

SOP CLI012/1  
Management of GCP/protocol deviation  
and notification to AIFA of critical deviations in Phase I trial

## Standard Operating Procedure

### Management of GCP and trial protocol deviations and notification to AIFA of critical deviations occurred during Phase I trials

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## 1. ABBREVIATION

ASST-PG23:	Azienda Socio Sanitaria Territoriale - Papa Giovanni XXIII
CA:	Competent Authority
CRA:	Clinical Research Associate
DM:	Data Manager
EC:	Ethics Committee
FROM:	Fondazione per la Ricerca Ospedale Maggiore
GCP:	Good Clinical Practice
ICH:	International Council of Harmonization
PI:	Principal Investigator
PM:	Project Manager
QAM:	Quality Assurance Manager
SOP:	Standard Operating Procedure

## 2. SCOPE

The purpose of the Standard Operating Procedure (SOP) is to provide indications on the management of GCP and protocol deviations occurred in relation to a clinical trial.

In addition, this SOP provides directives in relation to Phase I trials for the communication to AIFA of:

- *critical* deviations from the GCP guidelines and trial protocol/amendments
- loss of previously self-certified requirements of the Phase I unit, including those related to the self-certified laboratories
- corrective and preventive actions undertaken as consequence of deviations and verification of their effectiveness.

## 3. FIELD OF APPLICATION

The procedures described for management of GCP and trial protocol deviations apply to all clinical trials sponsored by FROM or ASST-PG23.

Procedures described for the notifications of critical deviations or loss of self-certified requirements to AIFA apply only to Phase I trials in accordance with the Determina AIFA n. 809/2015.

## 4. RESPONSIBILITIES

### Sponsor

- Provides the site staff with a guideline on possible GCP / protocol deviations
- Provides the site staff with a module for the collection of detailed information about deviations

### Principal Investigator (PI)

- Drafts the guideline on possible GCP / protocol deviations for a given trial with the support of the PM/DM

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#### Project Manager (PM) / Data Manager (DM)

- Collaborates with the PI for drafting the guideline on possible GCP / protocol deviations for a given trial
- Records the trial deviations on the module provided by the sponsor
- Collects all relevant information regarding a significant deviation and contacts the Quality Assurance Manager (QAM) to share such information
- Performs a root cause analysis and identifies corrective and preventive actions with the collaboration of the QAM
- Reports trial related deviations to the sponsor If the PM/DM
- Reports major protocol violations to the Phase I Medical Director and QAM

#### Quality Assurance Manager (QAM) and Principal Investigator (PI)

- Collaborate with the PM/DM in the assessment of a significant deviation (i.e. major or critical), in performing the root cause and in the identification of corrective and preventive actions

#### Clinical Research Associate (CRA)

- Verifies the investigator's compliance to the approved protocol/amendments during the monitoring visits
- Verifies the completion of the GCP/protocol deviation log during the monitoring visits and requests the completion in case the PM/DM failed to complete the log
- Follows-up the preventive and corrective actions taken in case of significant deviations.

### **PHASE I TRIALS**

#### PM/DM, QAM and Medical Director

- Assess promptly the criticality of a significant deviation, regardless of the path followed by the Sponsor (if any)
- Agree on the corrective actions to be implemented urgently and ensure their execution

#### PM

- Completes and sends the Communication Form to AIFA if the criticality of the deviation is confirmed

#### Medical Director

- Verifies the Communication Form to AIFA or the declaration about the loss of the previously self-certified requirements before signing them for approval
- Ensures that notification to AIFA has been made.

#### PM and QAM

- Verify the effectiveness of the corrective actions implemented.

## Head of Laboratory

- Informs the Medical Director and the QAM if the requirements quoted in the Determine n. 809/2015 are no longer fulfilled
- Puts on-hold the laboratory activities in respect to Phase I trials until the requirements are restored
- Identifies and implements urgent corrective actions for the requirements restoration
- Drafts and signs the declaration about the loss of the previously self-certified requirements to be submitted to the Medical Director for approval before delivery to AIFA

## 5. PROCEDURE

### 5.1 Deviations from the GCP and protocol / amendments

GCP or trial protocol deviations can be detected by all personnel involved in various aspects of a clinical trial. Among these, also the CRA and the auditor are responsible, in different ways, to verify the adherence of trial conduct to the approved protocol/related amendments and the adequacy of the documentation produced.

The CRA is responsible to verify the investigator's compliance to the approved protocol/amendments during the on-site monitoring visits. When the on-site monitoring is limited, remote controls are implemented to detect protocol deviations based on the clinical data recorded in the electronic Case Report Forms.

Before the trial start the sponsor should provide the site staff with a guideline that identifies general (i.e. those occurring frequently in clinical trials) and trial-specific deviations and a standard module to collect detailed information about deviations.

With regards to trials sponsored by FROM or ASST-GP23, the document for the identification of GCP and protocol deviations should be drafted by the PI and PM/DM before the trial start according to the **Guideline for GCP/Protocol deviations (T.CLI12.01/1)**.

The person of the site staff who has detected a deviation should contact the PM/DM who are responsible for completing the **GCP/Protocol deviation log (T.CLI12.02/1)**. The log applies to all sites participating in the trial and it is used at the time of the Clinical Study Report where the list of major protocol deviations must be included as Appendix.

The CRA should verify the completion of the log during the monitoring visits and request the completion in case the PM/DM failed to complete the log.

A deviation deemed as non-significant is managed through the issue of a query following the sponsor's indication.

If a deviation is considered significant the PM/DM collects all relevant information with the support of the person detecting the deviation and contacts the QAM and PI to share such information, to decide the level of criticality and to prepare an action plan.

For Phase I trials the process described for the collection of information and the assessment of the criticality must not exceed 3 days from the identification of the deviation. In this period, a root cause analysis and the identification of corrective and preventive actions to be taken with a matter of urgency

should be identified. The identified actions and the agreed level of criticality of the deviation are reported by the PM/DM on **GCP/Protocol deviation log (T.CLI12.02/1)**.

The Sponsor, if different from ASST-PG23, should be promptly informed both verbally and in writing in case of significant deviations. The deviation and corrective/preventing actions are discussed and agreed with the Sponsor and specifically for Phase I trials it should occurred within the fifth day of identification of the critical deviation.

Preventive and corrective actions are implemented by the PM/DM and followed-up by the CRA and the QAM.

## 5.2 Critical GCP and Protocol Deviations occurred during Phase I trials

In case a significant deviation occurred during a Phase I trial the concerned Medical Director is immediately informed by the PI and QAM to evaluate the level of criticality.

Critical deviations are those likely to affect:

- the safety or physical integrity of the patients of the trial
- patient's rights
- the scientific value of the trial

Once a critical deviation to conditions and principles of GCP and to trial protocol/amendments has been identified, the PM/DM should fill in the form **Deviazioni Critiche da GCP e protocollo di studio - Notifica ad AIFA (T.CLI12.03/1)**.

The form, verified and signed by the Medical Director of the Phase I Unit, is delivered by certified mail within 7 (seven) days of the knowledge to the following offices at AIFA:

- **UFFICIO ISPEZIONI GCP** ([ispettorato-gcp@pec.aifa.gov.it](mailto:ispettorato-gcp@pec.aifa.gov.it))
- **UFFICIO SPERIMENTAZIONE CLINICA** ([apa@pec.aifa.gov.it](mailto:apa@pec.aifa.gov.it))

If the information sent to AIFA needs to be integrated, a new transmission form will be used (i.e. Follow-up report).

The corrective / preventive actions are managed through a plan of corrective and preventive actions (CAPA) managed by the PM/DM who will follow-up the actions to be undertaken with the collaboration of the QAM.

This procedure must be shared and agreed before the trial start with the commercial sponsors (i.e. Pharmaceutical Company) who intend to involve ASST-PH23 and/or FROM in a Phase I study.

The Sponsor and the functions involved in the critical deviation are kept up to date on notification to AIFA by the Medical Director.

## 5.3 Loss of the minimum requirements of the Phase I Unit previously self-certified to AIFA

It is the responsibility of the Medical Director or Laboratory Director(s) of the Phase I Unit to notify AIFA about the absence of one or more of the requirements previously self-certified according to the Determina n. 809/2015.

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The QAM collaborates with the Medical Director or the Laboratory Director for the identification of potential or actual deficiencies in the requirements and for planning possible solutions.

A report describing the loss of the previously self-certified minimum requirements is delivered by certified mail within 7 (seven) days of the knowledge of the deficiency to the following offices at AIFA:

- UFFICIO ISPEZIONI GCP ([ispettorato-gcp@pec.aifa.gov.it](mailto:ispettorato-gcp@pec.aifa.gov.it))
- UFFICIO SPERIMENTAZIONE CLINICA ([apa@pec.aifa.gov.it](mailto:apa@pec.aifa.gov.it))

AIFA is maintained up to date about the corrective actions and the restore of requirements.

## 5.4 Archiving

The documentation relevant to *non-significant deviations* of a given trial is filed in the Trial Master File and in the Investigator Study File according to sponsor's procedures.

The documentation relevant to *critical deviations* from GCP and trial protocol / amendments and the notifications to AIFA is filed according to the following criteria:

- by the Sponsor in the Trial Master File (copy)
- by the site in the Investigator Study File (copy)
- in the QAM archive (original documents)

The documentation relating to *the loss of minimum requirements of the Phase I Unit, laboratories included*, and the relevant notification to AIFA is filed according to the following criteria:

- in the QAM archive (original documents) with the first self-certification sent to AIFA confirming the presence of the minimum requirements and relevant documentation (*see FROM Linea guida per il percorso di adeguamento di una Unità Operativa alla Determina n.809/2015 per la conduzione di studi clinici di Fase I*).
- by the Quality Referent of the UOC or Laboratory where the loss of previously self-certified requirement(s) occurred.

## 6. REFERENCES

- ICH GCP Guideline for good clinical practice E6 (R2) (CPMP/ICH/135/95, December 2016).
- Determina AIFA n. 809 del 19 giugno 2015 inerente i requisiti necessari per le strutture sanitarie che eseguono sperimentazioni di fase I di cui all'art. 1 del decreto del Presidente della Repubblica 21 settembre 2001, n.439 e di cui all'art.31, comma 3 del decreto legislativo 6 novembre 2007, n.200.
- Q&A alle Determine AIFA n. 809/2015 e n. 451/2016 inerenti ai requisiti minimi necessari per le strutture che eseguono sperimentazioni di Fase I
- Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products (EMA/CHMP/SWP/28367/07 Rev. 1 20 July 2017).

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## 7. TEMPLATES

- T.CLI12.01/1 Guideline for GCP/protocol deviations.
- T.CLI12.02/1 GCP/Protocol deviation log.
- T.CLI12.03/1 Deviazioni Critiche da GCP e protocollo di studio - Notifica ad AIFA.

## 8. VERSION HISTORY

Version	Date	Reason for revision
1	15 Dec 2019	<p>The management of GCP and protocol deviations, and the loss of requirements of a Phase I Unit self-certified to AIFA was part of the SOP CLI01-Protocol and Amendments.</p> <p>It was decided to create a specific SOP to better clarify processes and responsibilities.</p>