Joint BBS-EFSPI Seminar
Data Sharing in Clinical Development
13. November

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BIG THUNDER, LITTLE RAIN?

An academic viewpoint

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„Hiding“ of scientific data

- unethical
- non-scientific
- uneconomical

Whether it is intented or not should not matter at all!

Should we not have access to any data due to freedom of information acts anyway?

- You can request any document from any EU institution, eg from EMA

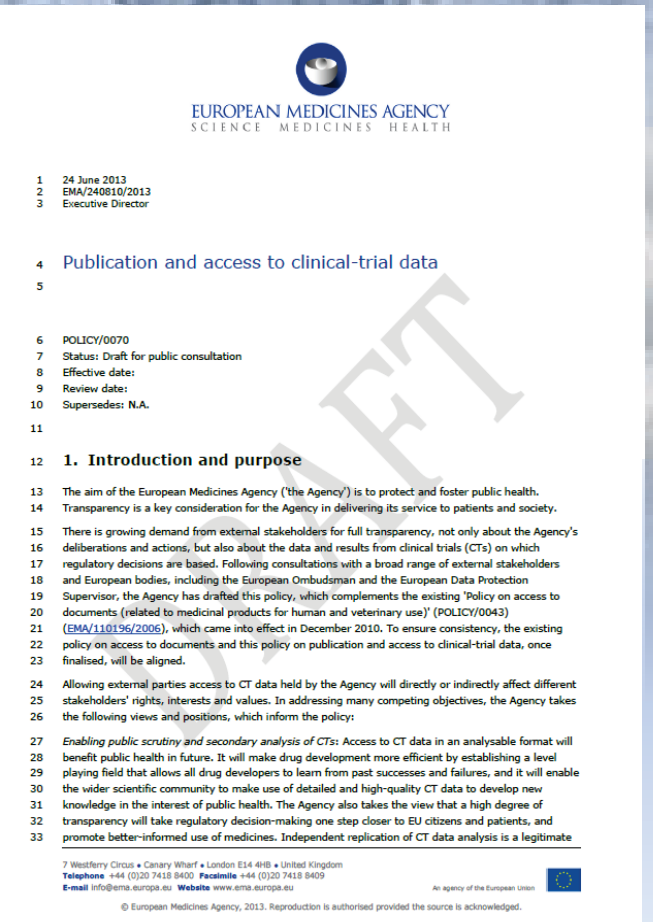
http://www.bmj.com/content/342/bmj.d2686?tab=responses

- E.g., 2010 EMA access-to-documents policy
- Since November 2010, the EMA has released more than 1.9 million pages in response to such requests.
- **Was put on hold!** Preliminary order by the General EU Court due to two on-going legal actions of the pharma companies AbbVie and InterMune.

Two years ago (22/11/2012) at the EMA Workshop on clinical-trial data and transparency an avalanche was set off …

Guido Rasi, Excecutive Director of European Medicines Agency (EMA):

"…we are not here to decide if we publish clinical-trial data, but how!"



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 June 2013
EMA/240810/2013
Executive Director

Publication and access to clinical-trial data

POLICY/0070
Status: Draft for public consultation
Effective date:
Review date:
Supersedes: N.A.

1. Introduction and purpose

The aim of the European Medicines Agency ('the Agency') is to protect and foster public health. Transparency is a key consideration for the Agency in delivering its service to patients and society.

There is growing demand from external stakeholders for full transparency, not only about the Agency's deliberations and actions, but also about the data and results from clinical trials (CTs) on which regulatory decisions are based. Following consultations with a broad range of external stakeholders and European bodies, including the European Ombudsman and the European Data Protection Supervisor, the Agency has drafted this policy, which complements the existing 'Policy on access to documents (related to medicinal products for human and veterinary use)' (POLICY/0043) (EMA/110196/2006), which came into effect in December 2010. To ensure consistency, the existing policy on access to documents and this policy on publication and access to clinical-trial data, once finalised, will be aligned.

Allowing external parties access to CT data held by the Agency will directly or indirectly affect different stakeholders' rights, interests and values. In addressing many competing objectives, the Agency takes the following views and positions, which inform the policy:

Enabling public scrutiny and secondary analysis of CTs: Access to CT data in an analysable format will benefit public health in future. It will make drug development more efficient by establishing a level playing field that allows all drug developers to learn from past successes and failures, and it will enable the wider scientific community to make use of detailed and high-quality CT data to develop new knowledge in the interest of public health. The Agency also takes the view that a high degree of transparency will take regulatory decision-making one step closer to EU citizens and patients, and promote better-informed use of medicines. Independent replication of CT data analysis is a legitimate

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Videos from EMA workshop can be downloaded from the EMA web

Open access to Clinical Study Report (CSR): designates the entirety of elements submitted as study reports in CTD Module 5, following the format of the ICH E3 document

Controlled access to Raw CT data (meaning individual patient data sets, individual patient line-listings, individual Case Report Forms (CRFs), and documentation explaining the structure and content of data sets

Further Clinical Trial Data Transparency Initiatives

- **BMJ Open Data Campaign**
  "As of January 2013, the BMJ will no longer publish any trial of drugs or devices where the authors do not commit to making the relevant anonymised patient level data available, upon reasonable request."
- **FDA Transparency Initiative**
  Availability of Masked and De-identified Non-Summary Safety and Efficacy Data
- **All Trials Initiative**
  "All Trials Registered, All Results Reported"
- **Individual Pharmaceutical Industry Initiatives**
  GSK Data transparency initiative, Roche Global Policy on Sharing of clinical Trial Data, …
  Researchers may receive access to raw data after requests have been reviewed by an independent panel of experts
- **Yale University Open Data Access (YODA) Project**
  … a model to facilitate access to patient-level clinical research data to promote wider availability of clinical trial data and independent analysis by external investigators
- **Cochrane Collaboration statement on access to clinical trial data**
  "All data from all randomised clinical trials, including raw anonymised individual participant data that do not allow identification of individual participants, and the corresponding trial protocols, to become publicly available free of charge and in easily accessible electronic formats"
- **Joint Statement of EFPIA and PHRMA**
  Principles for Responsible Clinical Trial Data Sharing
- **New EU regulation on clinical trials on medicinal products for human use**
- ….

Academia

EMA

Public Funding Agencies

Learned Societies

Physicians

Researcher

HTA

OPEN ACCESS TO DATA

What are the opportunities, challenges and risks of sharing clinical trial data?

Investigators

National Competent Authorities

Journal Editors

Industry

Pharmacovigilance

Patients

Ethics Committees

Life as academic researcher in medical resarch ...

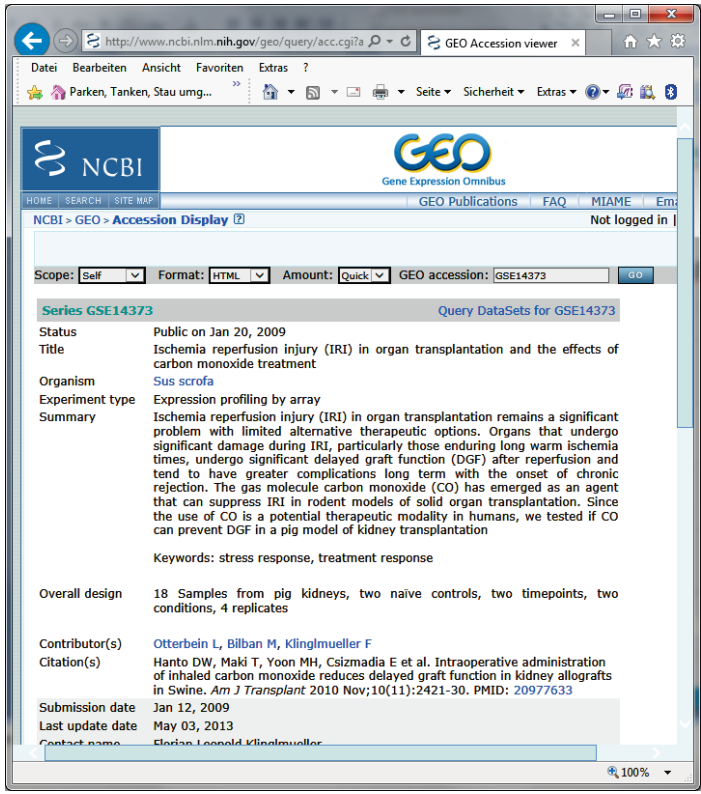
- Enhance knowledge in medicine
  (patients should receive better treatments)
- Career path at universities
- Scientific metrices
  # publications (as first/last author), IF, H-factor, grants, ...
- Collect data related to interesting research questions,
  publish as many paper as possible
  (but not all type of papers/journal will count)
- Who owns the data? Do you want someone else to publish „your“ data?
- How successful have we been so far in granting access to important information?

Life as (academic) researcher …
… Publish or Perish

Comic from http://science2enlighten.blogspot.co.at/2012_07_01_archive.html

Do medical researchers already share data?

- In some areas sharing of (raw) data is common,
  - E.g., genomics
- Some journals like BMJ require already commitment to give access to raw data (for some studies …)
- Also sharing of other documents becomes more common
  - Publication of study protocols
- We biostatisticians get also used to share our data
  - E.g., some journals require open access to software code used for analysis, simulation,



… to enhance reproducible research

Thus, is there room for improvement?

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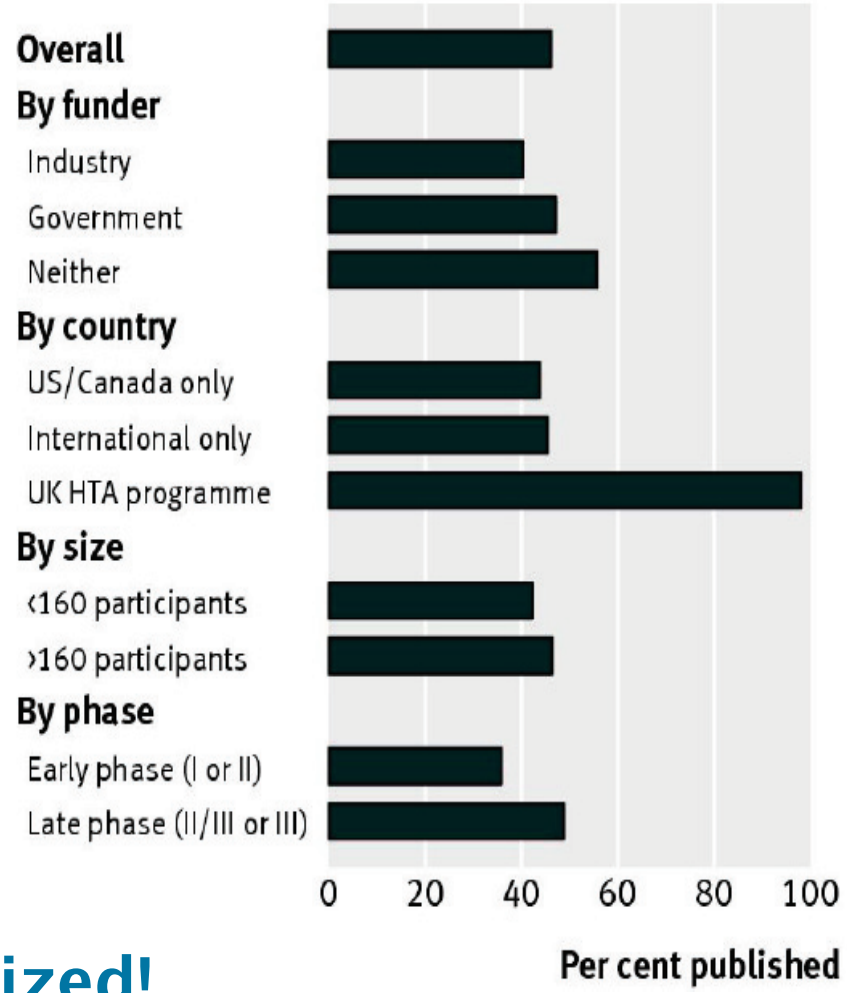
Presently, only for a fraction of clinical trials, results are published

Less than 50% of trials registered at clinicaltrials.gov after 31.12.1999 and completed before 31.12.2005 had been published by 31.12.2007.



Clinical trial data are underutilized!

Ross JS, et al. PLoS Med 2009, Chalmers et al. BMJ 2013

Transparency aspects in the proposal for new EU regulation on clinical trials on medicinal products for human use

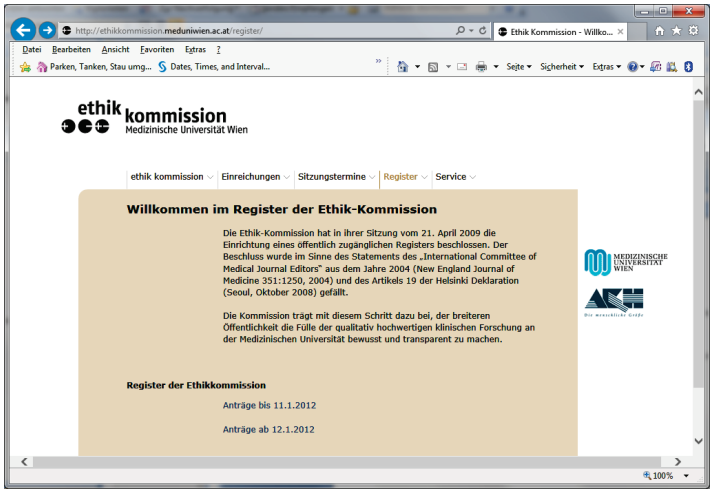
- *„For the purposes of this Regulation, in general the **data** included in clinical study reports **should not be considered commercially confidential** once a marketing authorisation has been granted or the decision-making process on an application for marketing."*
  http://www.europarl.europa.eu/sides/getDoc.do?pubRef=-//EP//NONSGML+REPORT+A7-2013-0208+0+DOC+PDF+V0//EN

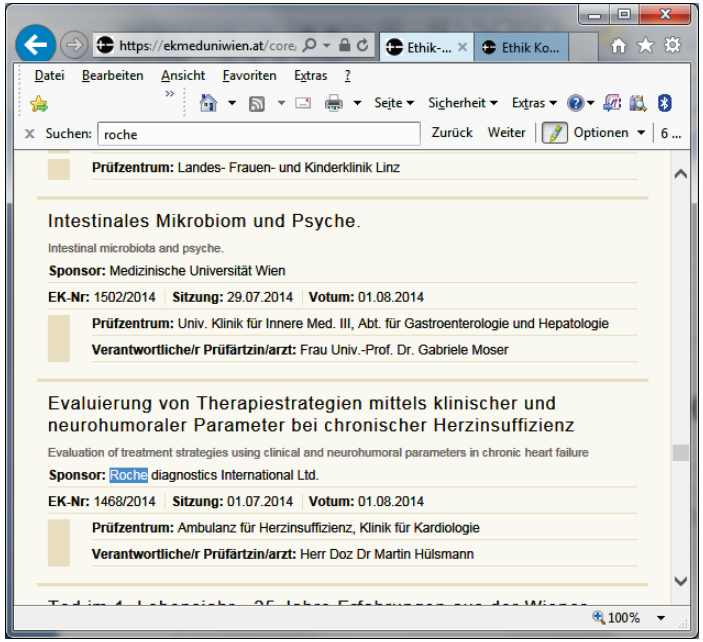
- Registration before the initiation of a trial
- Publication of summary results in a publicly and easily accessible database
- Access to clinical trial data

- Does not distinquish between acdemic or industry trials

Do we know which trials are currently conducted?

- Medical studies require approval by an Ethics committee before start
- Is this information publically accessible?





- Some trials are registered at public registries (WHO, ClinicalTrial.Gov, EudraCTm, ...)
- Depending on the registry more or less information on a trial is available

What happens to medical studies after Ehtical Approval?

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VIENNA: Publication of scientific research [Diploma thesis J. Neugebauer, 2010; supervisor M. Wolzt]

- Clinical studies Feb 1998 – Jan 99 approved by EC of the Medicial University of Vienna
- 447 studies approved
- Publication rate 35% (158/447 studies)
  - Industry sponsor 36/177 (20%)
  - Non-commerical sponsor 122/270 (45%)

FREIBURG: Fate of Clinical Research Studies after Ethical Approval [Blümle et al., PLOS One 2014]

- Clinical studies 2000-02 approved by EC of the University of Freiburg
- Publication rate: 419 / 807 (52%) with at least 1 publication (data of ~120000 study participants hidden)

Fate of Clinical Research Studies after Ethical Approval [Blümle et al., PLOS One 2014)

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Study characteristics	Approved (column %)	Started at local study site	Of those started:	
			Published (row %)	Not published (row %)
Total	917 (100)	807	419 (52)	388 (48)
Study design				
Randomised controlled trial	408 (45)	355	201 (57)	154 (43)
Non-randomised intervention study	72 (8)	65	33 (51)	32 (49)
Diagnostic study	41 (4)	36	21 (58)	15 (42)
Cohort study	23 (2)	19	8 (42)	11 (58)
Case-control study	6 (1)	6	3 (50)	3 (50)
Cross-sectional study	42 (5)	40	16 (40)	24 (60)
Uncontrolled study	186 (20)	163	75 (46)	88 (54)
Laboratory study	138 (15)	122	61 (50)	61 (50)
Health services research	1 (<1)	1	1 (100)	0
		Pearson χ^2 (df 8) = 10.173, p = 0.253		
Study size				
Size≥median of 120	449 (49)	391	224 (57)	167 (43)
Size<median of 120	429 (47)	379	177 (47)	202 (53)
Unclear	39 (4)	37	18 (49)	19 (51)
		Pearson χ^2 (df 2) = 8.808, p = 0.012		

Fate of Clinical Research Studies after Ethical Approval [Blümle et al., PLOS One 2014)

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Table 1. Publication status and characteristics of included studies.

Study characteristics	Approved (column %)	Started at local study site	Of those started:	
			Published (row %)	Not published (row %)
Collaboration				
Single-centre study	383 (42)	340	159 (47)	181 (53)
Multi-centre study	534 (58)	467	260 (56)	207 (44)
		Pearson χ^2 *(df 1) = 6.257, p = 0.012*		
Only multi-centre studies:				
International	310 (58)	276	173 (63)	103 (37)
Domestic	221 (41)	189	87 (46)	102 (54)
Unclear	3 (<1)	2	0	2 (100)
		Pearson χ^2 *(df 2) = 15.124, p = 0.00052*		
Funding (as stated in protocol)				
Commercial	422 (46)	368	203 (55)	165 (45)
Non-commercial	140 (15)	131	75 (57)	56 (43)
No funding stated	355 (39)	308	141 (46)	167 (54)
		Pearson χ^2 *(df 2) = 7.695, p = 0.021*		
Only commercially funded studies:				
Sponsor involved	362 (86)	318	182 (57)	136 (43)
Sponsor not involved	60 (14)	50	21 (42)	29 (58)
		Pearson χ^2 *(df 1) = 4.053, p = 0.044*		

If they are published …

…, **essential information is often missing**

Wieseler, Beate, et al. PLoS medicine 10.10 (2013)

Potential consequences:

- a distorted information base on the risks and benefits of therapies
- impaired meta-analyses
- clinical trials that are unnecessarily repeated

Potential reasons for

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Non- publication

- Competing interests (e.g. financial CoI)
- Poor project management
- Lack of time
- Low priority
- Disagreement
- Losing interest
- Moving to another institution
- Results not deemed important enough
- Journal rejection (publication bias)

Publication

- Funding (commerical or non-commerical)
- Study design (Multi-centre)
- Study size (large)
- Collaboration (international)

Thus more data need to be shared

Two types of secondary research in relation to open access to clinical trial data

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Trust & accountability

- **Reproducible Research**
  - Confirm sponsor‘s analysis
  - Validating the original study results and investigating their robustness
  - Transparency of regulatory decision making
  - no prospective „validation protocol“ necessary

Exploration & discovery

- **Investigation of additional research questions**
  - Reliable synthesis of study data (Meta-analyses)
  - Exploratory research
  - Different levels of evidence: from „quasi prospective research“ (with SAP written without any knowledge on results of the trial) to full data mining
  - To interpret such results – knowledge of time lines important (data access, background knowledge when formulating research questios, …)

How to assess the risk of „false positives“of multiple retrospective analysis of clinical trial data?

Koenig et al. Biometrical Journal 2014

Raw Data Sharing – Why?

- **Reproducible research**
- **Patient level meta- analyses**
- **Planning of new studies**
- **Enables development of tailored study designs and statistical methodology**
- **Avoiding the repetition of studies**
- **New discoveries through exploratory research**
- **Provide incentive to ensure accuracy of dataset**

Compare Vickers A. Trials 2006;7:15 doi:10.1186/1745-6215-7-15

Which data needs to be shared …

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- **Aggregated Clinical Trial Results**
  - Key outcomes in clinical trial registers
  - Research Articles in Scientific Journals (ideally open access)
  - Summary reports for patients (in trial, future, …)
  - Detailed clinical study reports (regulatory agencies, EC, …)

- **Raw (Patient Level) Data**
  - Held by individual sponsors
  - Data Repositories
  - Regulatory Authorities

Patient level data are of particular value …

- in small populations to enhance research for orphan drugs, personalized medicines, drug development for children, …
- Identification of patient subgroups
- Raw data of past studies may serve as historical controls
- Help to formulate prior for Bayesian analyses
- More tailored statistical models
  (selection of covariates, time points, …)

- However, even though small populations research may benefit most, it also poses the highest risk with regards to patient privacy.

Koenig et al. Biometrical Journal 2014
Bauer and Koenig, Nature RDD 2014

Challenges

- **Patient Privacy**
  - „Proportionate“ De-identification of data
  - Legal obligations of data requester
- **Ensuring the Qualitaty of Re- Analysis**
  - A pre-specified analysis plan increases the credibitility (as for all clinical studies).
  - Interpretation as retrospective analysis
- **Protecting Reseacher/Sponsor‘s Interests**
  - Suitable timing of data release
  - Give enough credits to data-generator (e.g., co-authorship in publication?)

How to make patient level data sharing happen?

- Open access to protocols and meta-data (Data-Dictionaries, CRFs) to plan secondary analysis
- Accessible data formats (standardization preferred)
- Learn from successful examples (e.g., NIH)

The NEW ENGLAND JOURNAL of MEDICINE

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Perspective

Access to Patient-Level Trial Data — A Boon to Drug Developers

Hans-Georg Eichler, M.D., Frank Pétavy, M.Sc., Francesco Pignatti, M.D., and Guido Rasi, M.D.

The provision of access to clinical trial results that include patient-level data is generating much debate. A growing chorus of transparency advocates is pushing for open access to these data, making a case on the basis of respect for patients' altruism, the need to safeguard public health, and distrust in the integrity and completeness of published trial information.[1] We at the European Medicines Agency (EMA) have been actively engaged in this debate, and the EMA has recently published a draft of a policy that would make patient-level data in its possession publicly accessible. The principle of privacy protection will inform the EMA's policy and activities; robust and proportionate measures will be adopted to safeguard patients' privacy, in compliance with applicable data-protection legislation.[2]

Pharmaceutical-industry organizations, however, have expressed concern that "one of the risks to innovation is disclosure to competitors of companies' trade secrets and proprietary information that could allow others to 'free ride' off of the substantial investments of innovators"; they fear "degradation of incentives for companies to invest in biomedical research."[3]

Industry leaders have rightly complained about the unsustainability of the current drug development and business model. The timelines and costs of clinical drug development are increasing relentlessly, and the attrition rate of assets in development remains high. At the same time, growing cost pressures in all health care environments are forcing restrictions on drug use, aiming to limit coverage only to patients who can be expected to benefit from a given intervention and for whom that intervention is clearly cost-effective.

Contrary to industry fears, we argue that access to full — though appropriately deidentified — data sets from clinical trials will benefit the research-based biopharmaceutical industry. We predict that it will help to increase the efficiency of drug development, improve cost-effectiveness, improve comparative-effectiveness analysis, and reduce duplication of effort among trial sponsors.

First, access to the full data sets of completed studies will lead to improvements in the design and analysis of subsequent trials. For example, available information about numerous variables can be used to identify and validate prognostic factors. Relevant validated prognostic factors can

„It is ironic that the organizations that most resist wider access to data are the ones that stand to benefit so much from greater transparency."

Eichler et al. NEJM, 2013.

Big thunder, little rain?

- The cat is let out of the bag!
- There is a public interest and discussion even outside the research community … (e.g., see SPIEGEL Online this week)

http://www.spiegel.de/wissenschaft/mensch/qualitaet-in-der-forschung-weg-mit-dem-forschungsmuell-

Qualität i...

sciencemag...

Datei Bearbeiten Ansicht Favoriten Extras ?

Parken, Tanken, Stau umg... Dates, Times, and Interval... ScholarOne Manuscripts

Seite Sicherheit Extras

Transparenz in der Wissenschaft: Kampf dem Forschungsmüll

Von Nicola Kuhrt

Corbis

Mehr Qualität gefordert: Der Druck für Forscher, in großen Journals zu veröffentlichen, sorgt für Probleme im Wissenschaftsbetrieb

Namhafte Forscher kritisieren seit Jahren die Veröffentlichungspraxis von Fachmagazinen. Darin stünde teilweise wenig Gehaltvolles. 30 internationale Magazine geloben Besserung. Hält ihre Qualitätsoffensive, was sie verspricht?

ANZEIGE

100%

Big thunder, little rain?

- This debate has already resulted in a huge paradigm-shift in medical research!
- Some time ago no public information was available on which studies were acutally conducted
  - … clinicaltrials.gov, EudraCT, register of ethics committee,…
- Some years ago regulatory agencies were sued for publishing summary report
  - Publication of EPARS, …
- Some years ago researchers complained that there was no way to publish results of negative trials
  - again registries, open journals
- Some years ago researchers very rarely shared raw data
  - Already after publication of EMA draft policy:
    Self commitment of industry sponsors to share raw data (past & future) in a controlled environment

Big thunder, little rain?

- This discussion has revealed that the question *„who owns the data in the first place?“* might have been wrongly tackled for many years!
- Helped to re-focus on what patients expect when agreeing to participate in trials and share their data!
- In the beginning there might be some problems to judge the evidence of secondary research. So what.
- Still a long way to go (100% publication rate, open access without restricition, …)
- Overall this journey should lead to an increase of quality

There is no way back to conduct research behind closed doors!

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Data is like children…

You like your own best, and do not like strangers to play with them

Slide from HG Eichler, Senior Medical Director EMA, Washington, IOM, Oct 2012
http://www.iom.edu/~/media/Files/Activity%20Files/Research/SharingClinicalResearchData/42%20%20Eichler%20%20Washington%20IOM%20%20Data%20Transparency.pdf

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Acknowledgement

Integrated DEsign and AnaLysis
of small population group trials

http://www.ideal.rwth-aachen.de/

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