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MINISTRY OF HEALTH

DECREE November 15, 2011.

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

THE MINISTRY OF HEALTH


Having regard to Legislative Decree no. 211 of June 24, 2003, published in the ordinary supplement to the Official Journal no. 184 of August 9, 2003, concerning the “Transposition of Directive 2001/20/EC relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use”;

Having regard specifically to article 20, paragraph 3, of the said Legislative Decree no. 211 of June 24, 2003, which specifies that the minimum requirements for private organizations that trial sponsors may appoint to conduct part or all of their clinical trial activities, as envisaged by standards of Good Clinical Practice, are established by Ministry of Health Decree, without prejudice to the trial sponsor’s own trial responsibilities, and considering that such organizations correspond to the Contract Research Organizations (CROs) set forth in paragraph 1.20 of attachment 1 to the said Ministerial Decree of July 15, 1997;

Having regard to Legislative Decree no. 200 of November 6, 2007, published in the ordinary supplement to the Official Journal no. 261 of November 9, 2007, concerning the “Implementation of Directive 2005/28/EC relating to the principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorization of the manufacturing or importation of such products”;

Having regard specifically to article 6, paragraph 3, of the said Legislative Decree no. 200 of November 6, 2007, that governs the sponsor’s ability to delegate its activities to private companies, institutes, organizations or persons satisfying the said minimum requirements;

Having regard to Decree of Minister of Health of March 31, 2008, concerning the “Definition of the minimum requirements which Contract Research Organizations (CROs) shall satisfy in order to work within clinical trials on medicinal products”;

Having regard to AIFA Director General Determination of December 23, 2008, “Self-certification of the minimum requirements of the Contract Research Organizations (CROs) within the field of clinical trials of medicines according to article 7, paragraphs 5 and 6, and of article 8 of the ministerial decree March 31, 2008”;

Having regard to Decree of Republic President dated November 18, 2010, through which, according to the complying opinion of the State Council no. 3922/2009, it has been accepted the extraordinary appeal to the Republic President for the revocation, prior suspension, of the same Decree of March 31, 2008;

Considered necessary to issue a new regulation that, completely replacing the one designated by the Minister of Health Decree of March 31, 2008, explicits and details further professional people and activities not covered by prior Decree;

Hereby issues:

Article 1.

Area of application

1. This decree establishes the minimum requirements that must be satisfied by private organizations as set forth in article 20, paragraph 3, of Legislative Decree no. 211 of June 24, 2003, or any other organization to which the sponsor has entrusted all or part of its clinical trial competencies and defined at the hereinafter article 2 as contract research organizations (CROs).

Article 2.

Definitions

1. For the purposes of this decree the following definitions shall apply:

a) Contract Research Organization (CRO): a private company, institute or organization with which the trial sponsor has drawn up a contract to transfer all or part of its clinical trial activities (drafting of protocol, selection of centers and investigators, selection and use of monitor, preparation of reports, statistical analysis, preparation of documents for submission to regulatory authorities, etc.), as envisaged by standards of Good Clinical Practice, without
prejudice to the trial sponsor’s own trial responsibilities;

b) Standards of Good Clinical Practice (GCP): standards set forth in attachment 1 to Ministerial Decree of July 15, 1997 and in Legislative Decree no. 200 of November 6, 2007, referred to in the recitals;

c) Trial Sponsor: a company, institute or body that assumes the responsibility of starting, managing and possibly financing a clinical trial. A person who, in addition to assuming this role, also acts as investigator in the facilities set forth in article 1, paragraph 2, letter a) of Ministry of Health Decree of December 17, 2004, is also considered a trial sponsor, in trials conducted for non-industrial purposes in the context of institutional duties only;

d) Monitor: the person who evaluates the trial’s progress at the clinical centers to guarantee that the research is conducted in compliance with the protocol, Standard Operating Procedures (SOP), applicable legislation and standards of Good Clinical Practice (GCP) and who is responsible for trial monitoring activities as set forth in attachment 1 to Ministerial Decree of July 15, 1997;

e) Quality Assurance (QA): the set of planned, systematic procedures prepared to ensure:

1) that studies entrusted to the CRO are conducted and data is produced, documented (recorded) and communicated in respect of GCP and applicable legislation;

2) that all CRO activities meet the quality requisites.

f) Inspection or Auditing: systematic, independent inspection of the study activities and documents to determine whether the study/trial center activities have been carried out and if data has been recorded, analyzed and accurately transmitted in compliance with the protocol, the CRO’s and sponsor’s Standard Operating Procedures, Good Clinical Practice (GCP) and applicable legislation:

g) Inspector or Auditor: person assuming responsibility for and coordinating the CRO’s auditing activities;

h) Medical or Scientific Director: person coordinating and assuming technical and scientific responsibility for the medical or scientific aspects of the CRO’s activities;

i) Supervising Statistician: person coordinating and assuming technical and scientific responsibility for the statistical aspects of the CRO’s activities;

j) Experienced Monitor: person having the requirements hereinafter defined at article 4, paragraph 1 or 2 as well as the requirements set forth in article 4, paragraph 5;

m) Experienced Auditor: person having the requirements hereinafter defined at article 5, paragraph 1 or 2 as well as the requirements set forth in article 5, paragraph 5;

n) Clinical Trial: clinical trial on medicinal product as set forth in Legislative Decree no. 200 of November 6, 2007, letter o), paragraph 1, article 1.

Article 3.

General minimum requirements

1. In order to operate, the CRO must satisfy at least the following general requirements:

a) organizational and structural requirements:

1) existence of a deed of constitution and articles of association coherent with the purpose of the CRO;

2) existence of a list of activities that the CRO is prepared to carry out;

3) presence of an organization chart that defines the positions responsible for the CRO’s activities and the people to which such activities are assigned;

4) presence of a medical or scientific director with a degree in medicine or a scientific subject relevant to the CRO’s activities, with documented experience of at least two years in one or more medical or scientific sectors in the CRO’s areas of competence;

5) presence of a sufficient number of staff qualified to carry out the envisaged activities;

6) availability of an operating site that is adequately structured to ensure the correct conduct of the CRO’s activities and the protected storage of confidential documents.

b) Quality requirements:

1) presence of standard operating procedures for the activities that the CRO is available to carry out;

2) presence of an implemented and active quality assurance system established and defined according to ISO or equivalent standards, and relative quality manual;

3) documented quality assurance (QA) activities;

4) presence of a degree-holding QA supervisor with documented experience of at least 1 year of practical activity in the sector and at least 15 days of theoretical training in general and specific CRO quality assurance activities in the last two years; this person is not necessarily overlapping to the clinical trials auditor hereinafter defined at article 5;

5) preparation and documented implementation of an annual training program for employees and external consultants;

6) compliance of all CRO activities with GCP;
7) record system capable of ensuring traceability of all CRO activities.

c) Staff refresher training requirements:

1) CRO staff involved in technical-scientific and quality assurance/check activities, which the CRO accepts to perform, as well as the staff as set forth at paragraph 1, letter a), dot 4), must perform, without prejudice to other specific provisions, at least 30 hours every 12 months, of refresher training in their areas of competence. Administrative, finance, human resources and general service staff is exempted from the said refresher training.

Article 4.

Monitoring activity requirements

1. CROs that perform monitoring activities must have staff with at least the following requirements:

a) degree in a healthcare/scientific subject relevant to the activities to be conducted;

b) at least 40 hours theoretical training in the 12 months prior to the start of monitoring activities on the following topics:

1) clinical trial methodology and legislation;

2) GCP;

3) standards of Good Manufacturing Practice (GMP), with specific reference to the investigational medicinal product;

4) pharmacovigilance;

5) quality systems and quality assurance;

6) monitor duties as set forth in paragraph 5.18 of attachment 1 to Ministerial Decree of July 15, 1997;

c) at least 20 days of monitoring activities shadowing expert monitors in the 12 months prior to the start of autonomous monitoring activities. At least 50% of this must have taken place at trial centers before the start, during the conduct and after the conclusion of a trial; for staff with documented experience in coordinating monitors activities, through specific on-site activity, performed for at least 6 months within the 12 months prior to the start of autonomous monitoring activities, a minimum of 5 days of accompaniment expert monitor is required, 3 of which during the visits at trial sites;

d) at least 4 months of activity in the 12 months prior to the start of autonomous monitoring activities in the sector of medicinal product or clinical trial control or vigilance; alternatively, a further 40 days of activity as set forth in letter c) in the 12 months prior to the start of autonomous monitoring activities; alternatively, attainment of a masters degree in clinical trials or regulatory sciences or an equivalent subject in the 36 months prior to the start of autonomous monitoring activities;

e) specific training in the trial to be monitored.

2. Anyone, from the effective date of this decree, who have performed the trial monitor activities as set forth in paragraph 5.18 of attachment 1 to Ministerial Decree of July 15, 1997, and is able to demonstrating said activities, is exempted from complying with the requirements set forth at paragraph 1, letters a), b), c) and d) and may continue to carry out their activities.

3. The CRO must use monitors who, in addition to the requirements set forth in paragraphs 1 and 2, undergo at least 30 hours specific annual refresher training on one or more of the following topics:

a) clinical trial methodology and legislation;

b) GCP;

c) GMP with specific reference to the investigational medicinal product;

d) quality systems;

e) pharmacovigilance;

f) clinical and scientific topics relevant to clinical trials;

g) other topics connected with the duties to be performed.

4. For the monitoring of trials or centers using advanced IT systems, such as electronic case report forms (e-CRFs), suitable training and refresher training in the specific sector must be demonstrated.

5. Experienced Monitor, as set forth in article 2, letter l) of this Decree, is the person able to perform autonomous monitoring activities and annually performs at least 15 days of monitoring visits.

6. For monitors and experienced monitors, the justified interruption of their activity does not prevent the resumption of the same activity and does not lead to the loss of status. However, only for the monitor, in case of justified interruption of the activity for more than 12 months, prior to the resumption of autonomous monitoring activities, it is required a minimum of 2 accompaniment visits with personnel having the same status and for the same activities.

Article 5.

Requirements for auditing of trials or trial centers

1. CROs that perform auditing activities of trials or trial centers must have staff with at least the following requirements:

a) University or master’s degree in a healthcare/scientific discipline relevant to the activities to be conducted;

b) at least 60 hours of theoretical training in the 12 months prior to the start of auditing activities on the following topics:

1) quality systems and quality assurance;
2) clinical trial methodology and legislation;
3) GCP;
4) Good Manufacturing Practice (GMP), with specific reference to the investigational medicinal product;
5) pharmacovigilance;
6) auditor duties as set forth in paragraph 5.19 of attachment 1 to Ministerial Decree of July 15, 1997;

a) at least 20 days of auditing activities shadowing expert auditors in the 12 months prior to the start of autonomous auditing activities; at least 50% of which shall take place during the visits at trial sites;

b) at least 4 months of activity in the 12 months prior to the start of autonomous auditing activities in the sector of medicinal product or clinical trial control or vigilance; alternatively, a further 40 days of activity as set forth in letter c) or 60 days of activity as a monitor in the 12 months prior to the start of autonomous auditing activities; alternatively, attainment of a post-graduate university master in advanced IT systems, such as electronic case report forms (e-CRFs), suitable training and refresher training on one or more of the following topics:

- quality systems;
- pharmacovigilance;
- clinical and scientific topics relevant to clinical trials;
- other topics connected with the duties to be performed.

4. For the auditing of trials or centers using advanced IT systems, such as electronic case report forms (e-CRFs), suitable training and refresher training in the specific sector must be demonstrated.

5. Experienced auditor, as set forth in article 2, letter m) of this Decree, is the person able to perform autonomous auditing activities and must undergo at least 12 days of auditing annually.

6. For auditors and experienced auditors, the justified interruption of their activity does not prevent the resumption of the same activity and does not lead to the loss of status. However, only for the auditor, if the activity is interrupted for more than 12 months, prior to the resumption of autonomous monitoring activities, it is required a minimum of 2 accompaniment auditing visits with personnel having the same status and for the same activity.

7. Persons who, from the effective date of Ministerial Decree of March 31, 2008, had requirements set forth in the said decree and performed at least 1 auditing visit, may continue to carry out their activities tough they attained a degree in a non-health/scientific subject.

Article 6.

Requirements for statistical analysis and data management

1. CROs that perform statistical analysis on data originating from clinical trials must use a qualified supervising statistician who satisfies at least the following requirements:

- degree in a statistical or equivalent subject for the conduct of his/her duties or degree in a scientific subject whose curriculum includes suitable training in statistics or a post-graduate specialization, masters or doctorate in statistics;

- at least two years’ experience in the areas of responsibility;

- annual refresher training on the areas of responsibility.

2. Data management activities must be carried out by qualified staff using suitable software validated as required 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.
qualifications set forth in article 6, paragraph 1, letter a).

4. Individual professionals or workers who carry out individual functions set forth in this decree as part of their freelance or consultant activities and under contract with the trial sponsor or a CRO, must possess the requirements specified by this decree for the conduct of such functions and must operate within the organization’s quality system.

5. CROs that, from the effective date of this decree, already notified their requirements, are not obliged to notify them again and may continue to carry out their activities. On the contrary, constituted CROs subsequent to the effective date of the Ministerial Decree of March 31, 2008 and which have not yet notified their registration into the National Monitoring Centre on Clinical Trials of Drugs “OssSc” (“Osservatorio nazionale sulla Sperimentazione Clinica dei Medicinali”), must, in order to continue their activities, give notification that they comply with such requirements through self-certification, drawn up in compliance with the attachments to this decree, to be sent to the GCP Inspectorate and Research and Clinical Trial Office of AIFA, within 15 days from the effective date of this decree.

6. In the event of the activation of new CROs subsequent to the effective date of this decree, notification as set forth in paragraph 5 must be made at least 30 days prior to the start of activities.

7. Satisfaction of the requirements set forth in this decree, notification of which is given pursuant to this article, may be subject to verification by AIFA as part of its inspection activities as set forth in article 15 of Legislative Decree no. 211 of June 24, 2003, and in Chapters V and VI of Legislative Decree no. 200 of November 6, 2007.

8. CROs, pharmaceutical companies and sponsor of clinical trials must issue to employees and/or consultants, legally claimants and applying for it, a certification attesting the performed activities related to this decree.

Article 8.

Legal representation and sponsors responsibility

1. CROs located outside Italy that intend to carry out activities in Italy must have legal representation in one of the European Union member States and must meet requirements at least equivalent to those set forth in this decree.

2. This decree does not exempt sponsors, who transfer all or part of their clinical trial activities to a CRO, from their responsibility attributed by current regulations on clinical trials.

Article 9.

Information notification