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Health Products Regulatory Authority

Overview of GCP inspections, including common findings

Peter Twomey, GCP/PV inspector

HPRA Information Day – GCP for IMP clinical trials

Dublin, 23 October 2018

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What we will cover

- Background to inspections and the inspection team
- Inspection types and scope
- Common inspection findings
- Inspection responses

GCP Inspection Programme

Inspections undertaken by Authorised Officers according to SI 190/2004 (as amended)

Objective of inspections is to verify compliance with regulations and relevant guidance, in particular ICH GCP E6

Inspections may take place at any location where clinical trial related activities occur

Average of 16* GCP inspections per year

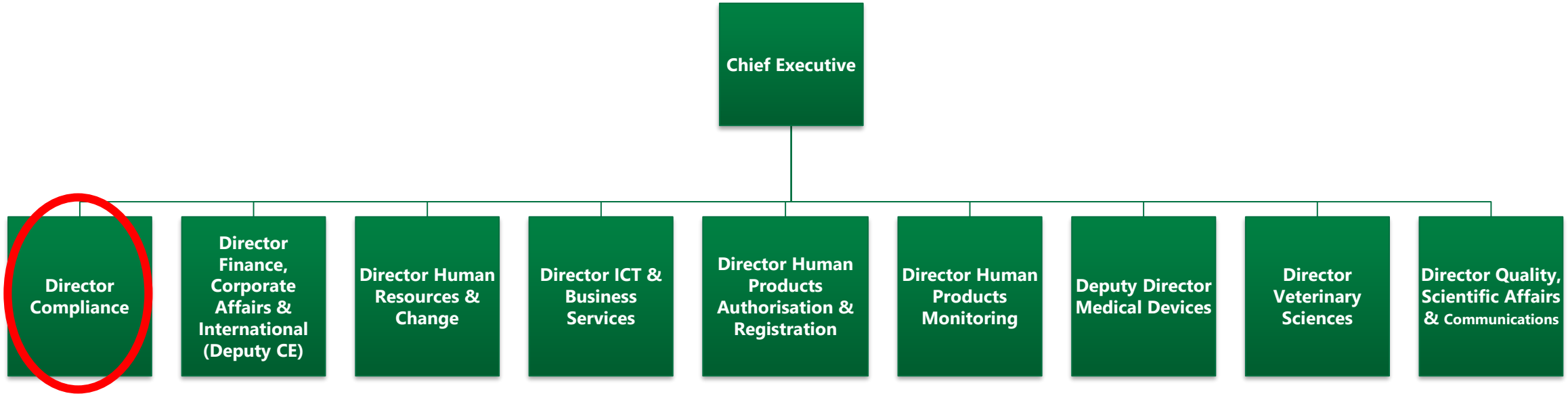
*From 2008 - 2017

GCP Inspection Programme

National routine surveillance programme or EMA requested inspections

Inspections conducted as per HPRA and Union Procedures (European)

Harmonisation across Europe via participation in EMA GCP Inspectors Working Group & Workshops


Chief Executive
Director Compliance
Director Finance, Corporate Affairs & International (Deputy CE)
Director Human Resources & Change
Director ICT & Business Services
Director Human Products Authorisation & Registration
Director Human Products Monitoring
Deputy Director Medical Devices
Director Veterinary Sciences
Director Quality, Scientific Affairs & Communications

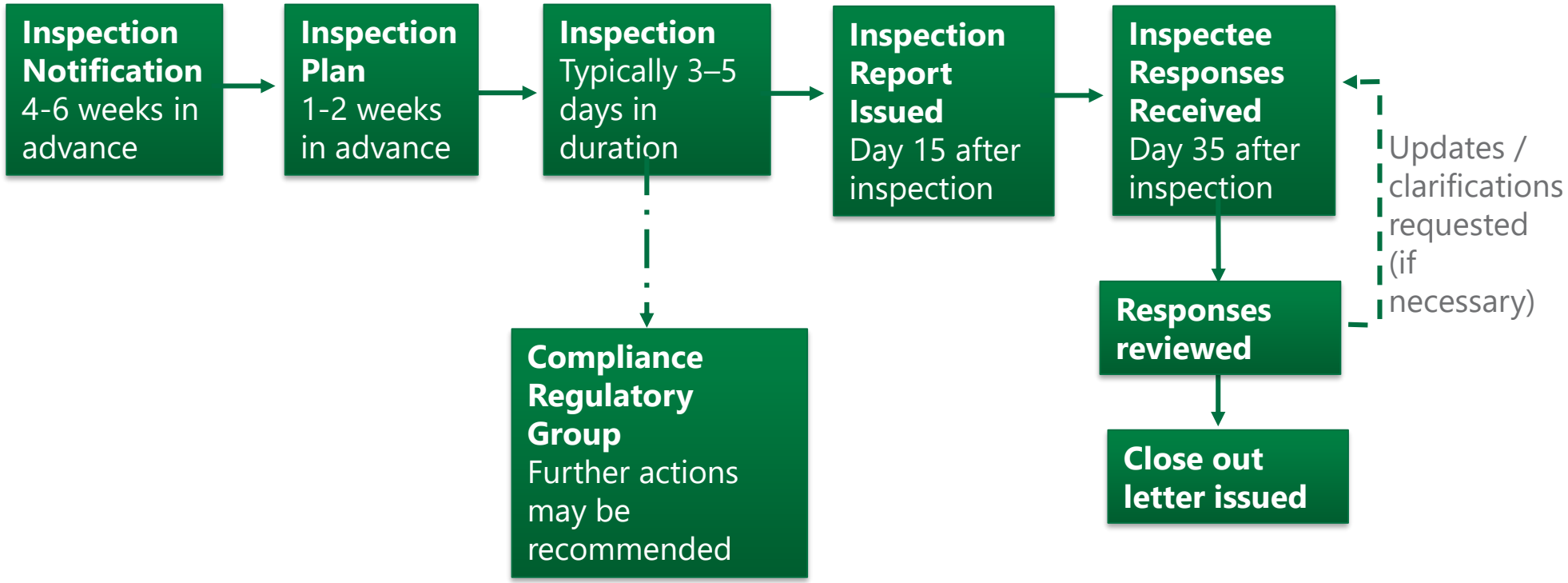
GCP/PV Inspection Team

Sinead Curran
GCP/PV Inspection Manager

Marie Callaghan
GCP/PV Inspector

Peter Twomey
GCP/PV Inspector

Routine Inspection Process



Inspection Findings: Grading

Critical deficiency

- Conditions, practices or processes **that adversely affect** the rights, safety or well-being of the subjects and/or the quality and integrity of data

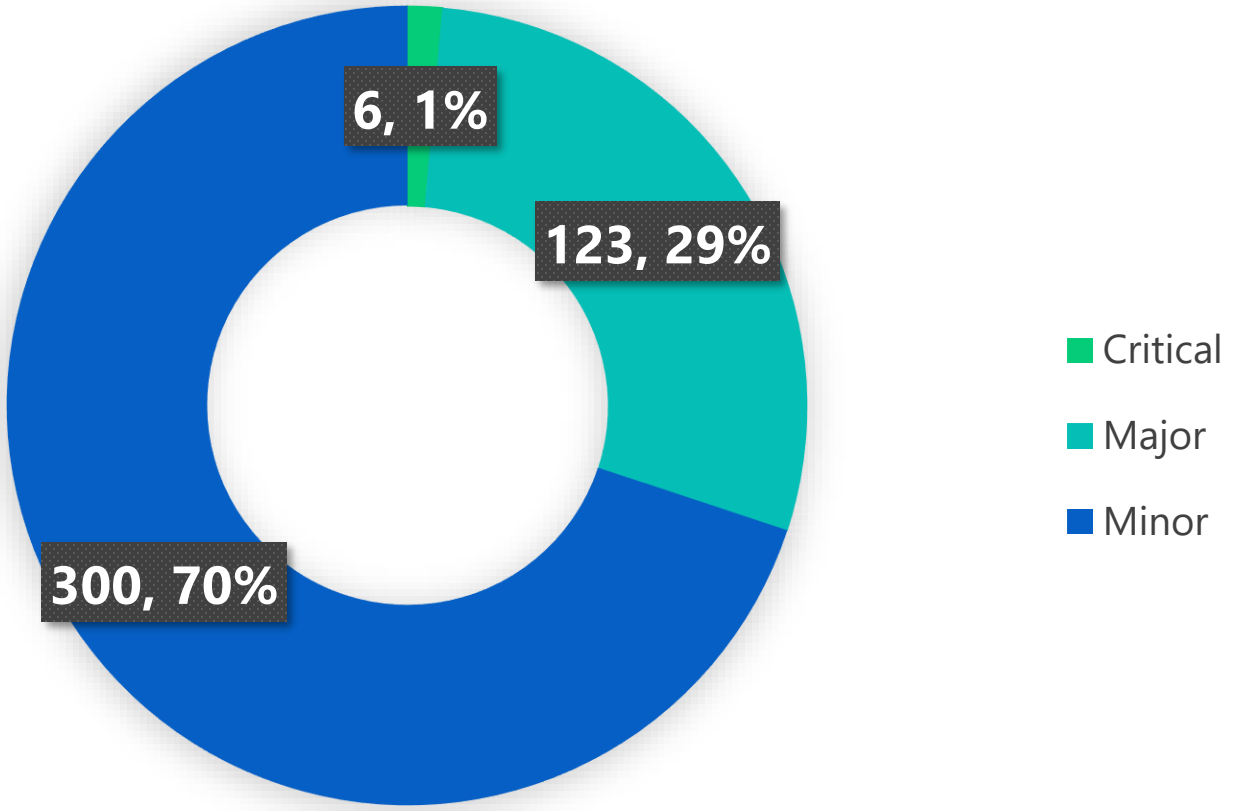
Major deficiency

- Conditions, practices or processes **that might adversely affect** the rights, safety or well-being of the subjects and/or the quality and integrity of data

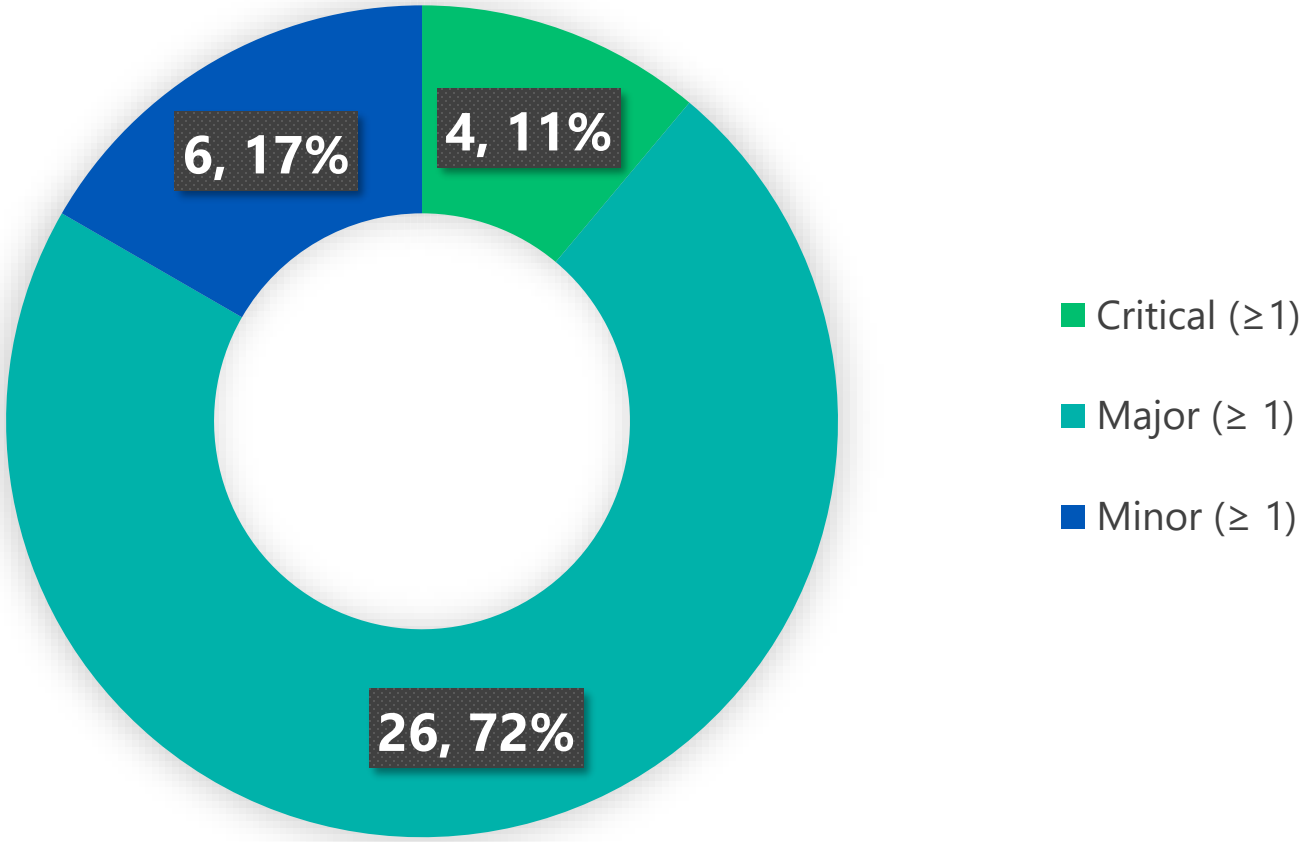
Minor deficiency

- Conditions, practices or processes **that would not be expected** to adversely affect the rights, safety or well-being of the subjects and/or the quality and integrity of data

Inspection Findings (n=429): by Grade



Inspection Outcome (n=36): by Highest Grade



Key Inspection Types

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Investigator site

- Generally study specific
- Most common type of HPRA GCP inspection
- Focus upon investigator role
- Aspects of sponsor role also examined, in particular where there is an interface
- Most often conducted at clinical site, or, an associated research facility where trial conducted

Sponsor site

- Generally systems based, but may choose study(s) as examples
- Less common type of HPRA inspection
- Focus upon sponsor role, including quality system & operational activities
- Most often conducted at sponsor office and/or at a CRO to whom tasks have been contracted

Key Inspection Types

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Clinical Trial Host

- Third party site, to whom the investigator has delegated tasks
- Newer type of HPRA GCP inspection
- Created in response development of specialised research facilities/ third party pharmacies
- Provides opportunity to broadly examine systems/processes, rather than study specific aspects
- To date, all inspections performed at clinical research facilities/centres

Inspection Scope: Investigator Site

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Organisation

e.g. delegation, personnel, training and facilities

Administrative Aspects

e.g. communication with HPRA/REC, contracts and insurance

Protocol compliance

e.g. satisfying incl./excl. criteria, adherence to schedule of assessments

Informed consent

e.g. initial & re-consent process, use of ethics approved form, delegated personnel, GP informed

Safety Reporting

e.g. AE collection, assessment, recording and reporting, including of SAEs

Inspection Scope: Investigator Site

Source doc, including SDV

e.g. ALCOAC, CRF and other reports

IMP management

e.g. Label, receipt, storage, accountability, subject compliance checks, returns, dose modifications, blinding

Clinical sample management

e.g. management of biological samples and communication of results

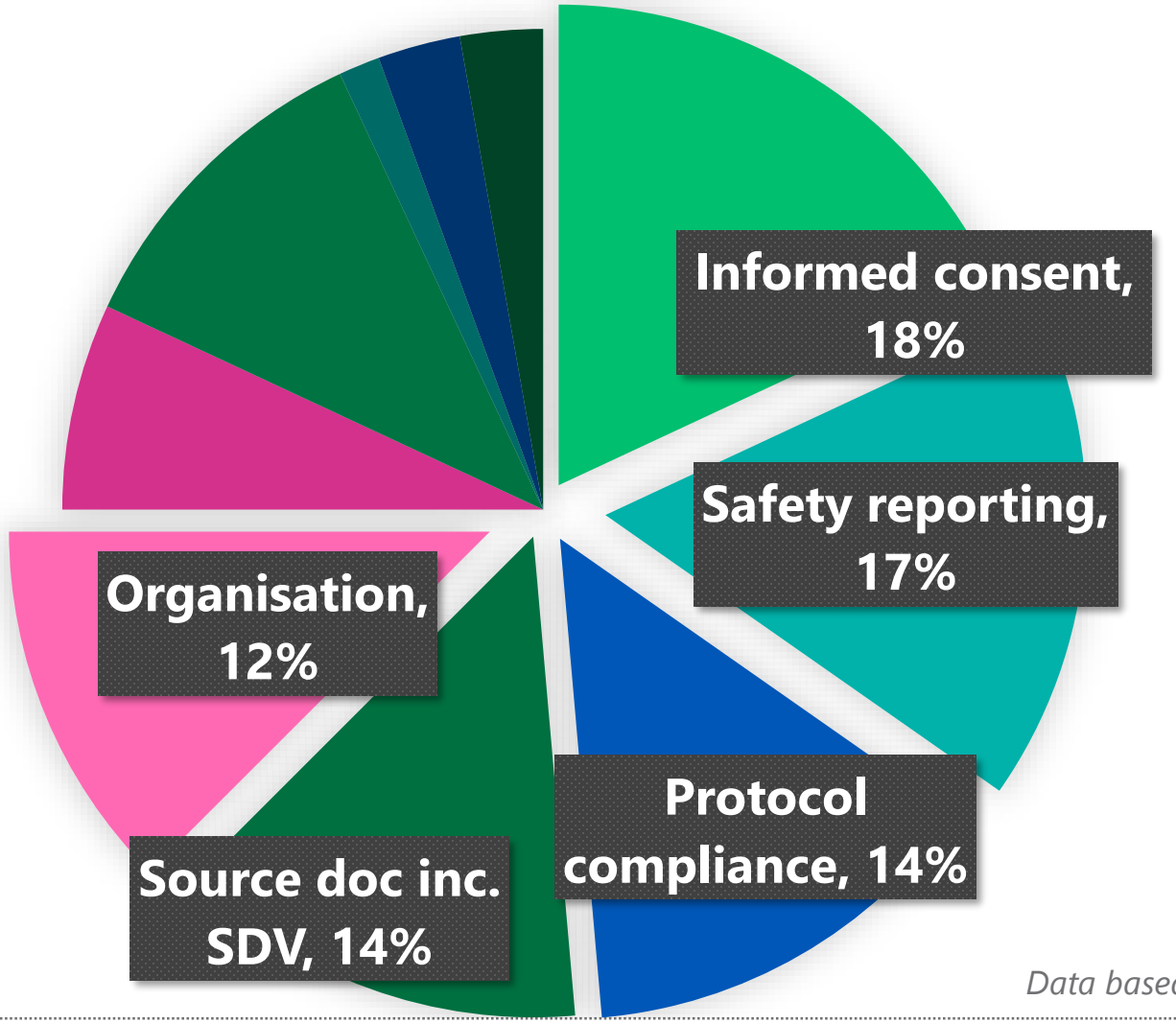
Investigator Site File

e.g. completeness and accuracy, archiving, computer systems

Trial Management & Monitoring

e.g. site monitoring, SOPs, contracts, reg/ethics

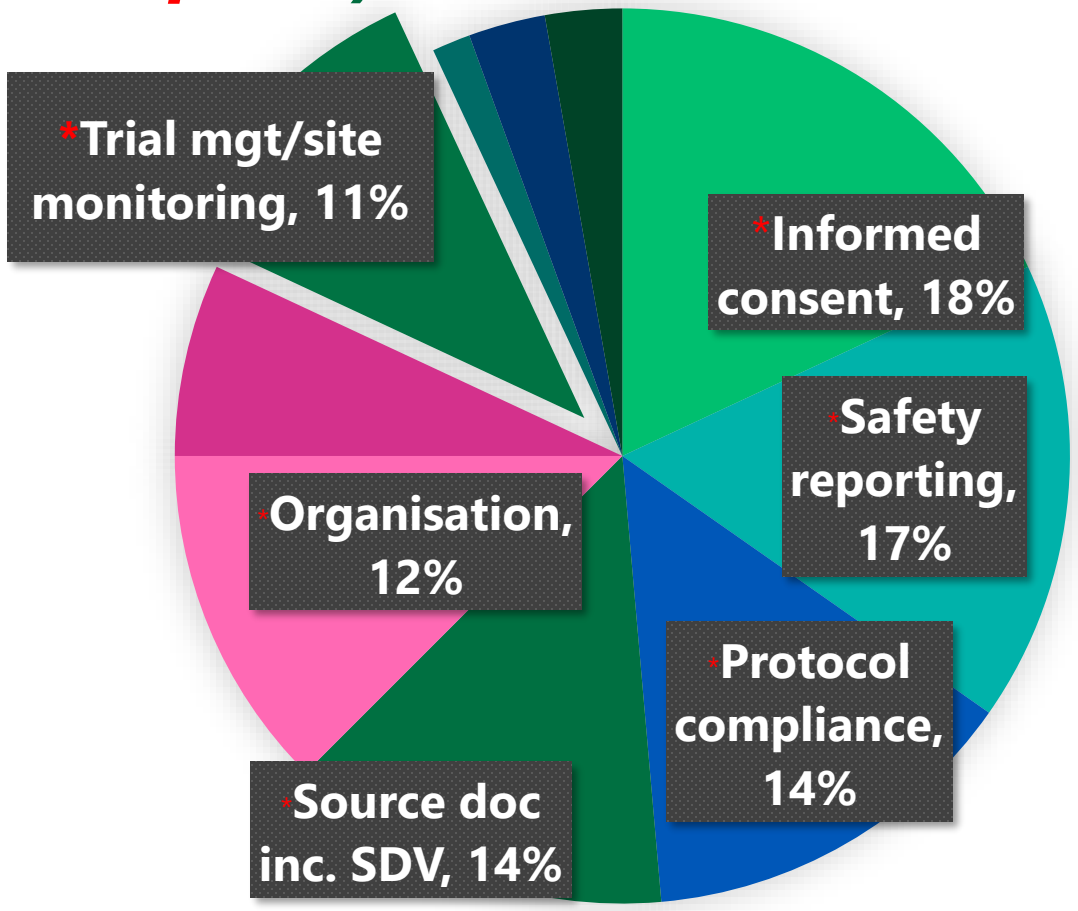
Findings By Area (≥Major) Investigator Site Inspections



- Informed consent
- Safety reporting
- Protocol compliance
- Source doc inc. SDV
- Organisation
- IMP
- Trial mgt/site monitoring
- Reg/ethics
- ISF
- Clincial sample mgt

Data based on 19 closed investigator site inspections from 2016

Findings By Area (≥Major): Investigator Site Inspections (*sponsor focus*)



- Informed consent
- Safety reporting
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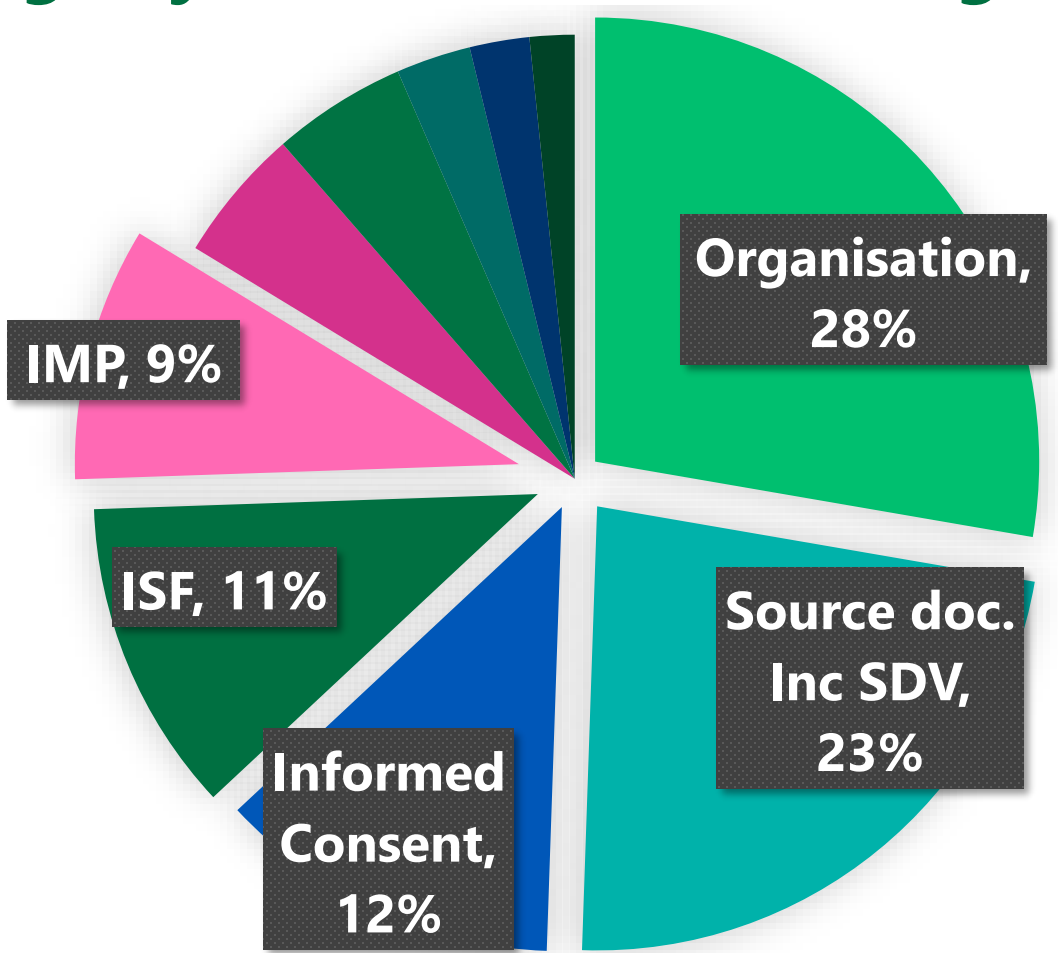
Data based on 19 closed investigator site inspections from 2016

Findings By Area (Minor): Investigator Site Inspections



Data based on 19 closed investigator site inspections from 2016

Inspection Scope: Sponsor

Organisation and Personnel

e.g. roles and responsibilities, CRO - written agreements, qualification and oversight

Facilities and equipment

e.g. validation of computerised systems, archive facilities

Quality System

e.g. quality risk management, document control, training, change control, compliance monitoring (e.g. deviations, audits)

Implementation and termination of clinical trial

e.g. availability of Reg/REC approvals, other reg. communications, regulatory green light, and insurance

Trial Monitoring

e.g. Trial management & oversight, site monitoring, medical monitoring

Inspection Scope: Sponsor

IMP

e.g. shipping, supply mgt, randomisation, blinding, instructions to sites

Pharmacovigilance

e.g. AE/SAE processing, SUSAR reporting, annual reports, ongoing safety evaluation

Non-compliance

e.g. process for dealing with significant or persistent non-compliance, including CAPA management

Data handling and clinical trial report

e.g. systems to collect, process, analyse and report clinical trial data, including statistics

Trial Master File

e.g. completeness, archive, direct access

Findings by Area: Sponsor

Experience in this area largely from non-commercial sponsor offices and EMA requested sponsor inspections

Non commercial: common/significant issues

- Systems and processes not established for all sponsor functions
- Quality management
- Monitoring
- Pharmacovigilance

Inspection Scope: Clinical Trial Hosts

Quality management system

e.g. organisation, document control, training, change control, compliance monitoring, archive

Third party interactions

e.g. qualification, roles and responsibilities, oversight

Clinical facility and equipment management

e.g. building mgt, study visit process, computer systems validation, maintenance of equipment & emergency process

IMP

e.g. processes for receipt, storage, allocation, preparation, accountability, labelling, destruction and recall

Biological sample management

e.g. sample management, storage, identification, chain of custody and shipment

Findings by Area: Clinical Trial Hosts

Of inspections performed to date, all in Clinical Research Facilities/Centres - majority of findings were minor

Key areas were findings cited;

- **Roles and responsibilities:** not clearly defined between investigator and CT Host, or, CT Host and third-parties
- **QMS:** deficiencies in document control, training and deviation management
- **QMS:** key steps/critical process not described in procedures
- **Facilities and equipment management:** oversight of equipment servicing/maintenance, emergency situation management

Inspection Responses

Response to an inspection report: a root cause analysis, further assessment and corrective and preventative actions (CAPAs) for all findings

A large proportion of inspections require more than one round of CAPA correspondence

Inform HPRA inspectors if a CAPA cannot be implemented within agreed timeframes or significant changes have been made to the CAPA

CAPA Expectations

- Identify and address the root cause to prevent future occurrences
- Developed in consultation with PI & all relevant personnel
- Clearly define section/personnel responsible for implementing actions
- Outline key steps required to implement the CAPA
- Include specific due dates which are reasonable and achievable
- Check for effectiveness after implementation
- Documentation and evidence available for review at future inspections or audits

Further Information – HPRA website

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Thank you!