30 April 2022
EMA/INS/GCP/271107/2022
Inspections Office
Quality and Safety of Medicines Department

Annual Report of the Good Clinical Practice Inspectors' Working Group 2020

Adopted by the GCP IWG on 30 April 2022

The activities outlined in the Annual Report for 2020 have been carried out in line with the Agency's Business Continuity Plan and prioritisation of activities for the COVID-19 pandemic and are therefore substantially reduced in comparison with the activities carried out by the GCP Inspectors Working Group in previous years.

The delay in the publication of this report is also due to the Agency's Business Continuity Plan and prioritisation of activities for the COVID-19 pandemic.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

1. Introduction

This document is the thirteenth Annual Report of the GCP IWG[1]. This group was established in 1997 under the scope of Article 51(e) of Regulation (EC) No. 2309/93, subsequently amended as Article 57(1)(i) of Regulation (EC) No. 726/2004.

The GCP IWG focuses on harmonisation and coordination of GCP related activities at EU[2]/EEA[3] level. The group's role and activities are described in more detail in its mandate, which was revised in 2013, its current Work Plan and also in volume 10, chapter IV of the publication "The rules governing medicinal products in the European Union".

The group supports the coordination of the provision of GCP advice and maintains a dialogue with other groups such as CHMP[4], CVMP[5], CMDh[6], PhV IWG[7], GMP/GDP IWG[8] and other groups, as needed, in areas of common interest.

This Annual Report is set out in line with the format and objectives of the 2020 GCP IWG Work Plan. However, due to the COVID-19 pandemic and imposed restrictions as well as the business continuity plans of the Agency and the Member States the majority of activities under training and development outlined in the Work Plan for 2020, had to be postponed.

2. Meetings

Seven GCP IWG meetings took place in 2020 (4 regular meetings and 3 extraordinary ones):

- 12th March 2020;
- 16th April 2020 (extraordinary);
- 23rd-24th June 2020;
- 21st, 23rd September 2020;
- 22nd September 2020 (extraordinary);
- 13th October 2020 (extraordinary);
- 10th-11th December 2020.

During 2020, the following GCP inspectors' subgroups/working parties were involved in the discussion of specific topics and drafting documents:

- GCP IWG/ EMA/ European Commission/ Clinical Trials Facilitation and Coordination Group (CTFG)/ Clinical Trials Expert Group (CTEG) collaboration on COVID-19 guidance document, numerous teleconferences;
- GCP IWG/CMDh working party (refer to section 6.5), 6 teleconferences;
- GCP IWG electronic systems subgroup (refer to section 4.1), 7 teleconferences/ full-day meetings;
- GCP IWG remote source data verification subgroup: 5 teleconferences;

[1] Good Clinical Practice Inspectors Working Group
[2] European Union
[3] European Economic Area
[4] Committee for Medicinal Products for Human Use
[5] Committee for Medicinal Products for Veterinary Use
[6] Coordination Group for Mutual Recognition and Decentralised Procedures - Human
[7] Pharmacovigilance Inspectors Working Group
[8] Good Manufacturing Practice/Good Distribution Practice Inspectors Working Group

- GCP IWG reflections on GCP inspections procedures – Integrated Inspection Reports (IIRs) Peer Review subgroup: 4 teleconferences;
- GCP IWG registry-based studies subgroup: 2 teleconferences and 1 workshop with industry;
- GCP IWG remote inspections subgroup: 4 teleconferences;
- GCP IWG Service providers of Home Healthcare services for clinical trials subgroup: 2 teleconferences;
- GCP IWG informed Consent Form- Lack of access to medical records by EU/EEA inspectors subgroup: 2 teleconferences;
- GCP IWG artificial intelligence subgroup: 1 virtual meeting with interested parties;
- GCP IWG requirements of principal investigator review and sign-off of data subgroup: 1 teleconference.

3. Inspections conducted in support of the centralised procedure

3.1. CHMP requested inspections

3.1.1. General overview

In total, 34 GCP inspections were requested by CHMP and carried out by the inspectorates of the EU/EEA Member States in 2020. However, it should be noted that several inspections requested in the last 5 months of the year 2019 were conducted in 2020 and that several inspections requested in 2020 were carried out in 2021 (as well as one inspection requested in October 2019). The decrease of conducted inspections in 2020 as well as the postponement of several inspections was due to the COVID-19 pandemic. The data in this report relates to inspections carried out in 2020.

Table 1: Number of inspections conducted per region and type of inspection.

Region	Non-Routine	Routine	Total
EU/EEA/EFTA[9]	8	4	**12**
UK	1	2	**3**
USA[10]	4	3	**7**
Middle East/Asia/Pacific	0	5	**5**
CIS[11]	0	5	**5**
Eastern Europe (non EU)	0	1	**1**
Australia/New Zealand	0	1	**1**
Total in all regions	**13**	**21**	**34**

[9] European Free Trade Association
[10] United States of America
[11] Commonwealth of Independent States

In Figure 1, the number of inspections carried out in 2020 is shown by region and type of inspection. Most inspections were carried out in the EU/EEA/EFTA region (44.1%) followed by the USA (20.6%) and the Middle East/Asia/Pacific countries and CIS (14.7% for each region).

Figure 1: Inspections conducted per region and type of inspection.

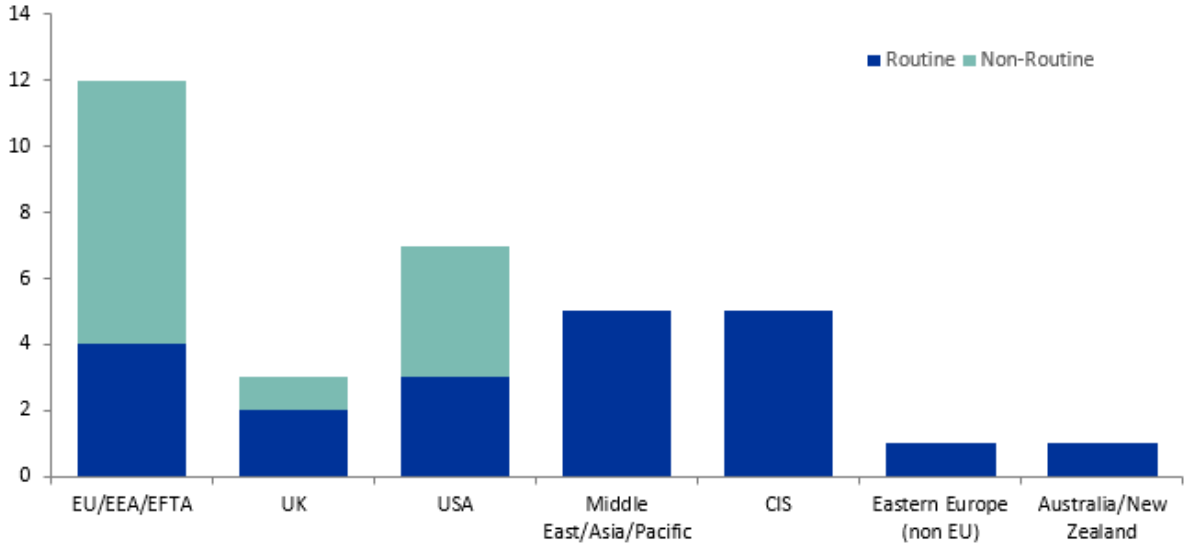

Table 2: Inspections conducted per type of site.

Site	No. of inspections conducted
Clinical investigator	16
Sponsor	12
CRO	6
Total in all sites	**34**

Figure 2: Inspections conducted per type of site.

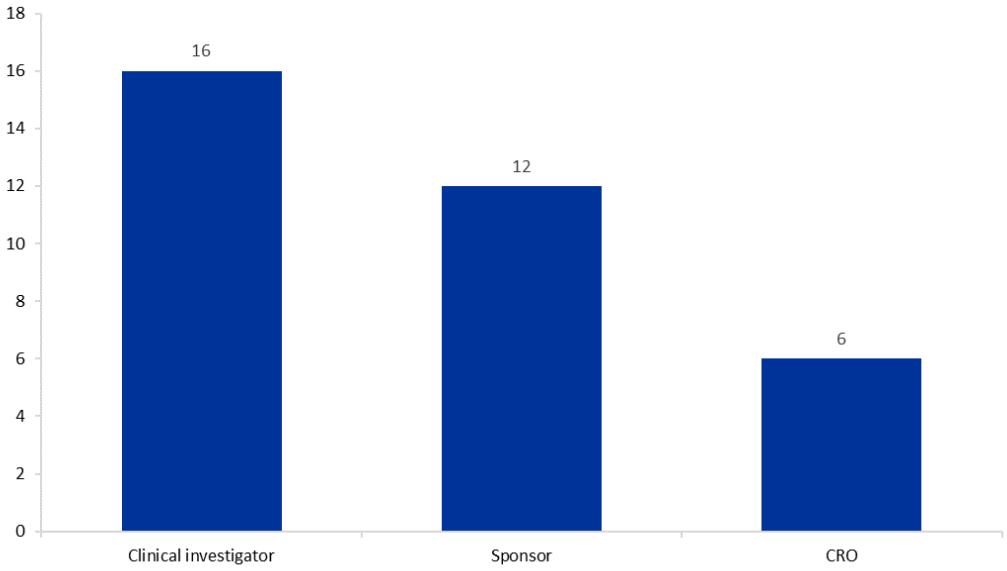

Figure 2 represents the number of inspections conducted in 2020 per type of site. Most of the inspections were conducted at clinical investigator sites, followed by sponsor and CRO sites.

3.1.2. Categorisation of findings

A total of 363 deficiencies, comprising 16 critical (4.4%), 200 major (55.1%) and 147 minor (40.5%) findings were recorded for the 34 CHMP requested inspections conducted in 2020.

The main findings observed in the 2020 inspections are detailed below in accordance with the GCP categorisation of findings agreed by the GCP IWG.

Figure 3.a: Number of findings by grading categories critical, major and minor.

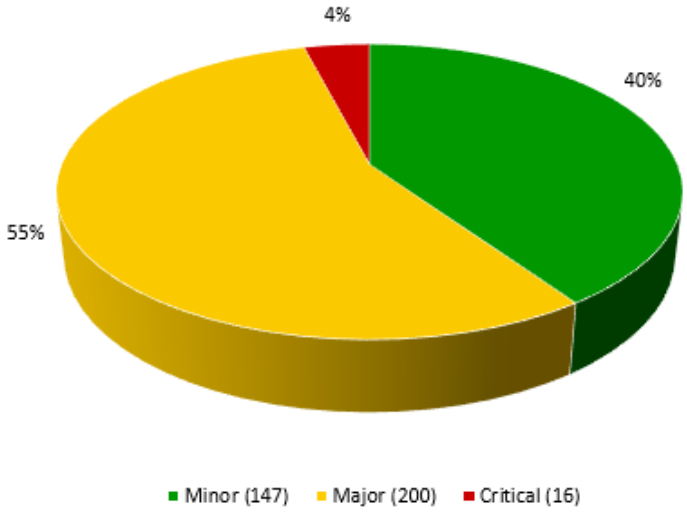

Table 3: Number of findings by main category and grading categories critical, major and minor.

Main category	Minor	Major	Critical	Total
Trial Management (Sponsor)	62	97	9	**168**
General	48	56	2	**106**
Investigational Medicinal Products (IMPs)	16	7	0	**23**
Investigational site	8	12	0	**20**
Computer System	3	15	1	**19**
Laboratory/Technical Facilities	7	10	0	**17**
Subject Protection	0	0	4	**4**
Informed Consent (IC)	1	2	0	**3**
IEC/IRB[12]	2	1	0	**3**
Total	**147**	**200**	**16**	**363**

Figure 3.b: Number of findings by main category and grading categories critical, major and minor.

[12] Independent Ethics Committee/Institutional Review Board

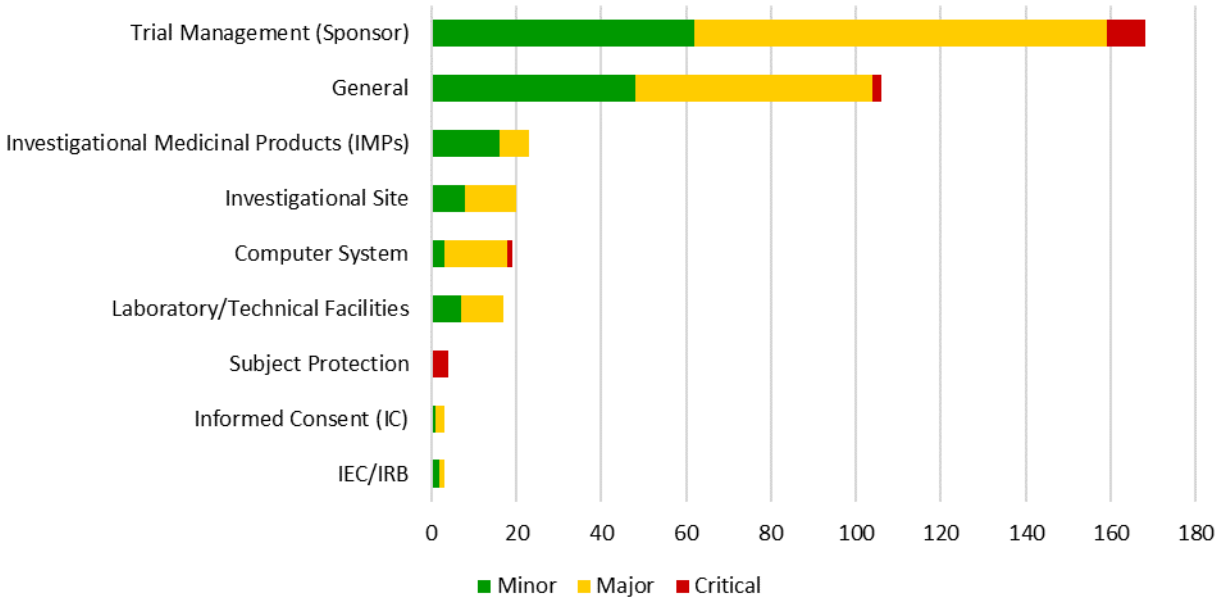
Trial Management (Sponsor)
General
Investigational Medicinal Products (IMPs)
Investigational Site
Computer System
Laboratory/Technical Facilities
Subject Protection
Informed Consent (IC)
IEC/IRB
0
20
40
60
80
100
120
140
160
180
Minor
Major
Critical

Table 4: Number of findings per sub-category of the top 3 main categories (trial management, general and investigational medicinal products) graded as critical, major and minor.

		# Inspected deficiencies			Total
Deficiency category name	**Deficiency sub-category name**	**Minor**	**Major**	**Critical**	
Trial Management (Sponsor)	Audit	5	13	2	**20**
	Clinical Study Report	3	6	0	**9**
	Data Management	21	31	1	**53**
	Document Control	21	28	4	**53**
	Monitoring	4	11	1	**16**
	Protocol/ Case Report Form/ Diary/ Questionnaires design	1	6	1	**8**
	Statistical Analysis	7	2	0	**9**
Trial Management (Sponsor) total		**62**	**97**	**9**	**168**
General	Contracts/ Agreements	6	12	1	**19**
	Essential Documents	6	6	1	**13**
	Facilities and Equipment	6	7	0	**13**
	Organisation and Personnel	6	7	0	**13**
	Qualification/ Training	6	10	0	**16**
	Randomisation/ Blinding/ Codes	1	0	0	**1**
	Standard Operating Procedures	6	8	0	**14**
	Source Documentation	11	6	0	**17**
General total		**48**	**56**	**2**	**106**
Investigational Medicinal Products (IMPs)	IMP Accountability	4	3	0	**7**
	Manufacturing/ Packaging/	2	2	0	**4**
	Prescription/ Administration/ Compliance	2	2	0	**4**
	Supplying/ Storage/ Retrieving/ Destruction	8	0	0	**8**
IMPs total		**16**	**7**	**0**	**23**

Examples of cross section (critical, major, minor) findings in the top sub-categories of the main three categories "Trial Management", "General", and "Investigational Medicinal Products" are listed below:

[13] Investigational Medicinal Product

Trial management (Sponsor)

Monitoring:

- lack of source data reporting;
- failure to escalate noncompliance adequately;
- review process of monitoring reports not consistently documented and such documentation was not retained;
- clinical trial monitoring failed to identify and remedy deficiencies.

Data Management:

- audit trails of the archival CRFs in pdf format incomplete or ambiguous;
- error in time settings of the eCRFs leading to incorrect reports of SAEs;
- eCRF completion guidelines finalised after the first subject enrolment.

Document Control:

- Shortcomings in the content and organisation of the Investigator Site File;
- No defined review process for the Investigator Site File;
- Discrepancy in information provided regarding the use of electronic medical records and the reporting thereof.

Clinical Study Report (CSR):

- discrepancies in the CSR with regard to protocol deviations and subjects excluded from analyses;
- inconsistencies with regard to the approval of the CSR;
- no clear mention of GCP non-compliance of a site in the CSR;
- the CSR contains erroneous data listings and omits relevant trial aspects.

Protocol/ Case Report Form/ Diary/ Questionnaires design:

- protocol wording not detailed enough or not ensuring a harmonized interpretation;
- missing precise and standardized instructions for (S)AE handling.

Audit:

- Lack of oversight by the sponsor on/over a number of crucial aspects related to study setup conduct and reporting;
- Lack of audit of key vendors and of audit of activities subcontracted to another party;
- process for vendor evaluation and accreditation not sufficiently robust;
- Process of remote audit not outlined in an SOP or other written procedure;
- No formal plan or procedure developed or adopted to assure and control quality during the integration of a company after an acquisition.

General

Essential Documents:

- lack of essential documents in TMF;
- location of files not easily identifiable by the structure of the eTMF system;
- Content of documents not easily identifiable by the naming.

Source Documentation:

- electronic medical record system not an acceptable source document;
- documents in the Investigator Site File and in some patient medical records available as photocopies of poor quality, rendering reading impossible;
- source documents were not clearly identified and verified;
- source data location list not generated at the beginning of the trial and not filed in the Investigator Site File.

Qualification/ Training:

- training of the site staff did not meet the requirements set out in the Monitoring Plan;
- training of the principal investigator on the updated version of ICHGCP (E6R2) not done until several months after it became effective;
- electronic training modules were performed by persons not listed on the site signature and delegation log.

Standard Operating Procedures (SOPs):

- no formal quality management system in place when the study started;
- review period for SOP too long in the light of changing regulatory environment;
- SOPs not reviewed within the timeframe established;
- missing SOPs for site-specific activities;
- SOP not version controlled.

Contracts/ Agreements:

- no GCP compliance clause and no regulatory inspection clause in contractual agreements (including mix up with audit terminology);
- task delegation in contracts was not clearly defined or did not correspond to the actual tasks performed;
- missing tasks in Clinical Trial Agreement;
- no signature of contract with external laboratories.

Organisation and Personnel:

- process of maintaining a list of people to whom trial related duties have been delegated not robust;
- trial team composition not properly and contemporaneously documented;
- discrepancies between team member lists in the TMF and CRO study team list.

Facilities and Equipment:

- documentation of temperature measurements not reliable;

- back up equipment not identified at the study start;
- documentation of evaluation of the (back up) equipment maintenance/suitability for study purposes not available.

Investigational Medicinal Products (IMPs)

IMP Accountability:

- incomplete or inconsistent inventory log;
- IMP accountability missing in the Investigator Site File;
- no consistent documentation at the site concerning whether the trial drug dispensed by the investigator's site staff matched the trial drug allocated by IWRS;
- no audit trial provided to the site at the end of the trial for the IWRS drug accountability documentation;
- inconsistencies between accountability log and patient diary regarding IMP intake.

Manufacturing/ Packaging/ Labelling:

- incomplete documentation of relabelling;
- lack of overview document including a direct link between the blinded IMP packaging/labelling lot numbers and the original manufacturing batches and expiry dates;
- lack of qualification of containers used for IMP shipment.

Prescription/ Administration/ Compliance:

- incomplete templates for recording the preparation of the IMP;
- study protocol and study manual/instructions ambiguous or discrepant regarding dilution of IMP concentrate;
- no documentation of (limited) in-use time;
- insufficient documentation on (per patient) dispensing;
- privacy information of participants potentially not adequately safeguarded due to additional labelling by the pharmacist.

Supplying/ Storage/ Retrieving/ Destruction:

- lack of appropriate documentation of storage conditions of the IMP/NIMP supplies;
- incomplete temperature log template (thermometer in use);
- observations regarding temperature excursion handling;
- lack of IMP handling instructions;
- inconsistencies between documents regarding IMP batch receipt date;
- lack of procedure for extending the expiration date;
- lack of procedure for site to site transfer of IMP.

Table 5. Findings graded as critical, major and minor per site type.

Inspection Site Type	Minor %, #		Major %, #		Critical %, #		Total %, #	
Sponsor	16.3%	59	27.8%	101	2.2%	8	**46.3%**	**168**
Clinical Investigator	19.8%	72	20.1%	73	0.6%	2	**40.5%**	**147**
CRO	4.4%	16	7.2%	26	1.7%	6	**13.2%**	**48**
Grand Total	**40.5%**	**147**	**55.1%**	**200**	**4.4%**	**16**	**100%**	**363**

Figure 4: Findings graded as critical, major and minor per site type.

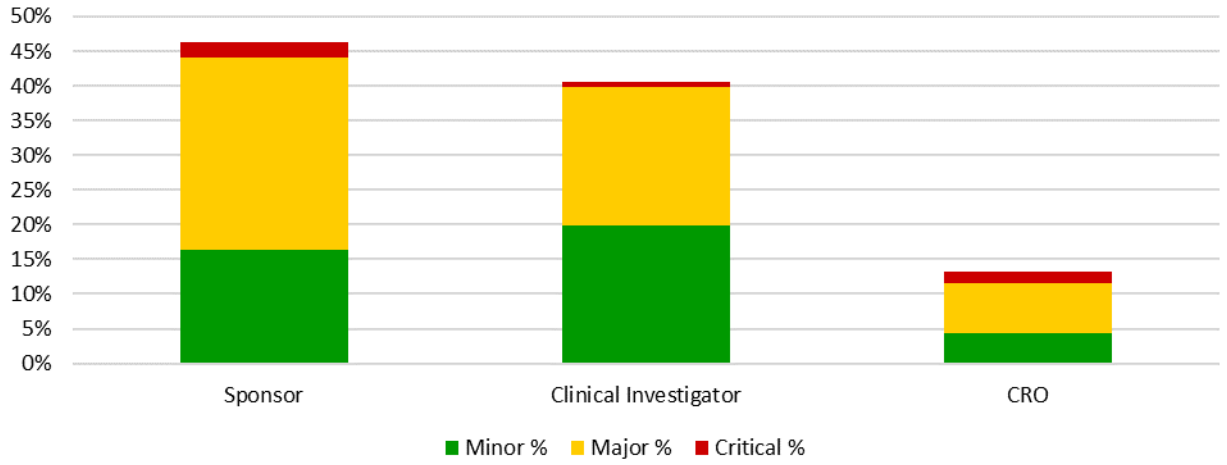

Table 6. Number and categorisation of findings at clinical investigator sites.

Main category	Minor	Major	Critical	Total
General	31	28	0	**59**
Trial Management (Sponsor)	15	16	0	**31**
Investigational Site	7	10	0	**17**
Investigational Medicinal Products (IMPs)	11	4	0	**15**
Laboratory/Technical Facilities	5	7	0	**12**
Computer System	0	5	0	**5**
Informed Consent (IC)	1	2	0	**3**
IEC/IRB	2	1	0	**3**
Subject Protection	0	0	2	**2**
Total	**72**	**73**	**2**	**147**

Figure 4.a: Number and categorisation of findings at clinical investigator sites.

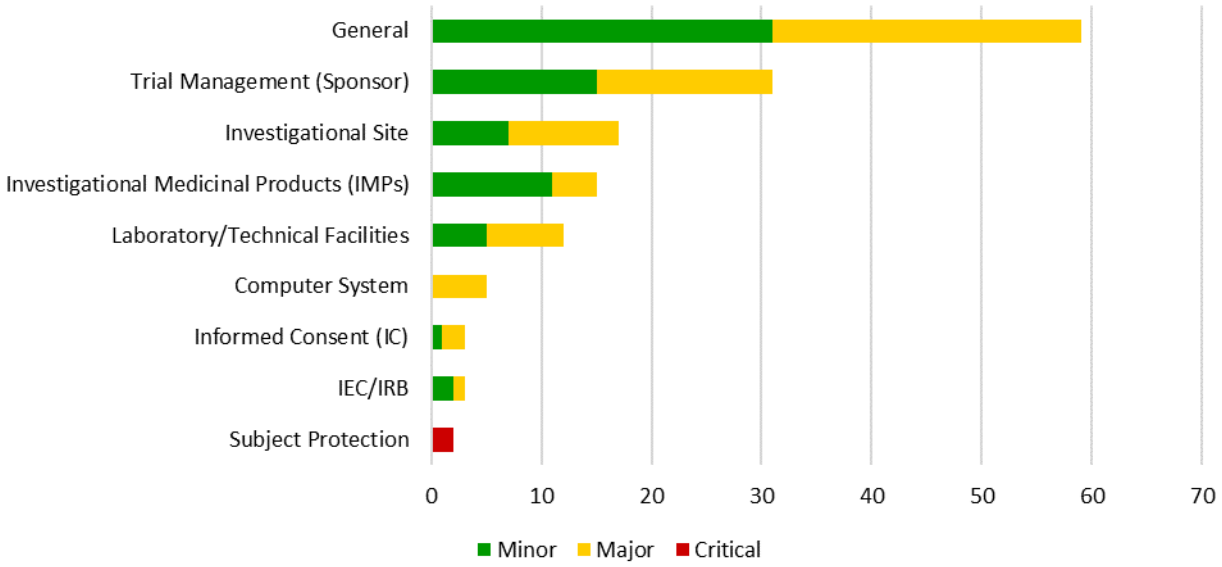

Table 7. Number and categorisation of findings at sponsor sites.

Main category	Minor	Major	Critical	Total
Trial Management (Sponsor)	36	68	5	**109**
General	14	20	0	**34**
Computer System	3	7	1	**11**
Investigational Medicinal Products (IMPs)	5	1	0	**6**
Laboratory/Technical Facilities	1	3	0	**4**
Subject Protection	0	0	2	**2**
Investigational Site	0	2	0	**2**
Total	**59**	**101**	**8**	**168**

Figure 4.b: Number and categorisation of findings at sponsor sites.

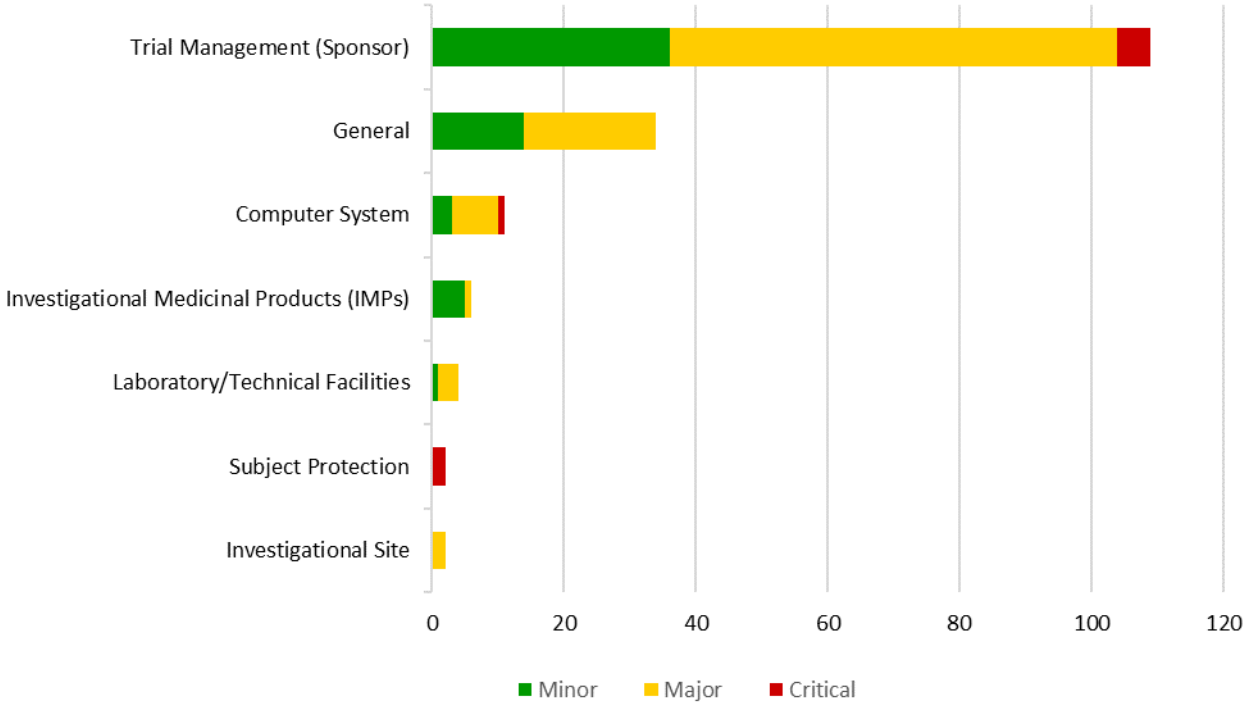

Table 8. Number and categorisation of findings at CRO sites.

Main category	Minor	Major	Critical	Total
Trial Management (Sponsor)	11	13	4	**28**
General	3	8	2	**13**
Computer System	0	3	0	**3**
Investigational Medicinal Products (IMPs)	0	2	0	**2**
Investigational Site	1	0	0	**1**
Laboratory/Technical Facilities	1	0	0	**1**
Total	**16**	**26**	**6**	**48**

Figure 4.c: Number and categorisation of findings at CRO sites.

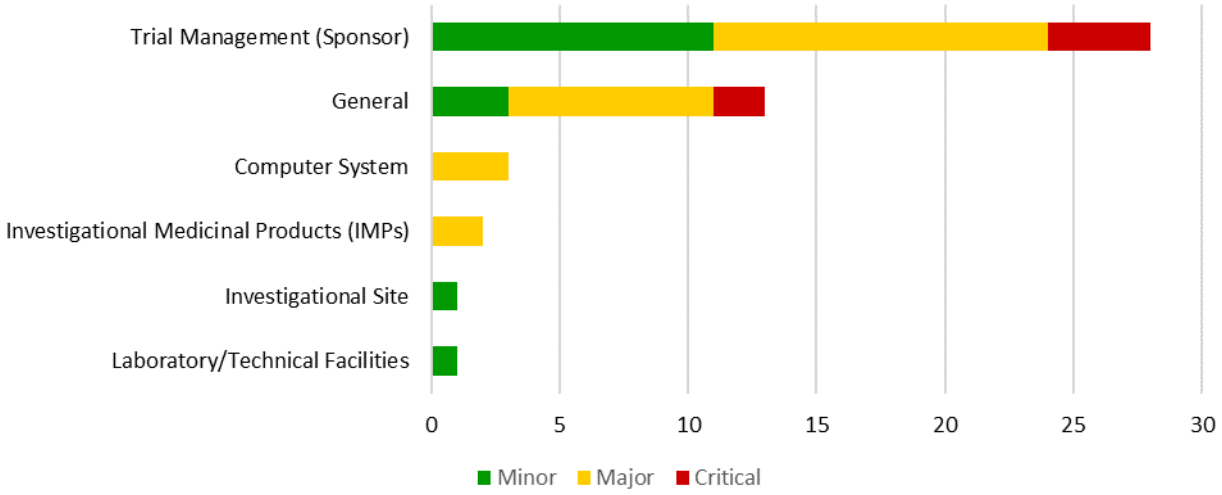

Table 9. Responsibility of findings from each type of site.

Responsibility	Minor findings		Major findings		Critical findings		Total #	Total %
	#	%	#	%	#	%		
CRO	12	8.2%	4	2.0%	1	6.3%	**17**	**4.7%**
Investigator	23	15.6%	17	8.5%	0	-	**40**	**11.0%**
Multiple Responsibility	41	27.9%	64	32.0%	7	43.8%	**112**	**30.9%**
Sponsor	69	46.9%	115	57.5%	8	50.0%	**192**	**52.9%**
Unclassified	2	1.4%	0	-	0	-	**2**	**0.6%**
Grand Total	**147**	**100%**	**200**	**100%**	**16**	**100%**	**363**	**100%**

4. Harmonisation topics

4.1. Procedures and guidance documents

The GCP inspectors worked (or continued working) on the following documents in 2020:

- Guidance on how to manage clinical trials during the COVID-19 pandemic;
- Guideline on electronic systems and electronic data in clinical trials;
- Guideline on registry-based studies;
- Justification paper for the need to update the CHMP guideline on data monitoring committees (DMCs) and revised guideline;
- Q&A on Informed Consent Form and the lack of access to patient's medical records and data by EU/EEA inspectors;
- Q&A 14 on whether the sponsor of a clinical trial has the right to audit the manufacturer of the IMP even if the manufacturer has been subcontracted by a CRO involved in the clinical trial.

Responses to several AskEMA queries within the remit of the IWG/sub-groups were also prepared.

The subgroup on registry-based studies met virtually to discuss topics relevant to the draft guideline during a workshop with industry held on 19 October 2020.

The GCP IWG published the following Q&As:

- Q&A 13, which provides guidance on the requirements for principal investigator review and sign-off of data.
- Q&A 14, which provides guidance on whether the sponsor of a clinical trial has the right to audit the manufacturer of the IMP even if the manufacturer has been subcontracted by a CRO involved in the clinical trial.

4.2. Remote inspections

During the COVID-19 pandemic, on-site inspections have not always been possible due to multiple factors such as difficulties and restrictions related to travelling between and within the borders of countries (including travel warnings / restrictions, border controls, transportation difficulties), restrictions to accessing facilities justified by health hazards and local authorities' recommendations / orders, as well as additional health risks for inspectors and inspectees.

To enable the continuity of GCP inspections requested by the CHMP remote inspections were conducted in lieu of on-site inspections where considered appropriate and feasible.

The GCP inspectors developed a Guidance on remote GCP inspections during the COVID-19 pandemic to outline the requirements and specificities of such inspections identifying the points to be considered during the preparation, conduct, and reporting phase.

In 2020, 7 CHMP requested GCP inspections were conducted remotely, and 3 inspections were conducted in a hybrid setting (part on-site, part remotely).

4.3. Inspection cooperation

- Cooperation between the EU/EEA Member States:

  Nearly all the inspections conducted in 2020 were joint inspections involving inspectors from at least two Member States. Only one inspection was carried out by one Member State only, for an accelerated ATMP procedure, due to resources constraints.

- Cooperation with third countries:

  Observers from countries outside the EU/EEA have always been invited to observe the EU/EEA GCP inspections performed in those countries in the context of the centralised procedure. In 2020, the following third country regulatory authorities observed GCP inspections requested by the CHMP: Bosnia and Herzegovina and Thailand.

4.4. GCP training and development

A bioequivalence (BE) forum took place online on the 17th and 18th November 2020. 63 participants including mainly BE experienced inspectors from EU/EEA, US FDA, WHO and UK MHRA were present. The following topics were covered:

- Statistical issues on bioequivalence inspections –update on the joint project.
- Data anomalies in BE trials.

- Interpretation of BE data trends.
- Widening the use of tools; Interpretation of the data; Consequences; Incorporating the use of data analysis tools in the evaluation process.
- Approach, steps taken and Regulatory actions in case of CRO GCP non-compliance.
- Differences between BE trials in healthy volunteers vs patients (in a hospital setting) and challenges that these kind of BE trials bring.
- Expectations for validation of Computerized Systems.
- Extrapolating (AUC) to infinity.
- Feasibility, Pros and cons of distant assessment/remote inspections of BE trials.

4.5. GCP IWG meetings and topics of interest

- During the plenary GCP IWG meetings, the following topics were discussed:
  - Work Plan (2021-2023) and Annual Reports (2018 and 2019) of the GCP IWG.
  - Ongoing guidelines and Q&A.
  - GCP inspection programme/strategy.
  - Update on ongoing inspections and specific inspection issues.
  - Feedback on remote inspections.
  - Updated inspection templates.
  - Response to queries received from third parties.
  - COVID-19 and impact on GCP/GxP inspections, including remote inspections, GCP compliance of clinical trials during the COVID-19 Pandemic and of COVID-19 clinical trials submitted for Marketing Authorisation Applications/Rolling Review.
  - Regulation (EU) No 536/2014 implementation and CTIS[14].
  - Updates on renovation of ICH E8 and E6, and new ICH E19 and M11.
  - Reflections on inspection processes.
  - Training and joint meetings.
  - International collaboration.
- During the extraordinary GCP IWG meeting held on 20 May 2019 on the qualification requirements for electronic systems and clinical databases acquired by sponsors from 3rd parties, inspectors' discussions focused on GCP findings related to electronic systems and clinical database qualifications.
- During the extraordinary GCP IWG meetings, the following topics were discussed:
  - GCP surveillance of COVID-19 clinical trials submitted to EMA for rolling review.
  - Version 3 of the Guidance on how to manage clinical trials during the COVID-19 pandemic.
  - Updates on renovation of ICH E8 and E6, and new ICH E19 and M11.

[14] Clinical Trials Information System

- During the GCP IWG reflections on GCP inspections procedures – IIR Peer Review subgroup meetings, the peer review of a sample of IIRs was initiated.

5. Collaboration with European Commission

The European Commission attended all plenary 2020 GCP IWG meetings.

5.1. Clinical trial legislation and related guidance documents

- The European Commission, the EMA and the Heads of Medicines Agencies collaborated on the development of the Guidance to sponsors on how to manage clinical trials during the COVID-19 pandemic, which was first published on 20 March 2020. This guideline was further revised twice in 2020 (version 2 dated 27 March 2020 then version 3 dated 27 April 2020). The guidance was agreed by the CTEG of the European Commission, supported by EMA, the CTFG of HMA and the GCP Inspectors' Working Group.
- The GCP IWG remote Source Data Verification (rSDV) subgroup liaised with the European Commission to initiate discussions on rSDV aspects and their compliance with GDPR. A meeting between the subgroup and the European Commission was held on 15 December 2020.

5.2. EU portal and database

During the September and December 2020 GCP IWG meetings, the inspectors were updated on the status of the development of the new EU portal and database, CTIS, including audits and go live. A GCP IWG subgroup had been previously involved in the preparation of the functional aspects of the EU portal and database, in particular in relation to gathering the business requirements for the inspection module. The inspectors were also involved in the testing of the EU Inspection Module.

5.3. EU enlargement

Bosnia and Herzegovina, Kosovo under UNSC Resolution 1244/99, Albania, Republic of North Macedonia, Montenegro, Serbia and Turkey did not attend, as observers, any of the GCP IWG meetings held in 2020.

6. Liaison with other EU groups

6.1. GMP/GDP IWG

The GCP IWG maintains a dialogue with the GMP/GDP Inspectors Working Group on areas of common interest. In 2020, topics included GxP remote inspections during the COVID-19 pandemic and the performance of audits of GMP vendors by sponsors.

6.2. PhV IWG

The GCP IWG maintains a dialogue with the Pharmacovigilance Inspectors Working Group on areas of common interest and in particular concerning pharmacovigilance issues observed in relation to GCP inspections. In 2020, topics included GxP remote inspections during the COVID-19 pandemic.

6.3. Heads of Medicines Agencies/ CTFG[15]

The GCP IWG maintains a collaboration with the CTFG on areas of mutual concern in the supervision of clinical trials conducted in the EU/EEA. In 2020, the collaboration focused on the Guidance to sponsors on how to manage clinical trials during the COVID-19 pandemic. Additional topics included complex and innovative clinical trials.

6.4. CHMP

The GCP IWG maintains a dialogue with the CHMP on areas of common interest and in particular on matters related to GCP and GCP inspections. In 2020, topics included the impact of COVID-19 on GCP inspections and the GCP compliance of clinical trials of the COVID-19 pandemic vaccine rolling reviews.

6.5. CMDh

The GCP IWG and the CMDh, mainly through the GCP/CMDh working party which met 6 times in 2020, have contributed to the following topics:

- preparation of the 2020 risk-based programme of routine GCP inspections of the CROs most often used in the conduct of bioequivalence trials included in a marketing authorisation application in the mutual recognition and decentralised procedures;
- CRO inspection coordination;
- selection of trial(s)/applications for inspection;
- development of guidance on the management of critical findings identified during bioequivalence (BE) inspections;
- discussion on new tools and methodology to be used by BE inspectors and assessors in support of the BE inspections;
- exchange of information on BE trials/CRO inspections planned and conducted within the EU/EEA and non-EU BE network;
- communication of CRO inspection outcome and inspection findings and recommendation for the CMDh;
- improving the exchange of information between inspectors and assessors;
- improving the exchange of information with non-EU regulatory authorities (i.e. FDA and WHO);
- discussion on monitoring of BE trials;
- discussion on statistical issues on BE inspections;
- CRO oversight during the COVID-19 pandemic;
- Development of the ICH M10 guideline on bioanalytical method validation.

6.6. Joint meetings with interested parties

- A Joint meeting with interested parties (EU/EEA and FDA regulators, industry, academia, patient organisations) on the use of Artificial Intelligence (AI) in the clinical trial area was held on 22 September 2020. Presentations included examples of key areas were AI can be applied in drug discovery and development and more specifically clinical trials, challenges when using AI, the

[15] Clinical Trials Facilitation and Coordination Group

concept of 'Augmented Intelligence - Human In The Loop Learning', and use cases. As presented by the speakers, AI can be used in critical steps of clinical research which have direct impact on clinical trial results and ultimately on regulatory decision-making. Additional presentations included risk assessment during the decision-making process, risk-based approaches, regulatory strategies and validation challenges for AI and Big Data.

- The draft guideline on registry-based studies developed by the concerned GCP IWG subgroup was published for consultation on 24 September 2020 (consultation open until 31 December 2020). A half-day virtual workshop was held on 19 October 2020 to give an overview of the draft guideline, discuss questions from stakeholders, perspectives on the usefulness of the document and recent experience on methodological aspects of registry-based studies, such as the use of a large registry for clinical trials.
- Joint meetings on complex and innovative clinical trials were organised by the European Commission together with EMA, CTFG and EFPIA[16].

6.7. Paediatric Committee (PDCO)

Communication on inspection issues with the PDCO continued in 2020 with the exchange of information on inspections of clinical trials with a paediatric population.

7. Liaison with international partners

7.1. Regulatory agencies from outside the EEA

- The EMA and the FDA have had a collaboration initiative in place since 2009 in the area of GCP[17]. This collaboration was extended in 2013 to bioequivalence, together with some of the EU/EEA Member States[18].
  - During 2020 there were 5 regular teleconferences of the EMA-FDA GCP collaboration and 4 teleconferences as part of the EMA-FDA-MS BE collaboration.
  - The FDA was systematically informed of EMA inspections performed in the USA. There was no formal observation of EMA inspections by the FDA or of FDA inspections by EU/EEA MSs in 2020. Only one closing meeting of an FDA inspection concerning a product of common interest was followed by an EU MS in 2020.
  - Several FDA representatives also attended the BE Forum.
- PMDA[19] (Japan):
  - PMDA joined the FDA-EMA initiative as observers in June 2017 for 18-month pilot phase. Based on the outcomes of this pilot initiative, EMA and FDA agreed to add PMDA as an official member of the GCP initiative and to continue this activity.
  - Regular exchanges of information have occurred during EMA and PMDA meetings.
  - PMDA participated in all regular teleconferences with EMA and FDA as part of the GCP collaboration.
- WHO:

[16] European Federation of Pharmaceutical Industries and Associations
[17] Announcement of the EMA-FDA GCP Initiative
[18] Announcement of the generic medicines application inspections initiative
[19] Pharmaceuticals and Medical Devices Agency

- EMA, WHO and the EU/EEA MSs that perform the highest number of BE inspections had several teleconferences to understand each other's inspections and regulatory procedures and responsibilities with a view to having a collaboration with regular exchange of inspection information.
- Since 2018, WHO has been an observer of the GCP IWG under the EMA, European Commission and WHO confidentiality arrangement.
- WHO participated in all regular teleconferences with EMA and FDA as part of the BE collaboration.

- Swissmedic:
  - The Swiss Agency for Therapeutic Products (Swissmedic) is an observer of the IWG GCP under the European Commission, EMA, Swiss Federal Department of Home Affairs and Swissmedic confidentiality arrangement, in place since 2015.
- Other regulatory agencies:
  - Collaboration is ongoing with the United Kingdom (now a third country following Brexit), Health Canada and any other regulatory agencies of interest.

7.2. International initiatives

- General information was exchanged with the regulatory authorities in Thailand, Singapore and Ghana on GCP inspections, training and international collaboration.
- COVID-19-specific information was exchanged with the regulatory authorities in the UK, Brazil, Argentina and South Africa.
- The EMA and EU/EEA inspectors, along with several non-EU regulatory authorities, were invited to a mini-symposium organised by the FDA on Myths and Perspectives About FDA Inspections and GCP Process, held on 05 November 2020.
- Capacity building in non-EU countries:
  - Some EU inspectors provided training in countries outside the EU/EEA e.g. South Korea (DE-PEI[20] provided training in collaboration with MFDS (APEC)[21]).
  - The Danish inspectors had a visit from two inspectors from the National Pharmaceutical Regulatory Agency (NPRA) in Malaysia. The two inspectors participated in an inspection at a Danish sponsor site, mainly focusing on the inspection of IT systems.

For details of the activities of the GCP IWG for next year see the Work Plan for 2021-2023.

[20] Paul-Ehrlich-Institut (PEI), Federal Institute for Vaccines and Biomedicines, Agency of the German Federal Ministry of Health
[21] Ministry of Food and Drug Safety of the Republic of Korea