Clinical Trial Data Sharing: Uses and Challenges in Implementation

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14th Statistical Leaders Meeting

Clinical Trial Data….

are generated with a large investment of

- Economic resources
- Time
- Burden and risk patients are taking when entering a clinical trial

Therefore, „hiding“ the data is considered

- Unethical
- non-scientific
- non-economical

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 anyhow?

One can request any document from any EU institution, e.g from EMA

- 2010 EMA access-to-documents policy. EMA has released millions of pages in response to such requests. http://www.bmj.com/content/342/bmj.d2686?tab=responses

Ten 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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An agency of the European Union

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

EMA Policy 0070

European Medicines Agency policy on publication of clinical data for medicinal products for human use (EMA/240810/2013)

- **Phase 1** (effective from 01/01/2015): EMA will publish the study reports 60 days after a decision on the application, Last update of guidance **(03/2019)**
- Publication of CSR suspended in 2017 (with exception of COVID-19 related trials)
- EMA intends to gradually resume clinical data publication from September 2023
- **Phase 2:** Sharing of individual patient data (IPD) (pending)

Further Clinical Trial Data Transparency Initiatives

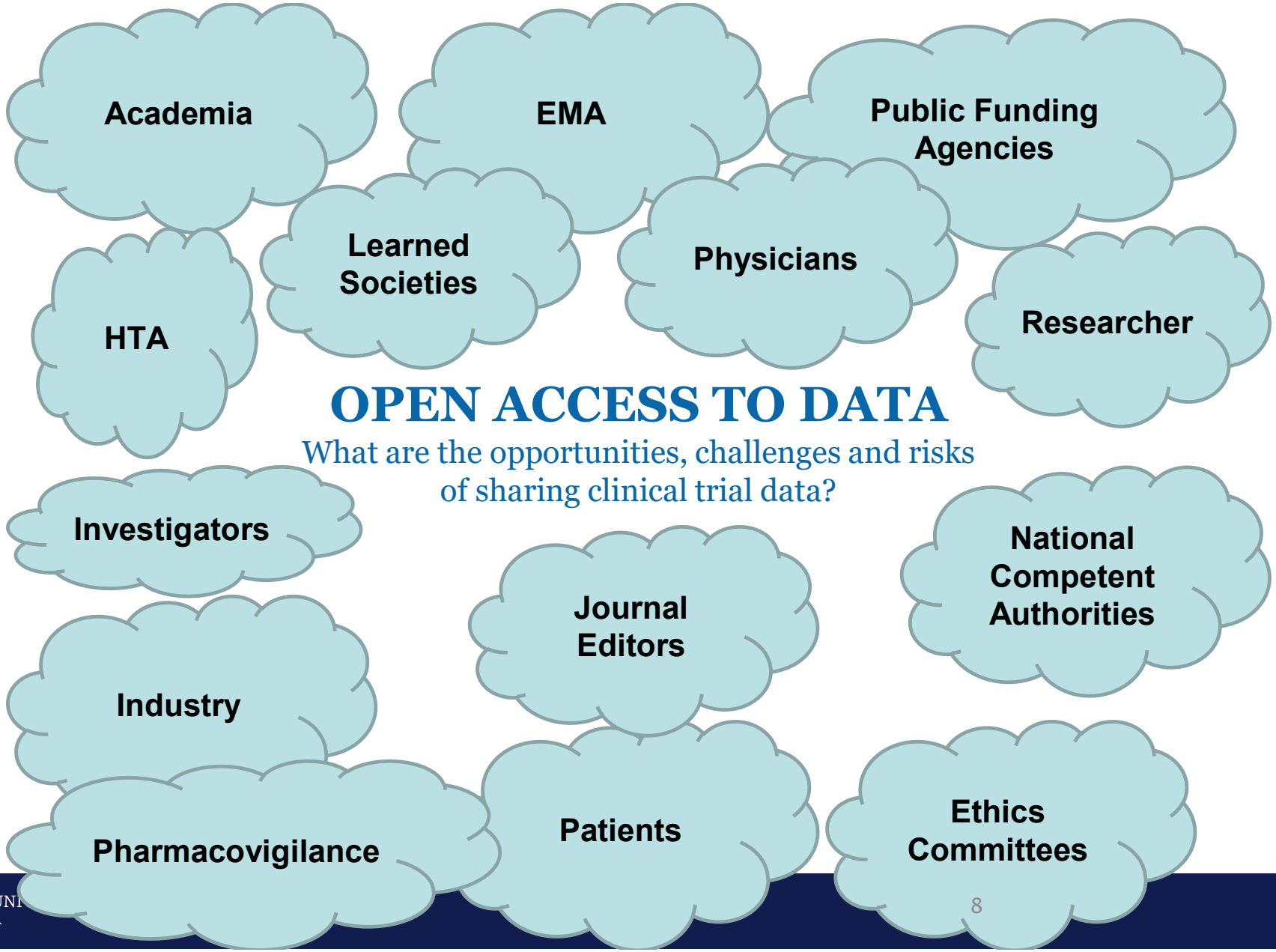
- **FDA Transparency Initiative**
  Availability of Masked and De-identified Non-Summary Safety and Efficacy Data
- **ICMJE's data sharing policy**
  Since 2018 data sharing statement, for trials starting after January 2019 data sharing plan in the trial's registration.
- **Individual Pharmaceutical 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
- **Data Sharing platforms**
  Clinical Study Data Request (CSDR), Yale University Open Data Access (YODA) Project, Vivli,…
- **Project Data Sphere** Sharing of comparator arm data from historic cancer clinical trials
- **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
- ….

CT Regulation No 536/2014

- "… **in general the data included in a clinical study report** should **not be considered commercially confidential** once a marketing authorisation has been granted …".

- **All information submitted to EMA shall be in principle publically accessible** unless the confidentiality can be justified based on protection of commercially confidential information, personal data, confidential communication in relation to the preparation of the assessment report, (…).

- The regulation does not distinquish between academic or industry sponsored trials


Academia
EMA
Public Funding Agencies
Learned Societies
Physicians
HTA
Researcher
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

Who owns the data?

The sponsor, the patients in the trial, or the public and future patients?

- The **sponsor** has invested considerable resources to generate the data (and seeking research data from companies was in general considered as „industrial espionage“; „research parasites“, ..)
- **Patients** have taken risks and burdens to participate in the trial.
- The **public** who eventually has to pay for the drug (and patients who are treated with it)?

Life as academic researcher in medical resarch …

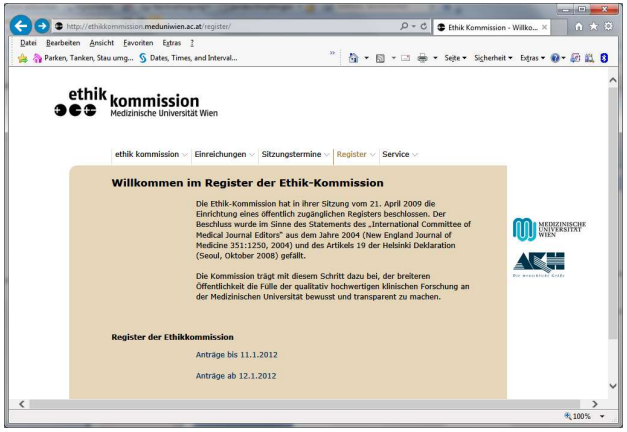
- Enhance knowledge in medicine
  (patients should receive better treatments)
- Career path at universities
- Scientific metrices
  # publications (as first/last author), IF, H-factor, grants, …
- Collect data related to interesting research questions,
  publish as many paper as possible
  (but not all 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?

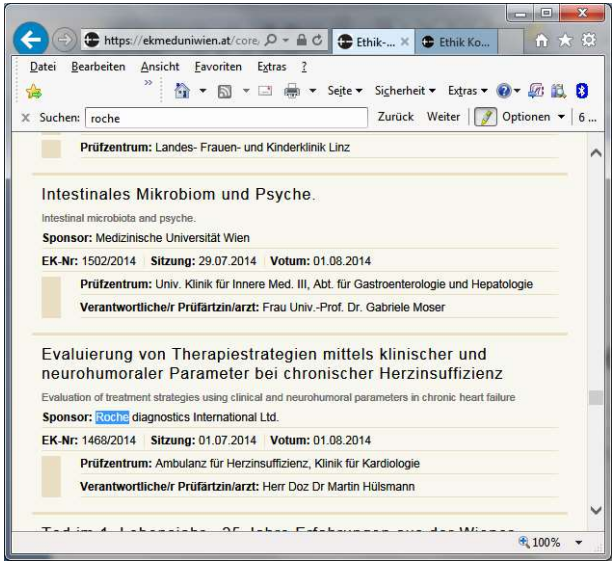
Life as (academic) researcher …
… Publish or Perish

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

Do we know which trials are currently conducted?

- Pre-registration for drug trials mandatory
- Medical studies require approval by an Ethics committee before start
- Is this information publically accessible?





If they are published …

… **inconsistencies between published results and protocols / trial registry data**

e.g., Goldacre (2019)

… **essential information is often missing**

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

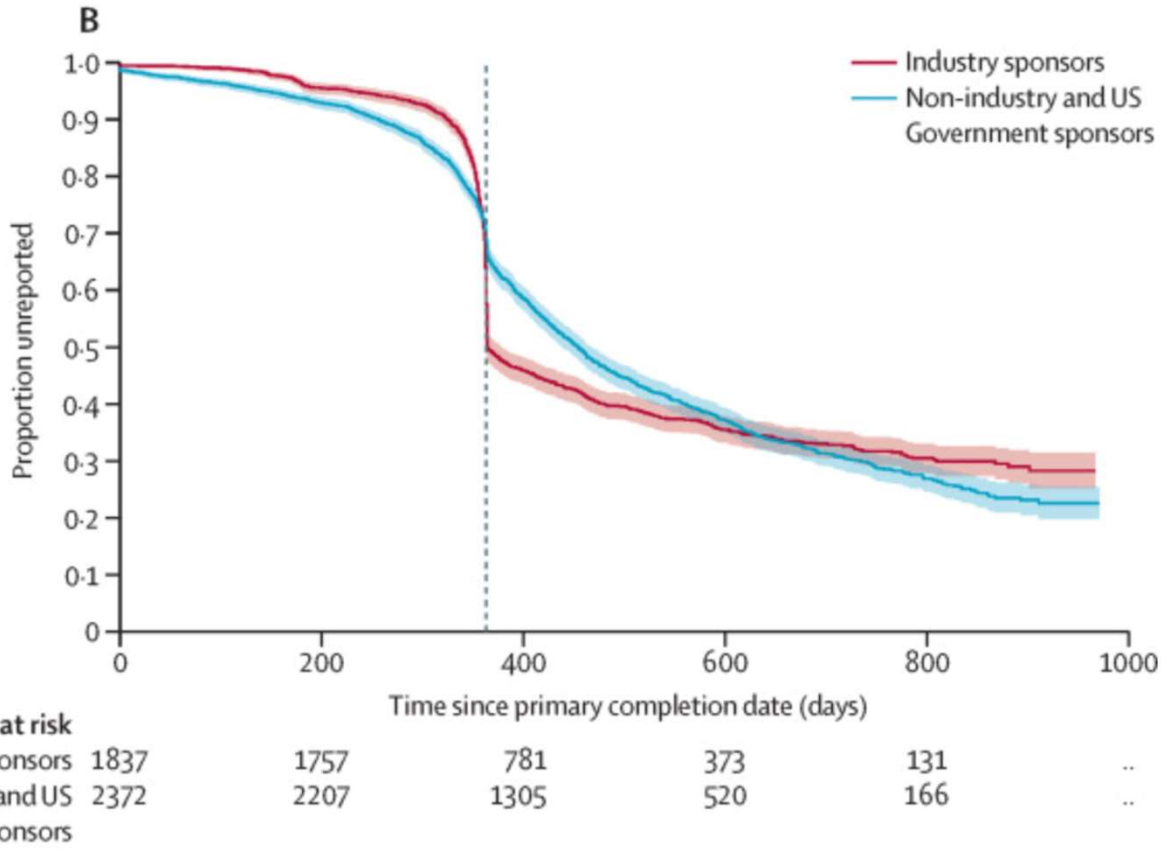
Potential consequences:

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

After they have been conducted, do we know the results?

Trials on ClinicalTrials.gov 03/2018- 09/2019 with obligation to report results on ClinicalTrials.gov

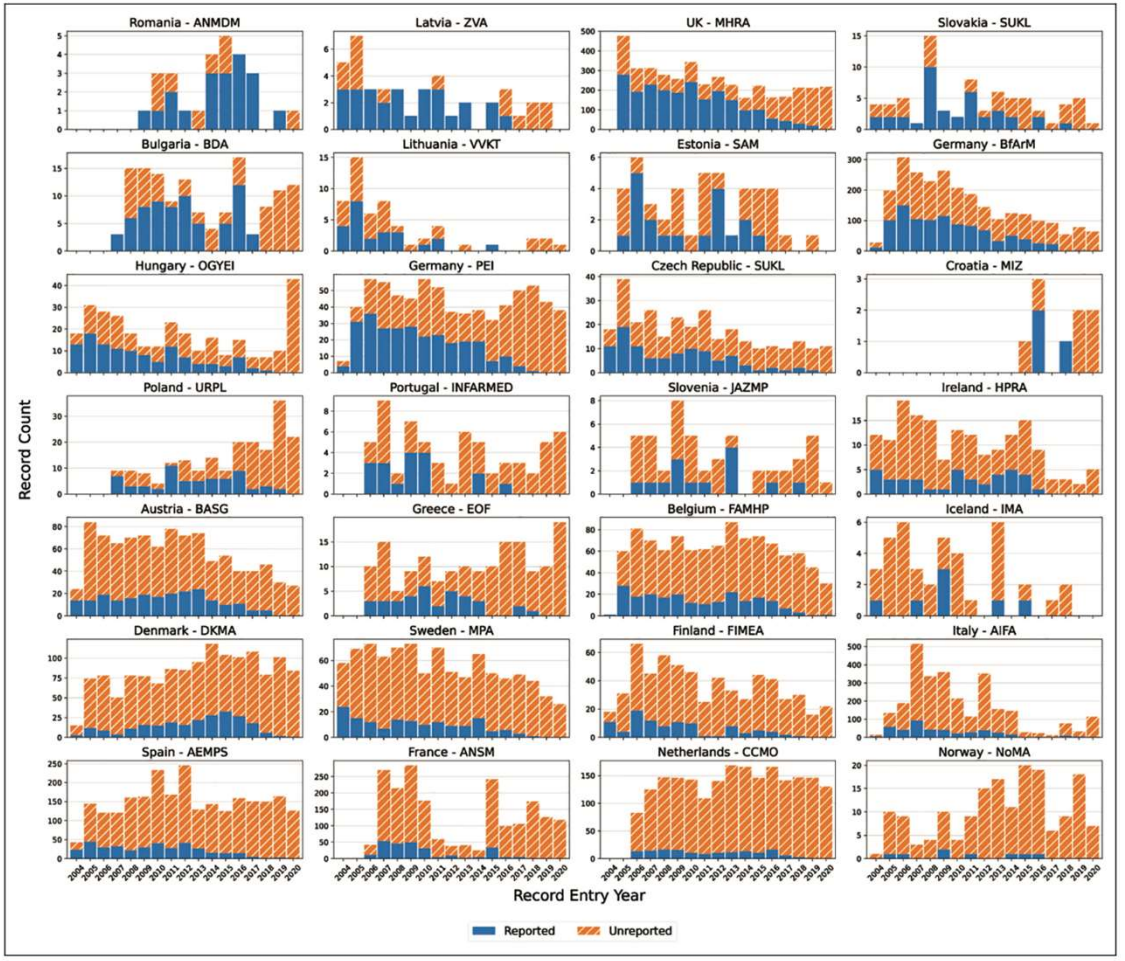
DeVito, N. J., et al. The Lancet, 2020



Results Reported in the European Union Clinical Trials Register

De Vito, Goldacre, Clinical Trials (2022)

Data cutoff: 01/12/2020



Potential reasons for

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

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

Which data needs to be shared …

- **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

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

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?

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

Which type will be more frequently?

- **Reproducible Research**
  - Co… …sor's analysis
  - Va… …nd investigating their robustnes
  - Transpa…
  - no prospective „validation proc…

3 proposals

- **Investigation of additional research questions**
  - Re… …udy data (Meta-analyses)
  - Ex…
  - Different levels … …" (with S… …f the trial) to full data mining
  - To interpret such results – knowledge of time lines … …g research questios, …)

144 proposals

Data Sharing — Is the Juice Worth the Squeeze?

Brian L. Strom, M.D., M.P.H., Marc E. Buyse, Sc.D., John Hughes, B.Sc., and Bartha M. Knoppers, Ph.D.

The past few years have seen considerable interest in the sharing of patient-level data from clinical trials. There is a clear and logical "ethical and scientific imperative"[1] for doing so, to permit activities ranging from verification of the original analysis to testing of new hypotheses. This interest has resulted in many publications and meetings, attention from the Institute of Medicine,[2] proposed changes in journals' policies,[3] and enormous effort from pharmaceutical sponsors and other groups to provide access to patient-level data.[4] It is critical that we learn from these early experiences as we move forward.

Beginning in May 2013, GlaxoSmithKline made available to investigators the patient-level data and study documents from more than 200 trials that had started since January 1, 2007; the later addition of others resulted in access to data from more than 1500 trials sponsored by GlaxoSmithKline, including all their global intervention trials since the formation of GlaxoSmithKline in 2000. Beginning in January 2014, requests for data could be made through a public website, clinicalstudydatarequest.com (CSDR), and were subject to approval by an independent review panel.[4] Other trial sponsors joined CSDR.

In March 2015, the Wellcome Trust took over running the independent review panel for CSDR. In an attempt to increase participation even further, a small number of sponsors were given the right to veto data requests for commercial reasons, although such vetoes were strongly discouraged. Wellcome recruited a new panel, which started reviewing proposals in December 2015. As the members of the original independent review panel, we can report on the first 2 years of applications for access to data and on the results of a brief survey about project status that was sent to the lead investigators of all approved protocols, as well as a survey of sponsors about publications of which they were aware. At the time, data from 3049 trials were available through the website, from Astellas, Bayer, Boehringer Ingelheim, Daiichi Sankyo, Eisai, GlaxoSmithKline, Lilly, Novartis, Roche, Sanofi, Takeda, UCB, and ViiV Healthcare.

Overall, 177 research proposals were submitted between May 7, 2013, and November 14, 2015. The panel had 30 working days within which to complete their reviews; all reviews were completed before December 31, 2015. Access was granted for 144 of these proposals; 33 were withdrawn after the panel requested additional details, and in all but 6 of those cases a new proposal was submitted because data from additional studies were needed. In 58 cases, the panel required the requesters to improve their lay summary. These 177 proposals included requests for data from 237 studies not yet in the system; access was granted to data from 179 of these. The commercial veto option was never exercised.

Most proposals (148) were for a new study and publication, with confirmation of original studies' results (3) being quite uncommon. Statistical methods ranged widely and included predictive models (63), meta-analysis (28), survival analysis (15), and tests of new analysis methods (14). The most

1608 N ENGL J MED 375;17 NEJM.ORG OCTOBER 27, 2016

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

First experiences with https://clinicalstudydatarequest.com/

- **Good news, some fears seem unfounded:**
- *"It will be difficult to get the data"*
  - Commerical veto never executed
  - 144/177 granted access
    (33 withdrawn)
- *"data will mainly be used by researchers to disprove against pharma"*
  - Focus on new studies (144 proposals)
  - Only 3 for re-analysis of original results
- **Bad news, outcome disappointing**
  - Few requests, few publications

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http://www.nejm.org/doi/pdf/10.1056/NEJMp1610336

Usage of Data repositories

Metrics of CSDR, YODA and Vivli websites					
Platform	**Metrics date**	**Available studies**	**No of requests**	**No of requests agreed**	**No of publications / No of citations***
CSDR	01/05/2023	3052	722	368	114
YODA	15/11/2019	334	196	173	35
Vivli	28/04/2023	6660	739	413	422*

CSDR, Vivli websites, Ohmann et al. BMJ Open 2021

Raw Data Sharing – Why?

- Reproducible research
- Patient level meta-analyses
- Historic Control Groups
- Planning of new studies
  - Information on the distribution of endpoints
  - Information on placebo effects
  - Information on the natural course of the disease
  - Enables development of tailored study designs and statistical methodology
- Use in simulation studies to generate realistic data sets for the assessment of innovative methods
- 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
Burger et al. 2021

Sharing of 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?)

Statistical Challenges of Research based on Shared Data

- Potential bias due to knowledge of outcome data of already published trials
  - SAP is written based on published data
  - Criteria for the selection of trials are defined based on (some) information on the data.
- Potential bias if data availability is related to the outcome data
  - Trial registration
  - Transparency of data request processes

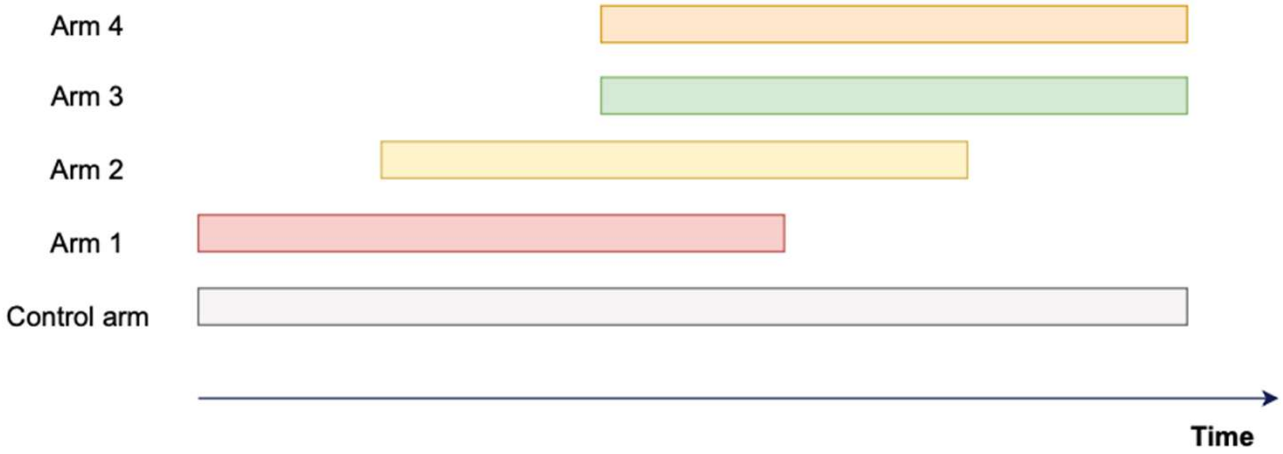
Potential bias depends on the amount of information available related to study objectives.

What means Pre-specification in the Analysis of Shared Data?

- No real pre-specification is possible as this is secondary research
- Information on the data available at the planning stage is important to assess potential bias.
- Verification of which information was available maybe difficult

Collaborative Platform Trials

- Multi-armed trials, Experimental arms from different sponsors, shared control
- Treatment may enter and leave the platform over time
- Recovery, Remap-Cap, Stampede

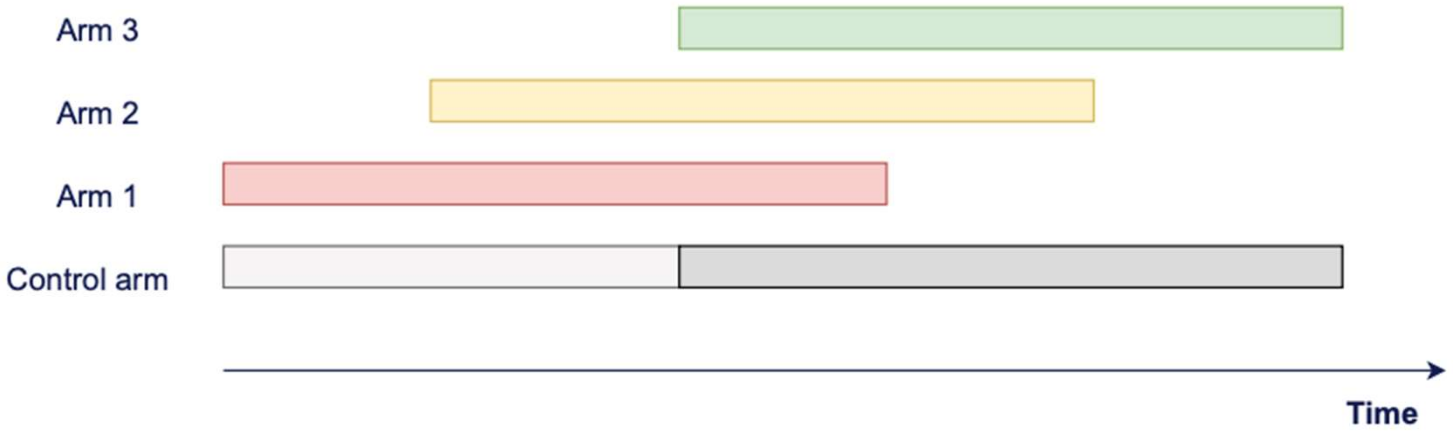


Issues of Data Sharing in Platform trials

- Sharing of data of control arms is less controversial
- Head to head comparisons are possible in PT trials but may not be in the interest of commercial sponsors
- Sharing of data from experimental arms
  - may be required for certain statistical analysis as non-concurrent controls, missing value imputation
  - can facilitate the planning of future arms (data on recruitment, covariate distributions, drop out mechanisms)
- Data transparency can impact trial integrity:
  Shall control data of completed arms, which will also be used later for the analysis of still on-going arms already be accessible?

Example: Non-concurrent controls

- Can we incorporate control data of patients recruited before an experimental arm joined the platform?



Bofill Roig et al. BMC Methods (2022)

Non-Concurrent controls

- If platform trials run over a long time period, with multiple treatments entering and leaving the platform over time, incorporating non-concurrent controls can substantially improve the efficiency

- However, non-concurrent controls may introduce bias due to different types of time trends

Non-Concurrent controls = Historical controls in RCT?

Non-concurrent and historical controls share several sources of potential bias
When using historical data for comparisons in clinical trials we accept that strict T1E control is not possible.

Eichler et al. 2016

So in platform trials?

Non-concurrent controls…

- are collected within a framework which has many features standardized (same infrastructure, assessment of endpoints, monitoring, …) and all changes are well documented.
- patients are randomized and blinding is possible

Randomized controlled trials & non-concurrent controls

- Non-concurrent controls can be randomized & blinded but
  - At a **different calendar time** such that randomization **does not ensure control on the distribution of prognostic factors** between NCC and experimental arms.
  - patients & investigators **are not blinded with respect to the experimental treatment and the non-concurrent control** it is compared to
- The lack of true randomization can induce time trends

Time Trends due to External and Internal Factors

- **External,** e.g.,
  - Changes in standard of care
  - Patient population
  - Pandemics
- **Internal**
  - Change in **recruiting centers**: an analysis stratified by center is no longer possible if centers enter or leave the platform.
  - Change in **recruitment strategies**, e.g. if promising treatments enter the platform.
  - Change in **inclusion/exclusion criteria** because of other experimental treatments under investigation
  - Change in **assessment of endpoints** (e.g., new diagnostic devices)

Analysing Platform Trials Incorporating Nonconcurrent controls

- Pooling of control data can lead to bias due to time trends.
- Using data from all arms, the time trend can be estimated and adjusted for with model based analyses.

Bofill Roig et al. 2022

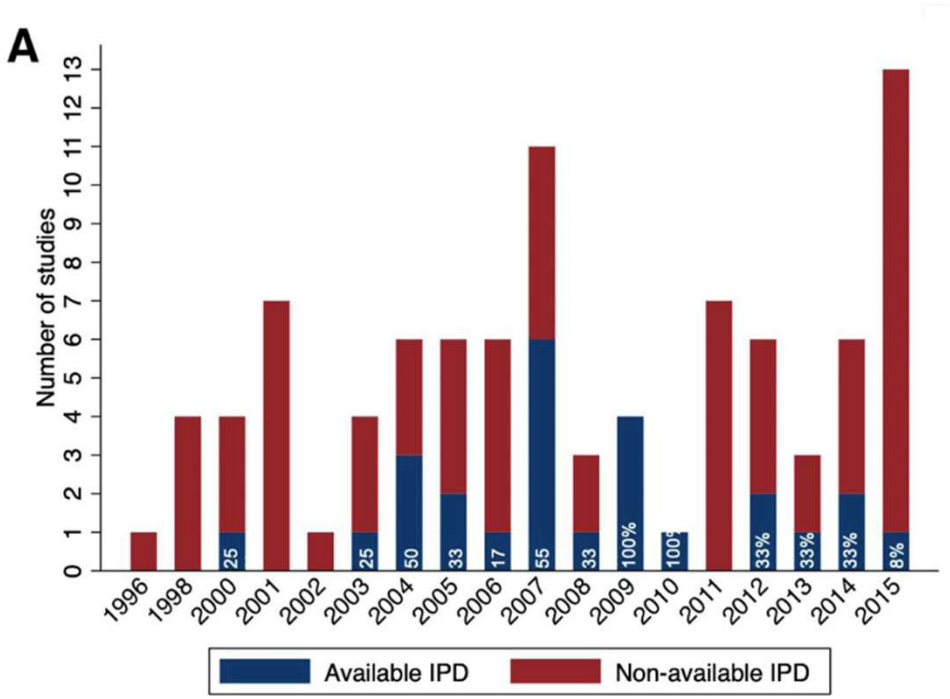
Implementing Data Sharing in Platform Trials

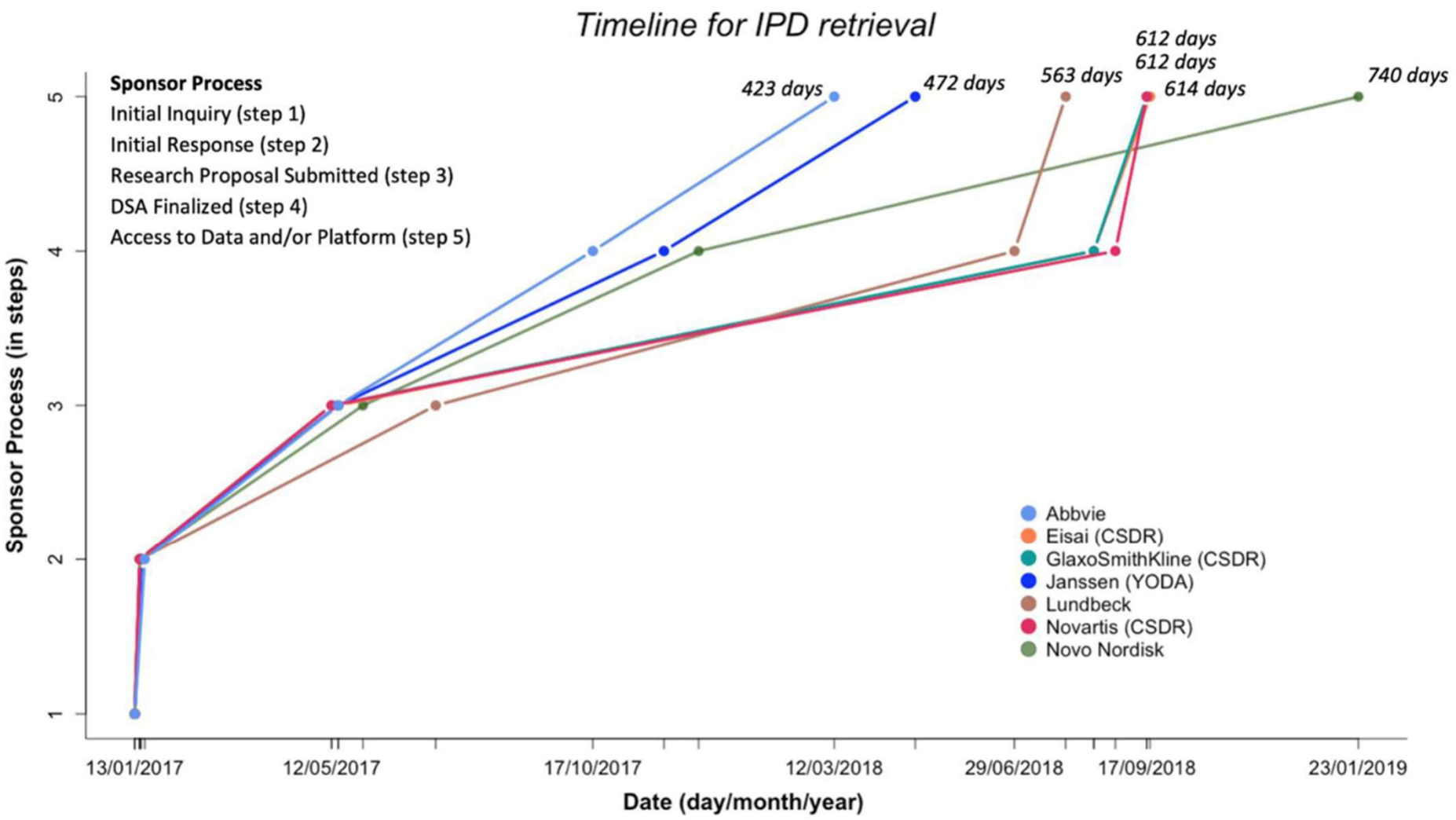
- Critical if intervention owners are direct competitors
- Data governance processes required to define which data can be shared when and to whom.
- Analysis by sponsor independent third parties as data handlers
- Communication & publication of results must be pre-defined
- Data-sharing with external parties to be pre-planned

Will data sharing and the potential of direct comparisons in secondary research prevent larger multi-company platform trials in Phases 2 and 3?

Example IPD Meta-analysis (BMJ EBM Veroniki, 2023)

- IPD availability in Alzheimer's dementia and type 1 diabetes
- From 125 RCT publications 0 authors shared their IPD
- For the 78 industry sponsored trials, the industry sponsor (17 different companies) was contacted. 7 (41%) sponsors agreed to share IPD.




Timeline for IPD retrieval
Sponsor Process
Initial Inquiry (step 1)
Initial Response (step 2)
Research Proposal Submitted (step 3)
DSA Finalized (step 4)
Access to Data and/or Platform (step 5)
423 days
472 days
563 days
612 days
612 days
614 days
740 days
Abbvie
Eisai (CSDR)
GlaxoSmithKline (CSDR)
Janssen (YODA)
Lundbeck
Novartis (CSDR)
Novo Nordisk
Sponsor Process (in steps)
1
2
3
4
5
13/01/2017
12/05/2017
17/10/2017
12/03/2018
29/06/2018
17/09/2018
23/01/2019
Date (day/month/year)

Challenges Reported

BMJ EBM Veroniki, 2023

- Reasons for data not provided
  - Difficulty with study identification (especially for trials before 2005)
  - Multi-sponsored trials (data ownership unclear)
  - Lack of Response/ IPD no longer available/ other
- Legal process for setting up data sharing agreement
- Costs for licences of coding dictionaries, Limited time & costs for extension
- Missing Data (covariates, outcome data)
- Data availability on separate proprietary platforms only (no combination of data, e.g. for one stage NMA)
- Limited software availability on the platforms
- no clear evidence of IPD retrieval bias

Data-sharing and re-analysis for main studies assessed by the European Medicines Agency Siebert et al. BMC Medicine (2022)

- Random sample (62/192) of 'main' studies (according to EPARs) on new medicines, biosimilars & orphan medicines approved in 01/2017 – 12/2019

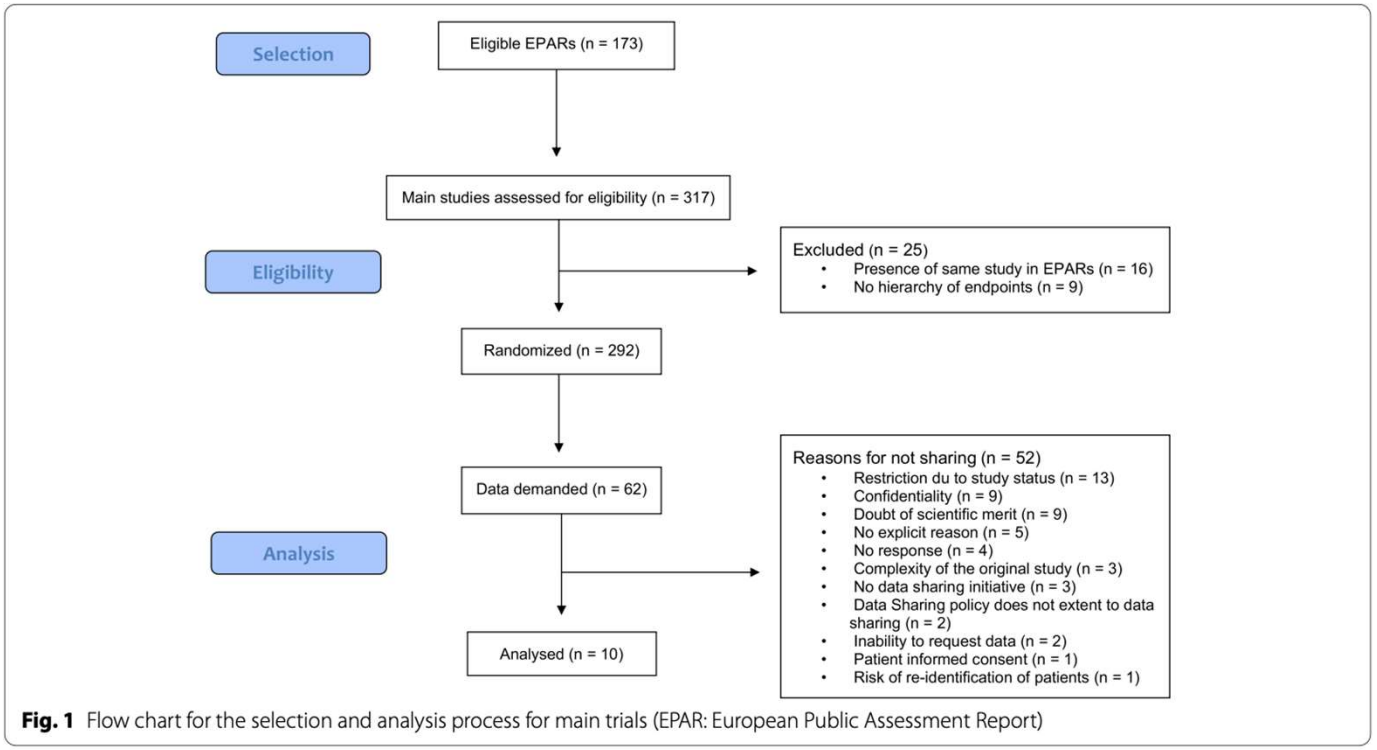


Fig. 1 Flow chart for the selection and analysis process for main trials (EPAR: European Public Assessment Report)

- Challenges
  - Missing Data
  - Coding Dictionaries
- Re-analysis
  - The results of the10 studies could be reproduced
  - (similar as experience of medical journals when asking for re-analysis)

SHARE-CTD: Sharing and re-using clinical trial data to maximise impact

EU-Horizon Doctoral Network (2024-2028)

- Doctoral network (10 PhDs) and 17 institutions
- Training and Research in Data sharing
- Study level: requesting, preparing, sharing and re-using data
  Global level: adopting and optimizing data-sharing policies)
- Multidisciplinary approach: regulations, ethical, legal and social issues, informatics, data science, biostatistics and meta-research, domain expertise across different medical fields.
- Data sharing experts needed by Journals, academic institutions (trial centers), sponsors and funders
- Meta-research can improve the impact of data sharing.

https://doi.org/10.1038/s41591-022-02080-y

Implementing clinical trial data sharing requires training a new generation of biomedical researchers

Ulrich Mansmann, Clara Locher, Fabian Prasser, Tracey Weissgerber, Ulrich Sax, Martin Posch, Evelyne Decullier, Ioana A. Cristea, Thomas P. A. Debray, Leonhard Held, David Moher, John P. A. Ioannidis, Joseph S. Ross, Christian Ohmann & Florian Naudet

Data sharing enhances the value of medical research and builds trust in clinical trials, but more biomedical researchers need to be trained in these approaches, which include meta-research, data science and ethical, legal and social issues.

Clinical trials form foundational evidence to inform contemporary medical decision-making. They provide evidence widely used by regulatory bodies and health technology assessment agencies and are considered the gold standard for assessing treatment effects. The value and trustworthiness of medical research may be enhanced by sharing of patient-level clinical trial data together with the code on which analyses are based[1,2], as well as other materials such as the protocols, case report forms and data dictionaries.

Nature Medicine (2023)

SHARE-CTD: Sharing and re-using clinical trial data to maximise impact

EU-Horizon Doctoral Network (2024-2028)

Preparing Data to be Shared

Fairification
Data Enrichment
Anonymization

Patient's Perspectives
Impact of CTDS
Automated Tools

Using Shared Data

Validation
Cross Design Synthesis
Outcome Reporting Bias
Shared Observational Data

Added value of IPD-MA
Impact in specific disease areas

Academia – Industry Collaborations

- Joint Data and analysis centers
- Methods and CT-Design development utilizing existing data
  - Evaluation of methods and designs based on resampling of CT data
- Improving Safety Assessment
- Broader use of IPD meta-analysis

Stakeholder's Interests in Data Sharing

- Trial Participants
  - Patients have the most to gain of efficient use of their data, e.g., research syntheses, comparative effectiveness
  - Confidentiality (through de-identification and governance)
  - Patients must consent to the sharing of their data
- Data Requesters
  - Provision of useable data and meta data
  - Fast access to data, high data quality and complete documentation
  - No unnecessary administrational burden
- Public: Ensuring the Qualitaty of Re-Analysis
  - Pre-specified analysis plans
  - Interpretation as retrospective analysis
  - Risk of „false positives" of multiple reanalyses of CT data.

Mansmann et al. 2023
Koenig et al. 2014

Stakeholder‘s Interests in Data Sharing (II)

Investigators and intervention holders running CTs

- Appropriate time schedule when data has to be shared (embargo period?)
- Compliance to GDPR

Industry

- Confidentiality to protect commercial interests

Academics

- Data deposition in registries is not considered as prior publication.
- Source of the data must be referenced using a unique identifier
  Authors of secondary analyses must explain completely how theirs differ from previous analyses.
- Those using data collected by others should seek collaboration with those who collected the data.
- Alternative means of providing credit need to be developed