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DRAFT

Guidance 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 (EMA), in accordance with Article 41 of Regulation No. (EC) 1901/2006

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1 Introduction

Regulation (EC) No 1901/2006, of the European Parliament and of the Council of 12 December 2006¹ on medicinal products for paediatric use, as amended by Regulation (EC) No. 1902/2006, of the European Parliament and the Council of 20 December 2006², hereafter the Paediatric Regulation, entered into force on 26 January 2007. Article 41(3) requires the Commission to draw up guidance on the nature of the information on paediatric clinical trials to be entered into the database of clinical trials (EudraCT), created by Directive 2001/20/EC as amended, on which information shall be made available to the public, on how clinical trials results shall be submitted and be made public and on the European Medicines Agency (EMA)'s responsibilities and tasks in this regard.

This obligation aims to increase the availability of information on the use of medicinal products in the paediatric population and to avoid unnecessary repetition of studies in the paediatric population which do not add to the collective knowledge.

In addition to clinical trials covered by Directive 2001/20/EC³, Regulation (EC) No 1901/2006 requires that clinical trials conducted in third countries and contained in a PIP to be also subject to the same transparency rules.

The information on clinical trials that include any or all paediatric population subsets is aimed at the public which includes lay persons, patients and families, health professionals, researchers and academics as well as industry and regulators.

This information comprises clinical trial protocol-related information and trial results. Such trial information is to be entered into EudraCT in cases where the respective trial has at least one investigator site in the European Economic Area (EEA), and/or is part of an agreed Paediatric Investigation Plan (PIP). This information concerns paediatric trials planned, ongoing or completed in the EEA and those that are planned, ongoing or completed in any other country (“third countries”) provided these latter trials are included in a PIP.

In so far as entry of information into EudraCT and releasing this information to the public is concerned, paediatric trials conducted outside the EEA will, as much as possible and where applicable, follow the same processes as EEA trials, in order to ensure streamlined and consistent processes and support efficient development of the database.

At the time of publication of this guideline the EudraCT data fields are for the most part consistent with international initiatives relating to clinical trial registries, e.g. WHO International Clinical Trials Registry Platform (ICTRP) and the International Committee of Medical Journal Editors (ICMJE). Although EudraCT may have additional fields, the convergence of the information to be made public with the WHO ICTRP facilitates the work

¹ OJ L 378, 27.12.2006, p.1.

² OJ L 378, 27.12.2006, p. 20.

³ OJ L 121, 1.5.2001, p. 34.

of sponsors and researchers submitting information to different registries for different purposes, and facilitates the access of patients, health professionals and citizens in general to this information.

2 Scope

The information referred to in this guidance to be included in the EudraCT database, and that to be made public shall cover paediatric clinical trials of all Phases I, II, III and IV, regardless of whether the medicinal product concerned has already received a marketing authorisation in the Community or not. These are paediatric trials with at least one site in the Community and / or those which are included in a Paediatric Investigation Plan (PIP) (regardless for where they are conducted).

The status of each trial will be identified (e.g. under assessment, authorised or refused, ongoing, prematurely ended or completed). This status will be listed for each Member State with the relevant dates.

Clinical trials, which have received a decision from the Competent Authority and/or an opinion from the Ethics Committee, in the Member State or non-EEA country/region in question, will be made public.

This guidance sets out the nature of the information to be entered into EudraCT, the information to be made accessible to the public, the clinical trial results to be submitted and made public and on the responsibilities of the EMEA and related tasks in this context.

Directorate-General for Enterprise and Industry (DG ENTR) will subsequently make available the list of the specific data fields to be included in EudraCT, and those to be made public, and additional information on the processes involved, notwithstanding the full details of the data and processes to be contained in the technical implementation documents developed by the EudraCT Telematics project at the EMEA.

The requirements for the current version of EudraCT have been published by the Commission in the form of detailed guidance, which will be revised subsequently in accordance with this guidance.

3 *Guidance on nature of the information to be entered into the European database and on its entry into the database*

3.1 Nature of the information

The nature of the required information to be entered into the European database is based on its importance to clinical trials contained in an agreed paediatric investigation plan. Two sets of information are required:

- Trial protocol related information - supplied prior to the start of the trial and updated if needed during the trial describing the trial protocol, investigational medicinal products (IMPs), therapeutic indication, trial population, the trial authorisation and the current status of the trial.

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- Trial results related information – supplied after the completion of the trial and containing a summary of the results and conclusions of the trial.

Any clinical trial for which protocol related or result related information is to be stored in the database should be identified by one unique EudraCT number.

These elements represent minimum scientific requirements for reporting clinical trials such as the ones included in the CONSORT statement produced by the CONSORT Group (Consolidated Standards of Reporting Trials) or the Good Clinical Practice (GCP) requirements for reporting clinical studies in the ICH E3 guideline of the International Conference of Harmonisation of Technical Requirements for the Registration of Medicinal Products (ICH). Scientific conclusions on the trial are added by the body that submitted it (see section 3.3).

3.2 Timing of entering of the information into the database

Protocol related information

All clinical trials that are included in an agreed PIP, whether the trials are planned, ongoing, or completed should be included.

All interventional clinical trials with at least one site in the EEA are required to be entered into EudraCT no later than the time of application to the National Competent Authorities (NCA) of the Member States in which applications, in accordance with Directive 2001/20/EC and this includes paediatric trials.

All trials conducted with at least one site in a third country and included in an agreed PIP, should be entered, into EudraCT. This should be done no later than one month after, either, the EMEA decision on the agreed PIP, or, the first approval/positive opinion of the trial by a third country competent authority and/or third country ethics committee, whichever is later.

Result related information

Results-related information for paediatric trials should be submitted to the Agency and the NCA without delay and no more than six months after the trial has ended, i.e. after the time at which the end of trial notification should have been submitted, whether the trial has been completed, or prematurely terminated or suspended, whichever occurs first.

A trial is considered completed when the last visit of the last patient has occurred, as foreseen in the latest version of the protocol (in keeping with protocol-related information submitted to competent authorities). Open trial extensions, e.g., for maintenance treatment, are not considered as part of the trial.

3.3 Submission of the information into the database

The sponsor, PIP holder or MAH of the concerned clinical trial submits the information (protocol related or results related) electronically to the EudraCT staging area.

The NCA(s) or the EMEA will receive an automatic alert from the database with information for their attention in order that they commence the further processes involved in validating the data and saving it to the main EudraCT database.

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4 Guidance on information to be made available to the public

4.1 Protocol related information

The information to be included in EudraCT and to be made public will include details of the following elements:

- Identification of the clinical trial and its protocol
- Sponsor
- Source of funding
- Contact point for public use
- Identification and description of the treatment arms of the study (IMPs) to be used
- Therapeutic objective of the trial (disease under investigation)
- Trial population
- Trial design
- Major objectives and endpoints
- Inclusion/exclusion criteria
- General information on the trial including the countries in which it is to be conducted
- Trial status (per country or region as applicable), and if refused for ethical reasons the reasons for refusal

4.2 Results related information

The information to be included in EudraCT and to be made public will cover the following elements:

- Administrative information and trial identification
- Trial design
- Scientific background and explanation of rationale for the trial
- Participants in the trial – information on the subject population including inclusion exclusion criteria and demographic information
- Interventions - the treatments used
- Objective(s) of the trial
- Outcome measures
- Randomisation implementation
- Blinding
- Statistical methods
- Patient disposition
- Protocol deviations
- Recruitment
- Baseline data
- Trial interruption
- Outcomes and estimation
- Ancillary analysis
- Adverse events
- Trial termination
- Discussion and interpretation of study results (interpretation of trial results by sponsor, if available and by competent authority, if available)
- A declaration of the submitting party on liability for the accuracy of the submitted information

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4.3 Timing of making information accessible to the public

The releasing to the public of protocol-related information takes place automatically after validation in EudraCT has been completed. Where a negative opinion by an Ethics Committee has been issued, this information will still be published, together with a field indicating the reason for the negative opinion.

Public release of results takes place automatically once they have been validated by the NCA concerned or the EMEA. A disclaimer related to the absence of a Competent Authority's assessment is set by default until the assessment summary is available. The summary of assessment of the results is presented next to the conclusions on the clinical trial, when available.

4.4 How information is made public

The information will be made available through a dedicated public website containing a subset of information regularly updated from EudraCT. The data stored will be queryable in a user-friendly manner including full-text and related keywords searches. Facilities for usability such as thesauruses and internationalisation of keywords and certain fields may be provided. Appropriate disclaimers will be included to reflect the stage of regulatory evaluation of the trial.

Studies not registered in EudraCT and for which protocol-related information is not available, e.g., because the conduct of the studies predated requirements for inclusion in EudraCT, should be specifically identified.

The process of receiving and publishing the results of paediatric trials, via EudraCT, will not routinely involve a detailed scientific assessment between the submission and the release of the results to the public. The submitted information should be subject to specified validation checks, both automated and by human intervention. The published results will display suitable explanation of this process, on its limitations and on the necessary caution to be applied in the use or interpretation of the data.

Once the results of the trial have been assessed during a marketing authorisation application and an assessment report has been published [European Public Assessment Report (EPAR) or Public Assessment Report (PAR)], links between the results published in EudraCT and the EPAR/PAR may be created. In a similar way, when the results of the trial are published in a peer reviewed journal, a link to that scientific publication may be made or a reference given.

5 *Guidance on responsibilities of the European Medicines Agency and tasks in this regard*

5.1 The EMEA's responsibilities

The EMEA should:

- make public part of the protocol-related information on paediatric clinical trials according to this guideline and the lists of data fields made public by DG ENTR.
- make public part of the result-related information on trials included in EudraCT and on any paediatric studies submitted according to Article 45 and 46.

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- coordinate the exchange of information
- manage the EudraCT database.

5.2 The related tasks

The responsibility for the initiation of the process, electronic submission of protocol and result related data, and maintenance of data (including, for certain data elements, directly in the database) lies with:

- the Marketing Authorisation Holder, in the case of provision of the results of an authorised medicinal product in accordance with the obligations in Articles 45 and 46.
- the sponsor of trials referred to by Article 41, whether or not they are the Marketing Authorisation Holder
- the PIP addressee.

The EMEA should:

- enter the protocol information received electronically to the staging area into the database for third-country trials including their authorisation status and end of trial information
- validate the protocol-related information for trials conducted in third countries
- enter the result information received electronically to the EudraCT system
- validate the result-related information for paediatric trials
- make public those data from the protocol-related and result-related information in accordance with section 4.4

The National Competent Authorities (NCAs) should:

- enter the protocol information received electronically into the database
- enter information concerning the review and oversight of the trial
- exchange information with the Agency on the studies submitted
- validate protocol-related information submitted by the applicant
- enter additional data relating to the review and authorisation, amendment and end of the trial, to be recorded directly into EudraCT by the NCAs or by transmission of specific XML files from national clinical trial databases.

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6 *Guidance on Implementation*

The European Commission DG ENTR will publish detailed data elements corresponding to the information that is to be included in EudraCT on clinical trials and on their results and on that part of the information that will be made public in accordance with this guidance.

The specific details of the processes involved will be addressed in documents setting out the detailed business rules to be developed by the Agency in conjunction with the EudraCT Telematics Implementation Group. The functionality of the database will be described in technical documents to be developed by the EMEA in conjunction with the EudraCT Telematics Implementation Group.

User manuals will be published by the EMEA.

The actual physical and logical data models to be used in implementing this guideline will be drawn up through object modelling. The specific processes to be used to send or retrieve data from EudraCT and other functionality will be defined by technical specifications to be prepared when this guideline is implemented.

A glossary will be provided in an appropriate location on the database website, explaining the relevant technical and regulatory terms and acronyms for the benefit of the general public.