EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 September 2022
EMA/INS/GCP/33934/2022
Quality and Safety of Medicines Department
Inspections Office

Annual Report of the Good Clinical Practice (GCP) Inspectors Working Group (IWG) 2021

Adopted by the GCP IWG on 15 July 2022

The activities outlined in the Annual Report for 2021 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 IWG in previous years.

List of Abbreviations

ANSM	*Agence nationale de sécurité du médicament et des produits de santé* (French competent authority)
BA	BioAvailability
BE	BioEquivalence
CHMP	Committee for Medicinal Products for Human Use
CMDh	Coordination Group for Mutual Recognition and Decentralised Procedures - Human
CRF	Case Report Form
CRO	Clinical/Contract Research Organisation
CSR	Clinical Study Report
CTFG	Clinical Trials Facilitation and Coordination Group
CTIS	Clinical Trials Information System
CVMP	Committee for Medicinal Products for Veterinary Use
DG SANTE	Directorate-General for Health and Food Safety
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Form
EEA	European Economic Area
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GDP	Good Distribution Practice
GMP	Good Manufacturing Practice
HMA	Heads of Medicines Agencies
IB	Investigator's Brochure
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMRA	International Coalition of Medicines Regulatory Authorities
IEC	Independent Ethics Committee
IIR	Integrated Inspection Report
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IWG	Inspectors Working Group
MAA	Marketing Authorisation Application
MS	Member State
PDCO	Paediatric Committee
PhV	Pharmacovigilance
PI	Principal Investigator
PMDA	Pharmaceuticals and Medical Devices Agency (Japanese competent authority)
Q&A	Question & Answer
ROW	Rest of the World
SDV	Source Data Verification
SOP	Standard Operating Procedure
UK	United Kingdom
UNSC	United Nations Security Council
US(A)	United States (of America)
WHO	World Health Organisation

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1. Introduction

This document is the fourteenth Annual Report of the GCP IWG. This group was established in 1997 under the scope of Article 51(e) of Council Regulation (EEC) 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 European Union (EU)/European Economic Area (EEA) 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 Committee for Medicinal Products for Human Use (CHMP), Committee for Medicinal Products for Veterinary Use (CVMP), Coordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh), Pharmacovigilance (PhV) IWG, Good Manufacturing Practice/Good Distribution Practice (GMP/GDP) IWG 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 2021-2023 Work Plan.

2. Meetings

Eight GCP IWG meetings took place in 2021 (4 regular meetings and 4 extraordinary ones):

- 04 February 2021 (extraordinary);
- 16 February 2021 (extraordinary);
- 02-03 March 2021;
- 26 April 2021 (extraordinary);
- 08 June 2021;
- 21 June 2021 (extraordinary);
- 28-29 September 2021;
- 30 November–01 December 2021.

During 2021, the following GCP inspectors' subgroups/working parties were involved in the discussion of specific topics and drafting documents:

Subgroup/ Working party	Number of participating GCP inspectorates
GCP IWG/CMDh working party (refer to section 6.5)	11
GCP IWG subgroup on decentralised and complex clinical trials	10
GCP IWG subgroup on Data Monitoring Committee (DMC) guideline update	2
GCP IWG subgroup on Integrated Inspection Report (IIR) Peer Review process	8

Subgroup/ Working party	Number of participating GCP inspectorates
GCP IWG subgroup on embedding the outcome of GCP inspections into the benefit-risk assessment and modernisation of the inspection process	6
GCP IWG subgroup on registry-based studies	3
GCP IWG subgroup on remote Source Data Verification (SDV)	7
GCP IWG subgroup on raw data	6
GCP IWG subgroup on remote inspections	5
GCP IWG subgroup on the development of the guideline on reporting serious breaches for clinical trials following the Clinical Trial Regulation	5

3. Inspections conducted in support of the centralised procedure

3.1. CHMP requested inspections

3.1.1. General overview

a) Foreword

The data in this report relates to inspections carried out in 2021. The selection of routine inspections was discontinued in 2020 due to the challenges associated with the COVID-19 pandemic; a pilot phase of re-starting to request routine GCP inspections was agreed at the September 2021 GCP IWG meeting and at the October 2021 PROM[1] meeting. The routine inspections adopted in 2021 were conducted in 2022.

For this reason, only triggered inspections were carried out in 2021 and are presented in this report. The fact that no routine inspections were conducted explains the low number of inspections in 2021.

In total, 27 triggered GCP inspections were requested by CHMP and carried out by the inspectorates of the EU/EEA Member States (MSs) in 2021. It should be noted that several triggered inspections requested in 2020 were conducted in 2021 – these are therefore included in this report – and, as also noted above, several inspections requested in 2021 were carried out in 2022 – these are therefore not included in this report. In addition, one inspection adopted in October 2019, which could not be conducted due to travel restrictions, and where a remote conduct was deemed not feasible, was postponed to 2021 and is therefore included in this report.

Due to the COVID-19 pandemic and associated restrictions, similarly to the year 2020, a number of inspections were conducted remotely or in a hybrid setting. Please refer to section 4.2 for more information.

b) Geographical distribution

The report is distinguishing the following regions:

[1] The CHMP PROM is a meeting to discuss CHMP organisational matters and other topics in preparation for the CHMP Plenary meeting.

- EU/EEA.
- North America:
  - United States of America (USA);
  - Canada.
- Rest of the World (ROW):
  - Africa;
  - Asia;
  - Eastern Europe, non-EU (Belarus, Bosnia, the Republic of North Macedonia, Moldova, Russia, Serbia, Ukraine);
  - Western Europe, non-EU (Switzerland, United Kingdom [UK]);
  - Latin America and the Caribbean;
  - Oceania.

Sub-regions in the ROW region were revised compared to the last report to take into account the modified political situation of some of the countries and to harmonise the country distribution with other published reports.

c) Inspection figures

In Figure 1 and Table 1, the number of inspections carried out in 2021 is shown by region and type of inspection. Most inspections were carried out in the EU/EEA region (33,3%) followed by Asia (25,9%) and Eastern Europe, non-EU (18,5%).

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

Region	Non-Routine	Routine*	Total
EU/EEA	9	0	9
North America	2	0	2
Africa	0	0	0
Asia	7	0	7
Eastern Europe, non-EU	5	0	5
Western Europe, non-EU	1	0	1
Latin America and the Caribbean	3	0	3
Oceania	0	0	0
Total in all regions	**27**	**0**	**27**

*As previously outlined, due to pandemic, all inspections were non-routine/triggered.

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

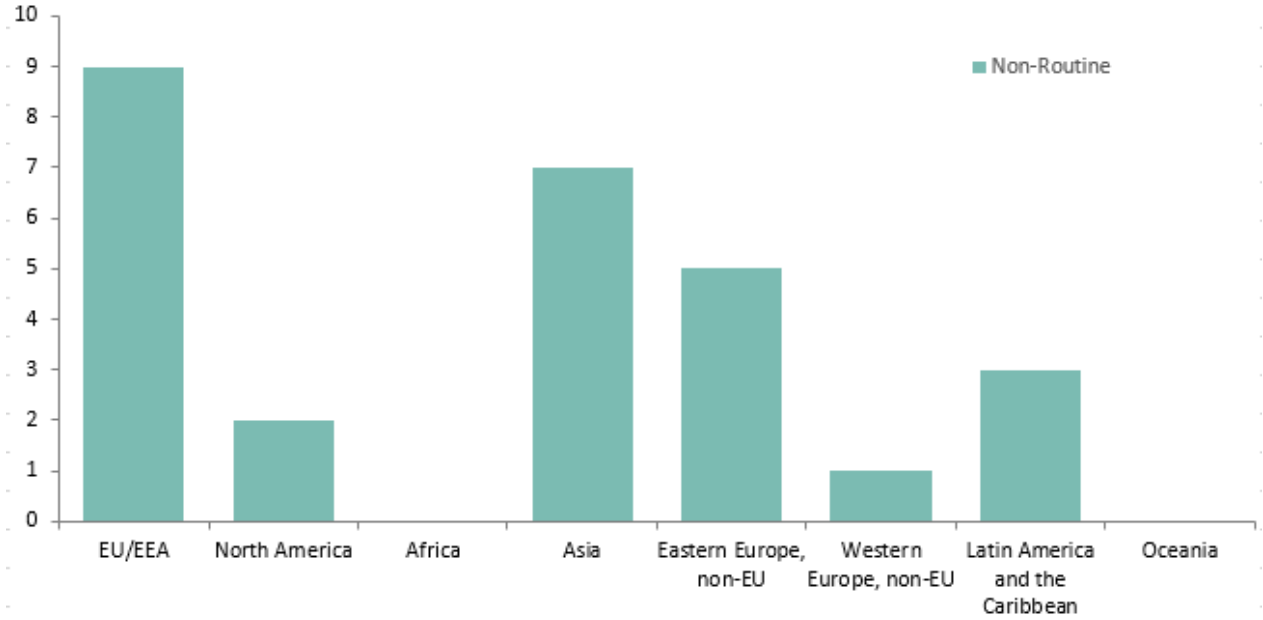
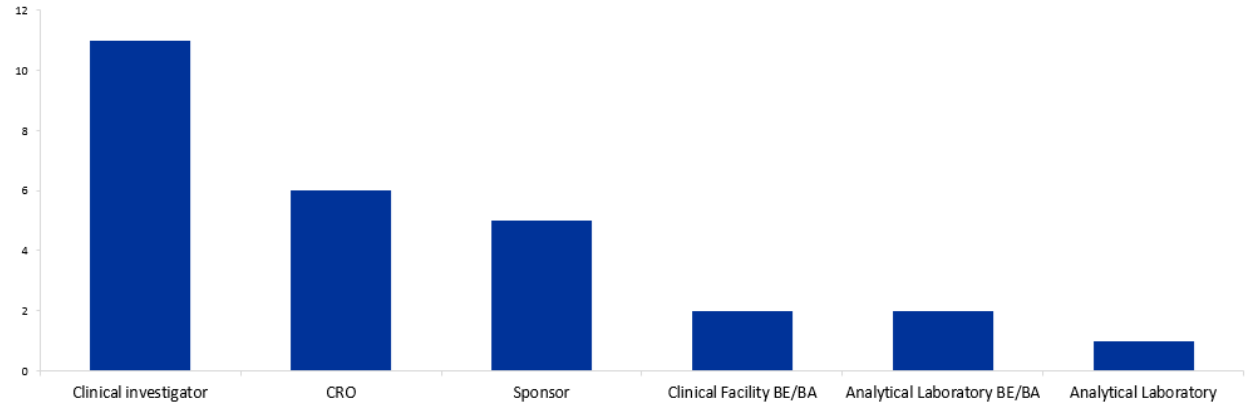


Table 2 and Figure 2 represent the number of inspections conducted in 2021 per type of site. Most of the inspections were conducted at clinical investigator sites, followed by Clinical/Contract Research Organisations (CROs) and sponsor sites. This is an increase in proportion of CRO inspections compared to the previous report.

Table 2: Inspections conducted per type of site.

Site	No. of inspections conducted
Clinical investigator	11
CRO	6
Sponsor	5
Clinical Facility BioEquivalence/ BioAvailability (BE/BA)	2
Analytical Laboratory BE/BA	2
Analytical Laboratory	1
Total in all sites	**27**

Figure 2: Inspections conducted per type of site.



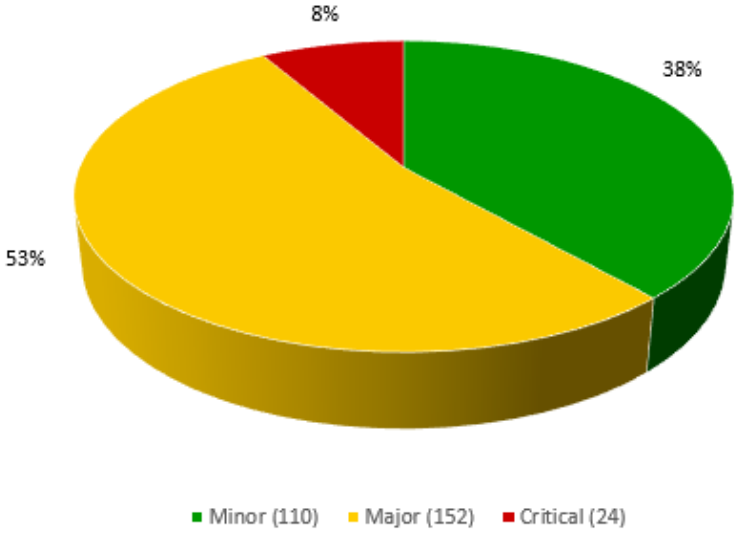
3.1.2. Categorisation of findings

a) General overview

A total of 286 deficiencies, comprising 24 critical (8,4%), 152 major (53,1%) and 110 minor (38,5%) findings were recorded for the 27 CHMP requested inspections conducted in 2021. This represents an average of 10-11 findings per site inspected.

The main findings observed in the 2021 inspections are detailed below in accordance with the GCP categorisation of findings agreed by the GCP IWG.

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



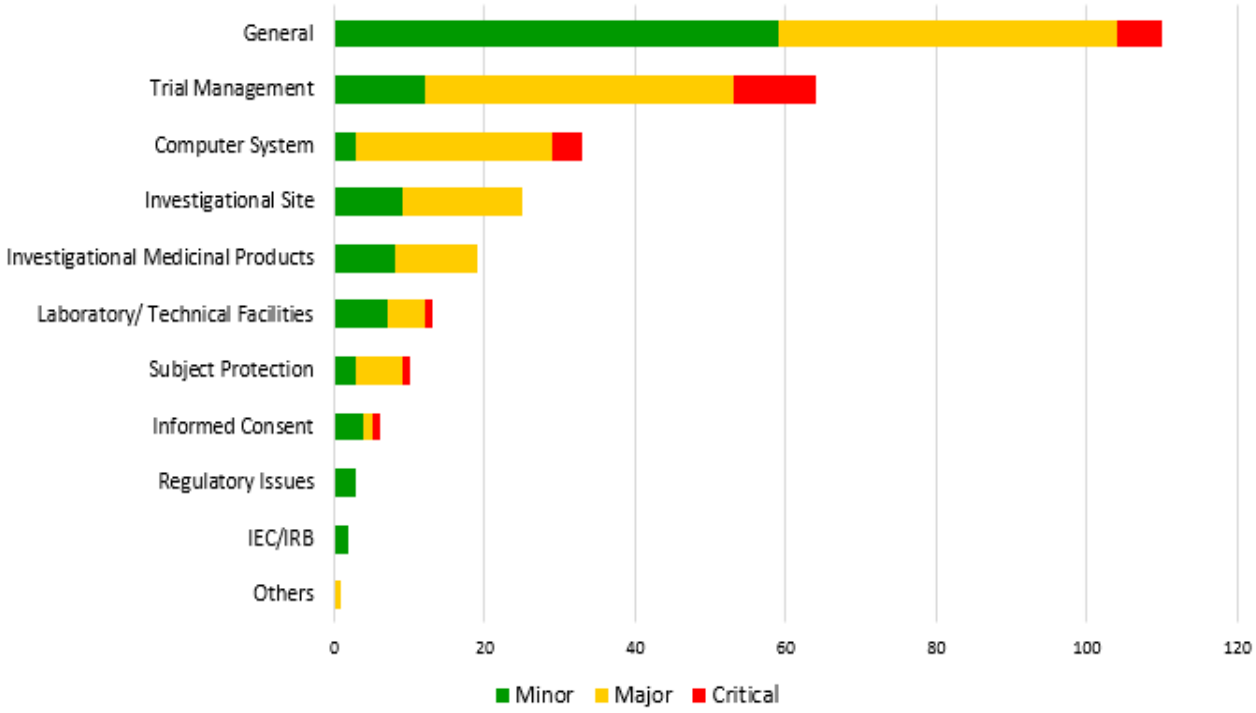
b) Distribution by categories and sub-categories

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

Main category	Minor	Major	Critical	Total
General	59	45	6	**110**
Trial Management	12	41	11	**64**
Computer System	3	26	4	**33**

Main category	Minor	Major	Critical	Total
Investigational Site	9	16	0	**25**
Investigational Medicinal Products (IMPs)	8	11	0	**19**
Laboratory/ Technical Facilities	7	5	1	**13**
Subject Protection	3	6	1	**10**
Informed Consent	4	1	1	**6**
Regulatory Issues	3	0	0	**3**
Independent Ethics Committee (IEC)/Institutional Review Board (IRB)	2	0	0	**2**
Others	0	1	0	**1**
Total	**110**	**152**	**24**	**286**

Figure 4: Number of findings by main category and grading categories critical, major and minor.



Findings are further detailed below for the three top categories: General, Trial Management and Computer System. An increase in findings related to computer systems is noted compared to the last reports.

Table 4: Number of findings per sub-category of the top 3 main categories (General, Trial Management and Computer System) graded as critical, major and minor.

		# Inspected deficiencies			Total
Deficiency category name	**Deficiency sub-category name**	**Minor**	**Major**	**Critical**	
General	Contracts/Agreements	1	5	0	**6**
	Direct Access to Data	1	0	0	**1**
	Essential Documents	25	12	3	**40**
	Facilities and Equipment	12	3	0	**15**
	Organisation and Personnel	5	4	2	**11**
	Qualification/Training	6	4	0	**10**
	Randomisation/Blinding/Codes IMP	0	6	0	**6**
	Standard Operating Procedures (SOPs)	5	8	1	**14**
	Source Documentation	4	3	0	**7**
General Total		**59**	**45**	**6**	**110**
Trial Management	Audit	1	1	0	**2**
	Clinical Study Report (CSR)	2	6	1	**9**
	Data Management	3	17	6	**26**
	Monitoring	2	8	0	**10**
	Protocol/ Case Report Form (CRF)/ Diary/ Questionnaires design	4	8	3	**15**
	Statistical Analysis	0	1	1	**2**
Trial Management Total		**12**	**41**	**11**	**64**
Computer System	Audit Trail and Authorized Access	3	9	2	**14**
	Computer Validation	0	9	0	**9**
	Physical Security System and Backup	0	8	2	**10**
Computer System Total		**3**	**26**	**4**	**33**

Examples of critical and major findings in the sub-categories of the main three categories "General", "Trial Management", and "Computer System" are listed below:

General

Contracts/Agreements:

- Lack of communication plan between sponsor and CRO.
- Lack of audit clause and retention time of data recording in clinical trial agreement between the sponsor, site and Principal Investigator (PI).
- Internal SOPs not adhered to.
- Performance of subcontracted activities before signature of a valid contract.

Essential Documents:

- Delays and late provision of requested inspection related documents/data before, during and post inspection.
- Documents missing in the Trial Master File (TMF)/Investigator Site File (ISF), or misplaced, or stored in another location without a note to file or filed with delay.
- TMF table of contents not granular enough to allow knowing which documents are located in each section.
- Deletion of documents allowed without the need for quality check and not traceable.
- Late provision of updated Investigator's Brochures (IBs) to sites.

Facilities and Equipment:

- Insufficient evaluation of temperature deviations for the equipment (e.g. freezer) and respective measures taken.
- Deficiencies in qualification of equipment.
- Deficiencies in maintenance/ calibration of equipment.

Organisation and Personnel:

- Unclarity and inconsistencies in organisational and contractual arrangements for the trial.
- Delay in initiation of a change in PI, thus impacting PI oversight.
- Delegation of tasks to inappropriate team members.

Qualification/Training:

- Late completion of GCP (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use [ICH] E6 R2) training or refresher.
- Late training in updated IBs and protocol amendments; self-training is not deemed adequate for significant amendments.

Randomisation/Blinding/Codes IMP:

- Lack of a system to allow for an investigator to undertake unblinding without the need to contact the sponsor/CRO.
- Lack of written procedure for how the integrity of the blind would be maintained, and lack of a defined mechanism and defined procedure covering unplanned unblinding.

- Lack of discarding procedures for the used IMP to ensure that no undetected breaking of the blind could occur.

SOPs:

- Lack of SOPs for critical processes.
- Lack of formal vendor prequalification and/or oversight for vendors.
- No evidence of review or update of SOPs for several years.

Source Documentation:

- Source data information not included in the electronic CRF (eCRF).
- Lack of a source data location list.
- Lack of filing of source data such as electronic communications with trial participants (e.g. telephone records, copy of instant messages).

Trial management

Audit:

- Lack of PI attendance during an audit of the site.
- Lack of audit plans.

CSR:

- Insufficient processes in place to prevent and/or detect significant flaws in the CSR.
- Incomplete description of the protocol amendments.
- Lack of patient listings in CSR annexes.

Data Management:

- Lack of review and sign-off of eCRF data by PIs or delegates.
- Late implementation of DMCs; lack of process/ documentation for selecting DMC members; lack of DMC contract/ charter.
- Persistent backlog in SDV.
- No robust reconciliation of the clinical and the safety database prior to database lock.

Monitoring:

- Insufficient resources available for the appropriate management and monitoring of the trial.
- Deficiencies in trial monitoring based on the number of deficiencies not identified and not corrected or corrected with delay.
- Delay in site responses to monitoring findings.
- Late identification of protocol deviations; poor classification of protocol deviations and serious breaches.

Protocol/ CRF/ Diary/ Questionnaires design:

- Issues in eCRF system allowing randomisation of subjects before all inclusion/exclusion criteria were confirmed.

- Lack of defined criteria or guidance for medical follow-up of subjects.
- Continuous occurrence of protocol deviations due to lack of protocol clarity/ ambiguities.
- Implementation of a trial-wide waiver for an exclusion criterion.

Statistical Analysis:

- Interim analysis supporting the Marketing Authorisation Application (MAA) performed on incomplete data.
- Statistical programming not finalised at the time of unblinding.

Computer System

Audit Trail and Authorized Access:

- Lack of procedure for period review of user accesses.
- Lack of audit trail to reconstruct the course of events.
- Deficiencies in/ late provision of access to electronic systems for relevant team members (PI, monitors).

Computer Validation:

- Lack of risk assessment of the computer system.
- Lack of procedure for validation of computerised systems.
- Lack of testing documentation and conduct.

Physical Security System and Backup:

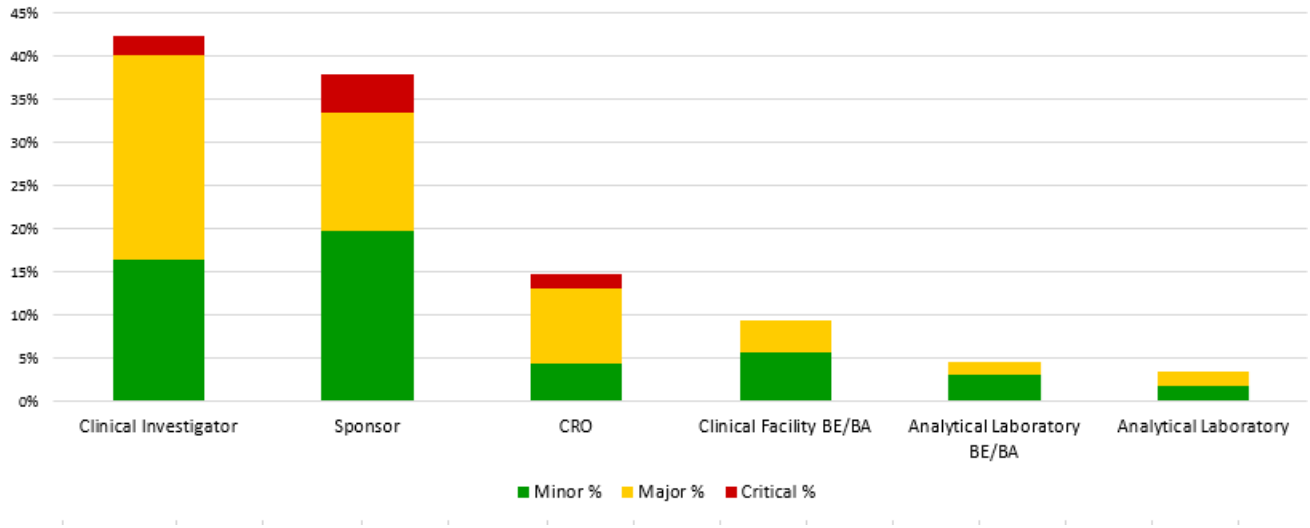
- Security issues for the remote internet access to the system (no encrypted channel).
- Lack of periodic reviews of firewalls protecting the system.
- Lack of record of security incidents.
- Lack of deployment of critical patches.

c) Distribution by type of site inspected

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

Inspection Site Type	Minor %, #		Major %, #		Critical %, #		Total %, #	
Clinical Investigator	16.3%	65	23.8%	68	2.1%	6	48.6%	139
Sponsor	19.8%	10	13.6%	39	4.5%	13	21.7%	62
CRO	4.4%	5	8.7%	25	1.7%	5	12.2%	35
Clinical Facility BE/BA	5.6%	16	3.8%	11	-	0	9.4%	27
Analytical Laboratory BE/BA	3.1%	9	1.4%	4	-	0	4.5%	13
Analytical Laboratory	1.7%	5	1.7%	5	-	0	3.5%	10
Grand Total	**38.5%**	**110**	**53.1%**	**152**	**8.4%**	**24**	**100%**	**286**

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



The figures below present the categories of findings at the three types of sites with the highest number of inspections and inspection findings: clinical investigators, CROs and sponsors.

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

Main category	Minor	Major	Critical	Total
General	35	23	0	**58**
Investigational Site	9	16	0	**25**
Trial Management	6	14	4	**24**
IMPs	3	6	0	**9**
Subject Protection	2	5	1	**8**
Informed Consent	4	1	1	**6**
Computer System	1	3	0	**4**
Laboratory/ Technical Facilities	2	0	0	**2**
IEC/IRB	2	0	0	**2**
Regulatory Issues	1	0	0	**1**
Total	**65**	**68**	**6**	**139**

Figure 6: Number and categorisation of findings at clinical investigator sites.

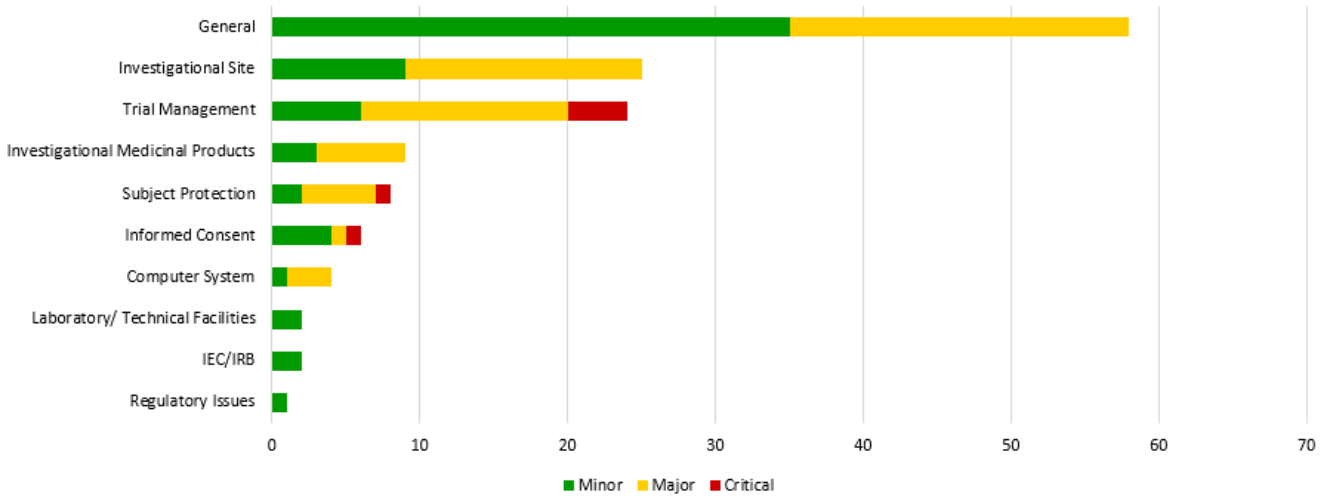


Table 7. Number and categorisation of findings at CRO sites.

Main category	Minor	Major	Critical	Total
Computer System	0	16	4	**20**
General	4	7	1	**12**
Trial Management	1	2	0	**3**
Total	**5**	**25**	**5**	**35**

Figure 7: Number and categorisation of findings at CRO sites.

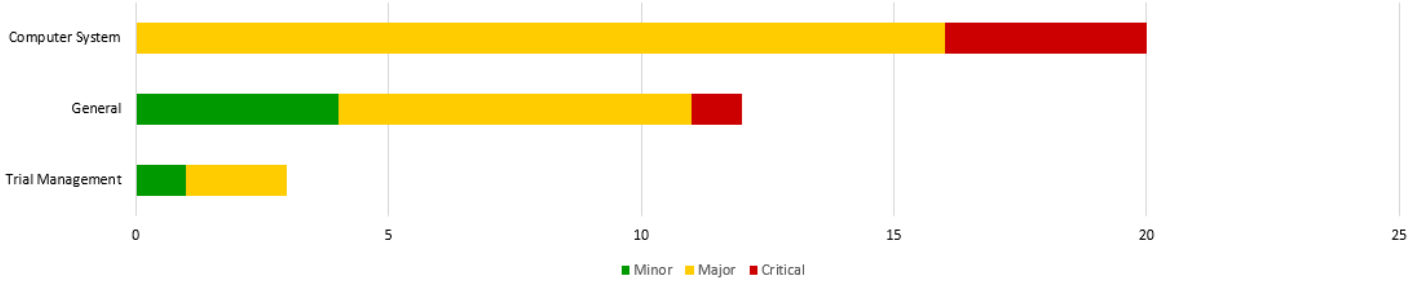
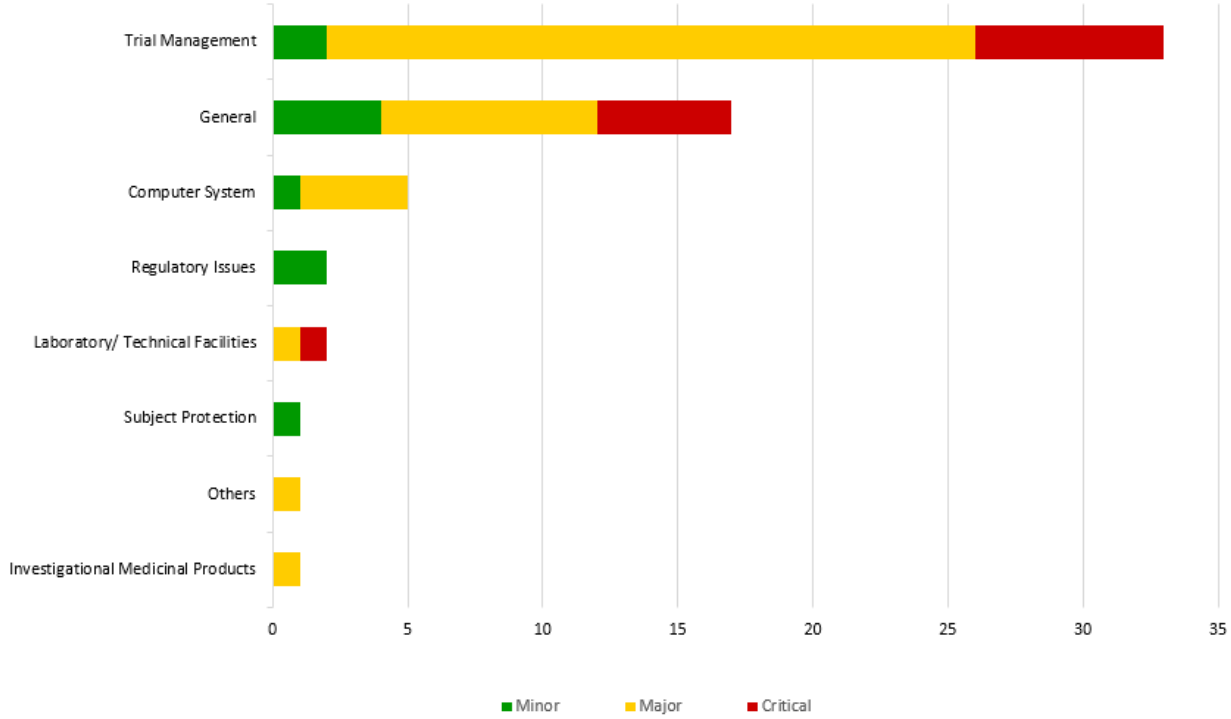


Table 8. Number and categorisation of findings at sponsor sites.

Main category	Minor	Major	Critical	Total
Trial Management	2	24	7	**33**
General	4	8	5	**17**
Computer System	1	4	0	**5**
Regulatory Issues	2	0	0	**2**
Laboratory/Technical Facilities	0	1	1	**2**
Subject Protection	1	0	0	**1**
Others	0	1	0	**1**
IMPs	0	1	0	**1**
Total	**10**	**39**	**13**	**62**

Figure 8: Number and categorisation of findings at sponsor sites.



d) Distribution by responsible party

Finally, Table 9 presents the distribution of responsibilities for each grading of finding.

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

Responsibility	Minor findings		Major findings		Critical findings		Total #	Total %
	#	%	#	%	#	%		
Sponsor	21	19.1%	47	30.9%	17	70.8%	**85**	**29.7%**
Multiple Responsibility	29	26.4%	47	30.9%	3	12.5%	**79**	**27.6%**
Investigator	45	40.9%	33	21.7%	0	-	**78**	**27.3%**
CRO	12	10.9%	21	13.8%	4	16.7%	**37**	**12.9%**
Laboratory	3	2.7%	4	2.6%	0	-	**7**	**2.4%**
Grand Total	**110**	**100%**	**152**	**100%**	**24**	**100%**	**286**	**100%**

4. Harmonisation topics

4.1. Procedures and guidance documents

The GCP inspectors worked (or continued working) on the following documents in 2021:

- Updated guidance on how to manage clinical trials during the COVID-19 pandemic;
- Draft guideline on computerised systems and electronic data in clinical trials;
- Guideline on the responsibilities of the sponsor with regard to handling and shipping of IMPs for human use in accordance with GCP and GMP;

- Guideline for the notification of serious breaches of Regulation (EU) No 536/2014 or the clinical trial protocol (adopted by the GCP IWG on 13 December 2021).

A new Question & Answer (Q&A) regarding the authority for GCP inspectors from regulatory authorities of an EU/EEA MS to inspect trial participants' medical records and other data was also published in February 2021 on the European Medicines Agency (EMA) website.

4.2. Remote inspections

As outlined already in the 2020 Annual Report, 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 sometimes conducted in lieu of on-site inspections, where considered appropriate and feasible.

In 2020, 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, which continued to be applied in 2021.

In 2021, 3 CHMP requested GCP inspections were conducted entirely remotely, and 3 inspections were conducted in a hybrid setting (part on-site, part remotely).

4.3. Inspection cooperation

- Cooperation between the EU/EEA MSs:

Nearly all the inspections conducted in 2021 were joint inspections involving inspectors from at least two MSs. Only one inspection was carried out by one MS only, due to resource constraints.

- Cooperation with third countries:

Observers from countries outside the EU/EEA are systematically invited to observe the EU/EEA GCP inspections performed in those countries in the context of the centralised procedure. In 2021, Switzerland, Brazil, USA and World Health Organisation (WHO) observed GCP inspections requested by the CHMP.

4.4. GCP training and development

4.4.1. 2021 GCP BE inspections forum

A BE forum took place online on 16 November 2021. 70 participants including mainly BE experienced inspectors from EU/EEA, US Food and Drug Administration (FDA), WHO and UK Medicines and Healthcare products Regulatory Agency (MHRA) were present. The forum focused on issues identified by the FDA at two Indian CROs (Synchron and Panexcell), and the actions taken, as well as sharing of information related to data analysis tools.

4.5. GCP IWG meetings and topics of interest

- During the plenary GCP IWG meetings held on 02-03 March 2021, 08 June 2021, 28-29 September 2021 and 30 November-01 December 2021, the following topics were discussed:
  - Organisational matters - revision of EMA policies, digital transformation, documentation sharing, new projects and calls for volunteers
  - Regulation (EU) No 536/2014 implementation and Clinical Trials Information System (CTIS)
  - Ongoing guidelines and Q&A
  - Renovation of ICH E8 and E6, and new ICH E19 and M11
  - Response to queries received from third parties
  - International collaboration and initiatives
  - COVID-19 and impact on GCP inspections, including remote inspections and COVID-19 clinical trials submitted for MAAs/Rolling Review
  - Update on ongoing and future inspections
  - Update from subgroups on their activities
  - Updated inspection templates
  - GCP compliance interpretation matters and GCP issues
  - Training, workshops, forums and joint meetings
  - European Commission revision of the pharmaceutical legislation
- The extraordinary GCP IWG meeting held on 04 February 2021 focused on COVID-19 issues – involvement of GCP IWG in rolling reviews and rapid scientific advice and EU guidance on managing clinical trials during the COVID-19 pandemic.
- The extraordinary GCP IWG meeting held on 16 February 2021 focused on IIR peer review project (Reflections on GCP inspections procedures) and on remote GCP inspections post-pandemic. Decentralised trials and variant vaccines were also addressed.
- An ad hoc GCP IWG meeting was organised on 26 April 2021 to discuss the International Coalition of Medicines Regulatory Authorities (ICMRA) Draft reflection paper on regulatory oversight of GCP and GMP facilities using digital means.
- The extraordinary GCP IWG meeting held on 21 June 2021 focused on decentralised trials, the ICMRA Draft reflection paper on the use of remote GCP and GMP inspections during the COVID-19 pandemic, and CTIS.

5. Collaboration with European Commission

A representative from the Directorate F – Health and food audits and analysis, of the Directorate-General for Health and Food Safety (DG SANTE) of the European Commission attended three out of four 2021 GCP IWG plenary meetings.

5.1. Clinical trial legislation and related guidance documents

- The European Commission, the EMA, the GCP IWG and the Heads of Medicines Agencies (HMA) collaborated on the revision of the Guidance to sponsors on how to manage clinical trials during the COVID-19 pandemic, which was revised to version 4 on 04 February 2021.
- The EMA, GCP IWG and European Commission collaborated on several additional topics such as decentralised clinical trials, direct to patient shipping of IMP and remote SDV.

5.2. EU portal and database

The inspectors discussed the status of the CTIS programme, including the inspections module and the training and communication plans, during all 2021 GCP IWG plenary meetings. In addition, a CTIS demo and feedback on testing were presented during the extraordinary GCP IWG meeting held on 21 June 2021.

Several guidelines relating to the implementation of the Clinical Trials Regulation No. 536/2014, on topics including serious breaches and redaction, are being developed in collaboration with the GCP IWG (see section 4.1).

5.3. EU enlargement

The EU (potential) candidate countries, Bosnia and Herzegovina, Kosovo under United Nations Security Council (UNSC) Resolution 1244/99, Albania, Republic of North Macedonia, Montenegro, Serbia and Turkey, were not invited to the GCP IWG meetings held in 2021 due to the Agency's Business Continuity Plan and prioritisation of activities for the COVID-19 pandemic.

6. Liaison with other EU groups

6.1. GMP/GDP IWG

The GCP IWG maintains a dialogue with the GMP/GDP IWG on areas of common interest. In 2021, the two IWGs collaborated on a query on mock preparation of IMP and on the Guideline on the responsibilities of the sponsor with regard to handling and shipping of IMPs for human use in accordance with GCP and GMP.

6.2. PhV IWG

The GCP IWG maintains a dialogue with the PhV IWG on areas of common interest and in particular concerning PhV issues observed in relation to GCP inspections.

6.3. HMA/ CTFG

The GCP IWG maintains a collaboration with the HMA and Clinical Trials Facilitation and Coordination Group (CTFG) on areas of mutual concern in the supervision of clinical trials conducted in the EU/EEA. In 2021, the GCP IWG and the CTFG collaborated on the revision of the Guidance to sponsors on how to manage clinical trials during the COVID-19 pandemic, the decentralised clinical trials initiated, the development of guidelines relating to the implementation of the Clinical Trials Regulation No. 536/2014, and the revision of ICH guidelines, in addition to ad hoc issues.

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 2021, topics included the collaboration between GCP inspectors and Rapporteurs for COVID-19 applications, the EMA project on reflections on GCP inspections procedures, the revision of ICH guidelines, the re-start of routine inspections, and referral procedures.

6.5. CMDh

The GCP IWG and the CMDh, mainly through the GCP/CMDh working party which met 8 times in 2021, have contributed to the following topics:

- List of CROs of interest.
- BE trials and CRO oversight during the COVID-19 pandemic.
- CROs inspection outcome and subsequent actions including referral procedures.
- 2021 CRO inspection program and planned national inspections.
- FDA-WHO-EMA-EU MSs collaboration in the area of BE inspections.
- EMA–MHRA–ANSM[2]–WHO–FDA–Health Canada collaboration on BE statistical project.
- Data manipulation at sponsor site.
- Development of the ICH M10 document - Bioanalytical Method Validation of Assays for Chemical and Biological Drugs.
- Q&A on Lack of monitoring for BE trials in the context of MAAs.

The GCP IWG was updated on the referral procedures during plenary meetings.

6.6. Joint meetings with interested parties

- A Joint meeting with interested parties (European Commission, EU/EEA regulatory authorities, US FDA, third country regulatory authorities, industry, academia, physician organisations, patient organisations) on the use of Artificial Intelligence in clinical trials was held on 14 and 15 September 2021.

6.7. Paediatric Committee (PDCO)

Communication on inspection issues with the PDCO continued in 2021 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[3]. This collaboration was extended in 2013 to BE, together with some of the EU/EEA MSs[4].

[2] *Agence nationale de sécurité du médicament et des produits de santé* (French competent authority)
[3] Announcement of the EMA-FDA GCP Initiative
[4] Announcement of the generic medicines application inspections initiative

- During 2021 there were 5 regular teleconferences of the EMA-FDA GCP collaboration and 4 teleconferences as part of the EMA-FDA-MSs BE collaboration.
- As part of the EMA-FDA GCP initiative the FDA observed one EMA inspection. Greece observed two FDA BE inspections. No inspections were performed jointly.
- Several FDA representatives also attended the BE Forum.

- Pharmaceuticals and Medical Devices Agency (PMDA, 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:
  - EMA, WHO and the EU/EEA MSs that perform the highest number of BE inspections had several teleconferences to purse the existing collaboration and exchange of BE 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 GCP IWG under the European Commission, EMA, Swiss Federal Department of Home Affairs and Swissmedic confidentiality arrangement, in place since 2015.
  - In 2021, Swissmedic observed one inspection requested by the CHMP.
- ICMRA:
  - Members of the GCP IWG contributed to the reflection paper "Reflections on the regulatory experience of remote approaches to GCP and GMP regulatory oversight during the COVID-19 Pandemic", published on 26 November 2021.
- Other regulatory agencies:
  - Collaboration is ongoing with the UK (now a third country following the Brexit), Health Canada and any other regulatory agencies of interest.

7.2. International initiatives

- General information was exchanged with the regulatory authorities in India, Brazil, Dominican Republic and Thailand.
- COVID-19-specific information was exchanged with the regulatory authorities in Peru, South Africa, Argentina, Brazil, Indonesia, South Korea, China and Chile.

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