



# Data sources to help inform drug development – what you give is also what you get

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# Introduction: Who are we?

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- **Disclaimer**  
The views and opinions expressed in this presentation are those of the individual presenter and should not be attributed to any organisation with which the presenter is employed or affiliated.

# Objectives of this session

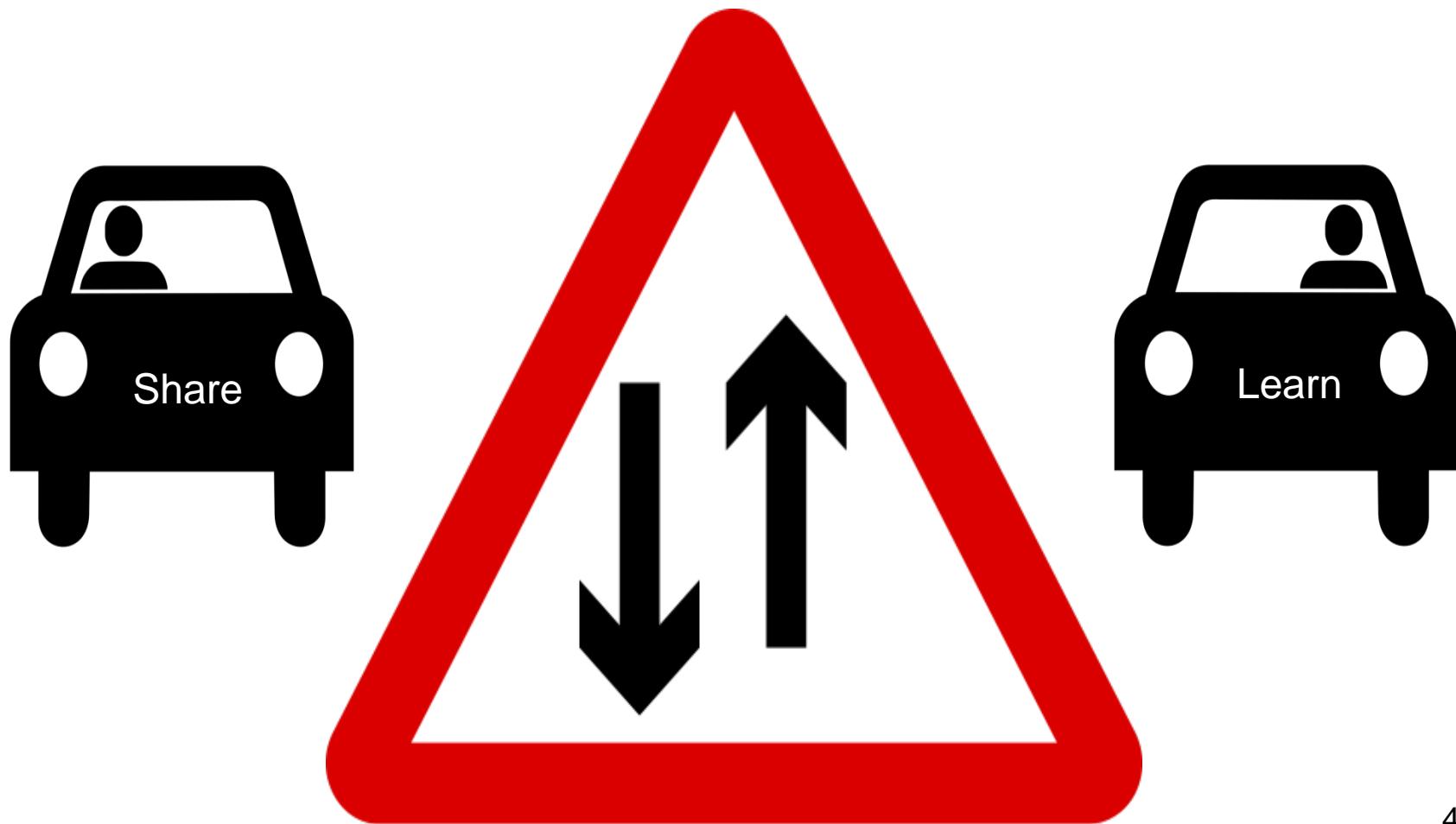
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Increase your

- **knowledge** of sources of clinical trial information outside of medical literature and registries and how to access them
- **awareness** of the sorts of insights that access to documents and/or datasets may afford
- **appreciation** that the clinical trials we work on have a life and scientific value beyond the protocol and regulatory filing .....

# Data sharing is a 2-way street ....

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# New mindset needed

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- Opportunities
  - New data sources that we can use in development planning and trial design
    - CSR level detail versus publication level detail
    - Operational aspects when embarking in a new disease area
- Challenges
  - All the “data” generated during a study has the potential to become publicly available
  - No longer limited to sharing with regulators

# Data sharing evolution continues ....

2013

2014

2015

2016

2017

2018



Campaign launched Jan 2013



efpia/PhRMA principles published July 2013



EMA Policy 70 effective Jan 2015

Report Jan 2015

INSTITUTE OF MEDICINE

CT.gov update effective Jan 2017 *ClinicalTrials.gov*

ICMJE Proposal for provision of PLD with journal articles



# What the regulators are doing



- EudraCT study and results registry
  - EMA Transparency Policy – redacted CSRs etc to 3<sup>rd</sup> parties (companies include redacted copies of documents as part of MA application)
  - Future phase will address patient level data
- The screenshot shows the homepage of the European Medicines Agency Clinical data website. At the top, there's a navigation bar with 'Home', 'Find Clinical Data', and 'About'. Below the navigation is a large blue header with the text 'EUROPEAN MEDICINES AGENCY Clinical data'. Underneath the header is a dashboard featuring several charts and graphs. One chart shows a line graph with values like 280, 780, 400, 610, 360, 470, and 600. Another chart shows a bar graph with values like 280, 780, 400, 610, 360, 470, and 600. Below the charts is a section titled 'Online access to clinical data for medicinal products for human use'. At the bottom of the page, there's a footer with small text about the website's purpose and regulatory authority.

Latest clinical data published

Medicine	Date Published
Amisulide (gemertexilic acid monohydrate)	published 24 November 2016
Capsofugan Acetate (capsofugan acetate)	published 24 November 2016
Kyprolis (carfilzomib)	published 20 October 2016
Zoledronic (lesimilumab)	published 20 October 2016
- CT.gov Sept 2016 update: expand criteria for posting, include all 2<sup>o</sup> endpoints, protocol and SAP. Scope for NIH funded research expanded.
  - Work with consortia to address disease wide issues – e.g. earlier endpoints to predict SVR in Hepatitis
  - Targeted opportunities to advance medical science

**Health Canada March 2017  
White Paper, similar to Policy  
70 approach**

# efpia/PhRMA Commitments Implemented from Jan 2014

1

- Enhancing data sharing with **researchers**

2

- Enhancing **public** access to clinical study information

3

- Sharing results with **patients** who participate in clinical trials

4

- Certifying procedures for sharing clinical trial information

5

- Re-affirming commitments to publish clinical trial results

# “Data” can have many meanings

Increasing level of detail



Regulatory Reviewer Assessment Reports



Registry posting (protocol and summary results)

Journal article



Regulatory summary document  
(multiple studies)



Clinical Study Report  
(single study / datacut)



**Aggregated data**

Statistical Analysis Plan



**Supporting info**

Trial correspondence – ICF, ethics  
committee communications



Patient Level Data files for a trial



**Individual Patient  
Data (IPD)**

Individual's patient record



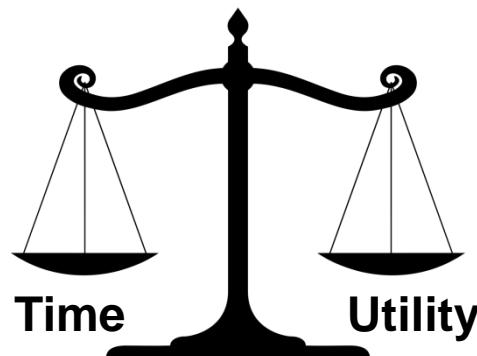
# Aggregate Data or PLD?

## Aggregate / Study Level Data

- Many CSRs, protocols and SAPs available online
- Generally open access when available
- Results available on CT.gov
- Considerably more detail than publications

## Patient Level Data

- EU and US approved products/indications only
- Research proposal required
- Time to access data from submission 6 months or more
- Commitment to publish your findings
- Complexity of different data models



# How could CSR access help me?

Meta-analyses using summary statistics

Access to 2° and exploratory results

Better understand details of analysis methodologies and assumptions used

Access to unpublished studies



Access to negative studies

Designing more efficient trials

Trial design

Sample size estimation

# Case Study: Using CSRs

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EMA provide redacted CSRs on request



Rare subgroup of disease population to be studied. 4 registrational studies identified using the same control arm.

6

weeks from request to receipt



Confirmed sample size assumptions for sub-group  
Additionally:

- Insights from protocol amendments
- Detailed efficacy endpoint definitions
- Analysis population definitions

# CSR Resources

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- CT.gov - summary results
- EU portal— proactive sharing and on request
- Company policies (e.g GSK and Novo Nordisk)
- CSRs available “on request” from some companies
- Equivalent full report may not be produced for academic studies

# How could access to PLD help me?

## 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



Study ID	Author	Title	Year	Country	Sample Size	Outcomes	Notes
1	Jones et al.	Effect of A on B	2010	USA	100	Outcome A	Good
2	Smith et al.	Effect of C on D	2011	UK	200	Outcome C	Good
3	Johnson et al.	Effect of E on F	2012	Canada	150	Outcome E	Good
4	Harris et al.	Effect of G on H	2013	Australia	180	Outcome G	Good
5	Wong et al.	Effect of I on J	2014	China	220	Outcome I	Good
6	Lee et al.	Effect of K on L	2015	Korea	160	Outcome K	Good
7	Perez et al.	Effect of M on N	2016	Mexico	190	Outcome M	Good
8	Reed et al.	Effect of O on P	2017	Germany	210	Outcome O	Good
9	Wilson et al.	Effect of Q on R	2018	France	170	Outcome Q	Good
10	Brown et al.	Effect of S on T	2019	Ireland	230	Outcome S	Good
11	White et al.	Effect of U on V	2020	Netherlands	190	Outcome U	Good
12	Black et al.	Effect of W on X	2021	Sweden	200	Outcome W	Good
13	Green et al.	Effect of Y on Z	2022	Denmark	180	Outcome Y	Good
14	Red et al.	Effect of A on B	2023	Portugal	220	Outcome Red	Good
15	Blue et al.	Effect of C on D	2024	Spain	160	Outcome Blue	Good
16	Yellow et al.	Effect of E on F	2025	Greece	190	Outcome Yellow	Good
17	Orange et al.	Effect of G on H	2026	Poland	210	Outcome Orange	Good
18	Pink et al.	Effect of I on J	2027	Croatia	170	Outcome Pink	Good
19	Grey et al.	Effect of K on L	2028	Slovenia	230	Outcome Grey	Good
20	Teal et al.	Effect of M on N	2029	Montenegro	190	Outcome Teal	Good
21	Indigo et al.	Effect of O on P	2030	Bosnia and Herzegovina	210	Outcome Indigo	Good
22	Violet et al.	Effect of Q on R	2031	Albania	170	Outcome Violet	Good
23	Maroon et al.	Effect of S on T	2032	North Macedonia	230	Outcome Maroon	Good
24	Dark Blue et al.	Effect of U on V	2033	Yugoslavia	190	Outcome Dark Blue	Good
25	Light Blue et al.	Effect of W on X	2034	Montenegro	200	Outcome Light Blue	Good
26	Dark Teal et al.	Effect of Y on Z	2035	North Macedonia	180	Outcome Dark Teal	Good
27	Light Teal et al.	Effect of A on B	2036	Yugoslavia	220	Outcome Light Teal	Good
28	Dark Grey et al.	Effect of C on D	2037	Montenegro	160	Outcome Dark Grey	Good
29	Light Grey et al.	Effect of E on F	2038	Yugoslavia	190	Outcome Light Grey	Good
30	Dark Indigo et al.	Effect of G on H	2039	Montenegro	210	Outcome Dark Indigo	Good
31	Light Indigo et al.	Effect of I on J	2040	Yugoslavia	170	Outcome Light Indigo	Good
32	Dark Maroon et al.	Effect of K on L	2041	Montenegro	230	Outcome Dark Maroon	Good
33	Light Maroon et al.	Effect of M on N	2042	Yugoslavia	190	Outcome Light Maroon	Good
34	Dark Violet et al.	Effect of O on P	2043	Montenegro	210	Outcome Dark Violet	Good
35	Light Violet et al.	Effect of Q on R	2044	Yugoslavia	170	Outcome Light Violet	Good
36	Dark Maroon et al.	Effect of S on T	2045	Montenegro	230	Outcome Dark Maroon	Good
37	Light Maroon et al.	Effect of U on V	2046	Yugoslavia	190	Outcome Light Maroon	Good
38	Dark Indigo et al.	Effect of W on X	2047	Montenegro	210	Outcome Dark Indigo	Good
39	Light Indigo et al.	Effect of Y on Z	2048	Yugoslavia	170	Outcome Light Indigo	Good
40	Dark Maroon et al.	Effect of A on B	2049	Montenegro	230	Outcome Dark Maroon	Good
41	Light Maroon et al.	Effect of C on D	2050	Yugoslavia	190	Outcome Light Maroon	Good
42	Dark Indigo et al.	Effect of E on F	2051	Montenegro	210	Outcome Dark Indigo	Good
43	Light Indigo et al.	Effect of G on H	2052	Yugoslavia	170	Outcome Light Indigo	Good
44	Dark Maroon et al.	Effect of I on J	2053	Montenegro	230	Outcome Dark Maroon	Good
45	Light Maroon et al.	Effect of K on L	2054	Yugoslavia	190	Outcome Light Maroon	Good
46	Dark Indigo et al.	Effect of M on N	2055	Montenegro	210	Outcome Dark Indigo	Good
47	Light Indigo et al.	Effect of O on P	2056	Yugoslavia	170	Outcome Light Indigo	Good
48	Dark Maroon et al.	Effect of Q on R	2057	Montenegro	230	Outcome Dark Maroon	Good
49	Light Maroon et al.	Effect of S on T	2058	Yugoslavia	190	Outcome Light Maroon	Good
50	Dark Indigo et al.	Effect of U on V	2059	Montenegro	210	Outcome Dark Indigo	Good
51	Light Indigo et al.	Effect of W on X	2060	Yugoslavia	170	Outcome Light Indigo	Good
52	Dark Maroon et al.	Effect of Y on Z	2061	Montenegro	230	Outcome Dark Maroon	Good
53	Light Maroon et al.	Effect of A on B	2062	Yugoslavia	190	Outcome Light Maroon	Good
54	Dark Indigo et al.	Effect of C on D	2063	Montenegro	210	Outcome Dark Indigo	Good
55	Light Indigo et al.	Effect of E on F	2064	Yugoslavia	170	Outcome Light Indigo	Good
56	Dark Maroon et al.	Effect of G on H	2065	Montenegro	230	Outcome Dark Maroon	Good
57	Light Maroon et al.	Effect of I on J	2066	Yugoslavia	190	Outcome Light Maroon	Good
58	Dark Indigo et al.	Effect of K on L	2067	Montenegro	210	Outcome Dark Indigo	Good
59	Light Indigo et al.	Effect of M on N	2068	Yugoslavia	170	Outcome Light Indigo	Good
60	Dark Maroon et al.	Effect of O on P	2069	Montenegro	230	Outcome Dark Maroon	Good
61	Light Maroon et al.	Effect of Q on R	2070	Yugoslavia	190	Outcome Light Maroon	Good
62	Dark Indigo et al.	Effect of S on T	2071	Montenegro	210	Outcome Dark Indigo	Good
63	Light Indigo et al.	Effect of U on V	2072	Yugoslavia	170	Outcome Light Indigo	Good
64	Dark Maroon et al.	Effect of W on X	2073	Montenegro	230	Outcome Dark Maroon	Good
65	Light Maroon et al.	Effect of Y on Z	2074	Yugoslavia	190	Outcome Light Maroon	Good
66	Dark Indigo et al.	Effect of A on B	2075	Montenegro	210	Outcome Dark Indigo	Good
67	Light Indigo et al.	Effect of C on D	2076	Yugoslavia	170	Outcome Light Indigo	Good
68	Dark Maroon et al.	Effect of E on F	2077	Montenegro	230	Outcome Dark Maroon	Good
69	Light Maroon et al.	Effect of G on H	2078	Yugoslavia	190	Outcome Light Maroon	Good
70	Dark Indigo et al.	Effect of I on J	2079	Montenegro	210	Outcome Dark Indigo	Good
71	Light Indigo et al.	Effect of K on L	2080	Yugoslavia	170	Outcome Light Indigo	Good
72	Dark Maroon et al.	Effect of M on N	2081	Montenegro	230	Outcome Dark Maroon	Good
73	Light Maroon et al.	Effect of O on P	2082	Yugoslavia	190	Outcome Light Maroon	Good
74	Dark Indigo et al.	Effect of Q on R	2083	Montenegro	210	Outcome Dark Indigo	Good
75	Light Indigo et al.	Effect of S on T	2084	Yugoslavia	170	Outcome Light Indigo	Good
76	Dark Maroon et al.	Effect of U on V	2085	Montenegro	230	Outcome Dark Maroon	Good
77	Light Maroon et al.	Effect of W on X	2086	Yugoslavia	190	Outcome Light Maroon	Good
78	Dark Indigo et al.	Effect of Y on Z	2087	Montenegro	210	Outcome Dark Indigo	Good
79	Light Indigo et al.	Effect of A on B	2088	Yugoslavia	170	Outcome Light Indigo	Good
80	Dark Maroon et al.	Effect of C on D	2089	Montenegro	230	Outcome Dark Maroon	Good
81	Light Maroon et al.	Effect of E on F	2090	Yugoslavia	190	Outcome Light Maroon	Good
82	Dark Indigo et al.	Effect of G on H	2091	Montenegro	210	Outcome Dark Indigo	Good
83	Light Indigo et al.	Effect of I on J	2092	Yugoslavia	170	Outcome Light Indigo	Good
84	Dark Maroon et al.	Effect of K on L	2093	Montenegro	230	Outcome Dark Maroon	Good
85	Light Maroon et al.	Effect of M on N	2094	Yugoslavia	190	Outcome Light Maroon	Good
86	Dark Indigo et al.	Effect of O on P	2095	Montenegro	210	Outcome Dark Indigo	Good
87	Light Indigo et al.	Effect of Q on R	2096	Yugoslavia	170	Outcome Light Indigo	Good
88	Dark Maroon et al.	Effect of S on T	2097	Montenegro	230	Outcome Dark Maroon	Good
89	Light Maroon et al.	Effect of U on V	2098	Yugoslavia	190	Outcome Light Maroon	Good
90	Dark Indigo et al.	Effect of W on X	2099	Montenegro	210	Outcome Dark Indigo	Good
91	Light Indigo et al.	Effect of Y on Z	2100	Yugoslavia	170	Outcome Light Indigo	Good

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

Connecting researchers / new collaborations?

- Increase research community understanding of pharma data
- Size and complexity of datasets
- Good statistical and programming practice

# PLD Resources

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- Clinicalstudydatarequest.com [CSDR.com]
  - 13 Pharma companies, 3374 studies listed, enquiry route available for unlisted trials
- Institution specific sites
  - Pharma companies outwith CSDR.com have request processes in line with efpia/PhRMA Commitment. Easy to access from corporate website, e.g. Pfizer, Amgen, AZ, Janssen (YODA)
  - Academic Institutions may have a process, but likely to be harder to find and access. Processes being put in place, e.g. UK Clinical Trial Units
- Disease Specific Resources
  - E.g. Project DataSphere, 90 oncology studies, control arm data

# How do we need to adapt?

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- Documents no longer “conversations with the regulators” – now public documents
  - Protocol and SAP will be submitted to CT.gov as part of results postings for studies starting from 18 Jan 2017
  - Protocol and SAP increasingly required as supplementary information to published article (e.g. NEJM)

# How do we need to adapt?

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- Preparation of public facing CSRs under EMA Policy 70
  - Need for expertise in data anonymization techniques and risk quantification
  - Development of scalable solutions
  - Opportunity for “redaction/anonymization” ready document templates
  - Plain language summary (lay summary) for EMA and for trial participants

# How do we need to adapt?

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- Clinical trial datasets (and documents) have a life beyond the CSR and filing
- All studies and data need to be available for future re-use
- Do your processes ensure that they are
  - Findable?
  - Accessible?
  - Interoperable?
  - Re-usable?

# Closing Thoughts

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Data sharing is a reality - opportunities for statisticians

- Data and insights to enhance drug development strategy
- Expertise and support in development of quantitative risk methods for data privacy
- Leaders in drug development will be those who know where the relevant data is, how to access it, aggregate it, analyse for meaning and communicate those insights



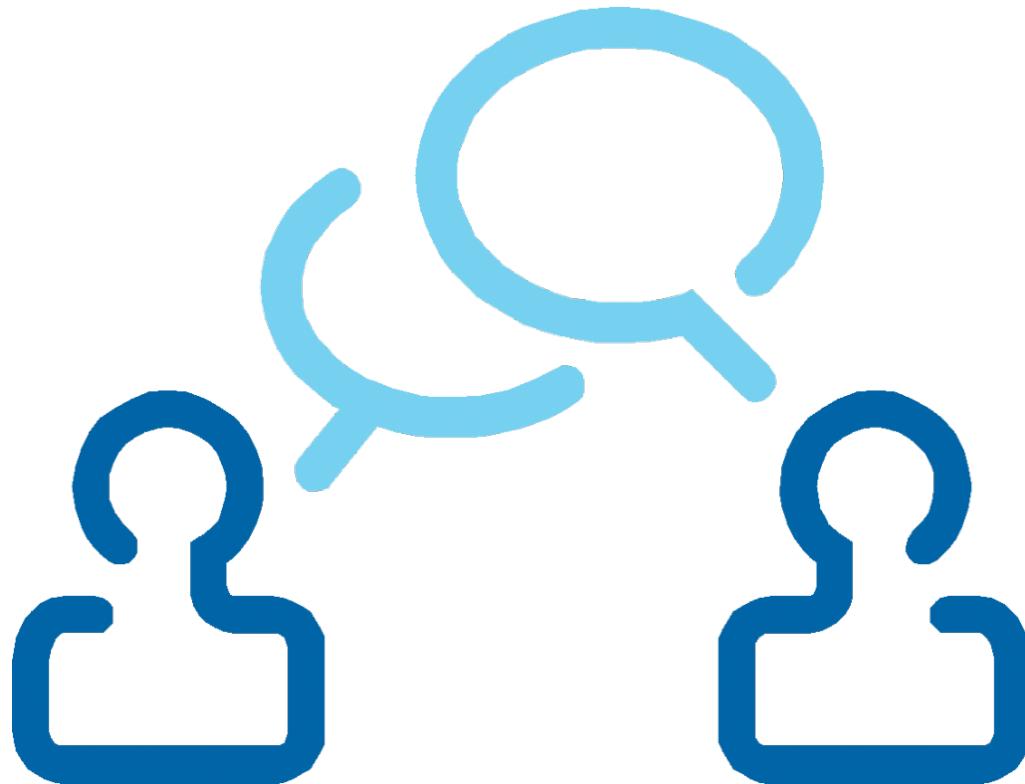
# Watch This Space ...

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- EMA Technical Anonymisation Group (TAG)
  - In March the European Medicines Agency (EMA) launched a call for applications to join a technical anonymisation group to assess best anonymisation practices, and any risks to privacy and re-identification of patients in the light of new technological developments. In addition, it will investigate how the anonymisation methodology used impacts the scientific utility of the published data, and establish whether secondary analysis of the data can be successfully undertaken.
- EFSP/EFPIA data sharing workshops
  - An initial workshop in September 2016 provided an opportunity to share experiences of the early implementation of the EMA publication of clinical data. A variety of case studies were shared, a number of challenges discussed and a range of stakeholders perspectives provided.
  - The second workshop will focus on different strategies for anonymizing clinical data and methods for assessing the risk of re-identification. The aim is for sponsors to share their approaches for anonymising clinical data and share experiences. Further information and details about the second workshop will be shared in forthcoming EFSPI newsletters.

# Questions & Feedback

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# Useful references

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- 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>
- Cross-pharma data sharing request website:
  - Link to site: <https://clinicalstudydatarequest.com/Default.aspx>
  - Publications by Independent Review Panel:  
<http://www.nejm.org/doi/pdf/10.1056/NEJMp1411794>,  
<http://www.nejm.org/doi/full/10.1056/NEJMp1610336>
- Data Sharing Statements for Clinical Trials - A Requirement of the International Committee of Medical Journal Editors
  - <http://www.nejm.org/doi/full/10.1056/NEJMe1705439>
- Reviews of Trial Transparency:
  - Compare Project: <http://compare-trials.org/>
  - Miller et al review: <http://bmjopen.bmj.com/content/5/11/e009758.full>

# References continued

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- EFPIA/PhRMA Principles:  
<http://transparency.efpia.eu/uploads/Modules/Documents/data-sharing-prin-final.pdf>
- GSK Clinical Study Register: <https://www.gsk-clinicalstudyregister.com/>
- EMA
  - Clinical Data website: <https://clinicaldata.ema.europa.eu/web/cdp/home>
  - Access on request:  
[http://www.ema.europa.eu/ema/index.jsp?curl=pages/document\\_library/document\\_listing/document\\_listing\\_000312.jsp&mid=WC0b01ac0580999a9c](http://www.ema.europa.eu/ema/index.jsp?curl=pages/document_library/document_listing/document_listing_000312.jsp&mid=WC0b01ac0580999a9c)
- EFSP/PSI Data Transparency articles  
<http://bmcmedresmethodol.biomedcentral.com/articles/supplements/volume-16-supplement-1>
- OpenTrials Initiative: <http://opentrials.net/2016/08/10/opentrialsfda-unlocking-the-trove-of-clinical-trial-data-in-drugsfda/>
- CT.gov Sept 2016 update: <https://www.nih.gov/news-events/news-releases/hhs-take-steps-provide-more-information-about-clinical-trials-public>

# Upcoming events



Course: Estimating sample sizes in clinical trials, 28 – 29 June 2017

Webinar: IMI PREFER — Patient preferences: why, how and when, 21 September 2017

Course: Improving Influence and Increasing Impact: Essential Skills for Industry Statisticians, 21 September 2017

One day meetings and webinars planned for late 2017, dates TBC

- Estimands
- Extrapolation
- Causal inference
- Health technology appraisals (joint with EFSPI)

[www.psiweb.org/events/psi-events](http://www.psiweb.org/events/psi-events)