# Transparency of Clinical Study Data
## Opportunities, Risks sand Side-effects

**SFdS Biopharmacie et Santé**

23. 11. 2015

Dr. Christoph Gerlinger

# Contents

Introduction

- A brief history of clinical trial data transparency
- How the pharmaceutical industry is making clinical trial data transparent
- Recent developments with academia

Opportunities

Risks

Side effects

Open issues

Conclusion

# What's the issue ?

Half of all clinical trials
have never been published.

This is a scandal.

Sign the petition here:

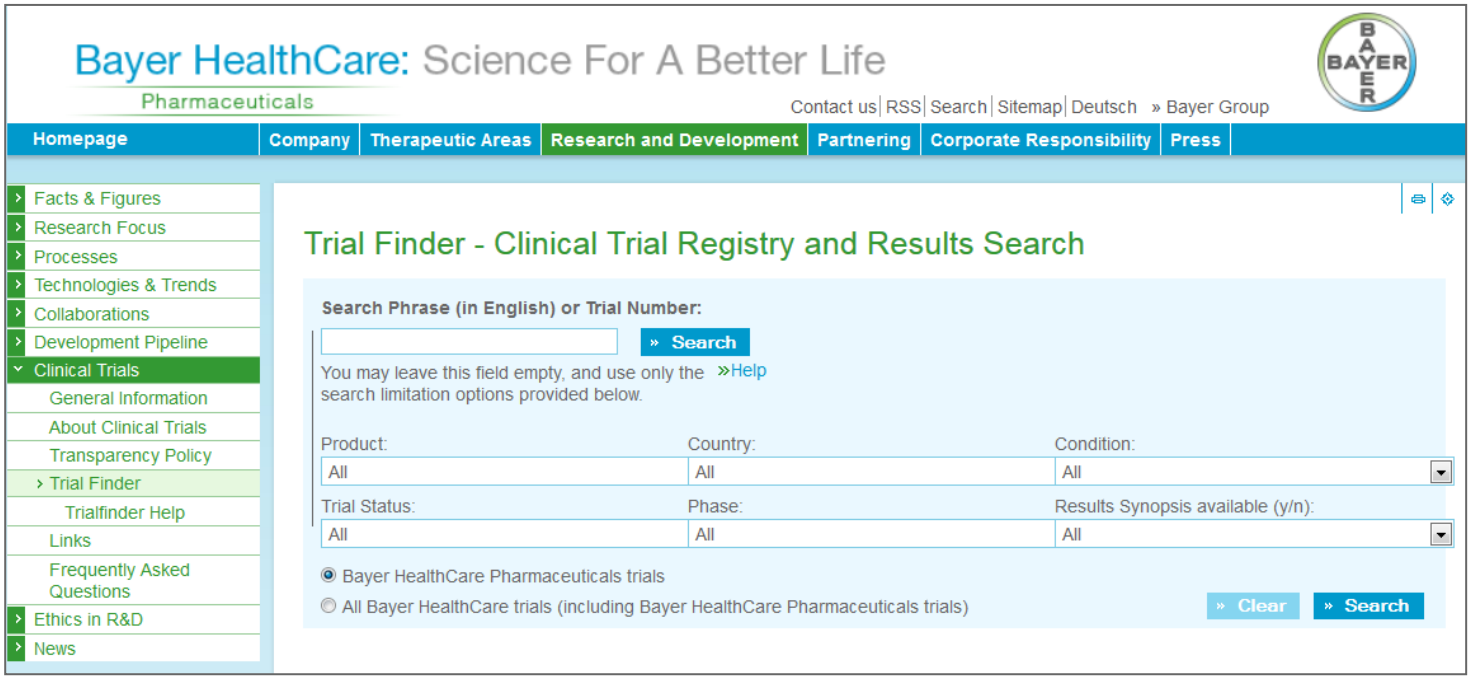
www.alltrials.net

alltrials.org 2014-04-28

# What's not the issue ?

Clinical trial registration and posting of summary results

- Mandatory in the US since 2005, EU since 2014
- Commitment by research manufacturers since 2005




http://www.bayerpharma.com/en/research-and-development/clinical-trials/trial-finder/index.php 2014-10-08

# 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 accessed 2013-09-26

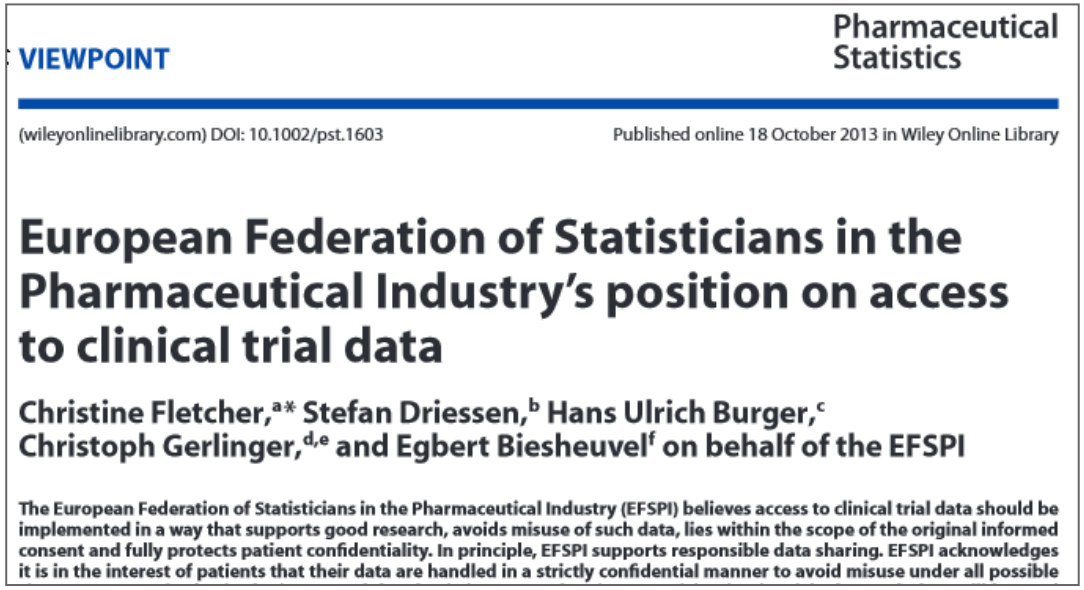
# EMA‘s plan for proactive disclosure

| | |
|---|---|
| Workshop | November 22nd 2012 |
| Advisory groups | April 30th 2013 |
| Draft EMA policy | June 24th 2013 |
| Consultation until | September 30th 2013 |

- 1,138 comments submitted by 169 entities

Final EMA policy by
~~November 30th 2013~~

- October 2nd 2014



VIEWPOINT

Pharmaceutical Statistics

(wileyonlinelibrary.com) DOI: 10.1002/pst.1603

Published online 18 October 2013 in Wiley Online Library

**European Federation of Statisticians in the Pharmaceutical Industry's position on access to clinical trial data**

Christine Fletcher,[a*] Stefan Driessen,[b] Hans Ulrich Burger,[c] Christoph Gerlinger,[d,e] and Egbert Biesheuvel[f] on behalf of the EFSPI

The European Federation of Statisticians in the Pharmaceutical Industry (EFSPI) believes access to clinical trial data should be implemented in a way that supports good research, avoids misuse of such data, lies within the scope of the original informed consent and fully protects patient confidentiality. In principle, EFSPI supports responsible data sharing. EFSPI acknowledges it is in the interest of patients that their data are handled in a strictly confidential manner to avoid misuse under all possible

# What shall be disclosed (according to EMA's draft policy)

Full overviews, clinical summaries, and study reports (text, tables, figures)

- For unrestricted download
- Redacted (e.g., case narratives)
- Without some of the appendices (e.g., individual patient data listings)

Patient level data

- De-identified for restricted download
- With (minimal) prior data sharing agreement

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

1 24 June 2013
2 EMA/240810/2013
3 Executive Director

4 **Publication and access to clinical-trial data**
5

6 POLICY/0070
7 Status: Draft for public consultation
8 Effective date:
9 Review date:
10 Supersedes: N.A.
11

# New approach by EMA

EMA held closed door stakeholder meetings in May 2014

For now only clinical study reports (CSR)

- CSRs (Module 5) + Clinical Overviews (Module 2.5) + Clinical Summaries (Module 2.7) + Appendices to CSRs No. 16.1.1, 16.1.2 and 16.1.9
- Controlled access to CSR (read on screen only)
- Contract between EMA and requestor
- Strengthened redaction principles
  - E.g. redact exploratory variables unrelated to regulatory decision (!)

Individual patient data (IPD) will be discussed with stakeholders later

# Hot debate ongoing

BMJ editorial: “The European Medicines Agency gets cold feet at the last minute”
*BMJ 2014;348:g3561*

IQWiG letter to BMJ: “EMA’s transparency policy: A placebo intervention?”
www.bmj.com/content/348/bmj.g3432?tab=responses

EMA press release: “European Medicines Agency agrees policy on publication of clinical trial data with more user-friendly amendments”
www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2014/06/news_detail_002124.jsp

# Final EMA policy

Released October 2nd 2014

Effective: new application: Jan 1st 2015
extension of indication: Jul 1st 2015

Scope: centralized procedure only (!)

Overviews, summaries and reports

- Redacted for data protection and commercial confidential information
- Redaction checked by EMA
- Publication after end of procedure

View on screen for all

Download for academia, HTA bodies

- With proper identification only


EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

2 October 2014
EMA/240810/2013

European Medicines Agency policy on publication of clinical data for medicinal products for human use

POLICY/0070
Status: Adopted
Effective date: 1 January 2015

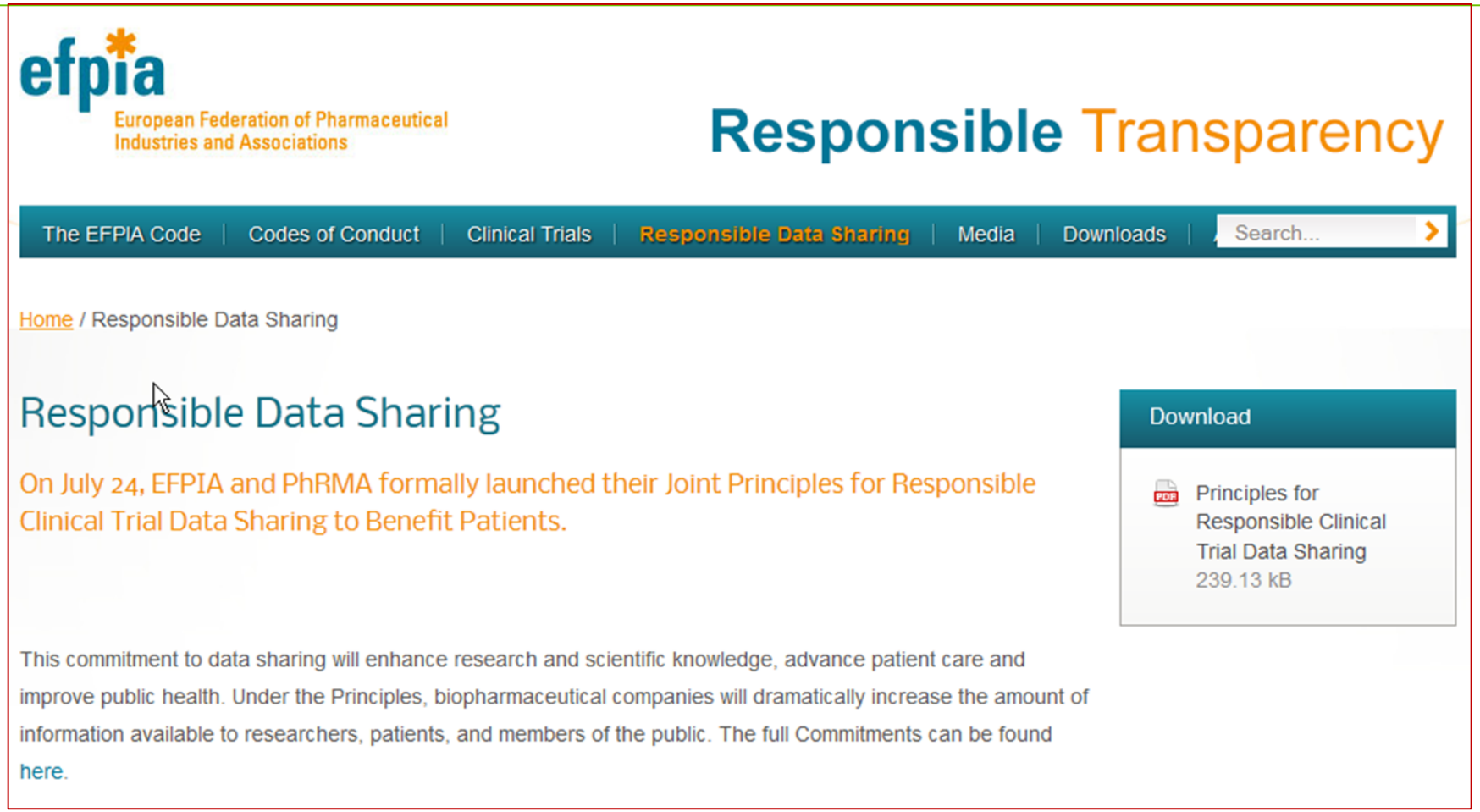
Release of patient level data postponed

Only data held by EMA (!)

Stakeholder discussion planned

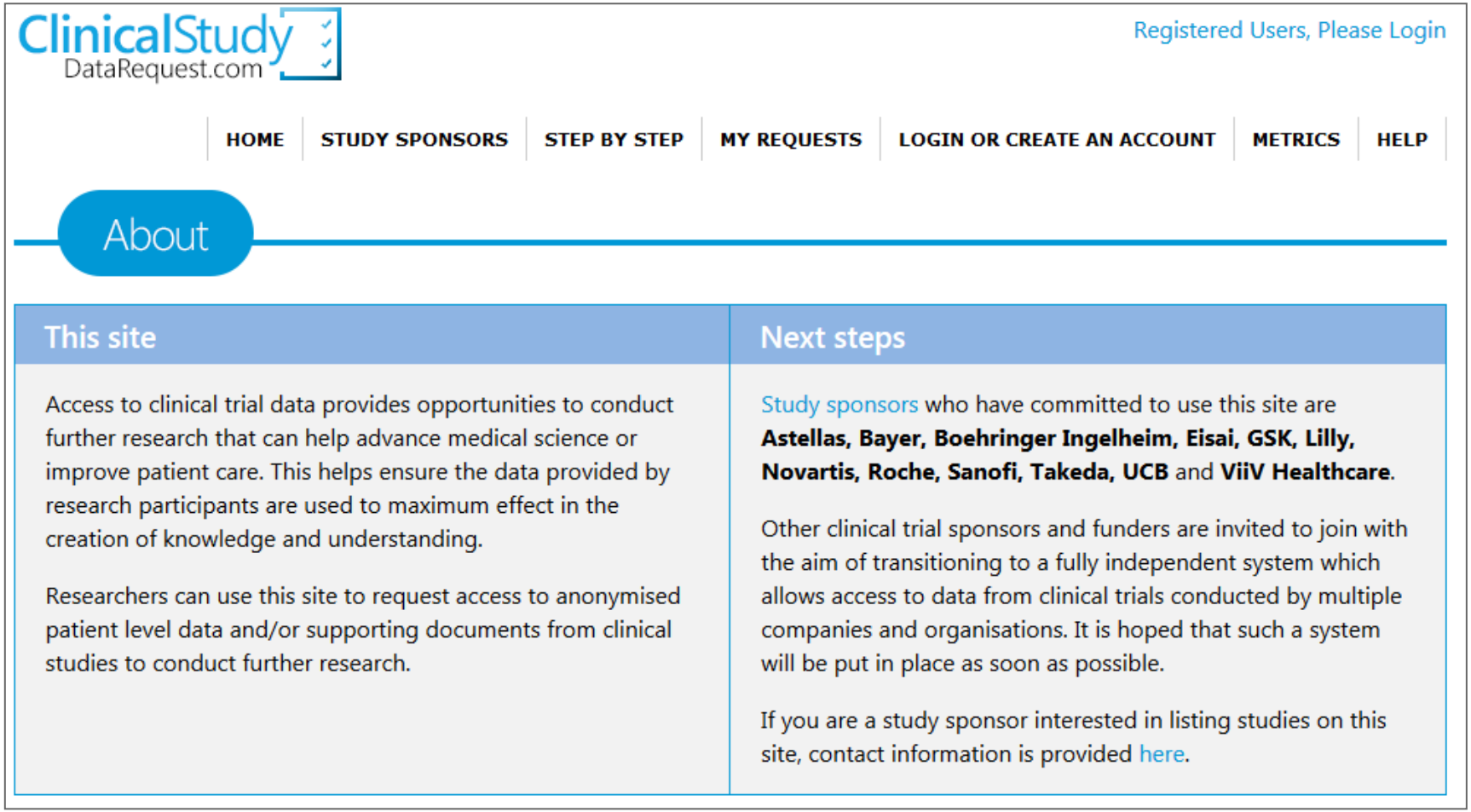
Revision of policy thereafter

# Industry commitment



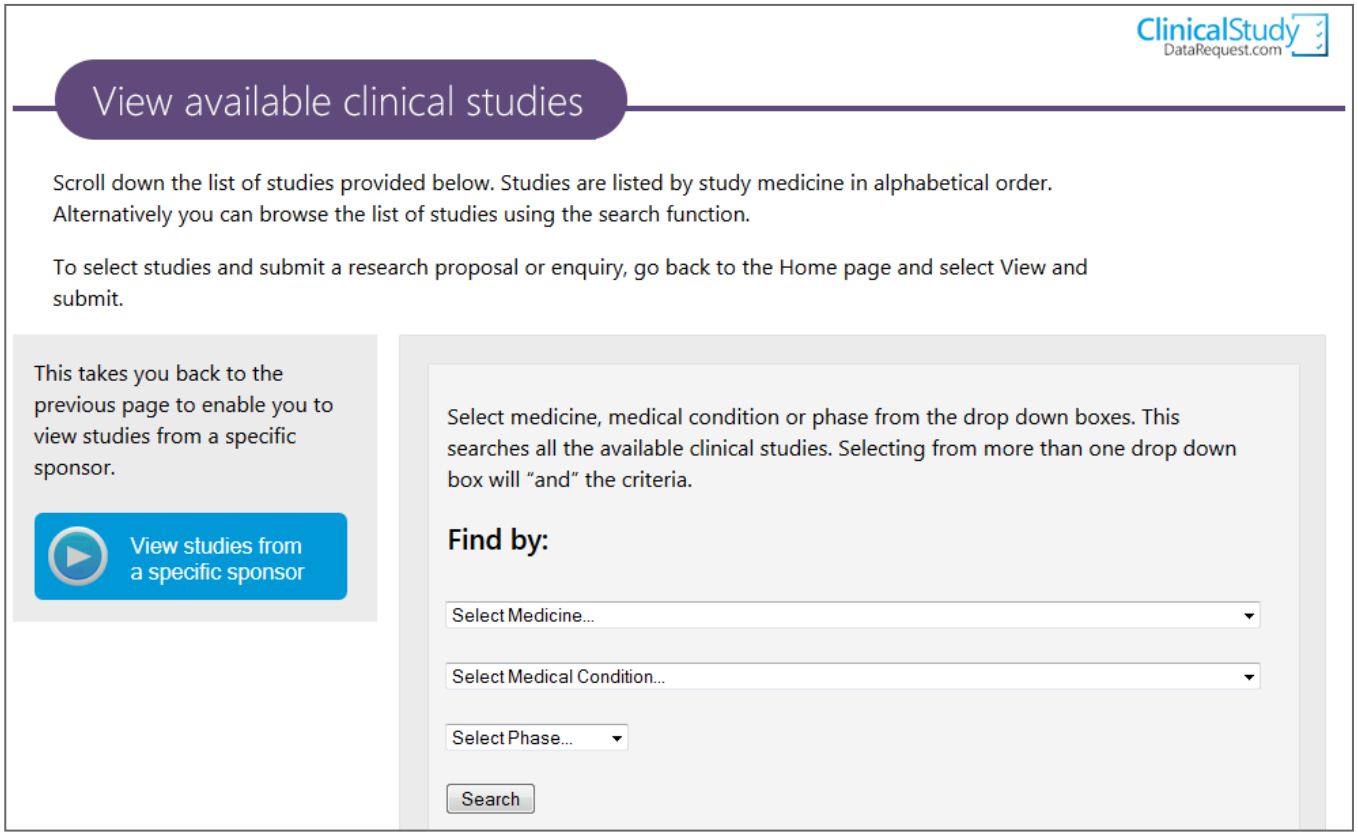

transparency.efpia.eu/responsible-data-sharing (accessed 2014-02-14)

# How data is made available




**www.clinicalstudydatarequest.com** 2015-11-04

# How data is made available




2760+ studies already available (Nov 2015)

clinicalstudydatarequest.com 2015-11-04

# How data is made available

## 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.

Find out more »

### Review

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

Find out more »

### 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.

Find out more »

**www.clinicalstudydatarequest.com** 2014-09-26

# How data is made available

## How it works

### Review of requests

### Review of research proposals

Research proposals are checked to make sure the information is complete and that they meet the requirements of this initiative and the sponsor's requirements for informed consent. They are then sent to the Independent Review Panel. The panel considers the following:

- The scientific rationale and relevance of the proposed research to medical science or patient care.
- The ability of the proposed research plan (design, methods and analysis) to meet the scientific objectives. This is a high-level review.
- The publication plan for the research.
- Real or potential conflicts of interest that may impact the planning, conduct or interpretation of the research and proposals to manage these conflicts of interest.
- The qualifications and experience of the research team to conduct the proposed research (a statistician with a degree in statistics or a related discipline should be part of the research team).

**www.clinicalstudydatarequest.com** 2014-09-26

# Scope of Studies to share Patient-Level Data

**www.clinicalstudydatarequest.com (status Mar 2014)**

| Company | Retrospective scope (No industry commitment) | Prospective Scope (= industry commitment) |
|---|---|---|
| GSK | Back to Dec 2000<br>Global interventional studies<br>Phase 1: included | All interventional studies that started in or after 2013 after first approval or termination of development project<br>Phase 1: included |
| Roche | Back to Jan 1999<br>Phase 2 - 4 studies<br>Phase 1: per enquiry only if > 50 patients | Phase 2 - 4 studies used as part of regulatory approval or from terminated development projects<br>Phase 1: per enquiry only if > 50 patients |
| Boehringer | Back to Jan 1998<br>All studies<br>Phase 1: only multi-center studies | All studies after completion of regulatory review or after termination of development program<br>Phase 1: only multi-center studies |
| ViiV | Currently unclear (earlier statement „back to 1999“ no longer posted on CSDR.com)<br>Global interventional phase 2 - 4 studies in adults living with HIV<br>Phase 1: unclear | Global interventional phase 2 - 4 studies in adults living with HIV listed on ViiVs trial registry after first approval or termination of development program |
| Sanofi / Bayer | None, only prospective use | Trials submitted to US and EU regulatory agencies for approved products in EU and US on or after Jan 01 2014 |
| Novartis | None, only prospective use | Studies for newly approved innovative medicines in the US and EU in 2014 [and onwards] |

# Planned Datasets and Documents to be Shared

**Where available, the following anonymized patient level data and information are planned to be provided for clinical studies in scope**

- Raw datasets
- Analysis-ready datasets
- Protocol with any amendments
- Annotated case report form
- Statistical analysis plan
- Dataset specifications
- Clinical study report
  - CSR appendices that contain no patient relevant data (e.g. audit certificates or manuals from providers of various diagnostic services) as well as individual patient level data (e.g. narratives) are not included.

**Documents will be redacted to protect personal data of study participants, study personnel, and Bayer employees, and to protect Bayer's commercially confidential information, including intellectual property rights.**

# Data anonymization

New patient identifiers

Center identification removed

Age censored for age 90+ (HIPPA rule)

Dates removed (only relative study time kept)

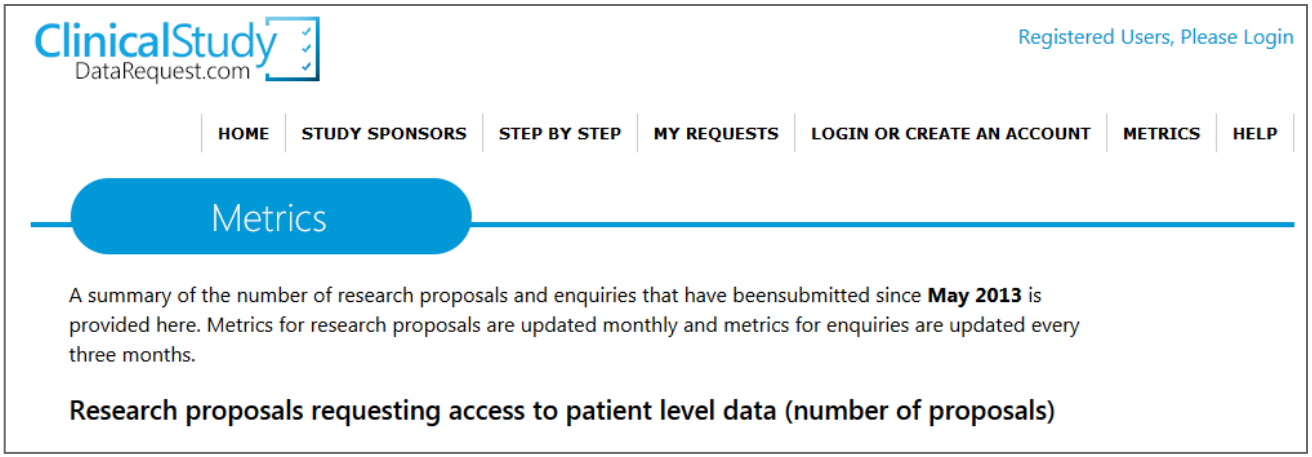
Verbatim texts removed (only coded information, e.g. MedDRA kept)

No images, e.g. MRT scans

Case check for rare combinations (e.g. 17-year old male with breast cancer)

See https://clinicalstudydatarequest.com/Documents/Bayer-Data-Anonymization-Standards-Apr-14-2014.pdf 2014-09-23

# Metrics




| | | |
|---|---|---|
| Number of Research Proposals submitted up to 30 September 2015 | | 165 |
| Requirements check | In process | 10 |
| | Withdrawn by the requestor | 18 |
| | Did not meet requirements (further details) | 11 |
| | Complete (data available) | 72 |
| Research project | In process | 72 |

- Transparancy works both ways
- Details of ongoing and finished research is made public

clinicalstudydatarequest.com
2015-11-04

# Recent developments with academia


**Promoting Clinical Trial Data Transparency Conference**

***When:*** March 30 & 31, 2015

***Where:*** Harvard Faculty Club, 20 Quincy Street, Cambridge, Massachusetts

***Who***: Data generators and data users, academic and government agencies, journal leadership, and other stakeholders (by invitation only)

***Conference Objectives***

- To discuss high-level principles with the explicit goal of developing an approach whereby participant level clinical trial data could be integrated, enabling researchers to access and combine data across the various platforms and sponsors.
- To present and deliberate centrally managed and federated models.
- To discuss implementable solutions to realize harmonization and enable broader data sharing across platforms.

http://mrct.globalhealth.harvard.edu/files/mrct/files/data_sharing_conference_agenda_03-16-2015_final_draft.pdf
accessed 2015-03-23

# Opportunities

Increase public trust in clinical trials

Verification of sponsor's pre-planned analysis

Re-analyses within initial objectives and randomization

- Deep drill within study
- Patient level meta-analyses

New research unrelated to initial objectives or randomization

# Opportunities: Increase public trust

In medical research

In regulatory action

In drugs' benefit / risk ratio

# Opportunities: Verification of sponsor‘s pre-planned analysis

Already done by FDA statisticians for pivotal phase III trials,
can be viewed in statistical reviews of new drug applications
e.g. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/202439Orig1s000StatR.pdf page 16

| | | | | | | |
|---|---|---|---|---|---|---|
| Per protocol[1] (out.hypo117) | From randomization up to follow up visit | Follow up visit | 283/7004 (4.0%) | 252/6958 (3.6%) | 0.90 (0.76, 1.07) | 0.244 |
| ITT[1] (out.hypo114) | From randomization up to follow up visit | Follow up visit | 285/7090 (4.0%) | 257/7081 (3.6%) | 0.91 (0.77, 1.08) | 0.285 |
| Per protocol[1] (out.hypo118) | From randomization up to the notification of site date | Site notification | 303/7004 (4.3%) | 263/6958 (3.8%) | 0.87 (0.74, 1.03) | 0.101 |
| ITT[1] (out.hypo115) | From randomization up to the notification of site date | Site notification | 306/7090 (4.3%) | 269/7081 (3.8%) | 0.88 (0.74, 1.03) | 0.116 |
| Per protocol[1] (out.hypo119) | From randomization up to reference end date** | Reference end date | 317/7004 (4.5%) | 285/6958 (4.1%) | 0.90 (0.77, 1.06) | 0.205 |
| ITT[1] (out.hypo116) | From randomization up to reference end date** | Reference end date | 320/7090 (4.5%) | 293/7081 (4.1%) | 0.91 (0.78, 1.07) | 0.263 |

(Source (in order of analyses): Clinical Study Report: Study ROCKET-AF;
Table 26 (page 136),
Attachment 6.1 (page 818),
Reviewer's results,
Reviewer's results,

Not always possible due to data anonymization (e.g. age censored at 90)

# Opportunities: Deep drill

Analyze study data further (but still within initial objectives and randomization)

- Subgroups
- Different  statistical methodology
  - Statistical model
  - Missing data / Questionable data
  - Intention To Treat / modified Intention To Treat / Full Analyses Set
- Endpoints
  - Composite
  - Separate

# Opportunities: Deep drill

Original Investigation

## Reanalyses of Randomized Clinical Trial Data

Shanil Ebrahim, PhD; Zahra N. Sohani, MSc; Luis Montoya, DDS; Arnav Agarwal, BSc; Kristian Thorlund, PhD; Edward J. Mills, PhD; John P. A. Ioannidis, MD, DSc

**IMPORTANCE** Reanalyses of randomized clinical trial (RCT) data may help the scientific community assess the validity of reported trial results.

**OBJECTIVES** To identify published reanalyses of RCT data, to characterize methodological and other differences between the original trial and reanalysis, to evaluate the independence of authors performing the reanalyses, and to assess whether the reanalysis changed interpretations from the original article about the types or numbers of patients who should be treated.

*JAMA.* 2014;312(10):1024-1032.

# Opportunities: Deep drill

**Table 2. Differences in Methods Used in the Reanalysis**

| Differences Cited in the Reanalysis | No. (%) | | | | |
|---|---|---|---|---|---|
| | | Did the Reanalysis Modify Inferences of the Original Trial? | | | |
| | Reanalyses (n = 37)[a] | No (n = 29) | Treat Different Patients (n = 3) | Treat More Patients (n = 13)[b] | Treat Fewer Patients (n = 1) |
| Differences in statistical or other analytical methods | 18 (48.6) | 11 (61) | 3 (17) | 3 (17) | 1 (5.5) |
| Nonparametric statistical technique | 1 | 1 | | | |
| Separation of composite end points for analysis | 1 | | | | 1 |
| Measure of clinical significance to confirm original findings | 2 | 2 | | | |
| Informative censoring approach | 3 | 3 | | | |
| Competing risks model | 1 | | 1 | | |
| Nonlinear model | 2 | 1 | 1 | | |
| Triangular and restricted sequential design | 1 | 1 | | | |

*JAMA.* 2014;312(10):1024-1032.

# Opportunities: Better Meta-Analyses

Currently most meta-analyses are based on publications

With access to patient level data

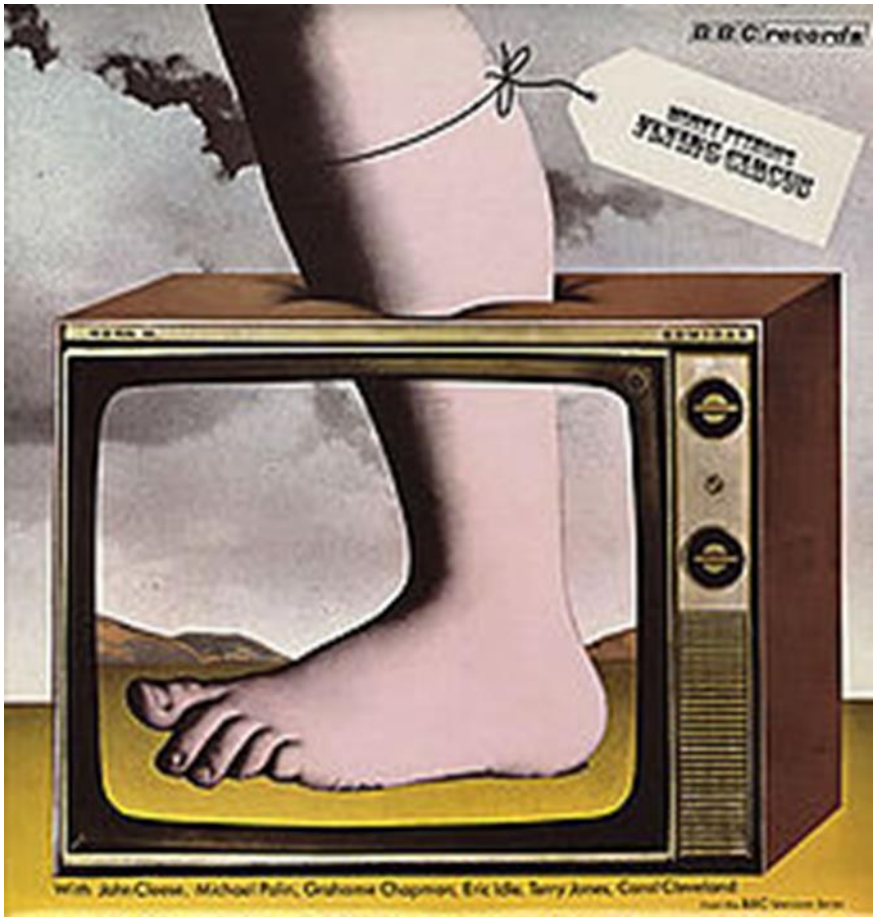
- Matching patient characteristics at baseline
- Subgroups of your choice (and not what is reported in the papers)

# Opportunities: New research

Use the data for new research
unrelated to initial objectives or
randomization

***And now to something completely different …***

CAVE! Might not be covered by
historic informed consent




https://en.wikipedia.org/wiki/Monty_Python%27s_Flying_Circus_%28album%29
accessed 2014-01-18

# Opportunities: New research

Assessing models for changes in tumour size over time and how they relate to survival times

Raluca Eftimie, PhD, Division of Mathematics, University of Dundee, UK

"There are still many unanswered questions regarding how, or even if, changes in tumour size relate to patient survival. In addition, to our best knowledge most survival models in the existing literature have never been tested on independent data sets. Such a test is the main purpose of this study. (…)

The research will be conducted using data from three drugs approved in the metastatic melanoma setting: Vemurafenib, Trametnib and Dabrafenib. The data from one of these studies will be used to select a tumour growth law model used to develop a survival model. The data from the other two drugs will be used as a validation set."

Data from 8 studies (6 GSK, 2 Roche) 1,789 patients

At ~60 T€ per patient, this more than 100 million € worth of data

https://clinicalstudydatarequest.com/Approved-requests-list-946-Roche.aspx 2014-09-09

# Risks

Patient privacy / re-identification

False positive findings

Commercial confidential information

Potential abuse

# Risks: Re-Identification of participants

Example of data record

| ID | Center | Age | Sex | Height | History | … |
|---|---|---|---|---|---|---|
| 1 | 1 | 54 | M | 187 | Myopia | … |

But from the study report you know also

- The study recruited from December 6th, 2013 to October 14th, 2014.
  - Date of birth is between December 7th, 1958 and October 14th, 1960
- Center 1 is located in Berlin-Wittenau
  - Participant most likely lives or works close by
- The studied illness is mad cow disease
  - Now you can guess …

# Risks: Re-Identification of participants

Real world example

Data known: year of birth, city, major subject at university

theguardian

Search

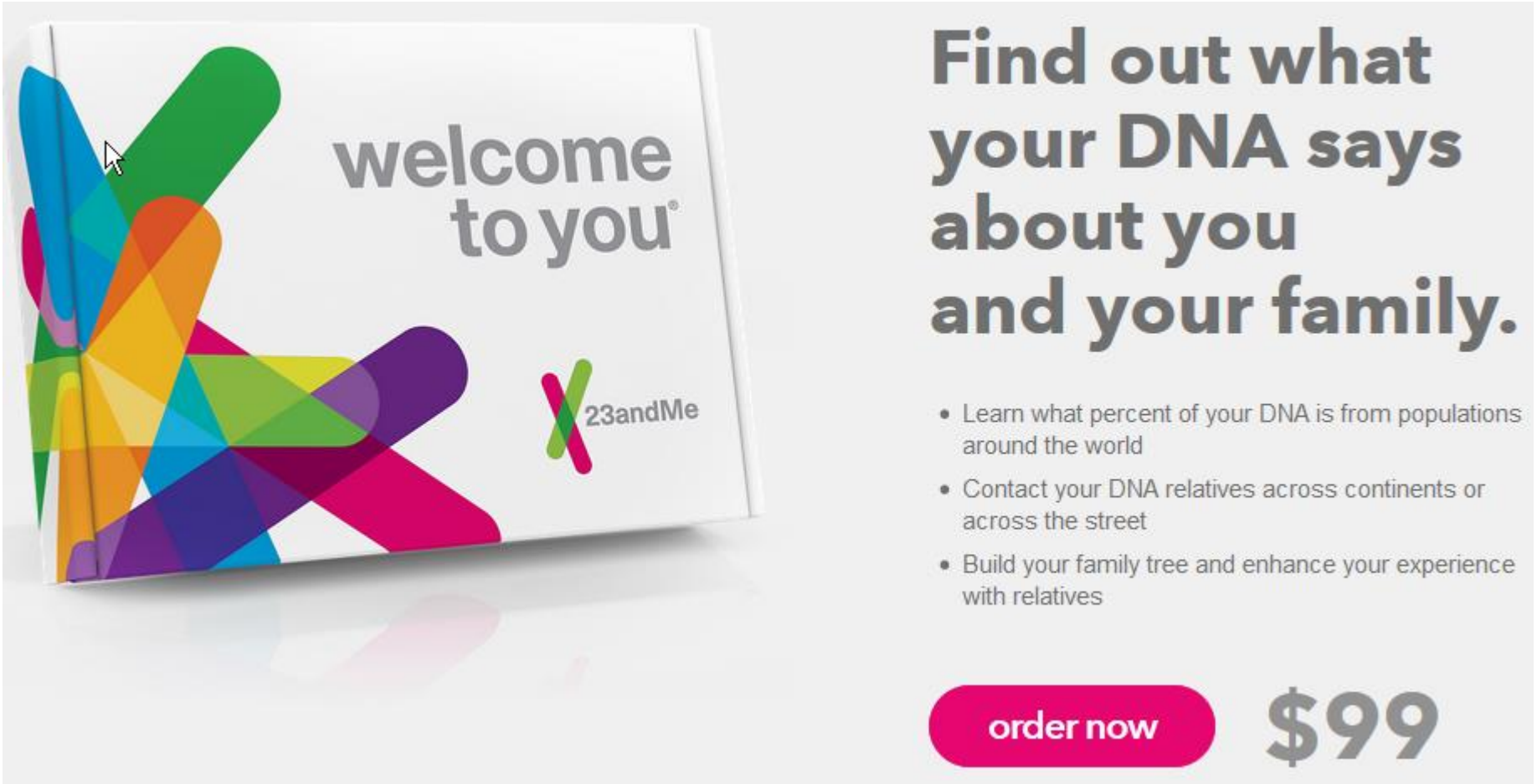
## Teenager finds sperm donor dad on internet

**Ian Sample**, science correspondent
The Guardian, Thursday 3 November 2005

Using nothing more than a swab of saliva and the internet, a 15-year-old boy has tracked down his anonymous sperm donor father, according to details released today.

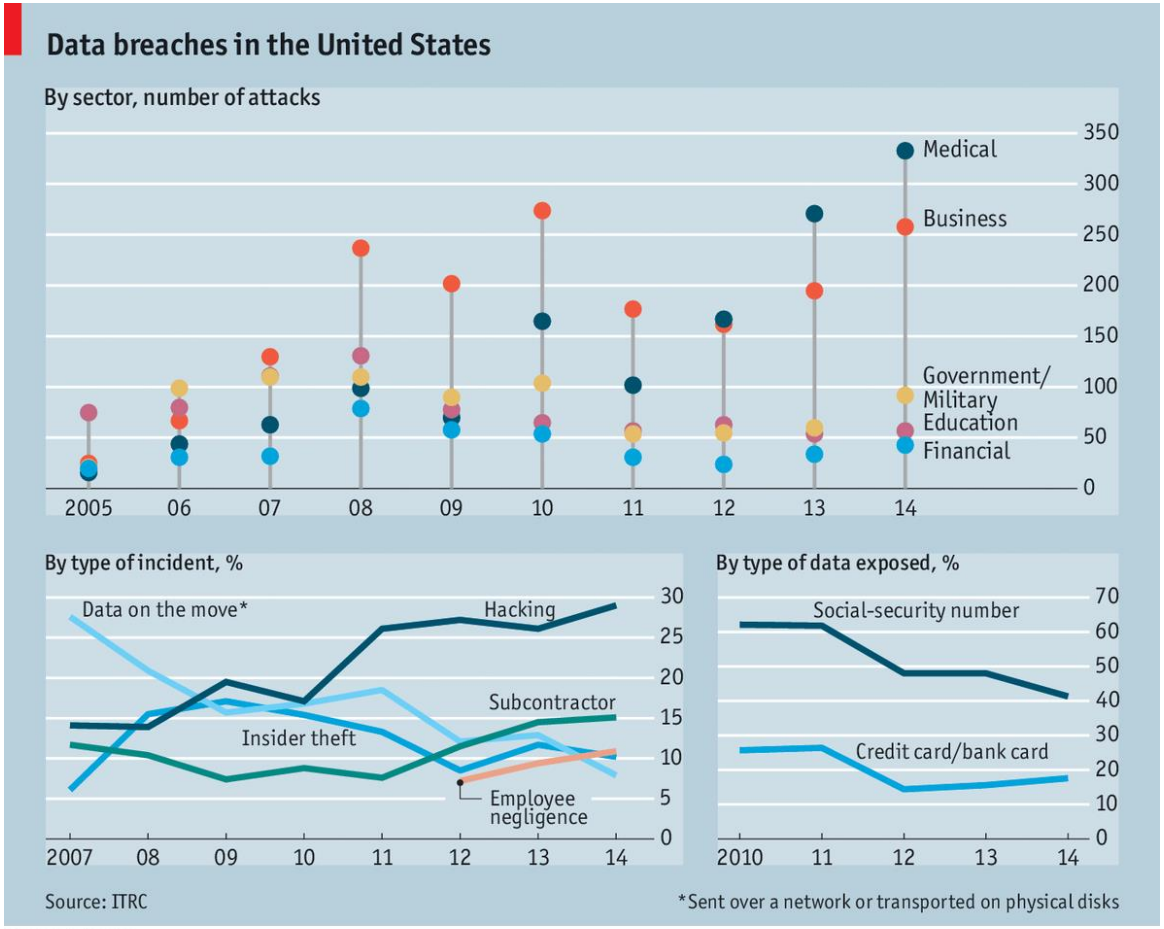
http://www.theguardian.com/science/2005/nov/03/genetics.news/print 2014-09-17

# Risks: Re-Identification of participants




23andme.com 2014-09-17

# Risks: Data breaches




Economist.com

http://cdn.static-economist.com/sites/default/files/imagecache/original-size/images/print-edition/20151107_WBC503_1.png 2015-11-15

# Risks: False positive findings

"pill scare" due to false positive finding

Have to account for multiplicity

A true positive finding is an opportunity - not a risk (!)

ZEIT ONLINE | GESUNDHEIT

RISKANTER GERINNUNGSHEMMER

**256 Menschen weltweit sterben nach der Behandlung mit Pradaxa**

Ein neuer Blutverdünner forderte fünfmal mehr Todesopfer als von Hersteller Boehringer zunächst angegeben. Das hat das Pharmaunternehmen jetzt bestätigt.

von Jutta Hoffritz | 12. November 2011 - 08:17 Uhr

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 November 2011
EMA/CHMP/903767/2011
Press Office

**Press release**

European Medicines Agency updates on safety of Pradaxa

http://pdf.zeit.de/wissen/gesundheit/2011-11/blutverduenner-boehringer.pdf 2012-12-31
http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2011/11/WC500117818.pdf 2014-09-29

# Risks: release of commercial confidential information

Not a statistical topic

Commercial confidential information unrelated to public health

- Which centers recruit many patients with only a few protocol deviations?
- Which suppliers were used

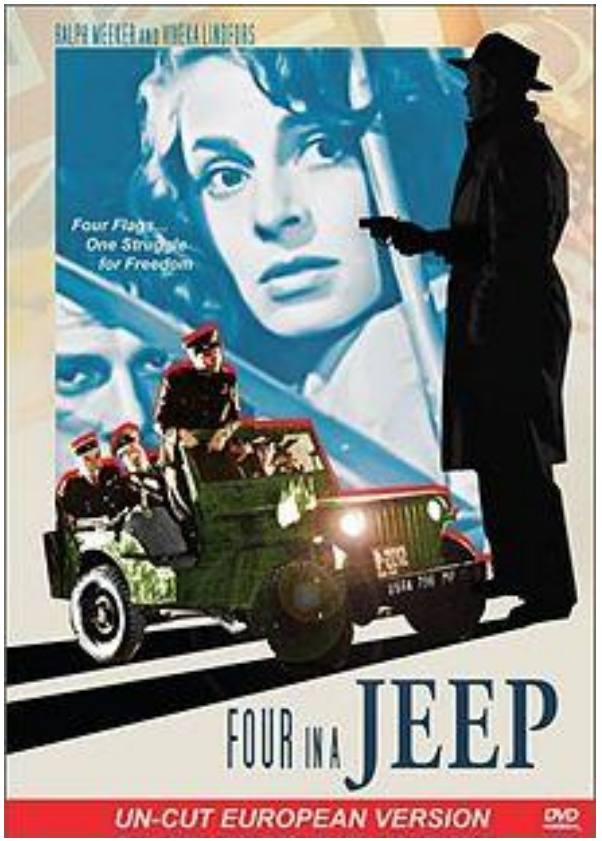
Usage of study reports and/or data to register a generic drug in third countries while the intellectual property is still protected in EU

Publication of results while a patent application is pending

# Risks: Potential abuse

Submit a sound analysis plan and get access

Do something else




en.wikipedia.org/wiki/Four_in_a_Jeep 2014-09-26

# Side effects

Data transparency is not for free

- Department at Bayer “Clinical Trial Transparency”
- Work to be done at
  - Statistics & Data Management
  - Medical Writing
  - Drug Discovery / Clinical Development / Medical Affairs
- External costs for
  - ClincalStudyDataRequest.com website
  - Review Panel
  - Protected data storage on external server
  - Software licenses (e.g. SAS)

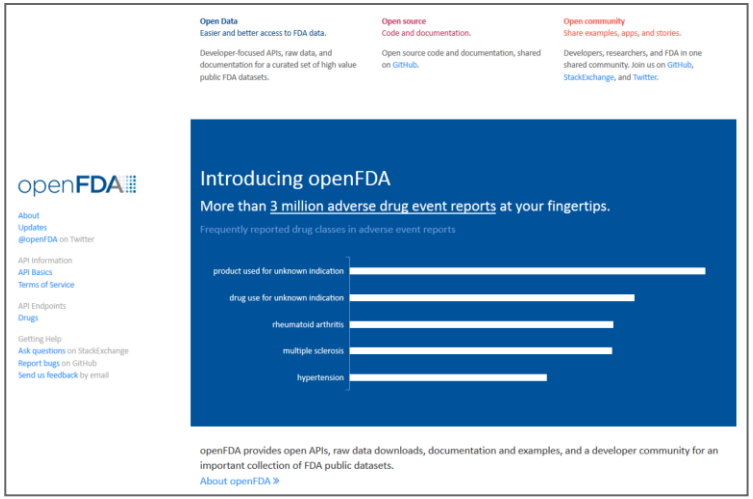
# Other data sharing initiatives

## German statutory health insurance data

www.dimdi.de/static/de/versorgungsdaten/index.htm
2014-03-03


## FDA open data initiative (spontaneous ADRs)

open.fda.gov 2014-06-20



# EFSPI working group on data sharing

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

European Federation of Statisticians in the Pharmaceutical Industry

Representing Statistical Associations in Europe

- More on www.efspi.org

# Conclusion

Clinical trial data is becoming rapidly more transparent

In my view, the opportunities do outweigh the inherent risks

We still need

- Good secondary data analysis practice
- Commitment from other sponsors than industry

# Recommended Reading


Eichler H-G, Abadie E, Breckenridge A, Leufkens H, Rasi G.
Open Clinical Trial Data for All? A View from Regulators.
PLoS Med 9(4) 2012: e1001202. doi:10.1371/journal.pmed.1001202

Fletcher C, Driessen S, Burger HU, Gerlinger C, Biesheuvel E; EFSPI.
European Federation of Statisticians in the Pharmaceutical Industry's position on access to clinical trial data.
Pharm Stat. 2013;12(6):333-6.

ClinicalStudyDataRequest.com 2015-11-04

EMA policy # 70
http://www.ema.europa.eu/docs/en_GB/document_library/Other/2014/10/WC500174796.pdf 2014-10-07

EMA draft policy # 70 www.ema.europa.eu/docs/en_GB/document_library/Other/2013/06/WC500144730.pdf 2014-04-28