Clinical Trial Data: Open For All? EMA’s Perspective

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CDISC Europe Foundation, Head of Strategic Projects

CDISC International Interchange
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A presentation in collaboration with Frank Pétavy
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Open clinical trial data! Why?

- **Scientific progress:** sharing of complex data can open new horizons
- **Ethical responsibility:** to the patients enrolled in clinical trials
- **Public health benefit:** independent (re)analysis of data broadens knowledge base
- **Build citizens trust and confidence in the system**
Release of Data – Current Status

- Release of documents on request since November 2010 (policy on access to documents) backed by EU REGULATION (EC) No 1049/2001
- Over 2 million pages of clinical trial data released – application dossiers, minutes etc.

- Documents submitted as part of applications for marketing authorisation
  - Includes clinical study reports – module 4
  - Once the decision-making process for the medicine in question has been completed
Access to documents

European Medicines Agency policy on access to documents (related to medicinal products for human and veterinary use)
POLICY/0043

Effective date: 1 December 2010
Supersedes: Not applicable

1. Introduction and purpose

Openness and transparency are paramount values enshrined in the TEU and in the TFEU as they contribute to strengthen the principles of democracy and good administration.

According to Article 15 of the TFEU, a right of access to documents of the EU Institutions, Bodies, Offices and Agencies is granted according to the principles and further conditions as defined by Regulations, namely Regulation (EC) No 1049/2001\(^1\).
Treaty of Lisbon TEC and TFEU
Ratifying the 2001 bill and Fundamental rights charter

Treaty of Lisbon
From Wikipedia, the free encyclopedia

For other uses, see Treaty of Lisbon (disambiguation).

The Treaty of Lisbon or Lisbon Treaty (initially known as the Reform Treaty) is an international agreement which amends the two treaties which form the constitutional basis of the European Union (EU). The Lisbon Treaty was signed by the EU member states on 13 December 2007, and entered into force on 1 December 2009. It amends the Maastricht Treaty (also known as the Treaty on European Union) and the Treaty establishing the European Community (TEC; also known as the Treaty of Rome). In this process, the Rome Treaty was renamed to the Treaty on the Functioning of the European Union (TFEU).

Prominent changes included the move from unanimity to qualified majority voting in several policy areas in the Council of Ministers, a change in calculating such a majority to a new double majority, a more powerful European Parliament forming a bicameral legislature alongside the Council of ministers under the ordinary legislative procedure, a consolidated legal personality for the EU and the creation of a long-term President of the European Council and a High Representative of the Union for Foreign Affairs and Security Policy. The Treaty also made the Union's bill of rights, the Charter of Fundamental Rights, legally binding.

Fundamental Rights Charter [edit]

Main article: Charter of Fundamental Rights of the European Union

The fifty-five articles of the Charter of Fundamental Rights of the European Union enshrine certain political, social, and economic rights for both European Union citizens and residents, into EU law. It was drafted by the European Convention and solemnly proclaimed on 7 December 2000 by the European Parliament, the Council of Ministers and the European Commission. However its then legal status was uncertain and it did not have full legal effect[29] until the entry into force of the Lisbon Treaty on 1 December 2009.

In the rejected Treaty establishing a Constitution for Europe the charter was integrated as a part of the treaty itself. In the Lisbon Treaty, however, the charter is incorporated by reference and given legal status without forming part of the treaties. The EU must act and legislate consistently with the Charter and the EU’s courts will strike down EU legislation which contravenes it. The Charter only applies to EU member states as regards their implementation of EU law and does not extend the competences of the EU beyond its competences as defined in the treaties.
REGULATION (EC) No 1049/2001 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL
of 30 May 2001
regarding public access to European Parliament, Council and Commission documents

Whereas:

(1) The second subparagraph of Article 1 of the Treaty on European Union enshrines the concept of openness, stating that the Treaty marks a new stage in the process of creating an ever closer union among the peoples of Europe, in which decisions are taken as openly as possible and as closely as possible to the citizen.

(2) Openness enables citizens to participate more closely in the decision-making process and guarantees that the administration enjoys greater legitimacy and is more effective and more accountable to the citizen in a democratic system. Openness contributes to strengthening the principles of democracy and respect for fundamental rights as laid down in Article 6 of the EU Treaty and in the Charter of Fundamental Rights of the European Union.
REGULATION (EC) No 1049/2001 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL
of 30 May 2001
regarding public access to European Parliament, Council and Commission documents

Exceptions

1. The institutions shall refuse access to a document where disclosure would undermine the protection of:

(a) the public interest as regards:
   — public security,
   — defence and military matters,
   — international relations,
   — the financial, monetary or economic policy of the Community or a Member State;

(b) privacy and the integrity of the individual, in particular in accordance with Community legislation regarding the protection of personal data.

2. The institutions shall refuse access to a document where disclosure would undermine the protection of:
   — commercial interests of a natural or legal person, including intellectual property,
   — court proceedings and legal advice,
   — the purpose of inspections, investigations and audits,
   unless there is an overriding public interest in disclosure.
Proactive publication of CT data

- PLOS article -

Open Clinical Trial Data for All? A View from Regulators

Hans-Georg Eichler¹*, Eric Abadie¹,², Alasdair Breckenridge³, Hubert Leufkens¹,⁴, Guido Rasi¹

¹ European Medicines Agency (EMA), London, United Kingdom, ² Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSAPS) Saint-Denis, France, ³ Medicines and Healthcare products Regulatory Agency (MHRA), London, United Kingdom, ⁴ Medicines Evaluation Board (CBG-MEB), Den Haag, The Netherlands

Reaction from Tami Flu debate and article by Peter Dosh et al

The EMA announced on 10 April 2012 that it intended to proactively publish clinical study reports and enable access to full data sets by interested parties.
Workshop on clinical-trial data and transparency (22 November 2012)

• “We are not here to decide if we publish clinical-trial data, but how” (G. Rasi)

<table>
<thead>
<tr>
<th>Selected speakers</th>
<th>Affiliation</th>
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<tbody>
<tr>
<td>Guido Rasi</td>
<td>EMA</td>
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<tr>
<td>François Houÿez</td>
<td>EURORDIS</td>
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<td>Mark Walport (moderator)</td>
<td>Wellcome Trust</td>
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<td>Susan Forda; Neil Weir</td>
<td>EFPIA</td>
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<td>Ben Goldacre</td>
<td>Author and journalist</td>
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<tr>
<td>Virginia Barbour</td>
<td>PLoS Medicine</td>
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<td>Peter Gøtzsche</td>
<td>Cochrane Collaboration</td>
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Currently, the only people who see all the data for a new medicine are those inside the company... the more eyes that look at the data, the better. **The days of secrecy must end.**

The biggest hurdles will be practical ones, and **the format in which the data is supplied** will be critical.

[I want to see] **appropriate access** to clinical data, especially for **legitimate scientific researchers.**

We ask that the **protection of intellectual property rights** is fully considered.
Patients (François Houÿez)

• « When I started working in rare diseases, I was surprised by how many people were eager to share data if it might benefit others. »

European Ombudsman’s representative

• Widest access possible.
• Any exceptions should be strictly interpreted.
• Any exception must be supported by adequate reasons.

Assistant European Data Protection Supervisor

• Welcomes the proactive approach to identifying key issues where transparency can be increased.
• Encourages further discussion on modalities of publication.
Workshop Outcome

- Creation of advisory groups to make proposals for a policy on pro-active publication of CT data
- Call for nominations to join the advisory groups in December 2012
- More than 200 individuals applied
- Only one member from the same organisation in each advisory group

Topics

- Protecting patient confidentiality
- Clinical trial data formats
- Rules of engagement
- Good analysis practice
- Legal aspects
Advisory groups: Stakeholder representation

The majority of affiliations were from Academia or Industry.
Advisory groups (1)

Protecting Patient Confidentiality

- How much should data be de-identified? It may not compromise analytical validity
- What standards for de-identification of data?
- What level of access to patient-level data depending on risk of de-identification?

Rules of engagement

- Consultation with MAH before data disclosure?
- What is commercially confidential information?
- Need for identification of requesters?
- Personal data protection: open or controlled access?
- Agreement to refrain from unintended commercial use?
- Data sharing agreement
Advisory groups (2)

Clinical Trial Data Formats
- Need of formatting data
- Accessibility and readability
- Levels of data (aggregate vs. patient-level)
- Which formats are most appropriate and why
- Strategy for guidance updates
- International harmonisation

Legal aspects
- Divergent views on publication of commercially confidential information
- Various options to avoid breach of copyright
- Reinforcement of the current system on legal remedies
Advisory groups: Good Analysis Practice

Good analysis practice

• Preparation of a protocol before analysis by the data requester (submit analysis plan)
• What guidelines should be followed, e.g. CHMP guidelines
• State relevant expertise in requester team, e.g. statistician or epidemiologist
• Modifications to data or code should be made public
# Project Schedule

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<tbody>
<tr>
<td>1.</td>
<td>Nominations for membership</td>
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<tr>
<td>2.</td>
<td>Initial sessions for each group to be convened during</td>
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<tr>
<td>3. <strong>Final advice</strong> from each Advisory Group (will be used to inform EMA policy, but the advice is not binding)</td>
<td>30 Apr 2013</td>
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<tr>
<td>4. <strong>Draft EMA policy</strong> completed and posted on website for public consultation</td>
<td>30 Jun 2013</td>
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<td>5.</td>
<td>End of public consultation phase</td>
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<td>6.</td>
<td>Publication of <strong>final EMA policy</strong> (including comments received)</td>
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<td>7.</td>
<td><strong>Policy</strong> becomes effective</td>
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EMA draft policy – Competing Objectives (1)

- Enabling public scrutiny and secondary analysis of clinical trials
  - Regulatory positions can be verified and challenged

- Protection of personal data
  - Fundamental right of EU citizens

- Respect for the boundaries of patient informed consent
  - Ethics committees should be consulted
EMA draft policy – Competing Objectives (2)

Ensuring future investment in bio-pharmaceutical R&D
- Pre-condition for future improvements in public health

Protecting public health against the consequences of inappropriate secondary data analysis
- Requesters should follow highest scientific standards

Ensuring transparency is a two-way street
- Requester’s analyses should be in public domain
Publication and access to clinical-trial data

4.2. Data standards

All documents listed in Annexes 1 and 2 — whether categorised 'O' or 'C' — shall be provided in portable document format (PDF), and should be fully searchable.

Section 5.2 of Module 5: for each product shall be published a full cumulative list of clinical trials, including a unique study identifier and basic information about each study (e.g. study title, interventions and indications). In addition to the study number provided by the applicant, relevant unique study identifiers shall be included in the list, e.g. EudraCT number, US NIH clinicaltrials.gov registry number and ISRCTN registry number.

Wherever technically possible, analysable, de-identified raw CT data shall be made available for downloading in the format in which they have been analysed by the applicant, submitted and evaluated. For the time being, this can be according to CDISC (Clinical Data Interchange Standards Consortium) or other appropriate standard. In future, CDISC shall be the required standard, in line with future guidance from the Agency. No conversion of formats is recommended, either by the marketing-authorisation holder or the Agency.
## Example list of clinical trial elements

<table>
<thead>
<tr>
<th>Section</th>
<th>Description</th>
<th>Access</th>
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<tr>
<td>2.5</td>
<td>CLINICAL OVERVIEW</td>
<td>O</td>
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<tr>
<td>2.5.1</td>
<td>Product Development Rationale</td>
<td>O</td>
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<tr>
<td>2.5.2</td>
<td>Overview of Biopharmaceutics</td>
<td>O</td>
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<tr>
<td>2.5.3</td>
<td>Overview of Clinical Pharmacology</td>
<td>O</td>
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<td>2.5.4</td>
<td>Overview of Efficacy</td>
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<td>2.5.5</td>
<td>Overview of Safety</td>
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<td>2.5.6</td>
<td>Benefits and Risks Considerations</td>
<td>O</td>
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<tr>
<td>2.5.7</td>
<td>Literature Reference</td>
<td>O</td>
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<tr>
<td>2.7</td>
<td>CLINICAL SUMMARY</td>
<td>O</td>
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<tr>
<td>2.7.1</td>
<td>Summary of Biopharmaceutic Studies and Associated Analytical Methods</td>
<td>CCI</td>
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<tr>
<td>2.7.1.1</td>
<td>Background and Overview</td>
<td>CCI</td>
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<tr>
<td>2.7.1.2</td>
<td>Summary of Results of Individual Studies</td>
<td>CCI</td>
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<tr>
<td>2.7.1.3</td>
<td>Comparison and Analyses of Results Across Studies</td>
<td>CCI</td>
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<tr>
<td>2.7.1.4</td>
<td>Appendix</td>
<td>CCI</td>
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### Annexes

#### Abbreviations used in Annexes I and II

- **O**: Open access.
- **C**: Controlled access.
- **CCI**: May contain commercially confidential information.
EMA draft policy – **Scope**

**In scope**
- Prospective
- All clinical trials submitted at EMA
- Examples of data: clinical study report, patient data listing, data set

**Out of scope**
- Clinical trial data not held at the Agency
- Pre-existing CT data of marketed products that will be submitted to the agency
- Pharmacovigilance data based on individual case safety reports
EMA draft policy – Rules of Engagement

- **Open access**
  - CT data/documents without PPD concerns: e.g., clinical overview, parts of the CSR, protocol, sample CRF
  - Policy comes into effect for data submitted on or after **1 March 2014**

- **Controlled access**
  - CT data/documents with PPD concerns: e.g., patient data listing, completed CRF
  - Policy comes into effect for data submitted on or after **1 January 2015**

- **Not available**
  - CT data/documents that may contain CCI: e.g., bioanalytical data
EMA draft policy – **Good Analysis Practice**

- Legally-binding data-sharing agreement for ‘controlled access’ data
  - Requester will be made aware of standards for good analysis practice (for information only)
  - Requester will be given the opportunity to upload a statistical analysis plan
  - Requester should make results available publicly

- The Agency will not judge the requester's professional competence to conduct analyses and the requester's statistical analysis plan
- The Agency will publish the following on the requester: identity, list of the aims of accessing data, any uploaded documents (e.g. SAP) within one year of the request
Comments on EMA Draft Policy

- 1,000+ comments
- 150+ individuals and organisations
- Individual citizens expressed support for EMA’s initiative to increase clinical trial data transparency
Next Steps

- **EMA draft policy** published on 30 June 2013
- **Public consultation** closed on 30 September 2013
- Comments to be reviewed by EMA
- **EMA final policy** expected to enter into force on 1 January 2014
- **Implementation plan** under development
Acknowledgements

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- & Frank Petavy (EMA)