ITALIAN LAW ON THE MINIMAL REQUIREMENTS FOR CRO PERSONNEL

BACKGROUND

- The role of CROs is increasing in the context of Clinical Trials
- Sponsors are delegating more and more activities to CROs
- Sometimes Sponsors are just "administrative subjects" who buy clinical studies "ready to submit" giving up any activity for checking quality and reliability of data (e.g.BE\studies)
- Quality of Clinical Trials depends particularly on provided monitoring

2

LEGAL BASIS

LEGISLATIVE DECREE no. 211 of 24 June 2003
Transposition of Directive 2001/20/EC relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for clinical use.

Article 20 (3) "General Provisions"

«The minimum requirements which must be met by private organisations to which the sponsor delegates all or part of its entitlement to conduct clinical trials as laid down by the rules of good clinical practice, without prejudice to the sponsor's liability for the trial, shall be established by decree of the Minister of Health.»

3

ITALIAN DECREE 15 NOVEMBER 2011

ITALIAN MINISTRY OF HEALTH

DECREE, 15 November 2011

Definition of the minimum requirements which Contract Research Organisations (CROs) shall satisfy in order to work within clinical trials on medicinal products.

4

ITALIAN DECREE 15 NOVEMBER 2011

- ***ART. 1*** *– Area of application*
- ***ART. 2*** *– Definitions*
- ***ART. 3*** *– General minimum requirements*
- ***ART. 4*** *–Monitoring activity requirements*
- ***ART. 5*** *– Requirements for auditing of trials or trial centers*
- ***ART. 6*** *– Requirements for statistical analysis and data management*
- ***ART. 7*** *– Effect and notification of requirements*
- ***ART. 8*** *– Legal Representation and sponsors responsibility*
- ***ART. 9*** *– Information notification*

5

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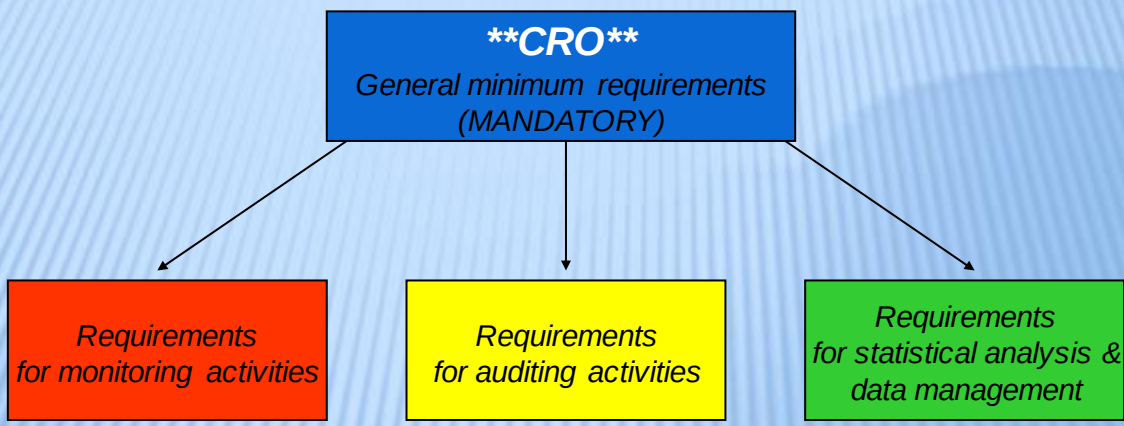

6

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ART. 3 – General minimum requirements

a) organisational and structural requirements:

1) official acts of the CRO (deed of constitution and articles of association) consistent with the objective of the CRO itself;
2) a list of the activities that the CRO is prepared to carry out;
3) organisation chart defining the positions responsible for the CRO's activity and names of people to which these activities are assigned;
4) there must be a medical director or a scientific director with respectively a degree in medicine and a degree in a scientific discipline that pertains to the tasks to be performed by the CRO, with documented experience of at least two years in one or more medical or scientific sectors in the CRO's areas of competence;
5) there must be personnel who is suitably qualified and in an adequate number to perform the activities foreseen;
6) the CRO must have operative headquarter adequately structured to ensure the correct undertaking of the CRO's activities, and the protected storage of confidential documents.

7

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ART. 3 – General minimum requirements

b) quality requirements:

1) standard operating procedures must be in force for the activities that the CRO has agreed to perform;
2) a quality assurance system must be set up and defined according to ISO or equivalent standards, which must be implemented and maintained and related quality manuals must exist;
3) documented quality assurance (QA) activities must be performed;
4) a quality assurance manager must be present holding a degree and with proven experience of at least one year of practice in the sector, who must also have undergone at least 15 days of theoretical training during the last two years in the area of general and specific CRO quality assurance activities in the last 2 years
5) an annual training program must be arranged, documented and implemented for employees and external consultants;
6) all the CRO activities must comply with GCP;
7) a suitable record system must be set up in order to ensure traceability of all CRO activities.

8

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ART. 3 – General minimum requirements

c) Staff refreshment training requirements:

1) the CRO personnel must perform annually at least 30 hours of refresher courses in their areas of competence

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ART. 4 – Requirements for monitoring activities

1. Should the CRO carry out activities of monitoring, the involved staff must satisfy at least the following requirements:

   a) a degree in a medical/scientific discipline that pertains to the type of work to be carried out;
   b) at least 40 hours of theoretical training during the 12 months before the start of the monitoring activities on the following topics:
      1) clinical trial methodology and regulations;
      2) GCP;
      3) Good Manufacturing practice (GMP) with specific reference to the investigational medicinal product being tested;
      4) pharmacovigilance;
      5) quality systems and quality assurance;
      6) monitoring tasks according to paragraph 5.18 of GCP

10

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ART. 4 – Requirements for monitoring activities

c) at least 20 days of monitoring activities shadowing expert monitors in the 12 months prior to the beginning of the autonomous monitoring activities. At least 50% of this must have taken place at the clinical sites before a trial commences, during the trial, and after the conclusion of a trial;

d) at least 4 months of activity in the 12 months preceding the beginning of the autonomous monitoring activities within the sector of control or vigilance of medicinal products and/or clinical trials; as an alternative, an additional 40 days of the activities described before at letter c) during the 12 months preceding the beginning of the autonomous monitoring activities; as an alternative the completion of a masters degree in clinical trials or regulatory science or in an equivalent discipline;

e) specific training in the type of trial to be monitored.

11

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ART. 4 – Requirements for monitoring activities

3. The CRO must use monitors who, in addition to the requirements of paragraph 1 and 2, will partake in specific annual refresher courses of a duration not inferior to 30 hours pertaining to one or more of the following subjects:
   1) clinical trial methodology and regulations;
   2) GCP;
   3) Good Manufacturing practice (GMP) with specific reference to the investigational medicinal product being tested;
   4) pharmacovigilance;
   5) quality systems;
   6) clinical and scientific topics relevant to clinical trials
   7) other topics connected with the duties to be performed.

4. For the monitoring of trials or clinical sites that use advanced technological systems, such as for example, electronic case report forms (e-CRF), it is necessary to demonstrate to have undergone suitable training and refresher courses in the specific sector.

12

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Experienced monitors, according to this decree, annually perform at least 15 days of monitoring visits.

13

ITALIAN DECREE 15 NOVEMBER 2011

ART. 5 – Requirements for auditing of trials or clinical sites

1. Should the CRO carry out activities of auditing of trials or clinical sites, he must have the related personnel who satisfy at least the following requirements:

a) University degree in a healthcare/scientific discipline;
b) at least 60 hours of theoretical training during the 12 months prior to the beginning of the auditing activities pertaining to the following subjects:

1) quality systems and quality assurance;
2) methods and regulations of clinical trials;
3) GCP;
4) Good Manufacturing Practice (GMP) with specific reference to the investigational product ;
5) pharmacovigilance;
6) auditor's tasks according to paragraph 5.19 of GCP

14

ITALIAN DECREE 15 NOVEMBER 2011

ART. 5 – Requirements for auditing of trials or clinical sites

c) at least 20 days of auditing activities shadowing expert auditors during the 12 months preceding the beginning of the autonomous auditing activities;

d) at least 4 months of activity in the 12 months preceding the beginning of the autonomous auditing activities in the sector of control or vigilance of medicinal products or clinical trials; alternatively, further 40 days of the activities described in letter c)

or 60 days of activities as a monitor performed during the 12 months preceding the beginning of the autonomous auditing activities;

e) specific training in the trial to be audited.

15

ITALIAN DECREE 31 MARCH 2008

ART. 5 – Requirements for auditing of trials or clinical sites

[…]

3. The CRO must make use of auditors who, in addition to the requirements of paragraph 1 and 2, folow specific annual refresher courses of a duration not less than 30 hours on one or more of the following subjects:

a) methodology and regulations relating to clinical trials;
b) GCP;
c) GMP with specific reference to the investigational medicinal product;
d) quality system;
e) pharmacovigilance;
f) clinical-scientific subjects that pertain to clinical trials;
g) other subjects pertaining to the tasks to be carried out.

16

ITALIAN DECREE 31 MARCH 2008

ART. 5 – Requirements for auditing of trials or clinical sites

4. For auditing of trials or clinical sites that use advanced technological systems, such as for example, electronic case report forms (e-CRF) it is necessary to demonstrate to have undergone suitable training and refresher courses in the specific sector.

17

ITALIAN DECREE 31 MARCH 2008

Experienced auditors, according to this decree, perform at least 12 days of auditing annually.

ITALIAN DECREE 31 MARCH 2008

ART. 6 – Requirements for statistical analysis and data management

1. Should the CRO carry out the statistical analysis of the data coming from clinical trials, they must make use of a qualified statistician who has at least the following requirements:

   a) degree in statistics discipline or in an equivalent discipline related to his tasks or a degree in a discipline of a scientific type with an adequate training in statistics or university specialization, doctorate or master in a statistical discipline;
   b) at least two years of experience on topics pertaining to his responsibilities;
   c) annual refresher courses on topics pertaining to his responsibilities;

19

ITALIAN DECREE 31 MARCH 2008

ART. 6 – Requirements for statistical analysis and data management

2. The data management activities must be carried out by qualified personnel and through appropriate software validated according to what is foreseen by GCP.

3. The CRO must have facilities and IT systems capable of ensuring physical and logical data security in order to carry out the activities set forth in this article.

ITALIAN DECREE 31 MARCH 2008

ART. 7 – Effect and notification of the requirements

1. From the date of effect of this decree, only CROs satisfying the requirements set forth above may operate in Italy.

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4. Individual professionals and technical workers who, within their independent professional activities or consulting activities, after having stipulated contracts with the sponsor of the trials or with a CRO, perform single functions referred to in this Decree, must satisfy the same requirements foreseen by this Decree in order to perform that functions and must operate within the quality system of such structures.

21

ITALIAN DECREE 31 MARCH 2008

ART. 7 – Performance and notification of the requirements

5. The CROs who, before the entrance into force of this Decree satisfy the foreseen requirements, in order to continue to operate must provide notification, before the Decree enters into force, of the possession of the aforementioned requirements by means of self-certification drawn up in compliance with a specific Determination by the Director General of AIFA, issued on the same date as this Decree, and to be sent to the GCP inspectorate and the Office or Clinical Trials of the Italian Medicines Agency (AIFA).

6. In the event of the activation of new CROs after the date this Decree enters into force, the notification be made at least 30 days before the beginning of the activity.

7. The possession of the requirements pursuant to this Decree, notified according to this article must be subject to verification by the AIFA, within the inspection activities […]

22

ITALIAN DECREE 31 MARCH 2008

ART. 8 – Legal Representation

1. The CROs with headquarters outside Italy who intend to carry out activities within Italian territory must have legal representation in one of the member states of the European Union and must have requirements that are at least equivalent to those set forth by this Decree.

ITALIAN DECREE 31 MARCH 2008

Definition

Contract Research Organisation (CRO):

a company, an institution or a private organisation contracted by the sponsor to perform any or all of his trial-related functions (protocols design, selection of clinical sites and investigators, selection and use of monitors, elaboration of reports, statistical analysis, preparation of the documentation to be submitted to competent authorities etc.) as foreseen by good clinical practice, without prejudice to the sponsor's responsibility for the related trial;

24

THANK YOU
FOR YOUR ATTENTION