EFSPI

European Federation of Statisticians in the Pharmaceutical Industry

Representing Statistical Associations in Europe

# European Statistical Workshop (EFSPI/PSI):
# EMA Clinical Trial Data Transparency

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# Overview

- How it all began
- Current status

- EFSPI‘s Position
- EMA‘s draft Policy

- Aim of this meeting

# How it all began …

- In 2007, Danish researchers turned to EMA and requested access to clinical study reports.
- EMA refused disclosure due to drug producers' commercial interests.
- EU Ombudsman called on EMA to disclose the documents or provide a convincing explanation as to why no access could be given.
- EMA decided to grant access to the documents requested.
- EMA further committed itself to reactive disclosure.

www.ombudsman.europa.eu/en/cases/summary.faces/en/5646/html.bookmark

# Timelines for EMA's proactive disclosure

- Advisory groups April 30th 2013
- Draft EMA policy June 24th 2013

- Consultation until September 30th 2013
- Final EMA policy by November 30th 2013
- Operational January 1st 2014
  - Open data posted for submissions from March 1st 2014
  - Controlled access for submissions from Jan. 1st 2015

# Statisticians in EMA advisory groups

- **Protecting patient confidentiality**
  - Stefan Driessen, EFSPI representative (Abbott)
- **Clinical trial data formats**
  - Hans-Ulrich Burger, Roche; Nick Manamley, Amgen
- **Rules of engagement**
  - Chrissie Fletcher, EFSPI representative (Amgen); Merete Jørgensen, Novo Nordisk
- **Good analysis practice**
  - Maylis Coste, Servier; Eric Genevois-Marlin, Sanofi; Merete Jørgensen, Novo Nordisk; Christoph Gerlinger, EFSPI representative (Bayer); Søren Kristiansen, Takeda; Hans-Jürgen Lomp, Boehringer Ingelheim; Laura Meyerson, Biogen Idec
- **Legal aspects**

# Current status

- Results of advisory groups posted
  - http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/document_listing/document_listing_000368.jsp
  - No consensus on most issues
- EMA issued draft policy for comments
  - http://www.ema.europa.eu/docs/en_GB/document_library/Other/2013/06/WC500144730.pdf
- Some companies sued EMA to prevent disclosure
- Some companies voluntarily disclose data

- EFSPI position statement issued
- EFPIA and PhRMA issued a joint statement
- Others are following: *FDA asked for comments on disclosure of de-identified data*

# EFSPI Position on EMA's Access to Clinical Trial Data Initiative

- EFSPI supports responsible data access
- EFSPI believes access to clinical trial data should be implemented in a way which
  - supports good research,
  - avoids misuse of such data and
  - fully protects patient confidentiality.

http://www.efspi.org/aadocs/efspipositiononema250413.pdf

# EFSPI supports

- open access to summary data
- access to patient level data, if
  - Protocol, SAP submitted upfront
  - Qualified individuals (ICH E9)
  - All analyses are published or posted
  - Opportunity of a dialog data owner and data requestor

# EFSPI concerns

- Removing/blurring data items (typically covariates) to protect patients' identity may
  - prevent reproduction of results
  - limit further analyses
- Further guidance on technical aspects of re - analyses and additional analyses needed
  - E.g., multiplicity, meta - analysis, subgroups, publication bias

# Key statistical elements of EMA‘s policy

- Definition of Clinical-trial (CT) data
- Levels of access

# CT data definition (line 90ff)

- CTD Modules:
  - 2.5 (Clinical Overview),
  - 2.7 (Clinical Summaries) and
  - 5 (Clinical Study Reports incl. appendices)
- Includes also:
  large simple trials, cohort studies, case control studies, or registry data

- But excludes data from independent trials

# CT data definition cont.

- documentation on data sets
  - e.g., annotated CRF, variable definitions, data-derivation specifications, data-set definitions
- supporting documents,
  - e.g., test outputs, Statistical Analysis Software logs and SAS statistical programs

# EFSPI Categories of CT data (line 125ff)

1. CT data containing commercially confidential information (CCI)
   - Not made public under this policy
2. CT data without personal data concerns (O)
   - Open access by download from EMA website
3. CT data with personal data concerns (C)
   - Controlled access

# CT data (O) (line 138ff)

- No personal data e.g. summary tables
- Personal data adequately de-identified
- There are public-health reasons why personal data can be made public
  - personal data of CT personnel

# CT data (C) (line 118ff, 155ff)

- individual patient data sets
- individual patient line-listings
- individual Case Report Forms (CRFs)
- supporting documents, such as test outputs, Statistical Analysis Software logs and SAS statistical programs

# Protection of (C) data

- De-identification
- Controlled access

# De-identification (line165ff)

- should preclude subject de-identification
  - even when applying linkages with other data (e.g. social media)
- all data sets or a subset,
  - e.g. the main analysis set
  - With a limited number of indirect identifiers
  - With ability to replicate the main analysis

# Controlled access (line 176ff)

- Agency verifies identity of requester
- requester, is established in the EU
- legally binding data-sharing agreement

# EFSPI Data sharing agreement (line 181ff)

- access data only in the interest of public health
- submit aims at the time of the request
- refrain from any attempt to retroactively identify patients in CTs
- refrain from using CT data for any purposes outside the patients' informed consent

# Data sharing agreement – 2

- refrain from using CT data to gain a marketing authorisation outside EU
- not share CT data with anyone else
  - all members of research groups will have to individually commit
- ethics-committee approval, as appropriate

# Data sharing agreement – 3

- be aware of good analysis practice
- agree to the Agency publishing their identity, aim(s), and (statistical) analysis-plan status
- make all results of their analyses public within a reasonable period of time
- destroy CT data, once analysis completed

# Good analysis practice (line 207ff)

- EMA will communicate its expectations relating to good analysis
  - but no obligations
- EMA considers a detailed protocol / statistical analysis plan before data access of utmost importance
  - but no obligations

# Good analysis practice – 2

EMA will NOT, at the time of allowing access to 'C' data:

- judge the requester's professional competence to conduct analyses
- judge the requester's (statistical) analysis plan (if uploaded)

# Aim of this meeting

- Discuss statistical/methodological issues of draft EMA policy
- Create and discuss EFSPI comments on draft EMA policy

- Finalize contents of EFSPI comments.
  - Wording will be finalized after today's meeting

EFSPI Σ

Thank you for your attention!

From: **The First 2 Years of the European Medicines Agency's Policy on Access to Documents: Secret No Longer**

JAMA Intern Med. 2013;173(5):380-382. doi:10.1001/jamainternmed.2013.3838

**Table. Requests for Documents Handled Under the European Medicines Agency's Policy Announced on November 30, 2010 (as of November 19, 2012)**

| | | | | | Analysis of Successful Requests | | |
|---|---|---|---|---|---|---|---|
| | | | | | Median (IQR) | | |
| Requestor's Affiliation | Total[a] | Pending[b] | No Access[b] | Access Granted[b] | Time to Access, d | Length Released, Pages per Request | Total Pages |
| Industry | 149 (33) | 6 (4) | 46 (31) | 97 (65) | 25 (18-60) | 78 (13-919) | 491 989 |
| Media | 84 (18) | 5 (6) | 20 (24) | 59 (70) | 26 (13-40) | 64 (17-358) | 380 563 |
| Legal | 71 (16) | 6 (8) | 15 (21) | 50 (70) | 37 (21-112) | 49 (14-1244) | 274 163 |
| Academia | 38 (8) | 6 (16) | 7 (18) | 25 (66) | 30 (19-68) | 210 (41-2796) | 286 045 |
| General public | 31 (7) | 1 (3) | 8 (26) | 22 (71) | 31 (16-62) | 183 (32-1873) | 134 782 |
| Institution | 28 (6) | 1 (4) | 13 (46) | 14 (50) | 21 (15-35) | 48 (6-167) | 17 620 |
| Consultant | 27 (6) | 5 (19) | 4 (15) | 18 (67) | 27 (14-62) | 75 (25-299) | 45 982 |
| Health care professional | 16 (4) | 1 (6) | 6 (38) | 9 (56) | 20 (19-24) | 89 (25-1534) | 18 795 |
| Patients' organization | 9 (2) | 0 | 3 (33) | 6 (67) | 51 (4-183) | 404 (404-1018) | 5942 |
| Financial sector | 4 (1) | 0 | 2 (50) | 2 (50) | 33 (1-64) | 202 (2-402) | 404 |
| **Total** | **457** | **31** (7) | **124** (27) | **302** (66) | 26 (16-60) | 81 (17-825) | **1 656 285** |

Abbreviation: IQR, interquartile range.
[a] Data are given as number of requests (proportion of total, overall).
[b] Data are given as number of requests (proportion of total, per category).

# Protecting patient confidentiality

- Mandate: “How can the Agency ensure through its policy that patient and other personal information will be adequately protected, i.e. that patients cannot be retroactively identified when clinical-trial data are released, and that applicable legislation, standards, and rules regarding personal data protection will be respected?”
- Key issues:
  - Complete datasets are needed to re-create original analyses
  - Thus, „blurring“ of data (i.e. by adding random noise) not feasible
  - Identification risk by comparing trial data e.g. to social media postings or search engine inquiries
  - Run secondary analyses in a protected mode on EMA server and give out only results but no raw data (resource intensive for EMA) ?

# Clinical trial data formats

- Mandate: “How can the Agency ensure through its policy that clinical-trial data can be shared, in the interests of public health, in a clear and understandable format that enables appropriate analyses and a swift implementation without undue burden to stakeholders?”

Key issues:

  - Provide trial data as used for the submission
  - Standardization will only be achieved over time, e.g. via CDISC
  - No re-formatting, e.g. to current version of MedDRA
  - No pooling of studies due to information loss

# Rules of engagement

- Mandate: “Are there rules or conditions that should be in place before an external stakeholder can download clinical-trial data (e.g. formal acceptance of the need to respect personal data rules, uploading of analysis plans etc.)?”

Key issues:

  - Patient confidentially (see before)
  - Good analysis practice (see below)
  - Need for scientific rationale?
  - Information / Consultation of MAH?
  - Approval of scientific rationale needed? By whom?
  - Tiered approach? CSRs for all and raw data only for few?
  - Publication of requests and/or results?

# Good analysis practice

- Mandate: “Are there good-analysis-practice guidelines that the Agency could ask external requestors of data to consider or be aware of, and that the Agency can apply when confronted with additional analyses from external parties?”

Key issues:

  - Pre-specification of Statistical Analysis Plan (SAP)
  - Possibility of data owner to comment on SAP
  - Publication of SAP and results (and derived datasets)
  - Qualification of personnel (ICH E9) ?

# Legal aspects

- Mandate: “Are there any legal aspects other than personal data protection that need to be addressed when drafting the Agency’s policy? Are there exceptional circumstances under which data can be claimed to be commercially confidential?”
- Key issues:
  - IP
  - Commercial confidential information

# General Court of the EU on access to clinical and non-clinical information

- The European Medicines Agency (EMA) has been ordered by the General Court of the European Union not to provide documents as part of two access-to-documents requests until a final ruling is given by the Court.
- These interim rulings were made as part of court cases brought by two pharmaceutical companies, AbbVie and InterMune. The companies are challenging the Agency's decisions to grant access to non-clinical and clinical information (including clinical study reports) submitted by companies as part of marketing-authorisation applications in accordance with its 2010 access-to-documents policy.

# GSK to make patient data available


https://clinicalstudydata.gsk.com/ (accessed 2013-05-09)

# Recommended reading

www.efspi.org/aadocs/finalefspiposition25april2013.pdf

www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000555.jsp

www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/document_listing/document_listing_000368.jsp


EMA workshop November 2012