

Standard Operating Procedure

Clinical Trial Application to AIFA and ECs for trial approval

Identification No: CLI07

Version: 2

| | Name | Role | Date | Signature |
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1. ABBREVIATION

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|------------|---|
| AIFA: | Agenzia Italiana del Farmaco (Italian Competent Authority) |
| ASST-PG23: | Azienda Socio-Sanitaria Territoriale – Papa Giovanni XXIII |
| CT | Clinical Trial |
| CTA | Clinical Trial Application |
| EC | Ethics Committee |
| EudraCT: | European Clinical Trials Database |
| FROM: | Fondazione per la Ricerca Ospedale di Bergamo |
| ISF: | Investigational Site File |
| OsSc: | Osservatorio Nazionale sulla Sperimentazione Clinica dei Medicinali (Italian regulatory database for CTs) |
| PI: | Principal Investigator |
| PM: | Project Manager |
| SOP: | Standard Operating Procedure |
| UOC: | Unità Operativa Complessa |

2. SCOPE

This Standard Operation Procedure (SOP) describes the responsibilities and procedures for the application to AIFA and to Ethics Committees (EC) in case of interventional trials with medicinal compound.

3. FIELD OF APPLICATION

This SOP is applicable to all clinical studies conducted in Italy, sponsored or supported by FROM or sponsored by ASST-PG23.

4. RESPONSIBILITIES

Trials sponsored or supported by FROM

Project Manager

- Applies for the EudraCT .
- Verifies that all information and documents needed for the application are available and collects the missing ones.
- Prepares the submission package to be submitted to AIFA and EC(s) for approval.
- Records the CT in the Osservatorio Nazionale sulla Sperimentazione Clinica dei Medicinali (OsSC).

- Submits the documental package to AIFA and ECs for approval (through OsSC).
- Ensures that the authorization / approval from AIFA and ECs are obtained and duly documented.
- Updates the OsSC in case of substantial amendment .
- Maintains contact with the company/cell factory providing support to the trial (e.g. trial products).
- Maintains contact and coordinates interactions with other participant centers (multicenter trials) and related ECs.

Project Manager at UOC of ASST-PG23

- Prepares and submit the local documents to the Ethic Committee of Bergamo.
- Interfaces with PM acting on behalf of Sponsor (below).

Operational Director

- Reviews and signs the Clinical Trial Application (CTA) form before submission of documental package to AIFA and ECs.

Trials sponsored by ASST-PG23

ASST-PG23 Representative

- Applies for the EudraCT .
- Verifies that all information and documents needed for the application are available and collects the missing ones.
- Prepares the submission package to be submitted to AIFA and EC(s) for approval.
- Registers the CT in the Osservatorio Nazionale sulla Sperimentazione Clinica dei Medicinali (OsSC) and submits the documental package to the Principal Investigator for review.
- Signs the CTA form after the Principal Investigator (PI) review and submits the documental package to AIFA and ECs for approval (through OsSC).
- Ensures that the authorization / approval from AIFA and ECs are obtained and duly documented.
- Updates the OsSC in case of substantial amendment.

Principal Investigator (PI) or delegated person

- Reviews the CTA form before submission of documental package to AIFA and ECs.

5. PROCEDURE

AIFA authorization and the Single Opinion of the coordinating EC as well as the favorable opinion of the EC at the collaborative sites should be requested and obtained before the trial start through the OsSC.

5.1 Obtaining EudraCT code

Each trial to be performed in the European Community is identified by a unique EudraCT number. The number is requested and obtained through the web site application <https://eudract.ema.europa.eu/results-web/>.

The EudraCT number should be reported at least on the first page of the trial protocol and clinical study report.

5.2 Registration of trial on OsSc and submission of package to AIFA and EC in order to request the authorization to conduct a CT

Documents (i.e. final and approved version) requested by the Italian Decree date 21 December 2007 and the information to be included in the OsSC should be collected by the appointed PM /ASST-PG23 Representative.

The submission package is generated through the CTA forms in the electronic platform OsSc. After all fields of the CTA forms are filled in with the relevant information and documental area is populated and completed by uploading the requested documents, the submission package is generated.

The PM/ ASST-PG23 Representative are responsible for printing the CTA form and for submitting it for review to the Operational Director and the Principal Investigator/delegated person, respectively.

The final CTA form for CTs sponsored by FROM is signed by the Operational Director while the final CTA form for CTs sponsored by the ASST-PG23 by the ASST-PG23 Representative as these people are the reference and contact person in OsSC for the concerned trials.

Then the submission package along with the CTA form are transmitted electronically to AIFA and concerned EC(s) for approval.

In addition, the following should be sent to AIFA by courier:

- Paper copy of Letter of intent/transmission letter (with 16,00 € stamp)
- CTA form originally signed
- CD containing the copy of whole submission package downloaded from OsSC

The trial package should be validated by AIFA and the EC of the coordinating site (i.e. multicenter trials). When the completeness of documentation is confirmed, the phase of trial evaluation begins.

During this period AIFA and EC of the coordinating site could ask the sponsor for document integration and/or clarifications. The FROM PM or the ASST-PG23 Representative is responsible for collecting and forwarding the documents/information requested by AIFA and coordinating EC within 30 days of the request.

Any new information and/or documents collected upon the AIFA and EC request is uploaded on OsSC and transmitted to AIFA and/or coordinating EC.

The PM operating on behalf of FROM also ensures the distribution of the submission package to ECs of the collaborative sites (in case of multicenter trial) for trial sponsored by FROM.

The ASST-PG23 Representative also ensures the distribution of the submission package to ECs of the collaborative sites (in case of multicenter trial) for trial sponsored by ASST-PG23 with the support of the concerned PM.

AIFA and coordinating EC approvals are posted in the OsSC website; paper copies of approvals are also remitted to FROM/ASST-PG23 by the AIFA and the coordinating EC.

The FROM PM/ASST-PG23 Representative are responsible for sending the AIFA authorization and the Single Opinion of the coordinating EC of their concerned trials to the ECs of the collaborative sites to allow the completion of the evaluation procedure.

A copy of the whole package transmitted to ECs is also sent to the Principal Investigators of the involved sites.

The FROM PM/ASST-PG23 Representative are responsible for collecting the approval/refusal released by the EC of each collaborative site.

5.3 Approval by the Institutions (General Director)

During the trial planning phase, the economic trial feasibility should be evaluated by the financial/administrative office at each institution. Generally, a site-specific document detailing estimated costs of a CT is issued. For trial conducted in ASST-Pg23, including those sponsored by FROM or ASST-PG23 the concerned trial PM is responsible for issuing the document in collaboration with the personnel of UOC Ricerca, Innovazione e Brand Reputation, section *COORDINAMENTO TRIAL CLINICI (Fattibilità locale sperimentazioni ASST-PG23, <http://oracolo.oorrbq.local/sperimentazioni/>)*.

The PM is also responsible for submitting administrative documents (e.g. contract) to each Institution participating in the trial as well as for collecting the institution trial approval (i.e. Delibera).

5.4 CTA amendment

Critical change(s) to the study protocol, Patient Information Sheet/Informed Consent Form or to any document of the Clinical Trial Application should be communicated as substantial amendment by FROM or ASST-PG23 to AIFA and the involved ECs following the same procedure of the original application.

The coordinating PI, with the collaboration of the PM where applicable, should issue the document **Riassunto di un Emendamento ad uno studio clinico (T.CLI01.05/2, attached to the procedure CLI01/2 Protocol and Amendments)**. The form can be adapted and used for any change to the CTA documents.

No changes should be implemented prior to the written AIFA and Single Opinion authorization, except in case of urgent safety measures to protect subjects participating in the trial. In the latest case the amendment is promptly implemented and sent afterwards to the AIFA and Single Opinion for approval/authorization.

Change(s) involving logistical or administrative aspects of the trial do not need the opinion of the AIFA and ECs for their implementation. They have just to be notified to the EC(s).

5.5 Other Trial Information to be communicated to AIFA and EC(s)

Opening, withdrawal, temporary halt or end of clinical trial at a site, conclusion of the clinical trial and the clinical trial report should be also notified to AIFA and the ECs through the OsSC. The relevant communications are also provided to the participating sites.

5.6 Archive

All documents included in the application/submission package as well as those relevant to CTA amendments, are duly and timely filed in the Trial Master File (SOP **Trial Files - CLI06/2**) by the PM and in the Investigator Site File (SOP **Trial Files - CLI06/2**) by the site staff. The Clinical Research Associate should check that Investigators received the initial ISF containing all documents duly filed and that any document relevant to a CTA amendment is filed during the trial life cycle.

6. REFERENCES

- Guideline for good clinical practice E6(R2) (CPMP/ICH/135/95).
- D.Lvo N. 211, 24/06/ 2003 Attuazione della direttiva 2001/20/ce relativa all'applicazione della buona pratica clinica nell'esecuzione delle sperimentazioni cliniche di medicinali per uso clinico.
- Decreto Ministeriale 21 dicembre 2007 Modalità di inoltro della richiesta di autorizzazione all'Autorità competente, per la comunicazione di emendamenti sostanziali e la dichiarazione di conclusione della sperimentazione clinica e per la richiesta di parere al comitato etico.

7. TEMPLATES

None.

8. VERSION HISTORY

| Version | Date | Reason for revision |
|---------|--------------|--|
| 1 | 30 Sept 2016 | Starting document. |
| 2 | 22 Jun 2020 | <ul style="list-style-type: none"> • Introduction of the Representative for ASST-PG23 sponsored trials. • Reference to "AIFA" in the SOP and not to "Competent Authority" as in the previous version (including SOP title). • Reference to the <i>Riassunto di un Emendamento ad uno studio clinico</i> included. • Minor changes in the text wording. |