-3 and CTFG guidance. The following issues were identified at this trial-specific inspection

    - CTU SOP on RSI stated that events are assessed using the RSI from the date of receipt and not event onset. Investigators were required to make an initial expectedness assessment. However, the training materials provided to the Investigators were not comprehensive and did not inform investigators which section of the IB/SmPC contained the RSI, when the RSI was approved by the MHRA via substantial amendment, or to use the MHRA approved RSI in place at the time of event onset for initial and follow up reports.

    - During interview it was confirmed that the expectedness assessment would be performed against the entire SmPC and not limited to section 4.8 undesirable effects (it is expected that only this section is used unless the use of an expanded set of information is justified and then approved by the MHRA).

    - It was explained during interview that synonymous terms could be used when making the expectedness assessment which had not been submitted and approved as part of the RSI for the trial.

- The following issues were identified with SAE case processing to ensure that SUSARs were reported within the regulatory timeframes:

    - There was ambiguity on what would be considered Day 0 for regulatory reporting of SUSARs. During interview it was confirmed that the CTU determined Day 0 to be the date on which a minimum information dataset was received which included causality assessment and expectedness assessment from the Investigator site. It is expected that day 0 is the date of receipt of an SAE when the minimum information required for capturing an SAE is provided.

    - All Fatal/ Life-threatening events or events identified as SUSARs based on Investigator review of expectedness would be sent for clinical review immediately or within a week for non-life threatening or fatal events. However, if information on causality or expectedness by the Investigator was missing for non-life threatening or fatal events, then these would be chased with the site and not sent for clinical review until the information was provided. For F/LT events, if investigator causality or expectedness assessment was missing, whilst a clinical review would occur, a Sponsor assessment would not be recorded until the information was received from the Investigator.

    - If investigator causality was missing, a conservative approach would not be taken during the assessment (e.g. to treat as related until informed otherwise) as per CT-3 and CTFG Q&A RSI November 2017 Question 17).

    - The safety tracker calculated the SUSAR reporting due date based on Day 0 which was defined as the date the SUSAR was confirmed. This could differ from the date the SAE was received which was recorded in a different field.

    - The Safety Management Plan was unclear on what happens in regard to expedited reporting for events where data were missing (e.g. clinical review would occur in 8 weeks and escalated to the Trial Management Group) but it was unclear on what actions would be taken for expedited reporting and if these events would be reported based on clinical review).

- There was a lack of oversight of SUSAR reporting by the CTU management. Trackers used to log SAEs in this trial were incomplete therefore it was not possible to have oversight of reporting timelines.

- Due to the issues identified with the use of RSI as per findings above there was a potential impact on the information reported in DSURs for the trial. In addition, the following issues were identified with the process for generation of the DSUR:

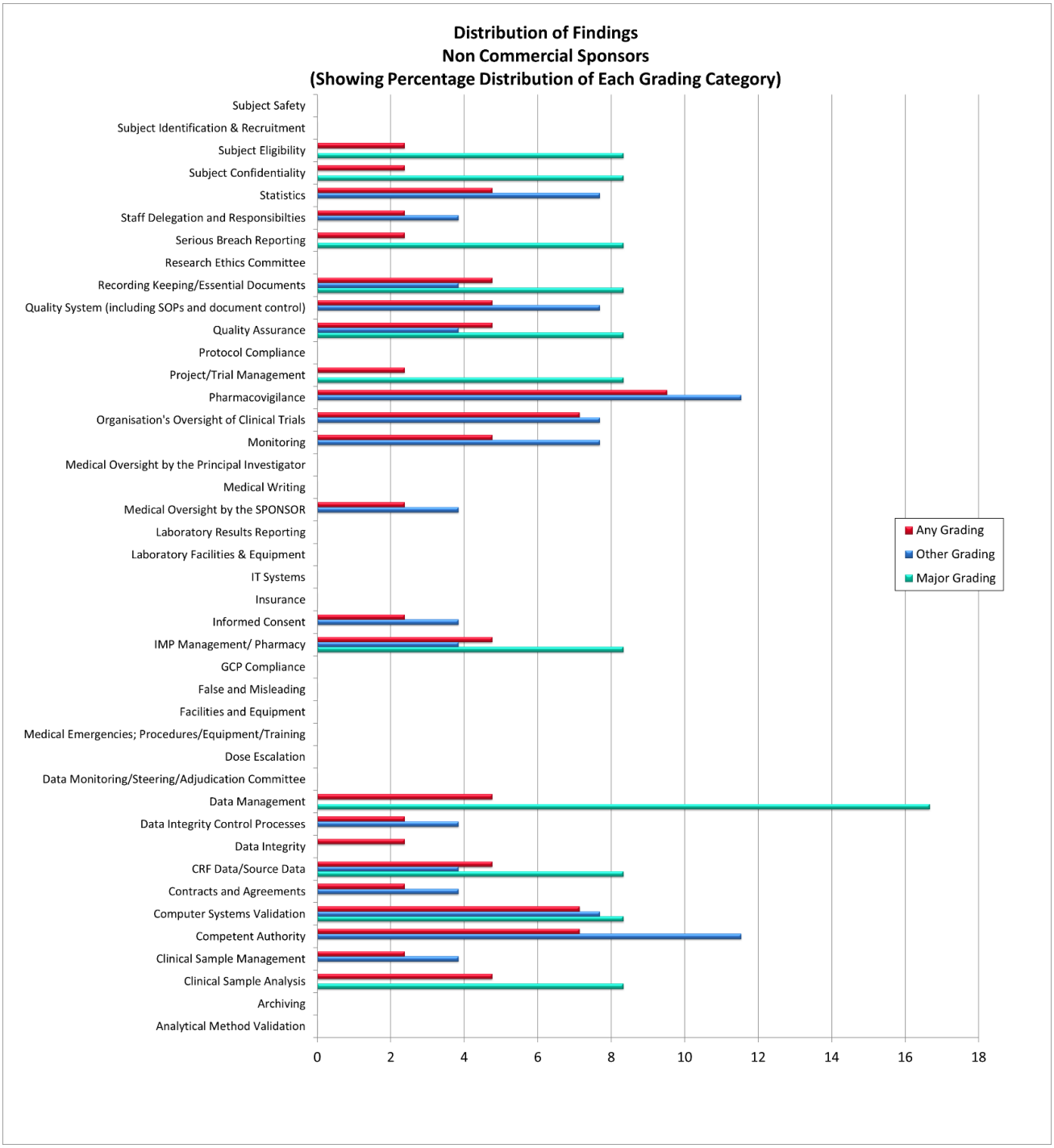
    - CTU SOP RSI was incorrect regarding which RSI was to be used for the DSUR reporting period and how events would be reassessed. It required the latest RSI to be used and not the RSI approved at the start of the reporting period.

    - Historically there was no documented reconciliation of SAEs for the DSUR and it was not mandatory that this was performed.

- The Work Instruction on DSUR Production stated that all DSUR reports should be blinded. This is misleading as DSUR reports should identify SUSARs which have occurred which can be unblinding.

Summary of Findings from Non-commercial Organisations

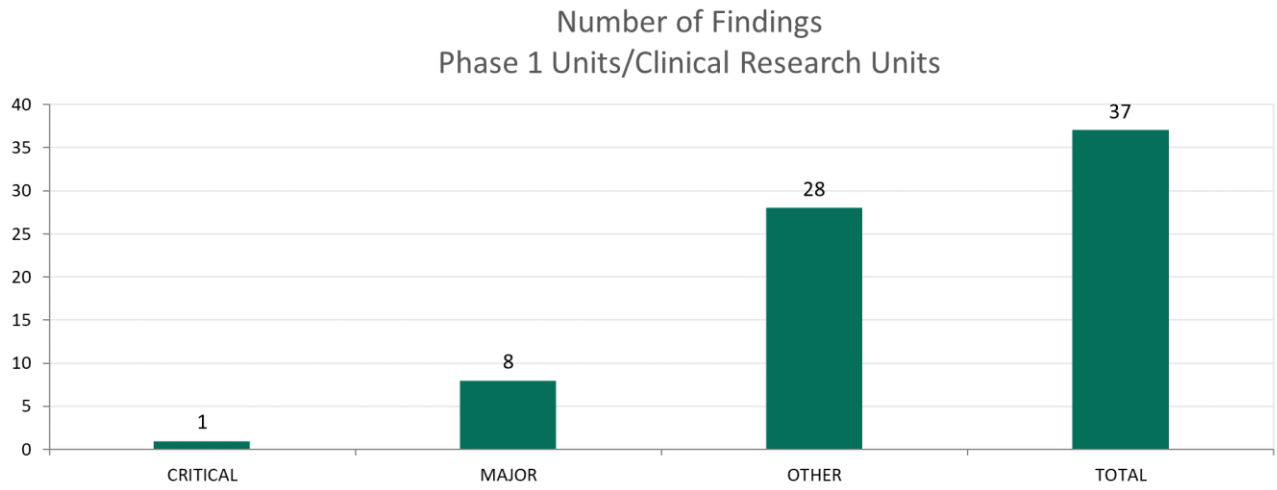
The figure on the following page shows the distribution of Major, Other and any grade of inspection findings. This identifies the areas where GCP inspectors have been making observations of non-compliance with GCP.



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

A total of four inspections were done of Commercial Phase 1 Units/Clinical Research Units. Three of the inspections were routine inspections for the MHRA voluntary phase 1 accreditation scheme. One of the inspections was triggered following concerns identified at a related inspection. Note that findings reported here relate to GCP only and not those related to the phase 1 accreditation scheme.

Of the four inspections, one (25.0%) had a critical finding and three (75.0%) 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 (Non-Commercial Organisations)

	Mean	Median	Mode	Maximum	n
Critical	0.3	0.0	0.0	1	4
Major	2.0	1.0	1.0	6	4
Other	7.0	9.0	9.0	10	4

There was one critical finding identified from one organisation.

Critical Finding 1

A triggered inspection at an accredited Phase 1 unit identified one critical finding during their inspection.

The critical finding was for **Dose Escalation**. This concerned breaches of UK Statutory Instrument 2004/1031 (as amended) Regulation 28 and Schedule 1, Part 2: (4, 9 & 11). Across the three First In Human (FIH) trials reviewed during the inspection, PK data from failed analytical runs had been provided to the Dose Escalation Committee (DEC) in order to decide whether to proceed to the next dose or not. In only one out of the three trials, documentation was present that the Principal Investigator (PI) or the delegated representative was made aware of the issue in order to determine if the issue may impact their decision to escalate the dose. As the PI has overall responsibility for the medical decisions made on behalf of participants, it is imperative in such higher risk early phase trials that the PI can make their own assessment of the issue. As there was a significant potential for impact to participant safety from release of data from failed analytical runs for dose escalation decisions, this finding was graded as Critical. Whilst for the three trials selected and reviewed it was confirmed during the inspection that the decisions taken would not have impacted on the stopping criteria based on PK data observed from previous cohorts, there was a lack of transparency in communicating the issues to the PI and documenting the issues (including any rationale/ justification to use the data) within the trial files.

- There was no formal procedure for how study teams (e.g. the Clinical Pharmacologist/ Pharmacokineticist and Medical Monitor) would be notified of, record and manage information from the laboratory of failed analytical data.

    - For a number of dose escalation meetings it had not been made apparent (to the attendees) that data presented had originated from failed analytical runs. There was a Pharmacokineticist present at the meeting, but there was no evidence if they or the study medical monitor (both of whom were aware of the failed runs) had communicated this PI in order for them to assess the impact on the PK stopping criteria/dose escalation decision.

- There were examples of where trial documentation was not reflective of decisions taken during dose escalation meeting one of the selected trials. For example:

    - It was evident in the minutes for dose escalation meeting minutes for one cohort that the unit were aware of the issue (with PK data from failed analytical runs). However, the DE documentation was not reflective of the rationale and justifications provided during interview by the Medical Monitor for why there was no impact on dose escalation and why it was decided to proceed to the next dose level.

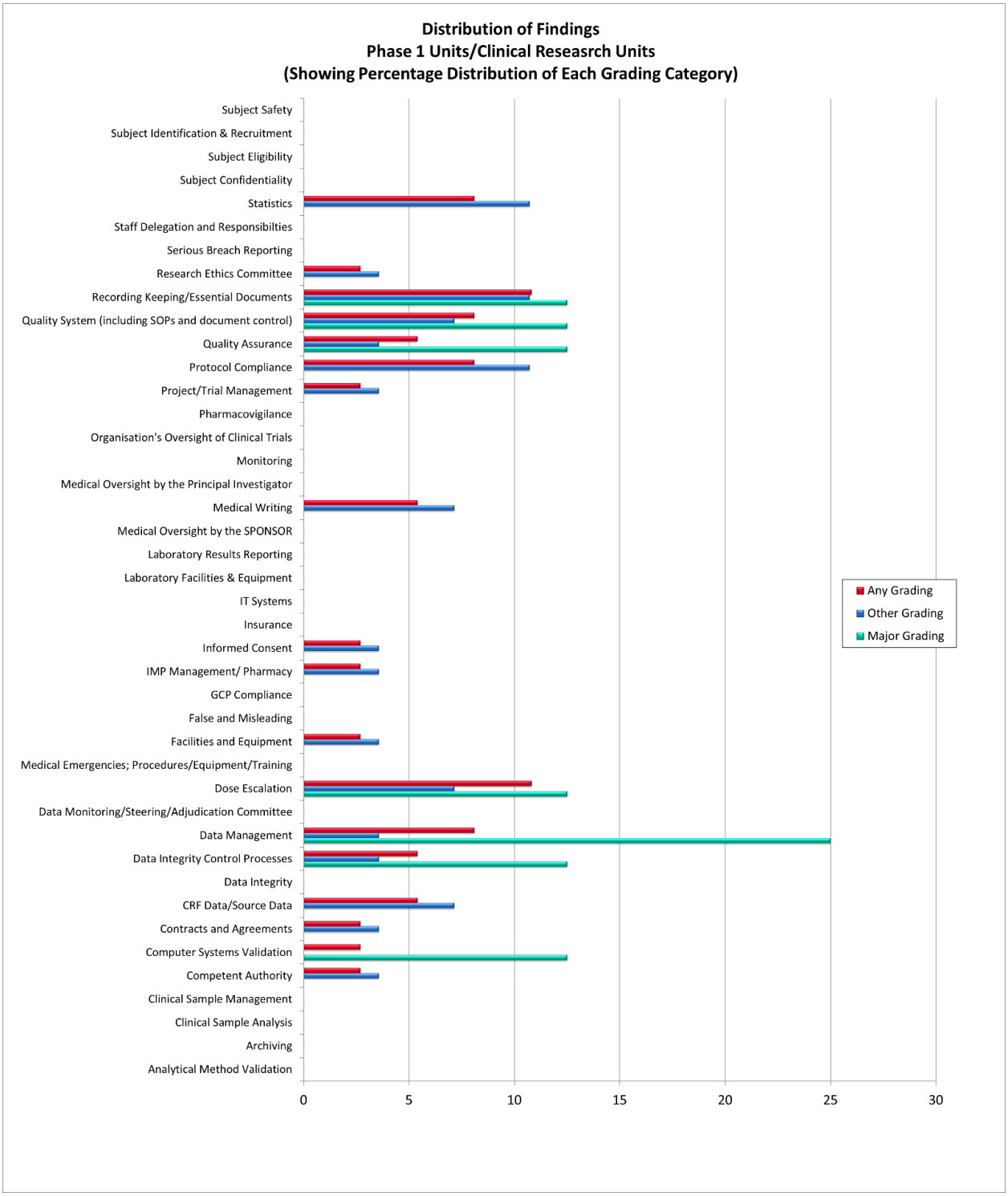
- Across all trials reviewed there were issues identified with the QC checks of PK data used for dose escalation decisions. For example:

    - There was no explanation within one trial’s dose escalation charter regarding how to handle any data that was not valid or had undergone QC (e.g. the failed runs for the PK data which could impact on the ability to make a safe decision on the protocol stopping criteria.

- For two other trials there was a lack of documented confirmation that PK data used during dose escalation meetings has undergone QC.

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

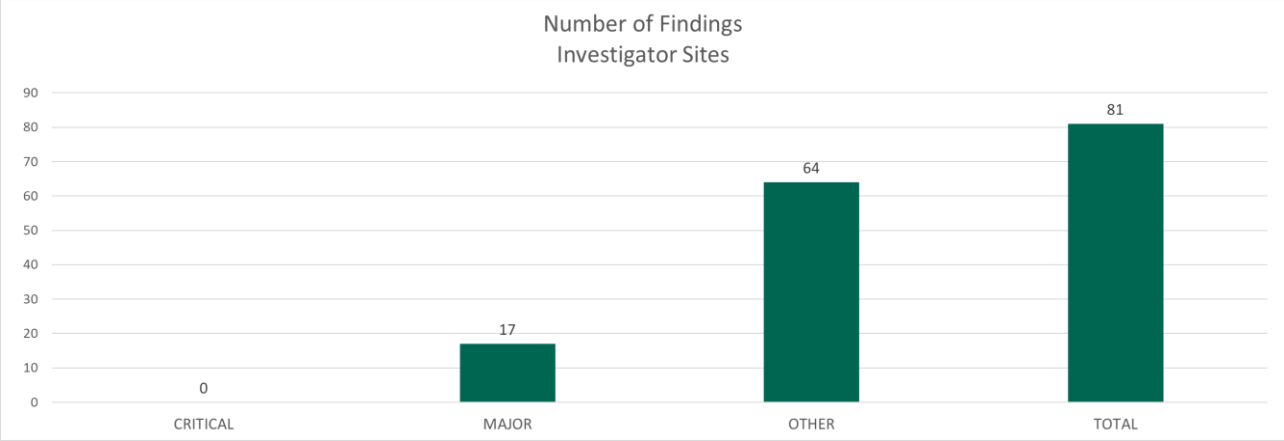
The figure on the following page shows the distribution of Major, Other and any grade of inspection findings. This identifies the areas where GCP inspectors have been making observations of non-compliance with GCP.



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

A total of 12 investigator sites in the UK were inspected and all were as an associated site with a sponsor/CRO/non-commercial/CTU inspection.

Of the 12 reported inspections, none (0.0%) had a critical finding and 10 (83.3%) 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.



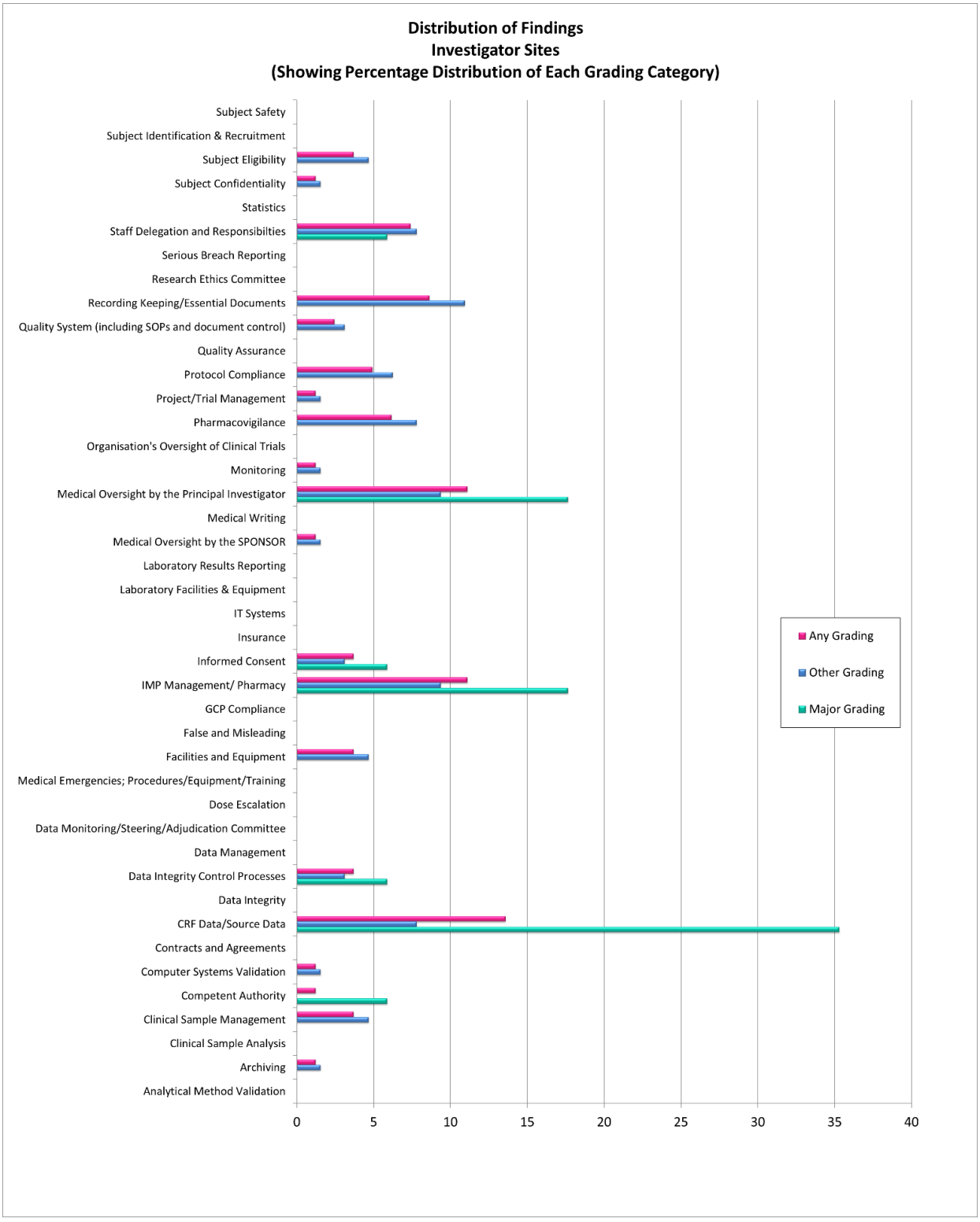
Number of Findings Per Inspection (Investigator Sites)

	Mean	Median	Mode	Maximum	n
Critical	0.0	0.0	0.0	0	12
Major	1.4	1.0	1.0	4	12
Other	5.3	5.0	5.0	9	12

There were no critical findings identified.

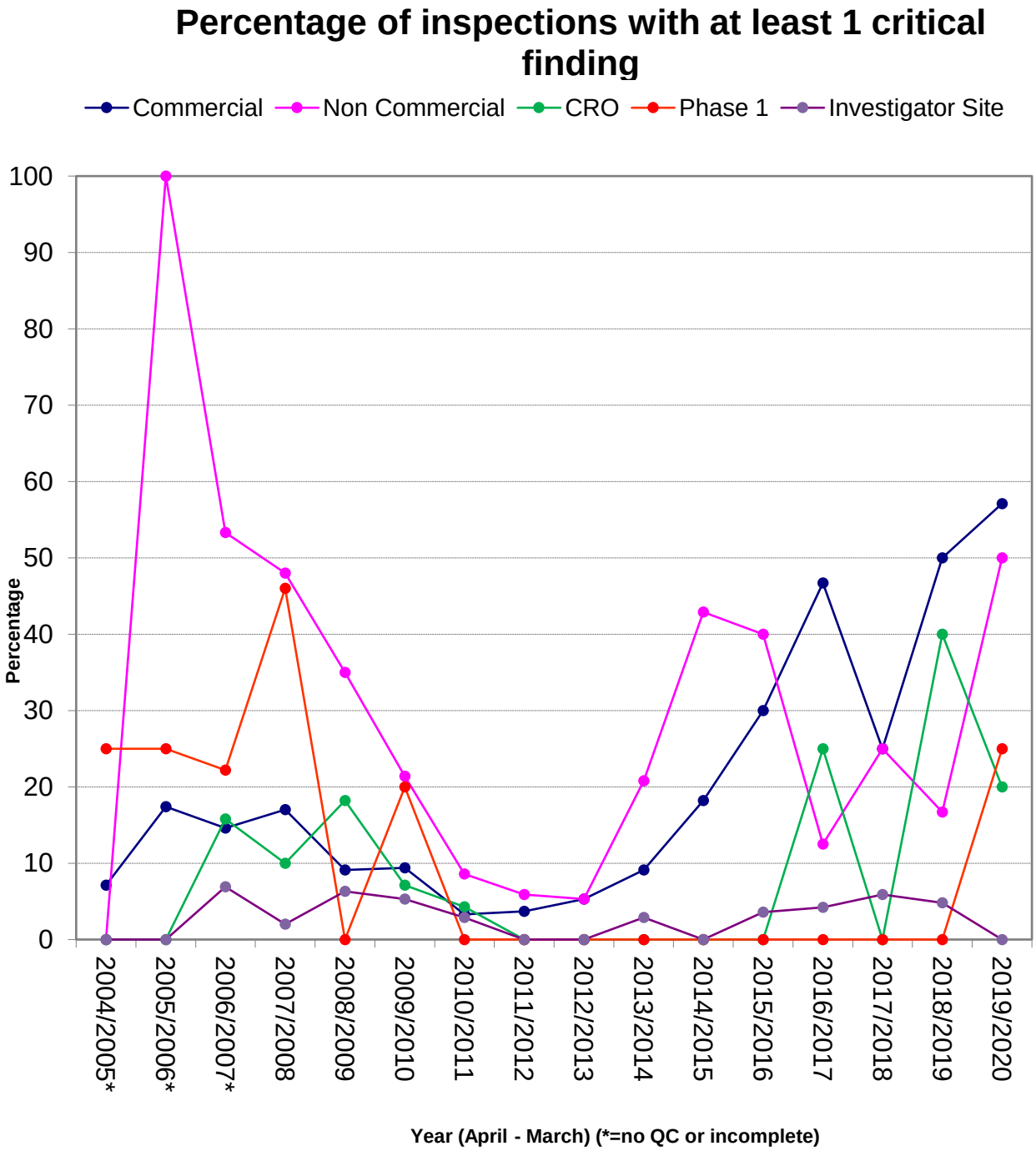
Summary of Findings for Investigator Sites

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.



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 and/or major finding