5 February 2021
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Inspections Office
Quality and Safety of Medicines Department

Annual Report of the Good Clinical Practice Inspectors' Working Group 2019

Adopted by the GCP IWG on 5 February 2021

The activities outlined in the annual report for 2019 have been carried out in line with the Agency's business continuity plan and prioritisation of activities for the preparation of the Agency's relocation and are therefore substantially reduced compared to the activities carried out by the GCP Inspectors Working Group in previous years.

The delay of the publication of this report is also due to the Agency's business continuity plan and prioritisation of activities for the preparation of the Agency's relocation in 2019 and 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
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1. Introduction

This document is the twelfth annual report of the GCP IWG[1]. This group was established in 1997 under the scope of Article 51(e) of Regulation (EC) No. 2303/93, subsequently amended as Article 57(1)(i) of Regulation (EC) No. 726/2004.

The GCP IWG focuses on the harmonisation and coordination of GCP related activities at EU[2] level. The group's role and activities are described in more detail in its mandate, which was revised in 2013, its work plans 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[3], CVMP[4], CMDh[5], PhV IWG[6], GMP/GDP IWG[7] and other groups, as needed, in areas of common interest.

2. Meetings

Two GCP IWG meetings took place:

- 20 May 2019 extraordinary meeting on the qualification requirements for electronic systems and clinical databases acquired by sponsors from 3rd parties (virtual meeting).
- 22-23 October 2019 plenary meeting.

During 2019, the following GCP inspectors' subgroups/working parties were involved in the discussion of specific topics and drafting documents:

- GCP IWG/CMDh working party (refer to section 6.5), 5 teleconferences.
- GCP IWG electronic systems[8] subgroup (refer to section 4.1), 3 meetings and 1 workshop with industry.

3. Inspections conducted in support of the centralised procedure

3.1. CHMP requested inspections

3.1.1. General overview

In total, 120 GCP inspections were requested by CHMP and carried out by the inspectorates of the EU Member States in 2019. However, it should be noted that several inspections requested in the last 3 months of 2018 were conducted in 2019 and some inspections requested in the last 3 months of 2019 will be carried out in 2020. The data in this report relate to inspections carried out in 2019.

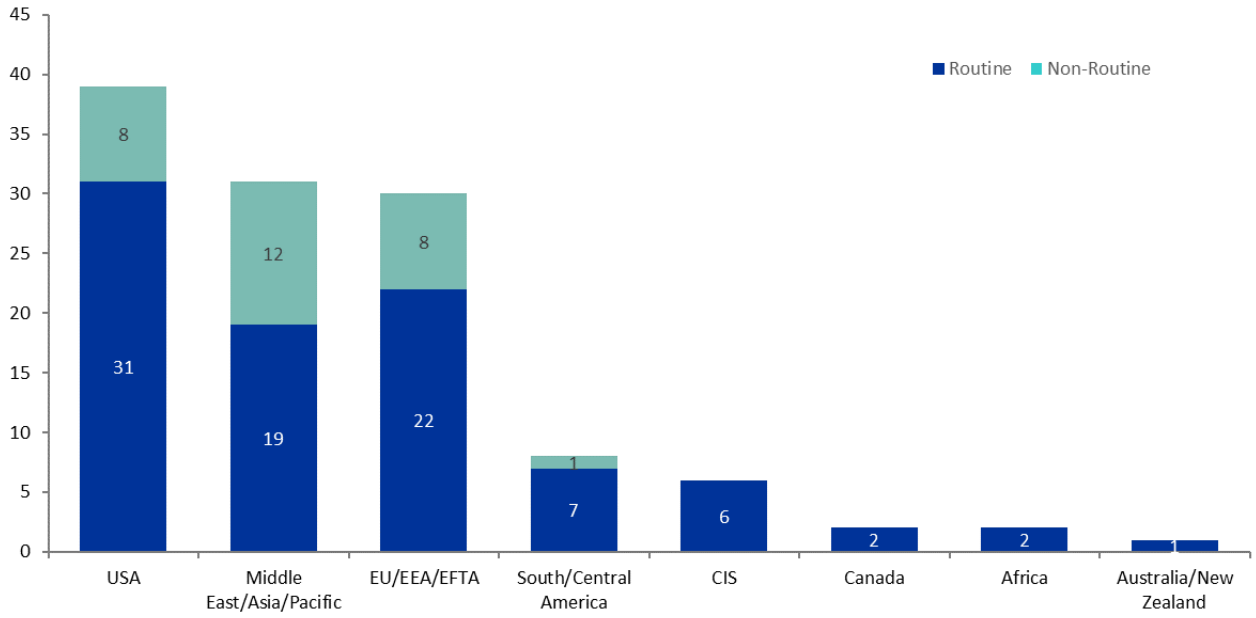
[1] Good Clinical Practice Inspectors Working Group
[2] European Union
[3] Committee for Medicinal Products for Human Use
[4] Committee for Medicinal Products for Veterinary Use
[5] Coordination Group for Mutual Recognition and Decentralised Procedures - Human
[6] Pharmacovigilance Inspectors Working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

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

Region	Non-Routine	Routine	Total
USA	8	31	39
Middle East/Asia/Pacific	12	19	31
EU/EEA/EFTA	8	22	30
South/Central America	1	8	9
CIS[9]	0	6	6
Canada	0	2	2
Africa	0	2	2
Australia/New Zealand	0	1	1
Total in all regions	**29**	**91**	**120**

In figure 1, the number of inspections carried out in 2019 is shown by region and type of inspection. Most inspections were carried out in the United States (32,5%) followed by the Middle East/Asia/Pacific (25,8%) and the EU/EEA[10]/EFTA[11] (25%).

Figure 1: Inspections conducted per region and type of inspection



[9] Commonwealth of Independent States
[10] European Economic Area
[11] European Free Trade Association

Table 2: Inspections conducted per type of site

Site	No. of inspections conducted
Clinical investigator	78
Sponsor	28
CRO	9
Analytical laboratory	2
Analytical laboratory BE/BA	2
Analytical and Clinical laboratory BE/BA	1
Total in all sites	**120**

Figure 2: Inspections conducted per type of site

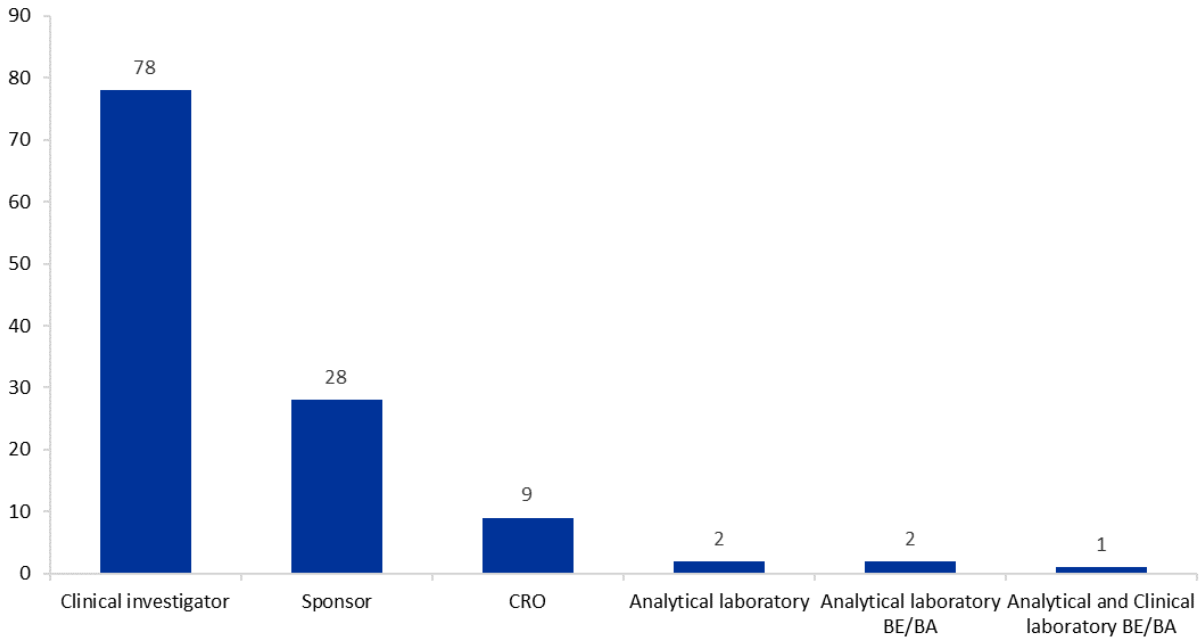


Figure 2 represents the number of inspections conducted in 2019 per type of site. Most of the inspections were conducted at clinical investigator sites, followed by sponsor sites, CRO, analytical laboratory, analytical laboratory of BE/BA and analytical and clinical laboratory of BE/BA studies.

3.1.2. Categorisation of findings

A total of 1491 deficiencies, comprising 151 critical (10%), 807 major (54%) and 533 minor (36%) findings were recorded for the 120 CHMP requested inspections conducted in 2019.

The main findings observed in the 2019 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

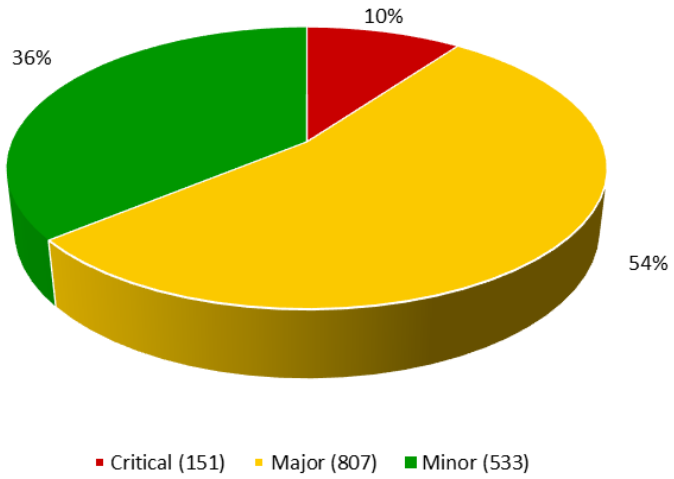


Table 3: Number of findings by grading categories critical, major and minor

Main category	Critical	Major	Minor	Total
General	39	282	255	576
Trial Management (Sponsor)	56	262	122	440
Investigational site	9	86	48	143
Investigational Medicinal Products (IMPs)	5	67	48	120
Computer System	16	48	15	79
Informed Consent (IC)	13	21	12	46
Laboratory/Technical Facilities	4	19	21	44
Subject Protection	6	15	5	26
IEC/IRB	2	5	5	12
Others	1	2	2	5
Total	**151**	**807**	**533**	**1491**

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

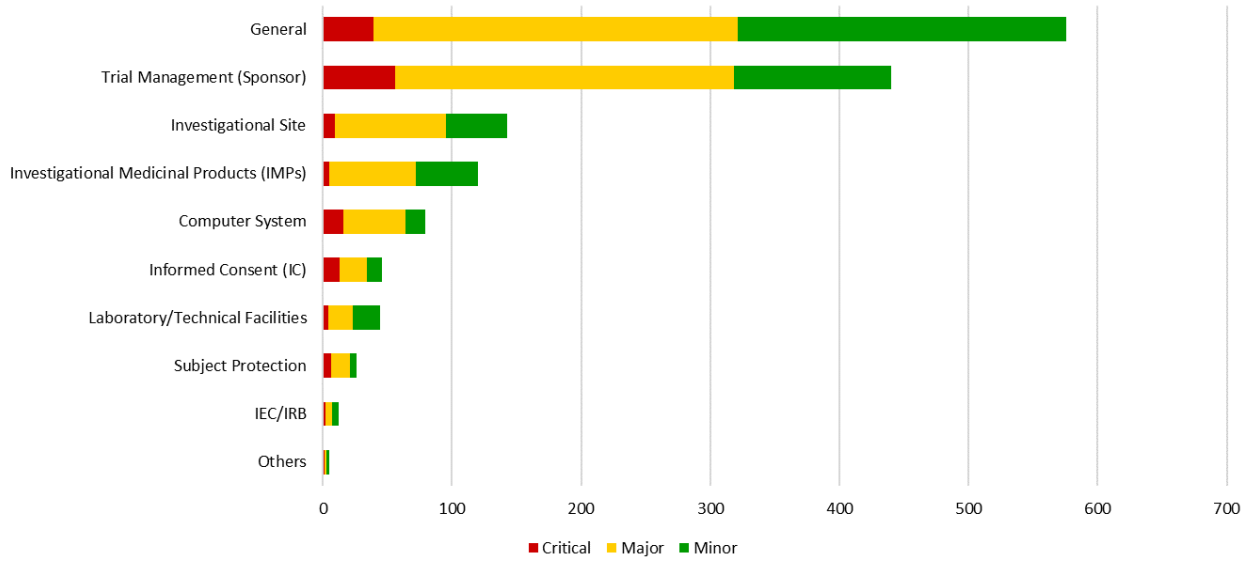


Table 4: Number of findings per sub-category of the top 3 main categories (general, trial management and investigational site) graded as critical, major, and minor.

		# Inspected deficiencies			# Inspected deficiencies total
Deficiency category name	**Deficiency sub-category name**	**Critical**	**Major**	**Minor**	
General	Contracts/agreements	6	30	23	59
	Direct access to data	2	4	2	8
	Essential documents	11	74	62	147
	Facilities and equipment	2	26	30	58
	Organisation and personnel	3	24	35	62
	Qualification/training	0	39	43	82
	Randomisation/Blinding/Codes IMP[12]	2	6	2	10
	Standard Operating Procedures	4	29	10	43
	Source documentation	9	50	48	107
General total		**39**	**282**	**255**	**576**
Trial management (sponsor)	Audit	4	14	8	26
	Clinical Study Report	4	21	9	34
	Data management	23	70	40	133
	Document control	10	59	37	106
	Monitoring	10	58	18	86
	Protocol/Case Report Form/diary/questionnaires design	3	25	4	32
	Statistical analysis	2	15	6	23
Trial Man. (Sponsor) total		**56**	**262**	**122**	**440**
Investigational site	Protocol Compliance (Assessment of Efficacy)	1	7	2	10
	Protocol Compliance (Others)	3	23	7	33
	Protocol Compliance (Safety Reporting)	1	32	26	59
	Protocol Compliance (Selection Criteria)	3	13	3	19
	Reporting in CRF/Diary	1	11	10	22
Investigational site total		**9**	**86**	**48**	**143**

[12] Investigational Medicinal Product

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

General

Essential documents:

- The TMF was not ready for inspection and relevant documents were either not filed, filed late or located outside the TMF structure.
- Lack of essential documents, e.g. receipt of IMP shipment to site, records of blood samples shipment to the central laboratories.
- Incomplete documentation, e.g. incomplete screening list.
- Lack of contemporaneous independent copy of the CRF[13] filed on site.

Source documentation:

- Discrepancies between source data and data reported in the CSR[14].
- Missing source documents.
- Lack of document specifying location of source data.

Qualification/training:

- Incomplete training documentation.
- Deficiencies regarding assessment of qualification of trial related persons.
- Inappropriate oversight of the vendors.
- lack of training of study personnel on trial related procedures.

SOPs[15]:

- Lack of evidence that sponsor SOPs have been followed and used.
- SOPs not updated as required.
- Sponsor failure to implement an efficient quality management system.

Contracts/agreements:

- Incomplete contracts in place.
- Responsibilities not clearly defined.
- Lack of consistency between contract and protocol.

Organisation and personnel:

- Incomplete site personnel signature log.
- Deficiencies regarding the delegation of trial related duties.
- Tasks performed by staff not authorised to do so.

Trial management (Sponsor)

[13] Case Report Form
[14] Clinical Study Report
[15] Standard Operating Procedures

Monitoring:

- Monitor has not identified number of deficiencies on site.
- Inadequate monitoring activities performed at site.
- Lack of escalation process to resolve issues identified by monitor.
- Monitor not following monitoring plan.

Data management:

- Inappropriate system for reporting protocol violations.
- Laboratory reports were submitted late to the site.
- Data management activities were only undertaken after the clinical conduct of the trial was completed.
- The decisions made by the DSMB[16] were not communicated to the site.

Clinical study report (CSR):

- Inconsistencies between source data and data reported in the CSR.
- Inaccurate information reported in CSR.
- Relevant information missing in the CSR.

Protocol/CRF[17]/diary/questionnaires design:

- Insufficient design of the study protocol, e.g. no instructions related to concomitant medication or unscheduled visits.
- The design of the CRF is not suitable to accurately collect the data specified within the protocol.

Investigational site

Protocol Compliance (Safety Reporting):

- Discrepancies and inconsistencies in the management of safety information.
- Inconsistencies in adverse event evaluation.
- Discrepancies in SUSAR reporting (time and manner).

Protocol Compliance (Others):

- Discrepancies and inconsistencies related to activities, procedures and assessment.
- Instructions related to patient visits and the study itself were not carefully followed.
- Deficiencies regarding the completeness of the investigator site file.

Reporting in CRF/Diary

- Lack of accuracy, completeness and timeliness of data reported in the CRF.
- Discrepancies between source data and data entered in the CRF.
- Relevant information missing in the CRF.

[16] Data Safety Monitoring Board
[17] Case Report Form

Protocol Compliance (Selection Criteria):

- Deficiencies related to the screening of subjects.
- Implementation of an additional screening procedure and exclusion criteria without following the protocol.

Protocol Compliance (Assessment of Efficacy):

- No adherence to protocol in terms of entering data collection.
- Non-qualified people intervened in the trial.
- Inconsistencies with the questionnaires used.

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

Inspection Site Type	Critical %	#	Major %	#	Minor %	#	#	Total %
Clinical Investigator	3.7%	55	31.5%	470	26.4%	394	**919**	**61.6%**
Sponsor	5.2%	77	16.2%	242	7.1%	106	**425**	**28.5%**
CRO	0.8%	12	4.4%	65	1.3%	20	**97**	**6.5%**
Analytical Laboratory BE/BA	0.2%	3	0.7%	11	0.6%	9	**23**	**1.5%**
Analytical Laboratory	0.1%	2	0.9%	13	0.1%	1	**16**	**1.1%**
Analytical and Clinical Laboratory BE/BA	0.1%	2	0.4%	6	0.2%	3	**11**	**0.7%**
Grand Total	**10.1%**	**151**	**54.1%**	**807**	**35.7%**	**533**	**1491**	**100.0%**

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

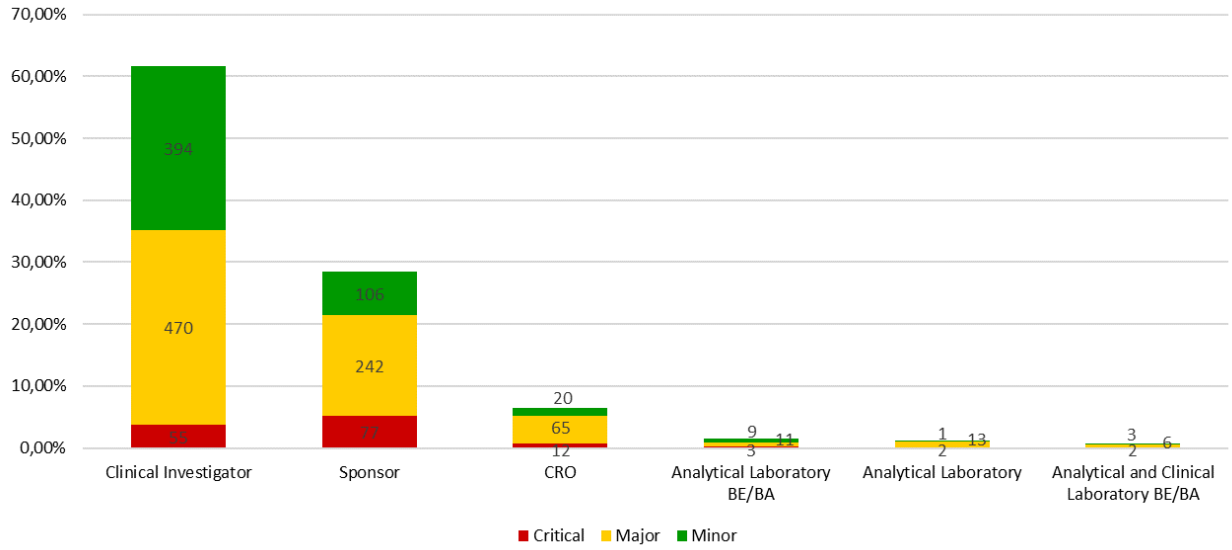


Table 6. Number and categorisation of findings at clinical investigator sites

Main category	Critical	Major	Minor	Total
General	11	177	216	**404**
Trial Management (Sponsor)	17	108	54	**179**
Investigational site	8	73	42	**123**
Investigational Medicinal Products (IMPs)	4	48	40	**92**
Informed Consent (IC)	10	20	11	**41**
Computer System	3	22	7	**32**
Laboratory/Technical Facilities	1	4	15	**20**
Subject Protection	0	12	5	**17**
IEC/IRB	1	4	4	**9**
Others	0	2	0	**2**
Total	**55**	**470**	**394**	**919**

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

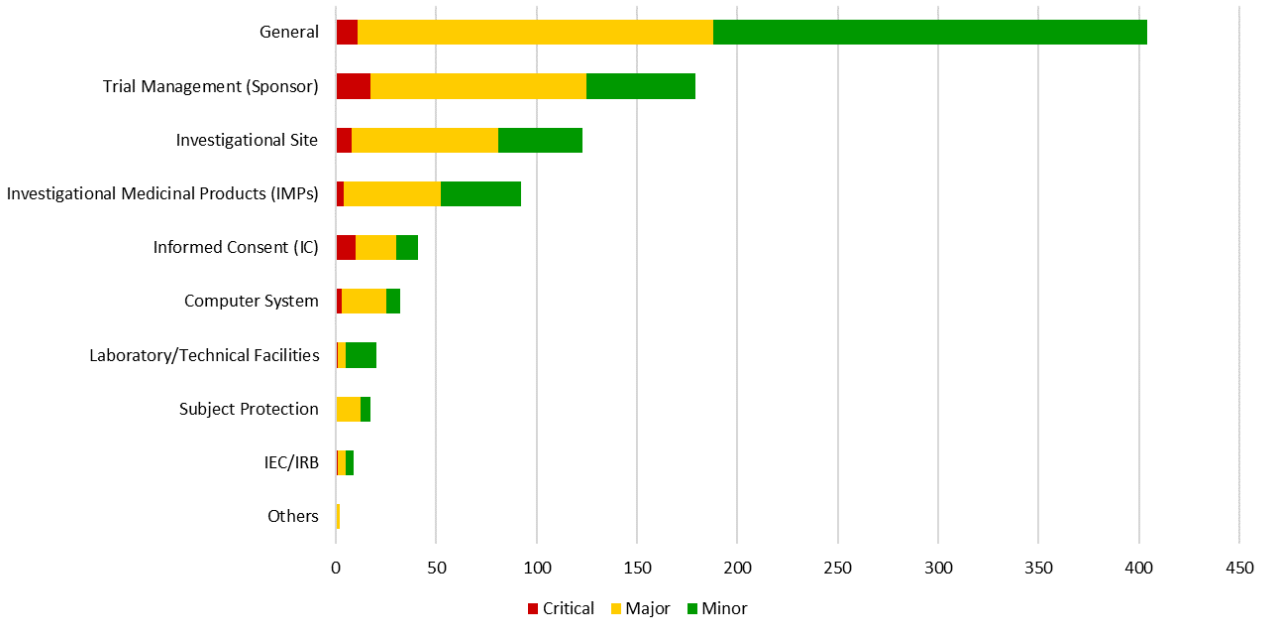


Table 7. Number and categorisation of findings at sponsor sites

Main category	Critical	Major	Minor	Total
Trial Management (Sponsor)	36	125	61	**222**
General	21	64	26	**111**
Computer System	12	20	7	**39**
Investigational Medicinal Products (IMPs)	0	17	4	**21**
Investigational site	1	11	6	**18**
Subject Protection	4	3	0	**7**
Informed Consent (IC)	1	1	1	**3**
IEC/IRB	1	0	1	**2**
Others	1	0	0	**1**
Laboratory/Technical Facilities	0	1	0	**1**
Total	**77**	**242**	**106**	**425**

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

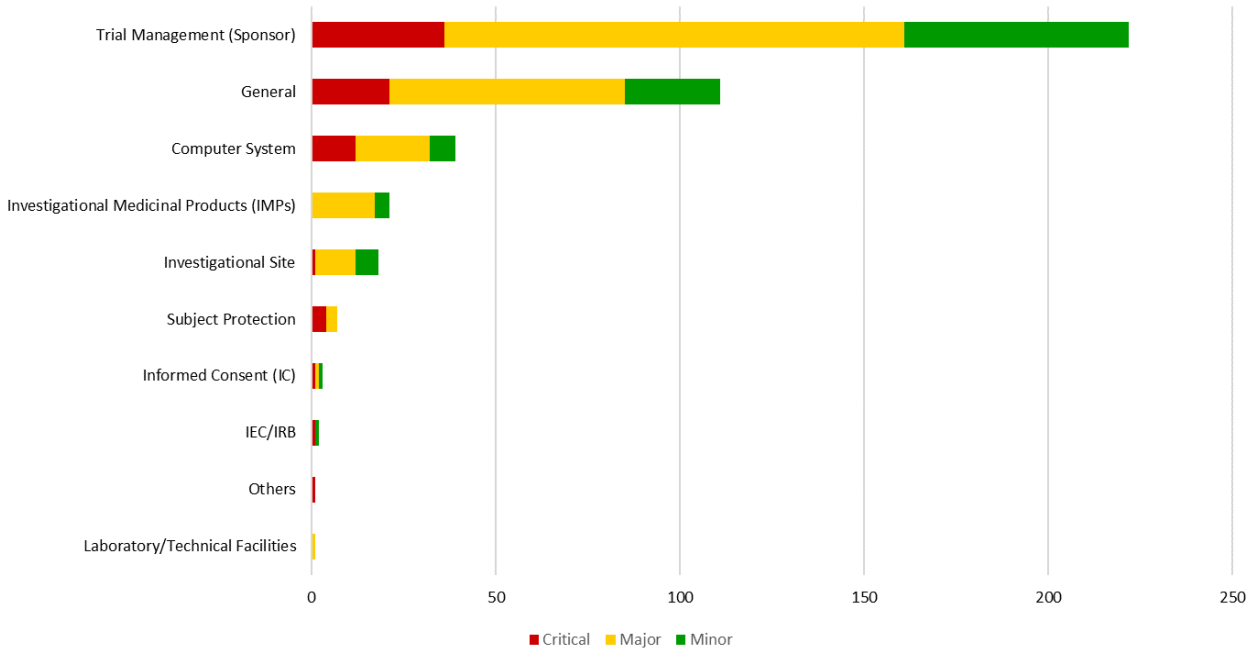
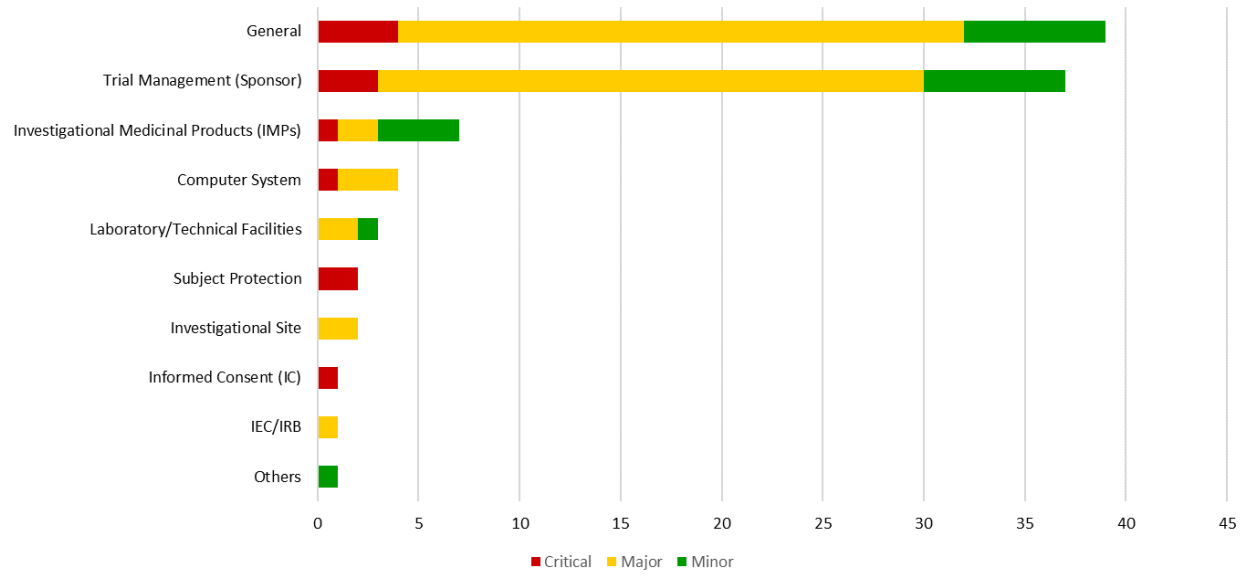


Table 8. Number and categorisation of findings at CRO sites

Main category	Critical	Major	Minor	Total
General	4	28	7	**39**
Trial Management (Sponsor)	3	27	7	**37**
Investigational Medicinal Products (IMPs)	1	2	4	**7**
Computer System	1	3	0	**4**
Laboratory/Technical Facilities	0	2	1	**3**
Subject Protection	2	0	0	**2**
Investigational site	0	2	0	**2**
Informed Consent (IC)	1	0	0	**1**
IEC/IRB	0	1	0	**1**
Others	0	0	1	**1**
Total	**12**	**65**	**20**	**97**

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



4. Harmonisation topics

4.1. Procedures and guidance documents

- The GCP inspectors continued working on the following document:
  - Guideline on electronic systems and electronic data in clinical trials.

  In 2019, the subgroup working on this guideline held 3 face-to-face meetings. In addition, the subgroup met to discuss topics relevant to the draft guideline during a workshop with industry held on 25 June 2019 in Bonn.

4.2. Inspection cooperation

- Cooperation between the EU/EEA Member States:

  In 2019, most of the inspections requested by the CHMP were joint inspections involving inspectors from at least two Member States. However, 10 inspections were carried out by one Member State only, due to inspection resource constraints.

- Cooperation with third countries:

  Observers from countries outside the EU have always been invited to observe the EU GCP inspections performed in their countries in the context of the centralised procedure. In 2019, the following third country regulatory authorities observed GCP inspections requested by the CHMP: Belarus, Canada, Japan, Switzerland, Peru, Taiwan, Thailand and the US.

4.3. GCP training and development

4.3.1. 2019 EU GCP bioequivalence inspections forum

A bioequivalence forum took place in Vienna (Austria) on the 2nd of October 2019. 19 participants including mainly BE senior inspectors from EU/EEA, US FDA, WHO and Health Canada (remotely) were present. The following topics were covered:

- Statistical issues on bioequivalence inspections –update on the joint project.
- Assessment versus inspection of statistical part of BE studies; Expectations and experiences.
- Statistical issues on bioequivalence inspections and inspection strategies.
- Critical aspects regarding statistical analysis of bioequivalence studies.
- Inspection of ligand binding assays: Inspection strategies and observed deviations.
- Ligand binding assays: Critical parameters and things that can go wrong from a laboratory perspective.

4.4. GCP IWG meetings and topics of interest

- 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.

As an outcome of this meeting, the GCP IWG published a notice for clinical trial sponsors to highlight the requirements for the qualification and validation of computerised systems used for managing clinical trial data. This is based on inspection findings and taking into account implications on the integrity, reliability, robustness and acceptability of data in marketing authorisation applications.

In line with this notice, the GCP IWG also updated questions 8 and 9, which provide further related guidance on computerised systems.

- During the plenary GCP IWG meeting held on 22-23 October 2019, the following topics were discussed:
  - GCP IWG annual report 2018.
  - GCP IWG workplan 2020.
  - Status of the CTIS programme (EU Portal and Database).
  - Modernisation of ICH E8 and the sub-consequent renovation of ICH-E6 and the new ICH E19.
  - Draft Guideline on electronic systems and electronic data in clinical trials.
  - Selection of EMA inspections, inspection teams and inspection timelines.
  - Revision of templates: Announcement letter to Applicant and GCP Information provided by applicant.
  - GCP interpretation issues e.g. country requirements for e-signature.
  - AskEMA queries: Queries were discussed and a harmonised response for each was adopted by the group.
  - Q&A on inspectors' access to patients' medical records/data when the access of EEA inspectors to medical information is not clearly stated in the ICF.
  - Preparation for the 2020 GCP IWG workshop.
  - Discussion and development of the peer review of product/company inspection related issues. (bioequivalence and non-bioequivalence studies).
  - Discussions on EU-FDA-WHO inspection collaboration.

5. Collaboration with European Commission

5.1. Clinical trial legislation and related guidance documents

- A subgroup of GCP inspectors contributed to the finalisation of the detailed guidelines on good clinical practice for advanced therapy medicinal products, following the public consultation of the document (see section 5.4).

5.2. EU portal and database

During the October GCP IWG meeting the inspectors were updated on the status of the development of the new EU portal and database. A GCP IWG subgroup has been 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, The Former Yugoslav Republic of Macedonia, Montenegro and Serbia did not attend the GCP IWG meetings held in 2019 as observers.

5.4. Regulation on advanced therapies

A subgroup of GCP inspectors and members of the Committee for Advanced Therapies collaborated in the progress of development and finalisation of the detailed guidelines on good clinical practice for advanced therapy medicinal products, following the public consultation of the document. The document was published in October 2019. https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/atmp_guidelines_en.pdf

6. Liaison with other EU groups

6.1. GMP/GDP IWG

The GCP IWG maintains a dialogue with the GMP/GDP Inspectors Working Group in areas of common interest.

6.2. PhV IWG

The GCP IWG maintains a dialogue with the Pharmacovigilance Inspectors Working Group in areas of common interest and in particular concerning pharmacovigilance issues observed in relation to GCP inspections.

6.3. CTFG

Collaboration in areas of mutual concern in the area of supervision of clinical trials conducted in the European Union.

6.4. CHMP

The GCP IWG maintains a dialogue with the CHMP in areas of common interest and in particular on matters related to good clinical practice and GCP inspections.

6.5. CMDh

The GCP IWG and the CMDh, mainly through the GCP/CMDh working party, have contributed to:

- The preparation of the 2019 and 2020 risk-based programme of routine GCP inspections of the CROs most often used in the conduct of bioequivalence trials included in marketing authorisation applications in 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 inspections.
- Discussions 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 and non-EU BE network.
- Communication of CRO inspection outcomes and inspection findings and recommendations for the CMDh.
- Improving the exchange of information between inspectors and assessors.
- Improving the exchange of information with non-EU regulatory authorities (e.g. FDA and WHO)
- Discussions on the monitoring of BE trials.

6.6. Heads of Medicines Agencies

See section 6.3.

6.7. Joint meetings with interested parties

See section 4.1

6.8. Paediatric Committee (PDCO)

Communication on inspection issues with the PDCO continued in 2019 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

- EMA and US FDA have had a collaboration initiative in place since 2009 in the area of GCP[18]. This collaboration was extended to bioequivalence, together with some of the EU Member States[19].
  - During 2019, there were 5 regular teleconferences of the EMA-FDA GCP collaboration, 4 teleconferences as part of the EMA-FDA-MS BE collaboration and 9 product/company-specific teleconferences.
  - As part of the EMA-FDA GCP initiative 11 inspections were observed (FDA observed 9 EMA inspections and EMA observed 2 FDA inspections) and 4 were performed jointly.
  - A total of 9 teleconferences were held with US FDA to discuss two projects on the comparison of EMA/FDA GCP inspection conduct.
  - Several US FDA representatives also attended the BE Forum.
  - During 2019, 136 documents were exchanged, including 63 inspection reports.
- PMDA[20] (Japan):
  - PMDA joined the FDA-EMA initiative as observers in June 2017 for an 18-month pilot phase.

[18] Announcement of the EMA-FDA GCP Initiative
[19] Terms of Engagement
[20] Pharmaceuticals and Medical Devices Agency (PMDA)

- Regular exchanges of information occurred during EMA and PMDA meetings.
- PMDA participated in all regular teleconferences with FDA.

- WHO:
  - EMA, WHO and the EU MSs that perform the highest number of BE inspections held several teleconferences to understand each other's inspections, 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, EC DG Santé and WHO confidentiality arrangement, all documentation and discussions are open to WHO representatives.
- Other regulatory agencies:
  - Provided support in the preparation of the framework for sponsor inspections in Singapore.

7.2. International initiatives

- PIC/S[21] GCP/PhV working group was formed in July 2014 and reports to the PIC/S Sub-Committee on Expert Circles. The primary purpose of the group is to facilitate technical cooperation and harmonisation of practices (including the development of guidance and training material), capacity building and information sharing in the area of GCP and GVP[22] inspections. The group's membership includes representatives from Argentina, Australia, Belgium, Canada, Chinese Taipei, Croatia, Denmark, France, Hungary, Israel, Italy, Slovenia, Spain, Switzerland, the UK and the US.

  The group also coordinates the PIC/S GCP and GVP joint visit programme, where three visits are carried out by groups of three inspectors from different PIC/S participating authorities over a period of 24 months. The purpose of the visits is to:
  - provide further training for inspectors through the exchange of experience between them;
  - provide the means of harmonising inspection procedures and developing inspection guidance;
  - ensure and maintain mutual confidence between inspectors of PIC/S participating authorities.

In 2019, EU GCP inspectors participated in four GCP inspections under the PIC/S GCP joint visit programme (two in Germany and two in the Czech Republic).

- Capacity building in non-EU countries
  - In 2019, some EU inspectors provided training in countries outside the EU/EEA e.g. Tunisia (inspections of BE trials training provided by ANSM[23]), South Korea (DE-PEI[24] provided training in collaboration with MFDS (APEC)[25])

[21] Pharmaceutical Inspection Cooperation Scheme
[22] Good Pharmacovigilance Practice
[23] Agence nationale de sécurité du médicament et des produits de santé (French National Agency for Medicines and Health Products Safety

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