Welcome to the new world of data transparency

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Disclaimer (Chrissie Fletcher)

- The views expressed herein represent those of the presenter and do not necessarily represent the views or practices of Amgen or the views of the general Pharmaceutical Industry.

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Agenda

- Why data transparency is so important
- Industry’s guiding principles for sharing clinical data
- Data sharing - experiences to date
- Key aspects of the final EMA policy on publication of clinical data
- Current areas of focus
- Conclusions
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Data Sharing / Disclosure Milestones

- **ICMJE (2004)**
  - requires protocol registration in clinicaltrials.gov in order for paper to be published

- **JAMA (2005)** [reversed in 2013]
  - requires independent replication of statistical analysis

- **AAMC (2006)**
  - proposed raw data be made publicly available

  - Joint Position on registration, publication of summaries and journal publication

- **FDAAA (2008)** requires basic results of CTs to be made publicly available

- **EU Regulation EC/726/2004** requires publication of summaries (live 2013)

- **BMJ (2013)** authors must commit to make anonymised patient level data available

- **EU CT Regulation (2014)** obligatory posting for all EU trials (2016)

- **EMA Clinical Data Disclosure Policy (2014)** proactive posting of clinical data upon approval

...but still not enough!
What does “sharing” mean?

- Sponsor
- Original researchers
- Other approved researchers
- Any researchers
- Everyone

Risk or Reward vs. Inclusiveness
Goals, Barriers and Risks

Data sharing stakeholders make numerous claims:

• **Goals of data sharing**
  • Help practitioners and patients
  • Inform scientific discourse
  • Advance medical technology
  • Enable public scrutiny and application of new knowledge in future research

• **Barriers and risks**
  • Patient privacy; patient consent
  • Process of de-identifying and standardizing data
  • Perceived loss of intellectual independence by academics
  • Erroneous secondary analysis
  • Research incentives

• Can goals be balanced against risks?
Existing Data Sharing Initiatives

Numerous data sharing initiatives exist; level of disclosure and to whom is varied:

- **BMJ Policy**
  - Authors must make data available upon ‘reasonable request’.

- **Multi-stakeholder platform / single sponsor initiatives**
  - Researchers can request access to anonymized, participant-level data.

- **Mini-Sentinel**
  - FDA pilot uses pre-existing electronic data from multiple sources.

- **C-Path Consortia**
  - Pre-competitive sharing of data; obtain broad data use agreements.

- …Many others
Data Sharing Models

There are also several data sharing models:

- Learned intermediary
  - Third party board reviews research requests; criteria applied.
- Data generator
  - Data requester submits written request via website to data generator; criteria applied.
- Database query
  - Data sets available for queries; not directly accessed/downloaded.
- Open Access
  - Data generator posts on central portal maintained by independent organization.
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Five New PhRMA-EFPIA Commitments

1. **Enhancing Data Sharing with Researchers**
   - Including patient level clinical trial data and protocols from trials in patients for already approved medicines; external review of data requests

2. **Enhancing Public Access to Clinical Study Information**
   - At a minimum, the synopses of clinical study reports (CSRs), following approval of a new medicine or new indication in US and EU

3. **Sharing Results with Patients Who Participate in Clinical Trials**
   - Providing patients with a factual lay summary of trial results

4. **Certifying Procedures for Sharing Clinical Trial Information**
   - Each company to certify on a publicly available website that established policies and procedures are in place

5. **Reaffirming Commitments to Publish Clinical Trial Results**
   - At a minimum, results of all phase 3 trials (irrespective of positive or negative results) and any other results of significant medical importance, including from discontinued programs
EFPIA Clinical Trial Data Portal Gateway

EFPIA's gateway for available clinical trial data offers a published list of member companies' online portals aimed at advancing responsible clinical trial data sharing. A promise to develop these portals was established as part of joint EFPIA-PhRMA commitments on clinical trials data transparency, which came into full force on 1st January 2014. More information about Clinical Trials and the EFPIA-PhRMA Commitments can be found on EFPIA's Responsible Transparency platform.

› Abbvie
› Amgen
› Bayer
› Biogen Idec
› Boehringer
› BMS
› GSK
› Johnson & Johnson
› Lilly
› Merck & Co (MSD)
› Merck
› Novartis
› Novo Nordisk
› Pfizer
› Sanofi
› Shire
› Roche
› UCB
› Celgene

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Multi-Sponsor Platform Approach for Sharing Data with Researchers

About

This site

Access to the underlying (patient level) data that are collected in clinical trials provides opportunities to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by research participants are used to maximum effect in the advancement of knowledge and understanding.

Researchers can use this site to request access to patient level data and supporting documents from clinical studies to conduct further research.

Next steps

Study sponsors who have committed to use this site are Bayer, Boehringer Ingelheim, GSK, Lilly, Novartis, Roche, Sanofi, Takeda, UCB and Viiv Healthcare.

Other clinical trial sponsors and funders are invited to join with the clinical research community in using this site to make their data more accessible to researchers.

How it works

### Submission

Researchers can submit research proposals and request anonymised data from clinical studies listed on this site. Study sponsors will add more studies when the site is updated.

Information on sponsor’s criteria for listing studies and other relevant sponsor specific information is provided in the Study sponsors section of this site.

Researchers can also submit enquiries to some study sponsors to ask about the availability of data from studies they have not listed on this site.

### Review

Research proposals are reviewed by an Independent Review Panel. The study sponsors are not involved in the decisions made by the panel.

### Access

Following approval and after the relevant study sponsor or sponsors receive a signed Data Sharing Agreement, access to the data needed for the research is provided on a password protected website.
Preparation of individual patient data from clinical trials for sharing: the GlaxoSmithKline approach

Sara Hughes, Karen Wells, Paul McSorley, and Andrew Freeman

In May 2013, GlaxoSmithKline (980 Great West Road, Brentford, Middlesex, TW8 9GS, UK) established a new online system to enable scientific researchers to request access to anonymised patient level clinical trial data. Providing access to individual patient data collected in clinical trials enables conduct of further research that may help advance medical science or improve patient care. In turn, this helps ensure that the data provided by research participants are used to maximum effect in the creation of new knowledge and understanding. However, when providing access to individual patient data, maintaining the privacy and confidentiality of research participants is critical. This article describes the approach we have taken to measure data sharing with other researchers in a way that minimises risk with respect to the privacy and confidentiality of research participants, ensures compliance with current data privacy legal requirements and yet retains the datasets for research purposes. We recognise that there are different possible approaches and that there is a need for transparency.

1. INTRODUCTION

Greater transparency and access to clinical trial data is a goal for many bodies and institutions currently (e.g. [1–4]). In line with this goal, GlaxoSmithKline recently made a commitment to provide access to anonymised individual patient data from clinical trials. The scope of the commitment and the approach the company adopted is described here.

The integrated approach initially involves collecting data on patients recruited in clinical trials and making the data available online through a web interface. The data are stored in a secure database, and access is granted on a case-by-case basis to researchers who meet the predefined criteria. The data are anonymised to the greatest extent possible while still providing sufficient information to conduct meaningful analyses.

The model is based on a recommendation from the UK parliament and the subsequent Government that anonymised patient level data should be provided but instead accessed in secured, password-protected databases. To ensure the proposal is feasible and sustainable, GlaxoSmithKline has adopted an industry model of research and development. This model incorporates best practices and minimises risk with respect to the privacy and confidentiality of research participants, ensuring compliance with current data privacy legal requirements and yet retains the datasets for research purposes. We recognise that there are different possible approaches and that there is a need for transparency.

2. METHODS

The proposed approach for providing access to anonymised clinical trial data involves several key steps:

1. Data collection: Data on patients recruited in clinical trials are collected and stored in a secure database.
2. Data anonymisation: The data are anonymised to the greatest extent possible while still providing sufficient information to conduct meaningful analyses.
3. Data sharing: Access to the anonymised data is granted on a case-by-case basis to researchers who meet the predefined criteria.

The approach is intended to be transparent and minimises risk with respect to the privacy and confidentiality of research participants, ensuring compliance with current data privacy legal requirements and yet retains the datasets for research purposes.
Company strategies – clinical trial data in scope

- Approved by FDA and EMA
- Clinical trials since
  - Jan 1999 (FPE)
  - Dec 2000
  - 2001
  - Sept 2007
- Approved by FDA and EMA Sept 2007
- Approved by FDA and EMA Jan 2008
- Approved by FDA and EMA Jan 2014
- Regulatory review has been completed or termination of the development program and manuscript accepted for publication
- Unclear, not available to US healthcare professionals
- Not specified
- Exceptions:
  - rare diseases
  - single-center clinical studies, or clinical studies with a very small number of subjects.
Company strategies - proposal submission and review processes

Submission Process
• Consistent across multi-sponsor platform and individual sponsors: Researchers request access to anonymised patient level data and supporting documents from clinical studies to conduct further research.

Review Process
Multi-sponsor platform:
• Proposals are reviewed by an Independent Review Panel. The study sponsors are not involved in the decisions made by the panel.

Individual sponsors:
• If sponsors reject, independent review panel reviews and decides.

Other companies (examples):
• No mention of independent review.
• Final decision following independent review remains with the sponsor.
Company strategies - data access processes

**Data Access Process**

**Multi-sponsor platform:**
- Following approval and after the relevant study sponsor or sponsors receive a signed *Data Sharing Agreement*, access to the data needed for the research is provided on a password protected website.

**Individual sponsors:**
- Following approval and receipt of a signed Data Sharing Agreement, anonymization of the requested data will occur and then access to data (not using controlled system).

**Other companies (examples):**
- Unclear how data will be made available
- All data requests, decisions and requestor’s research results summaries will be made available on a public website to ensure full transparency of the process.
Company strategies - anonymization considerations

- Aggregate centres/countries
- Subject ID, site, INV recoded
- Age > 89 removed/grouped
- DOB partial/complete removal
- Deletion of recoding algorithms
- Relative days or dates replaced
- Verbatim/comments removed
- Genetic data removed
- QC
- Storage of new datasets
Amgen’s data sharing experiences (Dec ‘13 – Sep ‘14)

17 data enquiries

6 data sharing requests

- 1 rejected (pipeline product)
- 3 accepted
- 2 under review
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EMA final policy on publication of clinical data

• **The policy’s objectives**
  • Make medicine development more efficient
  • Enable new knowledge to be developed
  • Verify original analyses and conclusions, conduct further analyses, and examine regulatory positions and challenge them

• **The agency expects**
  • Same standard of transparency used by everyone
  • Receive a copy of secondary analyses before publication where the results may need regulatory action
  • Review available information in a timely manner

• **The agency cannot**
  • Guarantee all secondary data analyses are conducted and reported to the highest possible scientific standard
EMA final policy on publication of clinical data (cont.)

Key principles

• **Protecting personal data** – guarded approach to sharing patient-level data, respecting patient informed consent

• **Protecting commercially confidential information (CCI)** – limited circumstances where information constitutes CCI

• **Protecting the agency and EU commission decision making process** – focus on science and best interest of patients, protect against external pressures

• **Ensuring future investment in R&D** – guard against unintended consequences e.g. breaches of intellectual property
EMA final policy on publication of clinical data (cont.)

- **Publication process for clinical reports**
  - Terms of use (ToU): govern access to and use of clinical reports
    - On-screen view with simple and limited registration process
    - Downloadable to identified users
  - User-friendly tool allowing access to clinical reports

- **Key elements of ToU:**
  - No attempt to re-identify patients
  - Clinical reports cannot be used to support MAA/extensions/variations or unfair commercial use
  - Watermark to prohibit use for commercial purposes
  - No responsibility by agency for users compliance to ToU
EMA final policy on publication of clinical data (cont.)

• **Redaction principles**
  - Most information in clinical report not considered CCI
  - Limited circumstances where CCI exists

• **Balancing protection of patients privacy whilst retaining scientific value of data**
  - Further discussion with stakeholders on best way forward

• **Stepwise implementation**
  - First phase: publication of clinical reports
  - Second phase: making available individual patient level data (IPD)
EMA final policy on publication of clinical data (cont.)

- **First phase: publication of clinical reports**
  - Following EC decision (grant or refuse) or
  - Following scientific committee opinion or
  - Following scientific committee conclusion or
  - Following applicants withdrawal notification

- **Second phase: release of IPD**
  - Clarify first
    - Submission of IPD for scientific review by agency
    - How best to provide access to IPD
  - IPD will not be submitted for the sole purpose to publish IPD
  - Targeted public consultation with all key stakeholders
EMA final policy on publication of clinical data (cont.)

- **Effective date of policy**
  - New MAAs (centralised procedure) on or after 1\textsuperscript{st} Jan 2015 for new MAAs
  - MAA extensions (centralised procedure) on or after 1\textsuperscript{st} July 2015

- **Policy expected to be revised within 18 months from effective date (1\textsuperscript{st} Jan 2015)**
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EFSPJ/PSJ working group on data sharing

- Lead Sally Hollis (AZ) and Uli Burger (Roche)

- Objectives:
  - To identify and prospectively prioritize statistical issues in data transparency
  - To co-ordinate statistical contributions across Europe to the data transparency debate
  - To disseminate relevant information on the topic across the statistical community
  - To develop and share a vision of the potential longer term impact of data transparency.
EFSPI/PSI working group on data sharing

- Five work streams
  - Providing continuous input in EMA/EFPIA
    (Christoph Gerlinger, Bayer, Chrissie Fletcher, Amgen)
  - Recommendations for re-analysis practices
    (Sally Hollis, AZ, Chrissie Fletcher, Amgen)
  - Future impact on biostatistics
    (Nick Manamley, Amgen)
  - Minimal requirements for data sharing
    (Rebecca Sudlow, Roche, Janice Branson, Novartis)
  - Ensuring patient data confidentiality
    (Katherine Tucker, Roche)
De-identification Working Group

Vision:

“Develop data de-identification standards for CDISC data models”
Future evolution of the CSDR.com website

Short term

• Steering Committee oversees any changes to process and web pages
• Continue to invite other clinical trial data holders to join

Medium term

• IRP being organised and managed by a 3rd party

Long term

• Website and all systems run by an independent non-profit group
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• Data transparency brings a new era for clinical research

• EMA final policy on publication of clinical data enables access to clinical study reports (from 2015)
  • Future policy coming on access to individual patient data

• Industry is committed to enhance access to clinical trial data for existing medicines

• A number of aspects relating to data transparency remain under discussion and this area will continue to evolve

• Thank you PhUSE for your work in developing de-identification standards for CDISC data sets
References


• Clinical Study Data Request Site. https://clinicalstudydatarequest.com/ (Accessed 3-Oct-14)