21 March 2019
EMA/357536/2014, Rev. 2

Questions and answers on the European Medicines Agency policy on publication of clinical data for medicinal products for human use

What are the main objectives of the policy?

The European Medicines Agency (EMA) has committed to continuously extending its approach to transparency. A key goal in this process is the proactive publication of clinical-trial data for medicines once the decision-making process on an application for a European Union (EU)-wide marketing authorisation is complete.

The Agency has embarked on this process because it believes that the release of data, making it accessible to all who wish to see it, is about establishing trust and confidence in the system.

This policy will also enable the independent secondary analysis of the evidence reviewed by the Agency's scientific committees to determine their benefits and risks and is expected to lead to public health benefits.

What were the steps leading to the adoption of the policy?

In all steps leading to the finalisation of its policy, the Agency has taken a considered approach to develop a policy that respects the views and concerns brought forward by a broad range of stakeholders and European bodies, despite the absence of any specific current legal provision mandating the Agency to publish documents submitted by third parties:

- The Agency's decision to move towards proactive disclosure was first outlined in the article 'Open clinical trial data for all? A view from regulators', (PLoS Medicine, April 2012).
- The process then started with a workshop on clinical-trial data and transparency on 22 November 2012, to listen to the views, interests, and concerns from a broad range of institutions, groups and individuals.
- Following this event, the Agency issued a call for nominations to join advisory groups to inform the Agency on five topics. These topics related to protecting patient confidentiality, clinical trial data formats, rules of engagement, good analysis practice, and legal aspects. More than 200 people

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from all stakeholder groups applied to participate. The advisory groups met at the beginning of 2013 and gave their final advice in April 2013.

- In June 2013, taking into account the advice given, the Agency released for public consultation its draft policy on the publication and access to clinical-trial data, inviting comments from all stakeholders.
- After taking stock of the 1,138 comments received from 169 stakeholders, the Agency launched in May 2014, following discussions at its December 2013 and March 2014 Management Board meetings, a final round of targeted consultations with key stakeholders (i.e. patients/consumers organisations and healthcare professionals organisations; pharmaceutical industry associations including small and medium sized enterprises; and representatives from academia, research bodies and medical journals). The aim of these targeted consultations was to provide an update on progress made since the end of the 2013 public consultation, to inform on the envisaged amendments to the draft policy, and in particular, to consult on the characteristics of the publication process (including technical measures to make the data available under the policy including their terms of use (ToU)), and the principles for possible redaction of the clinical reports. These targeted consultations showed broad support for the policy, but highlighted concerns over a proposed view-on-screen access to the data.
- On 12 June 2014, the EMA's Management Board discussed the policy on publication of clinical data, together with more user-friendly amendments proposed by EMA Executive Director Guido Rasi, that will allow the Agency to proactively make available through a publication process clinical data that are submitted as part of marketing authorisation applications, and extensions/variations thereof, but also give the possibility to download, save and print the clinical data for academic and non-commercial research purposes.
- On 2 October 2014, the policy, including the user-friendly amendments, was unanimously adopted by the Management Board.

What are the policy's main evolutions since the first draft released in June 2013?

During the 3 month public consultation launched in June 2013, the Agency received 1,138 comments from 169 stakeholders. This unprecedented range of stakeholder responses included patients, healthcare professionals, pharmaceutical industry representatives, researchers, transparency campaigners, academic and public institutions, health technology assessment bodies, EU institutions and national medicines regulators.

The Agency's initiative was positively received. However, a number of concerns were raised during the public consultation.

Revision following the 2013 public consultation

The main concerns related to:

- The concept of commercially confidential information (CCI) and the protection from unfair commercial use.
- Protecting patient confidentiality.
- The concept of raw data.

For an overview of all comments raised during this first consultation round, please refer to the document "Outcome of public consultation on Policy 0070 on publication and access to clinical trial data" (EMA/342387/2014).

The main concerns have been addressed as follows:

- **The concept of CCI and the protection from unfair commercial use.** The policy has been shaped in the absence of any specific legal provision mandating the Agency to publish documents submitted by third parties, as is the case for some other EU agencies. Consequently, a compromise approach was needed taking into account different stakeholders' competing interests, within the limitations of the current legal framework with:
  - The introduction of a publication process through ToU which govern the access to and use of clinical data, and a user-friendly technical tool allowing such access.
  - The management of CCI in clinical reports through redaction principles and a process for publication of clinical reports.
- To respond to **concerns on the protection of patient confidentiality**, the most appropriate balance between protecting patient privacy and retaining scientific value of the data must be identified. To achieve this objective, the Agency considers further consultation with stakeholders is necessary on a methodology to avoid (re)-identification of patients, in the absence of a commonly agreed methodology available at this stage.
- In order to address the **concept of raw data**, a stepwise implementation of the policy will be undertaken. In a first phase only clinical reports will be published excluding raw data. In order to avoid confusion, as noticed during the public consultation, the term "raw data" will no longer be maintained, but instead the term "individual patient data" (IPD) will be used. In a second phase, various aspects relating to IPD will be clarified with stakeholders, addressing issues such as the submission of IPD for subsequent scientific review, how afterwards to provide access to IPD and under which conditions.

Revision following the May 2014 targeted stakeholders consultation

The main concern expressed during the second targeted consultation round related to the view-on-screen access. This concept was criticised by academia, research bodies and medical journals, consumer organisations and healthcare professional organisations, as well as some EU institutions. To address this concern more user-friendly amendments were introduced, giving the possibility to download, save and print the trial data for academic and non-commercial research purposes.

For an overview of all comments raised during the second consultation round, please refer to the document "Finalisation of the EMA policy on publication of and access to clinical trial data – Targeted consultation with key stakeholders in May 2014" (EMA/292746/2014).

What are the next steps to implement the policy?

The date for coming into effect of the policy is **1 January 2015**.

This means that the policy will apply from this date onwards to any new marketing authorisation applications and article 58 applications (medicines that are intended exclusively for markets outside the European Union) submitted after that date. Concretely, data will only start to become accessible once the final decision on a given procedure has been reached by the European Commission, which implies a timeframe of about 18 months.

The policy does not apply to clinical data held by the Agency for applications received under the centralised procedure before 1 January 2015.

For post-authorisation procedures for existing centrally authorised medicinal products, the effective date will be **1 July 2015** for extension of indication and line extension applications submitted as of that date. The policy does not apply to clinical data held by the Agency for these applications received before 1 July 2015. For all other post-authorisation procedures the effective date still needs to be determined, and will be communicated in due course.

The Agency has chosen a stepwise approach for the implementation of the policy:

- The first phase concerns the **publication of clinical reports only**. The Agency has defined a process for publication of clinical reports whereby the data that will be accessible on the EMA website are module 2.5 (clinical overview), module 2.7 (clinical summary), module 5 (clinical study reports (CSRs) and appendices 16.1.1 (protocol and protocol amendments), 16.1.2 (sample case report form) and 16.1.9 (documentation of statistical methods)). Such data either use the common technical document (CTD) format or another format.
- In a second phase, the Agency will endeavour to find the most appropriate way to make **IPD** available, in compliance with privacy and data protection laws. This will involve consultation with stakeholders on various aspects in relation to IPD. More information on this consultation process will be provided at a later stage.

Why does the policy foresee a publication process and what will it mean?

The policy has been shaped in the absence of any clear legal provision mandating the EMA to proactively (i.e. in the absence of a specific request under Regulation (EC) 1049/2001 on access to documents) publish documents submitted to the Agency by third parties. Consequently, a balanced approach was needed taking into account different stakeholders' competing interests, within the limitations of the current legal framework. This compromise allows access to clinical data but, at the same time, aims to discourage unfair commercial use of the data.

The Agency has defined a process for publication of clinical reports with:

- Clinical reports available on-screen for any user, with a simple registration process;
- Downloadable clinical reports available to identified users.

Both situations will be governed by dedicated Terms of use.

What will be the 'Terms of use'?

There will be two sets of ToU applicable depending on whether an individual wishes to access the data for general information purposes or if he/she intends to use it for academic and non-commercial research purposes.

- The ToU for general information purposes foresees a simple registration process. The person wishing to access the data will obtain a user ID/password and accept the aforementioned ToU. The intended use is for general information and non-commercial purposes including non-commercial research purposes.

  With this ToU, users can read and search the data which will be permanently available. No screening or tracking of any individual accessing the data will be undertaken by the Agency.

- The ToU for academic and other non-commercial research purposes allows for downloadable clinical reports to be available to identified users. Individuals will need to provide the Agency with elements concerning the identity of the user (i.e. name, date of birth, passport or ID card number, expiry date of the document; for juridical persons, the affiliation and position within the organisation of the user should also be provided). They will also need to obtain a user ID/password and accept the ToU. The data will be permanently available for these users to read and search. In addition, these users will be able to download, transcribe, cut and paste and print the data. They can reference the data in publications. No screening or tracking of any individual accessing the data will be undertaken by the Agency. However, it should be noted that Courts may require the EMA to disclose the identity of the users who do not comply with the ToU to the marketing authorisation holders (MAHs)/applicants.

  The ToU clarify that researchers, academics and other stakeholders (such as health technology assessment bodies) are entitled to use the data for academic and non-commercial research purposes. The Agency recognises the value of such uses, and has acknowledged the potential benefits for public health of secondary analysis of data by independent academics and researchers after a medicine has been approved. Commercial purposes would include using the data to support a marketing authorisation application anywhere in the world; selling, trading or supplying the data to a third party that has not agreed to the ToU.

  The ToU are not intended to impose liability on users who comply with the terms, nor are they intended to create any additional layer of liability for academics or researchers stemming from their professional activity.

In all cases, users of the data shall not re-identify trial subjects or other individuals, and the information shall not be used to support a marketing authorisation application/extensions or variations to a marketing authorisation. Likewise, no unfair commercial use shall be made of such information. The Agency recognises that enabling comparative effectiveness research is in the interest of public health. Usage of the data for scientifically sound relative effectiveness comparisons (produced by either HTA bodies or pharmaceutical companies) would not be reasonably deemed *per se* an unfair commercial use and therefore would not be considered by the EMA as in breach of the ToU[1]. A watermark will be applied to the published information to emphasise the prohibition of its use for commercial purposes.

Also, since the EMA is based in the Netherlands and the disclosure of documents will take place in that country, the ToU are governed by the law of the Netherlands. However, it should be noted that the Amsterdam District Court does not have exclusive jurisdiction to settle disputes or claims arising out or in connection with the ToU. As the law of the Netherlands was accepted by the user when accepting the ToU, such disputes or claims may be settled under the law of the Netherlands by the courts of another country, either within the Union or outside.

The Dutch Civil Code ("Burgerlijk Wetboek") opens an opportunity to applicants and MAHs to operate and enforce the ToU directly, even if the EMA were not to enforce them. It should also be noted that copyright does not protect information or data itself. It only protects the form in which such information or data is expressed.

[1] Sentences added on 8 June 2015: The Agency recognises that enabling comparative effectiveness research is in the interest of public health. Usage of the data for scientifically sound relative effectiveness comparisons (produced by either HTA bodies or pharmaceutical companies) would not be reasonably deemed *per se* an unfair commercial use and therefore would not be considered by the EMA as in breach of the ToU.

Will HTA bodies be adversely affected by the provisions in the policy?

No - in parallel to other processes for providing clinical reports to HTA bodies, if HTA bodies would like to have access to clinical reports within the frame of this policy, nothing in the ToU will prevent HTA bodies from having access to and use of the clinical reports for the purpose of their institutional activities. The HTA bodies can download, transcribe, cut and paste and print the data in accordance with the specific ToU for academic and other non-commercial research purposes. Furthermore, the EMA will continue to explore additional routes of collaboration with HTA bodies.

What is the policy's definition of commercially confidential information and redaction principles?

The policy sets out clearly that the overwhelming majority of data in clinical reports is not CCI. As an example, a visualisation of what may be considered as CCI in a typical CSR is provided in annex 1. It shows in amber the sections of the CSR that may contain CCI and therefore may be redacted. However, it is important to clarify that not all the information in the sections shown in amber will be redacted but only the subset of the text considered being CCI.

The policy provides a common understanding with applicants on what information can be considered as CCI. CCI is defined, for the purpose of the policy, as '*any information contained in the clinical reports submitted to the Agency by the applicant/marketing authorisation holder (MAH) that is not in the public domain or publicly available and where disclosure may undermine the legitimate economic interest of the applicant/MAH'.*

The policy provides redaction principles which will ensure a clear and transparent understanding on the part of applicants, and indeed all stakeholders, of the redactions the Agency is prepared to consider. Under the policy, applicants will be asked to submit clinical reports in view of their publication. If they believe that some elements should be redacted, then they may propose this together with the justifications for the redactions. The starting point of the redaction principles is that clinical reports do not, in general, contain CCI. However, in a limited number of instances there might be pieces of information that could be considered CCI. In such cases the Agency is prepared to consider the justifications for redactions, as clarified in the policy. It is for the Agency to take the final decision on what is and is not to be redacted. The extent of what the Agency will redact will always be visible in the final documents that the Agency makes available.

The consultation process described above is to be completed within the decision making timelines following the review of the data by the scientific committee to allow for publication of the clinical data as soon as the procedure has been finalised.

In case of disagreement with the Agency's final decision on the redaction, the applicant/MAH will be given a defined period prior to the publication to seek an interim injunction from the Court. In this case, the Agency will only publish the undisputed parts of the clinical reports at stake.

How does the policy relate to the new Clinical Trials Regulation?

The Clinical Trials Regulation (Regulation (EU) No. 536/2014) was published on 27 May 2014 in the Official Journal of the European Union. The new Regulation provides, for the first time, a direct legal basis for the release of clinical trial results. However, it does not provide a legal basis for proactively making clinical trial results available until such time as the Regulation enters into application. It should

also be noted that this Regulation does not encompass non–EU clinical reports and is limited to clinical trial results deriving from clinical trials conducted in the EU and authorised under the provisions of this Regulation. Taking into consideration that (1) the first clinical trials will be authorised in accordance with the new legal provisions not earlier than May 2016, (2) the average duration of a clinical trial is 3 years, (3) the clinical trial results from these trials will have to be submitted for a marketing authorisation application, and (4) the decision-making will have to be completed, it can be foreseen that under the new legal provisions the first clinical reports will become publically available not before 2019/2020. Therefore, the policy will serve as a useful complementary tool ahead of the implementation of the new Clinical Trials Regulation when it comes into force no sooner than May 2016, and is without prejudice to the provisions of the Clinical Trials Regulation.

How does the policy relate to the existing policy on access to documents?

The policy does not replace the Agency's existing Policy on access to documents which came into effect in December 2010. The Agency will ensure that the policy will not prejudice citizens' rights under existing access to documents legislation. Any person may continue to submit a request for access to documents to the Agency independently of the proactive publication mechanisms established by this policy. Such requests will be handled by the Agency in accordance with Regulation (EC) No. 1049/2001 and the related Agency policy. The assessment of each request will be conducted on a case-by-case basis in accordance with the Agency's current handling of access to document requests including where relevant reactive third party consultation. As the process would have to be followed for each and every request for a clinical report, the normal procedures and timelines as foreseen under the existing policy on access to documents would apply. The mechanisms that are to be established by the policy on publication of clinical data will provide a more timely, systematic, public, easy and efficient access to all clinical reports following the Commission Decision or the end of a regulatory procedure.

There will be no difference in the understanding of CCI in the Agency's assessment of the documents held by the Agency that are requested through 'access to documents' or that will be proactively published by the Agency.

Annex I

The parts in amber MAY contain CCI and, therefore, MAY be redacted. It should be noted that NOT ALL the information in the sections shown in amber will be redacted but only the SUBSET of the text considered being CCI.

Structure and content of a clinical study report (CSR) (From ICH harmonised tripartite guideline, E3)
1. TITLE PAGE
2. SYNOPSIS
3. TABLE OF CONTENTS FOR THE INDIVIDUAL CLINICAL STUDY REPORT
4. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS
5. ETHICS
5.1 INDEPENDENT ETHICS COMMITTEE (IEC) OR INSTITUTIONAL REVIEW BOARD (IRB)
5.2 ETHICAL CONDUCT OF THE STUDY
5.3 PATIENT INFORMATION AND CONSENT
6. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE
7. INTRODUCTION
8. STUDY OBJECTIVES
9. INVESTIGATIONAL PLAN
9.1 OVERALL STUDY DESIGN AND PLAN – DESCRIPTION
9.2 DISCUSSION OF STUDY DESIGN, INCLUDING THE CHOICE OF CONTROL GROUPS
9.3 SELECTION OF STUDY POPULATION
9.3.1 Inclusion Criteria
9.3.2 Exclusion Criteria
9.3.3 Removal of Patients from Therapy or Assessment
9.4 TREATMENTS
9.4.1 Treatments Administered
9.4.2 Identity of Investigational Product(s)
9.4.3 Method of Assigning Patients to Treatment Groups
9.4.4 Selection of Doses in the Study
9.4.5 Selection and Timing of Dose for each Patient
9.4.6 Blinding
9.4.7 Prior and Concomitant Therapy
9.4.8 Treatment Compliance
9.5 EFFICACY AND SAFETY VARIABLES
9.5.1 Efficacy and Safety Measurements Assessed and Flow Chart
9.5.2 Appropriateness of Measurements
9.5.3 Primary Efficacy Variable(s)
9.5.4 Drug Concentration Measurements
9.6 DATA QUALITY ASSURANCE
9.7 STATISTICAL METHODS PLANNED IN THE PROTOCOL AND DETERMINATION OF SAMPLE SIZE

Structure and content of a clinical study report (CSR)
(From ICH harmonised tripartite guideline, E3)

9.7.1 Statistical and Analytical Plans
9.7.2 Determination of Sample Size
9.8 CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES
10. STUDY PATIENTS
10.1 DISPOSITION OF PATIENTS
10.2 PROTOCOL DEVIATIONS
11. EFFICACY EVALUATION
11.1 DATA SETS ANALYSED
11.2 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS
11.3 MEASUREMENTS OF TREATMENT COMPLIANCE
11.4 EFFICACY RESULTS AND TABULATIONS OF INDIVIDUAL PATIENT DATA
11.4.1 Analysis of Efficacy
11.4.2 Statistical/Analytical Issues
11.4.2.1 Adjustments for Covariates
11.4.2.2 Handling of Dropouts or Missing Data
11.4.2.3 Interim Analyses and Data Monitoring
11.4.2.4 Multicentre Studies
11.4.2.5 Multiple Comparison/Multiplicity
11.4.2.6 Use of an "Efficacy Subset" of Patients
11.4.2.7 Active-Control Studies Intended to Show Equivalence
11.4.2.8 Examination of Subgroups
11.4.3 Tabulation of Individual Response Data
11.4.4 Drug Dose, Drug Concentration, and Relationships to Response
11.4.5 Drug-Drug and Drug-Disease Interactions
11.4.6 By-Patient Displays
11.4.7 Efficacy Conclusions
12. SAFETY EVALUATION
12.1 EXTENT OF EXPOSURE
12.2 ADVERSE EVENTS (AES)
12.2.1 Brief Summary of Adverse Events
12.2.2 Display of Adverse Events
12.2.3 Analysis of Adverse Events
12.2.4 Listing of Adverse Events by Patient
12.3 DEATHS, OTHER SERIOUS ADVERSE EVENTS, AND OTHER SIGNIFICANT ADVERSE EVENTS
12.3.1 Listing of Deaths, other Serious Adverse Events and Other Significant Adverse Events
12.3.1.1 Deaths
12.3.1.2 Other Serious Adverse Events
12.3.1.3 Other Significant Adverse Events
12.3.2 Narratives of Deaths, Other Serious Adverse Events and Certain Other Significant Adverse Events

Structure and content of a clinical study report (CSR) (From ICH harmonised tripartite guideline, E3)
12.3.3 Analysis and Discussion of Deaths, Other Serious Adverse Events and Other Significant Adverse Events
12.4 CLINICAL LABORATORY EVALUATION
12.4.1 Listing of Individual Laboratory Measurements by Patient (16.2.8) and Each Abnormal Laboratory Value (14.3.4)
12.4.2 Evaluation of Each Laboratory Parameter
12.4.2.1 Laboratory Values Over Time
12.4.2.2 Individual Patient Changes
12.4.2.3 Individual Clinically Significant Abnormalities
12.5 VITAL SIGNS, PHYSICAL FINDINGS AND OTHER OBSERVATIONS RELATED TO SAFETY
12.6 SAFETY CONCLUSIONS
13. DISCUSSION AND OVERALL CONCLUSIONS
14. TABLES, FIGURES AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT
14.1 DEMOGRAPHIC DATA
14.2 EFFICACY DATA
14.3 SAFETY DATA
14.3.1 Displays of Adverse Events
14.3.2 Listings of Deaths, Other Serious and Significant Adverse Events
14.3.3 Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events
14.3.4 Abnormal Laboratory Value Listing (Each Patient)
15. REFERENCE LIST
16. APPENDICES
16.1 STUDY INFORMATION
16.1.1 Protocol and protocol amendments
16.1.2 Sample case report form (unique pages only)
16.1.9 Documentation of statistical methods