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European Regulatory Newsletter
April 2013



Introduction

CROMSOURCE is committed to sharing our expertise with our clients and future clients. This reflects the first part of our 'Advise Agree Deliver' motto! In this spirit we have pleasure in making available this the first issue of our Regulatory Newsletter.

This newsletter is put together by our expert regulatory team and tracks the changes occurring in European regulations relating to clinical research performed in both medicinal products and medical devices.

In future the Newsletter will be a quarterly publication distributed via email and posted on the CROMSOURCE website. We hope you find this information useful, and welcome feedback, questions and suggestions. Contact us on cromsource@cromsource.com at any time.



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your projects.
High quality, on time, on budget.
Guaranteed.

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At CROMSOURCE we believe experts should keep their word. After 18 years of success we provide the industry's only End-to-End Guarantee™. Starting at the RFP stage with our uniquely detailed Feasibility Plus™ process we guarantee:

1. Your study will start on time
2. We will enroll 100% of the contracted patients
3. We will finish on time with a set date for database lock
4. The price you contracted is the price you pay. No CRO-initiated changes-in-scope.

We know that budgets must be competitive, and you can rest assured that our End-to-End Guarantee™ does not come with a premium price. As an ISO-certified organization, you can also rest easy about quality. **Don't you owe it to your project to learn more?**

Contact us to request more information.

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TIME, COST & QUALITY GUARANTEED

 **ONE TRIAL ONE PRICE™**
GUARANTEED FIXED PRICE BUDGET

 **FEASIBILITY PLUS™**
GUARANTEED ENROLMENT & TIMELINES

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Update from the European Commission



Technical Guidance on the Format of the Data-Fields of Result- Related Information on Clinical Trials, published on 22 January 2013

In a context of transparency of information related to clinical trials, the EU legislation provides that certain information contained in the EudraCT is made accessible to the public. This accessibility concerns both protocol and results-related information. For the time being, protocol-related information has been made public; results-related information, not.

The technical guidance provides a visual representation on how the clinical trial results data field will be organised in the EudraCT database. It can be found on :

http://ec.europa.eu/health/files/eudralex/vol-10/2013_01_22_tg_en.pdf

The programming of the database is currently ongoing.

As soon as the programming of the database will be completed, the sponsor of a clinical trial, the Marketing Authorisation Holder performing a Paediatric trial or the holder of a Paediatric Investigation Plan are required to post the trial results into the EudraCT database, within the required timeframe (6-months for a paediatric trial, 1 year for all other trials).

Updates from the EMA



Guidance for the Format and Content of the Protocol of Non-Interventional Post-Authorisation Safety Studies (PASS), effective since 10 January 2013

From 10 January 2013, Marketing Authorisation Holders (MAH) have the obligation to submit the protocol of a non-interventional post-authorisation study imposed by a national competent authority, EMA or the Commission, in a format complying with the provisions laid down in Annex III of Regulation 520/2012. The use of the format is recommended for PASS initiated voluntarily by the MAH.

The EMA guidance document provides recommendation for drafting PASS study protocols.

The guidance can be found on:

http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/10/WC500133174.pdf

Guidance for the Format and Content of the Final Study Report of Non-Interventional Post-Authorisation Safety Studies (PASS), published on 23 January 2013

From 10 January 2013, Marketing Authorisation Holders (MAH) have the obligation to submit the abstract and the final study report of a non-interventional post-authorisation study imposed by a national competent authority, EMA or the Commission, in a format complying with the provisions laid down in Annex III of Regulation 520/2012. The use of the format is recommended for PASS initiated voluntarily by the MAH.

The EMA guidance document provides recommendation for writing the abstract and the final study report of a PASS.

The guidance can be found on:

http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2013/01/WC500137939.pdf

Reflection paper on GCP Compliance in relation to trial master files (paper and/or electronic) for management, audit and inspection of clinical trials, published on 1 February 2013

This paper has been prepared by the EU GCP Inspectors Working Group, further to the repeated inspection findings concerning TMF and the numerous questions raised about TMF.

The paper aims to precise the requirements for TMF as laid down in Dir 2005/28/EC and the GCP guidelines and to provide recommendations in maintaining a TMF.

In particular, the paper addresses the following topics: archiving, e-TMF, retention timings and destruction of paper documentation.

The paper is on draft stage and is open for public consultation, up to 30 April 2013.

It can be found on:

http://www.ema.europa.eu/ema/doc_index.jsp?curl=pages/includes/document/document_detail.jsp?webContentId=WC500138893&murl=menus/document_library/document_library.jsp&mid=0b01ac058009a3dc

From Regulators in Individual European Countries

France

CNOM (Commission Nationale de l'Ordre des Médecins) – Contract Issue

According to French legislation, the draft contract(s) between the sponsor and the investigator and where applicable between the sponsor and the investigator's scientific association needs to be submitted for approval to CNOM, at least 2 months before site initiation.

In December 2011, the law Bertrand was voted, forbidding the pharmaceutical industry to provide gifts to physicians and scientific associations, with an exemption: fees paid to physicians, in the frame of a clinical research study.

In the past, many investigators were requiring to have their fees paid via their scientific association. Today, with its interpretation of the law Bertrand, CNOM does not accept sponsor/association contract, without a precise description of the tasks performed by the association versus those performed by the investigator and if the contract is only mentioning the bank account details of the scientific association. Indeed CNOM is requesting separate contracts: a contract sponsor/association covering the coordination and administration fees and a contract sponsor/investigator covering his/her medical activities in the clinical study.

A tri-partite contract , where the tasks of the investigator are clearly separated from those of the association, with a clear budget split, indication of two separate bank accounts and two fiscal certificates can however still be envisaged.

Italy

- **AIFA Determina 1/2013 “Management of clinical trials with drugs following the transfer of the role of Competent Authority to the Italian Medicines Agency”, published on 12 January 2013**
Temporary closure of Osservatorio and RSO, since 1 January 2013

On 8 November 2012, Law no189 providing for urgent measures to promote the country’s development through a higher level of protection of health, was published.

With the aim of streamlining the submission process of clinical trials with medicinal products, this law, modifying the existing Decree 211/03, sets up the following measures:

AIFA (Agenzia Italiana del Farmaco): sole Competent Authorities, for the approval of clinical trials with medicinal products.

It should be remembered than before the entry into force of this new law, 3 Competent Authorities were involved (Istituto Superiore di Sanità for Phase I trials, AIFA for ATMP’s trials, Site General Director for all other trials)

- ☐ By 1 July 2013, electronic submission of all clinical trial documentation through the electronic platform managed by AIFA (i.e. OsSC- Osservatorio Nazionale sulla Sperimentazione Clinica dei Medicinali)
- ☐ By 30 June 2003, each Italian region shall have re-organized the authorised EC’s within in its territory.

However, it should be noted that until the publication of the Decree of the Ministry of Health, the Istituto Superiore di Sanità remains the Competent Authorities for Phase I trials.

Modalities for the transfer of responsibilities from the Istituto Superiore di Sanità to AIFA will be specified in this decree. Accordingly, the re-organization of the transfer of responsibilities between Istituto and AIFA is under transition phase. Therefore, AIFA released on 12 January 2013, the Determina 1/2013, in order to provide guidance to applicants on how the two instances are cooperating, within this transition period.

Transitional dispositions are as follows:

- ☐ Until the publication of the Decree, the Istituto continues to manage approval for Phase I trials and provides support to AIFA.
- ☐ No fees are to be paid to AIFA

As AIFA is currently re-organizing its electronic platform for all electronic applications, the OsSC (Osservatorio Nazionale sulla Sperimentazione Clinica dei Medicinali) and the RSO (Register of Observational Studies) have been temporary closed, since 1 January 2013.

This means that the Italian system for both the submission and the communication of decisions between CA, EC, Regions, CRO and sponsors is currently unavailable.

Accordingly, AIFA has issued a communication, to explain to all stakeholders how to deal with clinical trial obligations, in this transition period.

United Kingdom

MHRA – Revised Guidance for the Notification of Serious Breaches of GCP or the Trial Protocol, published on 7 February 2013

In accordance with Statutory Instrument 2004/1031 (Medicines for Human Use (Clinical Trials) Regulation), the sponsor shall notify the UK authorities in writing of any serious breach to GCP or the trial protocol, within 7 days of become aware of that breach.

MHRA revised guidance provides instructions for notifying UK authorities

Serious breach notifications should now be notified by e-mail only, at the following address:

GCP.SeriousBreaches@mhra.gsi.gov.uk.

The revised guidance is also providing an appendix with Frequently Asked Questions relating to specific serious breaches topics. The list of examples of serious breaches to be notified has also been extended.

The guidance can be found on:

<http://www.mhra.gov.uk/home/groups/is-insp/documents/websiteresources/con060111.pdf>



Updates from the European Commission

Updated References of Harmonised Standards under Directives 90/385/EEC, 93/42/EEC and 98/79/EEC, published on 24 January 2013

In order to demonstrate the conformity of a medical device with the essential requirements laid down in Annex I of Directives 90/385/EEC, 93/42/EEC and 98/79/EEC, the medical device manufacturer must use harmonised standards.

The updated list of the Harmonised Standards to be used was published on 24 January 2013 and can be found on:

http://ec.europa.eu/enterprise/policies/european-standards/harmonised-standards/medical-devices/index_en.htm

With respect to clinical investigation, the harmonised standard remains ISO 14155:2011.

Regulation 207/2012, in force on 1 March 2013

This regulation sets up the conditions under which a manufacturer may provide the Instructions for Use of a medical device in electronic format instead of in paper form.

Electronic format can be used for the following medical devices: active implantable, implantable, fixed installed, devices fitted with a built-in system visually displaying the instructions, stand-alone software. For these devices, electronic format may be used provided the devices and accessories are intended for exclusive uses by professional users and the use by anybody else cannot reasonably be foreseeable.

MEDDEV 2.12-1 rev 8, published on 24 January 2013

This guideline describes the European Medical Device Vigilance System, i.e. the European System for the notification and evaluation of incidents and field safety corrective actions for CE marked medical devices. It specifies the action to be taken once the Manufacturer or National Competent Authorities receives information concerning a medical device incident.

It applies to the following devices: CE-marked, custom-made, placed on the market before the entry into force of the medical device directives.

It can be found on : http://ec.europa.eu/health/medical-devices/files/meddev/2_12_1_ol_en.pdf

The revised guideline will be applicable as of July 2013.