New life for old data:
An overview of the clinical trial data sharing environment

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Outline of presentation

- Data Transparency: Where we are now
- What do we mean by “data”?
- Accessing and use of clinical study reports
- Accessing and use of patient level datasets
- Looking to the future

Data Transparency Movement Continues to Evolve …..

2013 → 2014 → 2015 → 2016

AllTrials Campaign launched Jan 2013

EMA Draft policy issued June 2013

efpia/PhRMA principles published July 2013

EMA Policy published October 2014

INSTITUTE OF MEDICINE Report Jan 2015

ICMJE Proposal for provision of PLD with journal articles

What the regulators are doing

- EMA Transparency Policy – redacted CSRs to 3rd parties
- EudraCT study and results registry
- Companies to include redacted copies of documents as part of MA application
- Future: Disclosure of clinical trial documents to public
- Future phase will address patient level data

- Now oversee aspects of CT.gov
- Watching closely what's happening in Europe regarding patient level data
- Work with consortia to address disease wide issues – e.g. earlier endpoints to predict SVR in Hepatitis
- Targeted opportunities to advance medical science
- Federal Register request for comments (04June2013)

What industry is doing : EFPIA/PhRMA principles (2013)

Principle	Details
1. Enhancing data sharing with researchers	On request from qualified medical and scientific researchers, companies will provide protocols, reports and patient-level clinical trial data for medicines that have been approved in both the EU and US. Each company will establish a scientific review board that will include scientists and/or healthcare professionals who are not employees of the company. Access will be consistent with patient informed consent and safeguarding privacy.
2. Enhancing public access to clinical study information	Companies will make available synopses of CSRs submitted to US and European regulatory authorities from 1 Jan 2014.
3. Sharing results with patients who participate in clinical trials	Companies will work with regulators to adopt mechanisms for providing a factual summary of clinical trial results and make the summaries available to research participants.
4. Certifying procedures for sharing clinical trial information	Companies will certify on a publicly available web site that they have established policies and procedures to implement these data sharing commitments.
5. Re-affirming commitments to publish clinical trial results	Results from all phase 3 clinical trials and any clinical trial results of significant medical importance should be submitted for publication, whether positive or negative, including results from discontinued development programs.

What academia is doing

- Some disease area specific examples,
  - e.g. ADNI database
- Funding bodies – NIH, MRC, Wellcome Trust
- Many barriers to sharing
  - Funding models
  - Sparse support for data curation, archiving and sharing
  - Recognition via publications

What do we mean by “data”?

Increasing level of detail and accessibility

Results registry posting

ClinicalTrials.gov

Journal article

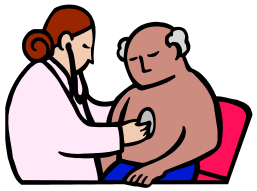
JOURNAL OF CLINICAL ONCOLOGY

Regulatory summary document
(multiple studies)

Clinical Study Report
(single study / datacut)

Patient Level Data files for a trial

Individual’s patient record



Do I need access to the CSR or the datasets?

How a CSR can help you

Meta-analyses using summary statistics

Access to 2° and exploratory results

Better understand details of analysis methodologies and assumptions used

Designing more efficient trials

Access to unpublished studies

Access to negative studies

Trial design

Sample size estimation

Do I need access to the CSR or the datasets?

How the patient level datasets can help you

Secondary research questions:

- Exploring effects across trials (IPD meta-analyses)
- New indications
- Refine/relevant endpoints
- Sample sizing (diff endpoint or population)
- Prognostic factors
- Investigating patients most likely to ….
- HTA analyses

Independent replication

Time to understand data and utlilize it to its full potential inc. failed studies/drugs

Connecting researchers / new collaborations?

Increase research community understanding of pharma data

- Size and complexity of d/sets
- Good statistical and programming practice

How do I know what studies have been conducted?

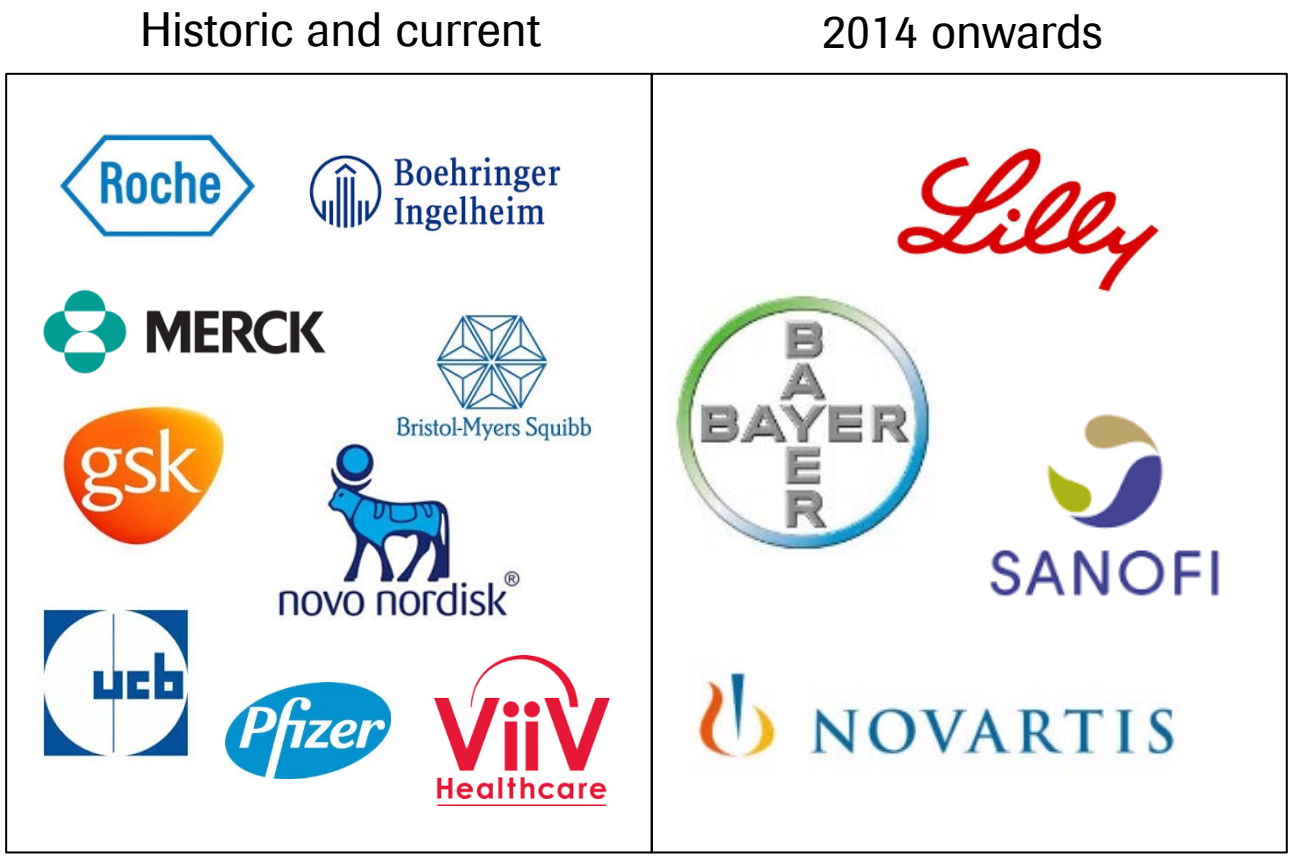
- Literature searches
- Registry searches
- Drug approval labels (e.g. FDA and EMA websites)
- Regulatory review reports
- Challenges:
  - Multiple names for the same study (e.g in-house id, “name”, NCT number on CT.gov)
  - Whose study/data is it? (collaborations, mergers and acquisitions, selling of assets)

Access to CSRs – Who is sharing what?

”

Based on website search as of Dec 2014

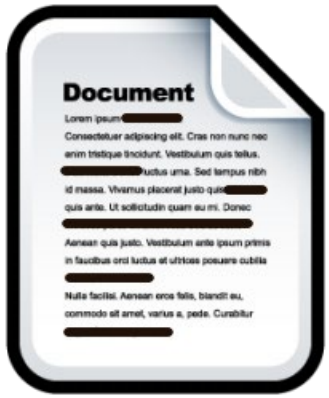
Access to CSRs: what can I ask for?



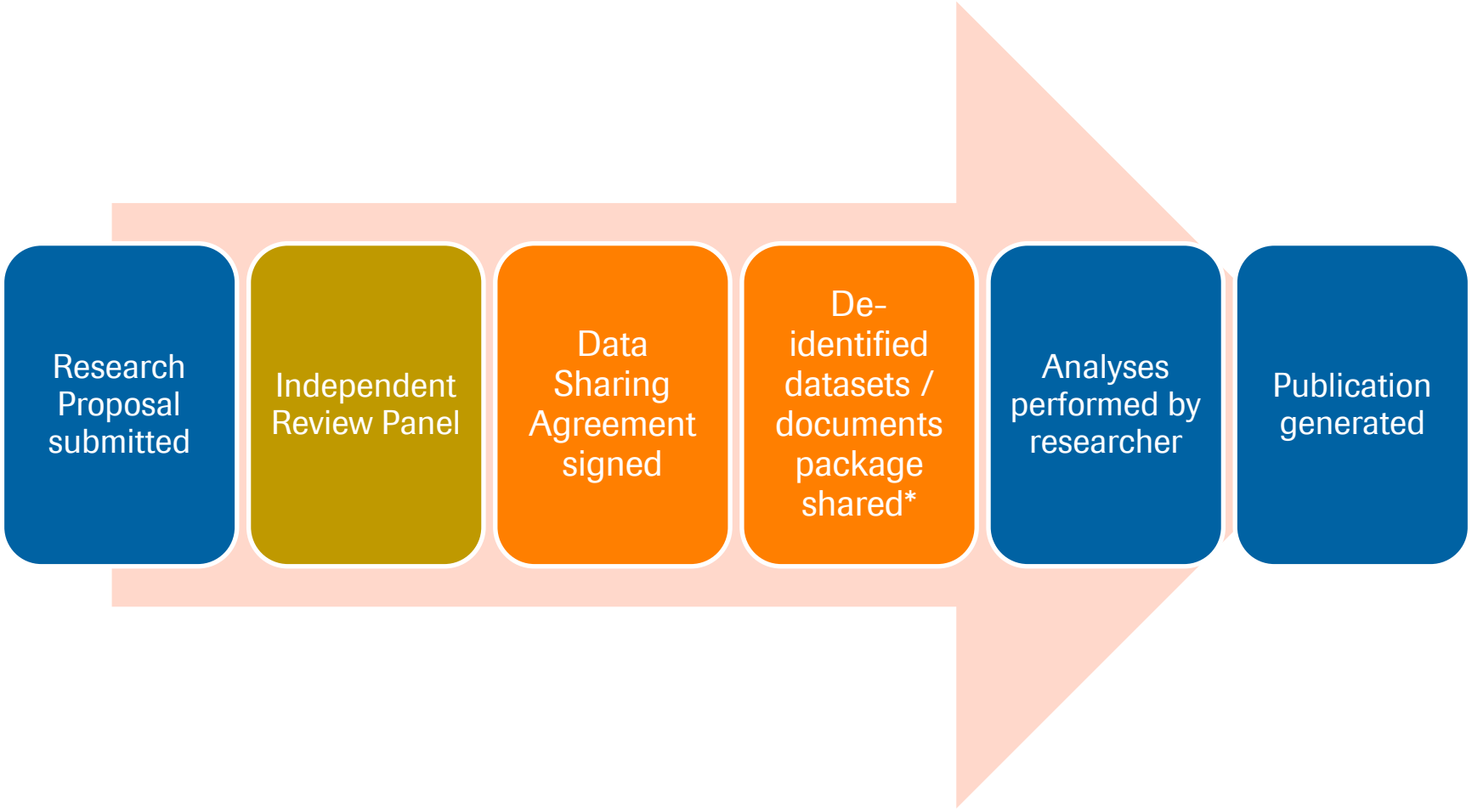
Based on website search
as of Dec 2014

Access to CSRs: What you'll get

- Body of the CSR – the written report part
  - Introduction
  - Study design
  - Results
  - Conclusions
- Limited appendices – e.g. No patient level data listings
- Report will be redacted for :
  - Any commercially confidential information
  - Any patient identifying information



Access to PLD: Typical Patient Level Data Access Model

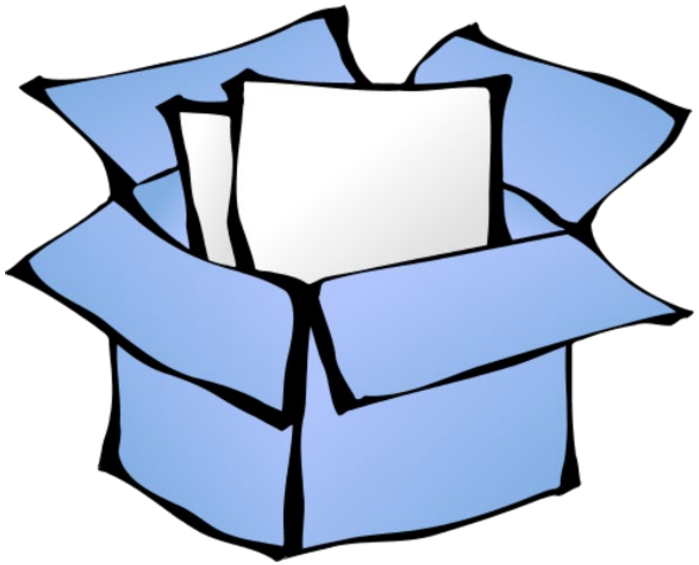


* Datasets generally shared via a secure analysis website and not sent directly to researchers

Access to PLD: What you'll get

Typical contents of a patient level data package:

- Raw datasets (anonymized)
- Analysis datasets (anonymized)
- Protocol
- Annotated Case Report Form
- Dataset Specifications
- Statistical Analysis Plan
- Clinical Study Report (redacted)



Access to PLD: Who's sharing?

- Cross-company collaboration

ClinicalStudy DataRequest.com

- Collaboration with an academic group
  - Johnson & Johnson with Yale ('YODA')
  - Bristol-Myers Squibb with Duke

- "Home grown" solutions
  - INSPIIRE portal
  - Pfizer EngageZone
  - MERCK Be well Data Request Portal
  - On-line form
  - AMGEN
  - novo nordisk®

AstraZeneca

Some stats about ClinicalStudy DataRequest.com

- Launched May 2013 (gsk)
- Cross-company version : 01 Jan 2014
- wellcome trust join as the IRP Secretariat: Jan 2016
- 2281 studies listed as available for request
- Enquiry route available if study not listed (225 studies added via this route to date)

Site Metrics (as of 31st Dec 2015)

Activity	Number
Research Proposal (RP) submitted	186
RP met requirements*	144
IRP approved**	124
Data Sharing Agreement signed	89
Research on-going	84
Research complete	2
Research published	1

*11 did not meet requirements, 21 withdrawn by researcher

**11 rejected or advised to re-submit

Descriptive Statistics - Disease Area

First 100 Research Proposals	Number
Cancer	23
Infectious diseases	20
Cardiovascular diseases	14
Autoimmune diseases	11
Central nervous system	10
Other	17
Co-morbidities	5

Acknowledgements: Marc Buyse, Jennifer O'Callahan

CSDR Data Sharing - Broad Trends

Of 100 projects:

- 58 requested multiple trials (11 from multiple sponsors)
- Only 2 aim to confirm original trial results
- 20 aim to develop/validate new methods
- 49 aim to find predictive factors (precision medicine)

Acknowledgements: Marc Buyse, Jennifer O'Callahan

Roche ClinicalStudy DataRequest.com metrics (09Dec15)

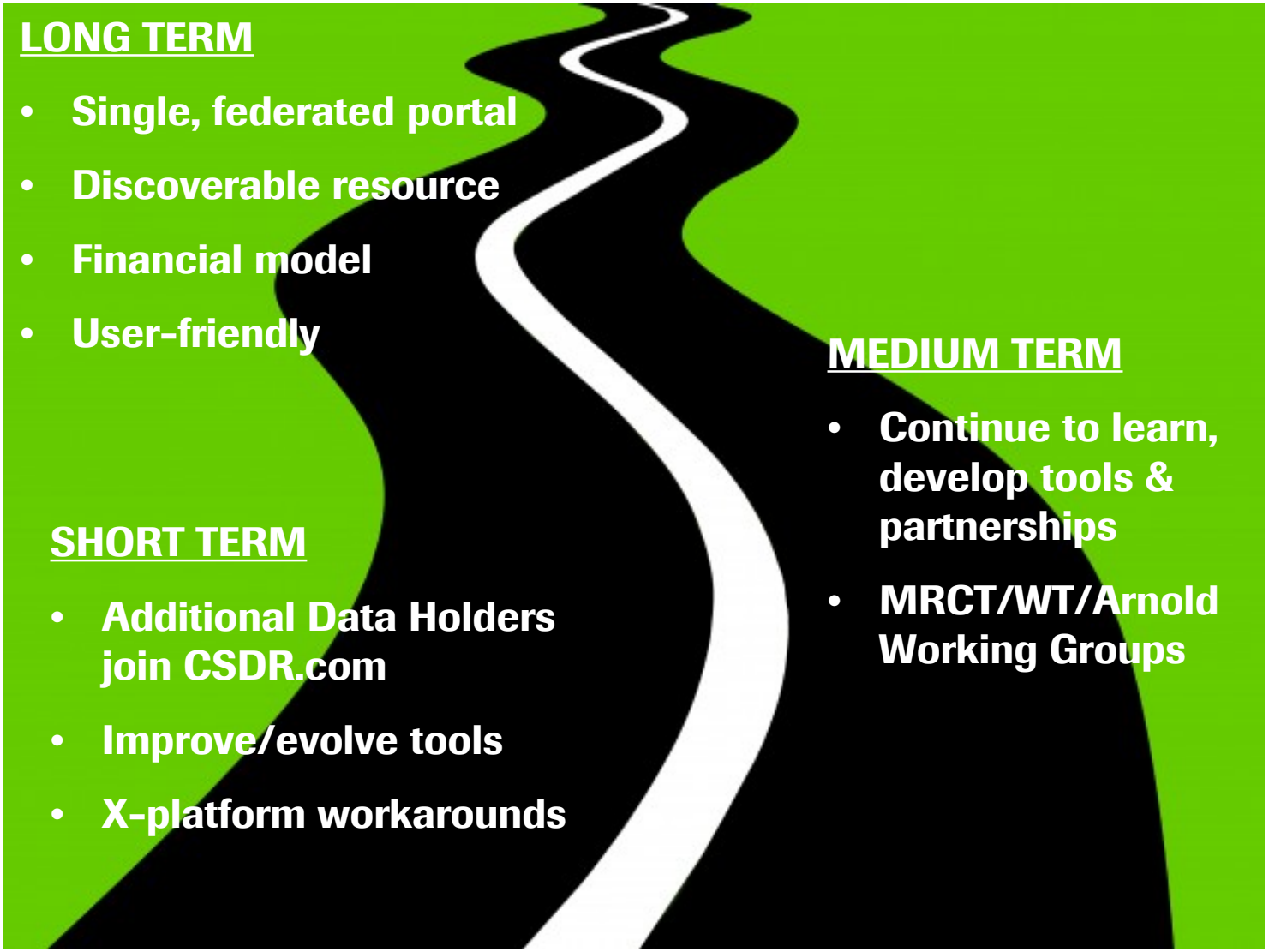
- 17 **'research proposals'** received to date
  - 2 were actually requests for documents-only
  - 2 proposals withdrawn and resubmitted with additional studies
- From the 13 PLD research proposals:
  - 1 in progress
  - 11 proposals approved by IRP
  - 1 proposal did not proceed with Roche studies due to requirement to share tumour images (out of scope as per policy)
- Data shared with **8 external research teams** to date

- 29 CSDR '**enquiries**', mixture of:
  - Requestors asking about studies not listed on the request site
  - General questions (how much does it cost, process questions)

CSR Redaction Requests Jan-Nov 2015:

- Total = 300
- 208 (69%) completed
- 39 (13%) rejected
- Remainder "in progress"

The Future : Patient Level Data Access



The Future: Study Reporting and Transparency Scrutiny

- Registries
  - Compliance (e.g. Jennifer Miller review)
  - New registry element: Data access field
  - Consolidation or fragmentation?
  - Fines imposed?
- Content comparisons:
  - Registry versus Publication (Compare Project)
  - Publication versus CSR

Academia – what we want from you?

- Understanding
- Feedback
- Participation

Data Sharing will benefit patients and society.

We all need to work together.

Useful References

- IoM report : http://iom.nationalacademies.org/Reports/2015/Sharing-Clinical-Trial-Data.aspx
- Wellcome Trust report : http://www.wellcome.ac.uk/About-us/Policy/Spotlight-issues/Data-sharing/Access-to-clinical-trial-data/index.htm
- Link to shared website: https://clinicalstudydatarequest.com/Default.aspx
- NEJM article by CSDR original IRP members: http://www.nejm.org/doi/pdf/10.1056/NEJMp1411794
- Sharing Clinical Trial Data – a proposal from the ICJME: http://www.nejm.org/doi/full/10.1056/NEJMe1515172
- Compare Project: http://compare-trials.org/
- Jennifer Miller et al review: http://bmjopen.bmj.com/content/5/11/e009758.full

Doing now what patients need next