Commission Guideline — Guidance on posting and publication of result-related information on clinical trials in relation to the implementation of Article 57(2) of Regulation (EC) No 726/2004 and Article 41(2) of Regulation (EC) No 1901/2006

(2012/C 302/03)

1. CONTEXT

This guidance document sets out aspects of the implementation of Article 57(2), third subparagraph of Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing the European Medicines Agency ([1]), and of Article 41(2) of Regulation (EC) No 1901/2006 on medicinal products for paediatric use ([2]).

It addresses the posting and publishing of result-related information relating to clinical trials, thus implementing the EU legislation aiming to make the results of clinical trials publicly available — a policy aim which is maintained in the proposal of the Commission for a regulation of the European Parliament and of the Council on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC ([3]). This guidance document also gives guidance as to how non-compliance and factual inaccuracy are addressed.

This guidance document completes the following Commission guidance documents:

— Guideline 2010/C82/01 on the request to the competent authorities for authorisation of a clinical trial on a medicinal product for human use, the notification of substantial amendments and declaration of the end of the trial (hereinafter 'detailed guidance CT-1') ([4]), and in particular Section 4.3 thereof,

— Guideline 2008/C168/02 on the data fields contained in the clinical trials database provided for in Article 11 of Directive 2001/20/EC to be included in the database on medicinal products provided for in Article 57 of Regulation (EC) No 726/2004 ([5]), and in particular Sections 3 to 5 thereof, and

— Guideline 2009/C28/01 on the information concerning paediatric clinical trials to be entered into the EU Database on Clinical Trials (EudraCT) and on the information to be made public by the European Medicines Agency (EMEA), in accordance with Article 41 of Regulation (EC) No 1901/2006 ([6]), and in particular Sections 3.2 to 3.4 and Section 5 thereof.

Those Commission guidance documents had been further detailed by two implementing technical guidances published in 'EudraLex — the rules governing medicinal products in the European Union' on the 'List of fields to be made public from EudraCT for Paediatric Clinical Trials in accordance with Article 41 of Regulation (EC) No 1901/2006' and the 'List of fields contained in the "EudraCT" clinical trials database to be made public, in accordance with Article 57(2) of Regulation (EC) No 726/2004.' ([7]).

2. SCOPE

This guidance document addresses the posting and publication of clinical trials as defined in Article 2(a) of Directive 2001/20/EC with at least one of the following characteristics:

— the clinical trial is regulated or was regulated by Directive 2001/20/EC, which took effect at the latest on 1 May 2004 (on the posting of result-related information on clinical trials which have ended in the past, see section 4.6.1). This implies that at least one investigator site of the clinical trial is located in the European Union (EU) or in a contracting State of the European Economic Area,

— the clinical trial forms part of a paediatric investigation plan including those where the investigator sites are outside the European Union (EU) ([8]),

— the clinical trial falls within Article 45 of Regulation (EC) No 1901/2006,

— the clinical trial falls within Article 46 of Regulation (EC) No 1901/2006.

3. CONTENT OF POSTED RESULT-RELATED INFORMATION

The result-related information should be posted in accordance with this Guideline for all clinical trials referred to in Section 2.

The content of the results-related information is set out in the Guideline 2009/C28/01. The information set out there applies for paediatric as well as non-paediatric clinical trials.

The implementing technical guidance on the format of the data fields (hereinafter 'full data set') is published in a separate

([1]) OJ L 136, 30.4.2004, p. 1.
([2]) OJ L 378, 27.12.2006, p. 1.
([3]) COM(2012) 369 final, 17.7.2012.
([4]) OJ C 82, 30.3.2010, p. 1.
([5]) OJ C 168, 3.7.2008, p. 3.
([6]) OJ C 28, 4.2.2009, p. 1.
([7]) http://ec.europa.eu/health/documents/eudralex/vol-10/index_en.htm
([8]) Article 41(1) of Regulation (EC) No 1901/2006.

document in 'EudraLex — the rules governing medicinal products in the European Union', thus completing the two implementing technical guidances on the 'List of fields to be made public from EudraCT for Paediatric Clinical Trials in accordance with Article 41 of Regulation (EC) No 1901/2006' and the 'List of fields contained in the "EudraCT" clinical trials database to be made public, in accordance with Article 57(2) of Regulation (EC) No 726/2004.' ([9]).

The data fields in that detailed technical guidance take account of international harmonisation efforts. The content of the data fields is kept identical with the U.S.-database 'clinicaltrials.gov', with limited exceptions to take account of particularities like the EU paediatric investigation plan, as well as evolving changes of international databases or international harmonisation efforts.

4. MODALITIES OF POSTING AND PROCESSING OF RESULT-RELATED INFORMATION

By posting result-related information to the European database referred to in Article 11(1) of Directive 2001/20/EC (hereinafter 'EudraCT') the sponsor, the addressee of the decision on a paediatric investigation plan or the marketing authorisation holder, as appropriate, comply with Article 41(2) of Regulation (EC) No 1901/2006. Moreover, this posting is considered as the submission of the clinical trial summary report as part of the end-of-trial-declaration to national competent authorities as set out in Section 4.3 of the detailed guidance CT-1. Where the result-related information is published (see Section 5), it is considered as submission to the Ethics Committee as set out in Section 4.2.1 of the detailed guidance CT-1.

4.1. Posting of data

The result-related information is posted to EudraCT either directly entering data using a web interface provided by the European Medicines Agency (hereinafter 'the Agency'), by uploading a XML file via the web interface, or using a gateway technology. The data are posted to a secure module of EudraCT.

The information should be provided in accordance with an XML schema established and published by the Agency.

The information is posted:

— by the addressee of the decision on a paediatric investigation plan, where the clinical trial forms part of a paediatric investigation plan,

— by the marketing authorisation holder, where the clinical trial falls within Articles 45 and 46 of Regulation (EC) No 1901/2006,

— by the sponsor of the clinical trial for all other clinical trials referred to in Section 2.

To this end the party responsible for posting the information is provided with a secure account to enable uploading and editing of these data in the system. That party has access only to their own data. This access will enable the posting and maintenance of the data in a secure part of the system. The further processing and making public of this information is controlled by the Agency.

Certain fields of the protocol-related data will be used to present the context of the trial facilitating the presentation of the result-related information. The corresponding protocol-related information will automatically be loaded, from EudraCT, into these fields when result-related information is provided via the web interface or on a pre-populated XML downloaded. On the occasion of posting result-related information, these fields may be updated by means of the web interface or alternatively via posting of an updated XML-file with protocol-related information.

In general, a comment field is made available linked to data fields other than free text fields. The comment field is intended to allow for inclusion of information supplementing the fixed field contents. The structure of the collected data accommodates the large majority of clinical trials; however, the comment field may be used if data fields do not adequately accommodate the required information.

4.2. Processing

In the secure part of the system, an automated technical validation may take place. In case issues are identified, the posting of the information will be blocked. A validation report will be provided to the posting party with instructions on how to resolve or clarify the issues.

The data are then entered into EudraCT, and information on clinical trials to be made public are selected by the applicable business rules and made public in the EU Clinical Trials Register of EudraPharm (see Section 5). They will be linked to the protocol-related data, where the latter are available in EudraCT.

It is not possible for the public to access the secure module. The posting of result-related information does not overwrite existing protocol-related information that is stored in EudraCT.

([9]) See footnote 7.

4.3. **Timing**

Result-related information should be posted within the time-frames set out in the Regulation (EC) No 1901/2006 and the guidelines referred to under Section 1, i.e. (relating to paediatric clinical trials) within six months ([10]) and otherwise within one year of the end of the trial ([11]).

It is recommended that result-related data should be posted prior to these dates if such information is already available. This is the case, for example, if results have already been published in scientific journals, or if a primary completion date is foreseen before the end of the trial.

If the clinical trial ends prematurely, that date should be considered the end of the trial.

Only one set of result-related data may be provided per planned analysis and trial. If the outcome is analysed on several occasions, each of these analyses should be posted.

4.4. **Language**

The result-related information is largely numerical, or based on value list definitions, using pre-defined options or terminology-lists.

Regarding free text fields the system will permit the entry of more than one language (from the official languages of the EU). In accordance with WHO standard and to facilitate the international use outside the EU, information should be posted in English. In addition, the information may be posted in any other official EU language.

4.5. **Data updates and follow-up posting**

Some protocol-related information, as well as the result-related information (e.g. contact points for further information or enrolment status), will be available for update by the posting party, in such a way that the updated information is made directly available in the public domain subject to technical controls being met.

Each version of protocol-related information and result-related data will be stored and posting of new versions will not result in deletion of previously posted versions, thus providing a record of changes.

4.6. **Provisions for results of clinical trials which have ended in the past**

4.6.1. *Clinical trials within the scope of Directive 2001/20/EC*

Result-related information on clinical trials which ended less than one year prior to finalisation of the programming referred to in Section 6 should be posted within one year of the finalisation of the programming by using the full data set (see Section 4.1).

Result-related information on clinical trials which ended one year or more prior to finalisation of the programming referred to in Section 6 may be posted either by using the full data set (see Section 3) or by using the method for clinical trials within the scope of Article 45 of Regulation (EC) No 1901/2006 (see below). This should be done within 24 months of the finalisation of the programming referred to in Section 6.

4.6.2. *Clinical trials referred to in Regulation (EC) No 1901/2006*

An alternative posting process will be made available for clinical trials referred to in Article 45 of Regulation (EC) No 1901/2006. For these clinical trials the posting of result-related information to the Agency for the purpose of publication may be done as a copy, authorised by the copy-right-holder, of a medical journal article (as PDF file), as the synopsis in accordance with Annex I to the ICH Topic E 3 guidance (as PDF file), or any other appropriate document containing the information of that synopsis (as PDF file). For these cases, a set of fields will be established in EudraCT to identify the clinical trial involved, to facilitate searching and to allow attachment of the PDF file. This result-related information should be posted within 24 months of the finalisation of the programming referred to in Section 6.

Result-related information of clinical trials included in an agreed paediatric investigation plan (Article 41(1) of Regulation (EC) No 1901/2006), and of marketing authorisation holder-sponsored trials which involve the use in the paediatric population of a medicinal product covered by a marketing authorisation (Article 46 of Regulation (EC) No 1901/2006), and which ended prior to finalisation of the programming referred to in Section 6, should be posted within one year of the finalisation of the programming by using the full data set (see Section 4.1).

4.7. **Non-compliance, factual inaccuracy**

Member States should verify that for clinical trials authorised by them the result-related information is posted to the Agency.

Clinical trials for which no result-related information has been posted 9 months after the end of the trial (see Section 4.3) for paediatric trials or 15 months for other trials will be flagged. This information will be publicly available. The anticipated duration of the trial is entered at the time of the clinical trial application. The actual end of the trial is notified through the 'Declaration of the end of trial form'.

All corrections to published information will be made by the party posting that information, sometimes upon request by the Agency.

([10]) Section 2.2.2 of Guideline 2009/C28/01.

([11]) For the term 'end of the trial' see Section 4 of the detailed guidance CT-1.

If inspections of compliance with good clinical practice (GCP) reveal that there are serious doubts about the accuracy or reliability of the result-related data, the Agency will be informed immediately.

The Agency will retain the possibility of:

— removing information from the public view,

— highlighting that the result-related information may not be valid in view of GCP non-compliance, or

— adding a notice to the public record, where necessary for reasons of factual accuracy or compliance with regulatory requirements.

5. PRESENTATION OF THE RESULT-RELATED INFORMATION TO THE PUBLIC

The posted result-related information is made public through the EU Clinical Trials Register of EudraPharm in accordance with the Commission guidance documents set out under Section 1, i.e. only result-related information on non-paediatric Phase-I clinical trials is not made public.

The result-related information is made public within 15 working days from the posting of a valid data set.

The results-related information of each clinical trial is linked to the corresponding protocol-related information which is already stored in the system.

Regarding follow-up posting (see Section 4.5), by default, the current version will be presented first for public access, but previous versions may also be viewed by the public.

In addition to being readable *in situ* on the web, the data will also be made available in a printable format and in a downloadable format.

The web interface is going to provide tools to facilitate the searching, reading and browsing of the public information on clinical trials and their results.

6. IMPLEMENTATION

This guidance document applies as soon as the programming of the relevant databases has been finalised.

Finalisation of the programming will be publicly announced by the Agency.