PhUSE Single Day Event
Clinical Trial Disclosure and Transparency

An academic researcher's perspective on data transparency

Sarah J. Nolan and Dr. Catrin Tudur Smith
University of Liverpool (sjn16@liv.ac.uk)

views expressed are our own personal views and do not necessarily reflect other academic researchers

An academic researcher's perspective on data transparency

- What does an academic researcher do?
- Why do we want access to participant level data?
- What does 'transparency' mean for us?
- What do we want from data providers?
- What are our obligations as researchers?

An academic researcher

Academic profile: Sarah J. Nolan

- 2006-2010: BSc Mathematical Sciences with a European Language, University of Liverpool
- 2010-2011: MSc Medical Statistics, University of Leicester
- October 2011: Started working at University of Liverpool under a 3 year NIHR research contract: *"Clinical and cost effectiveness of interventions for epilepsy in the NHS"*
- January 2012: Registered part time PhD

Research: Systematic Review

- "Identification, appraisal and synthesis of **all empirical evidence** that meets pre-specified eligibility criteria to answer a given research question"
- Researchers conducting systematic reviews use explicit methods aimed at minimising bias, in order to produce more reliable findings that can be used to inform decision making.
- Foundation of **evidence based medicine**

Research: Meta-analysis

- Results of the individual studies in the systematic review are combined statistically to produce an overall "average" result.
- This aims to provide a more precise estimate of the effects of a medical intervention and to reduce uncertainty based on **all available evidence.**
- This is not always feasible or appropriate

Research: Types of Data

Table 2 Time to treatment withdrawal and time to first seizure by VPA and CBZ strata for subgroups of patients with focal or generalised seizures only (intent-to-treat population excluding unclassified/unknown seizure types)

	LEV		Standard AEDs		
	N	Event	N	Event	HR (95% CI)*
Time to treatment withdrawal					
VPA stratum					
Focal seizures only	99	15	91	18	0.73 (0.37 to 1.44)
Generalised seizures only	226	54	232	49	1.16 (0.79 to 1.71)
CBZ stratum					
Focal seizures only	418	109	440	130	0.84 (0.65 to 1.09)
Generalised seizures only	46	5	40	8	0.49 (0.16 to 1.49)
Time to first seizure					
VPA stratum					
Focal seizures only	99	44	91	37	1.03 (0.67 to 1.60)
Generalised seizures only	226	78	232	67	1.28 (0.93 to 1.78)
CBZ stratum					
Focal seizures only	418	198	440	172	1.24 (1.01 to 1.52)
Generalised seizures only	46	15	40	10	1.17 (0.53 to 2.60)

*HR of <1 favours LEV.
AED, antiepileptic drug; CBZ, carbamazepine; LEV, levetiracetam; VPA, sodium valproate; N, number of patients; Event, number of patients who had the event (treatment withdrawal or seizure); HR, HR for time to event (treatment withdrawal or first seizure).

Trinka *et al. Journal of Neurology, Neurosurgery and Psychiatry* 2013;84:1138–1147.

AGGREGATE DATA (SUMMARY LEVEL DATA)

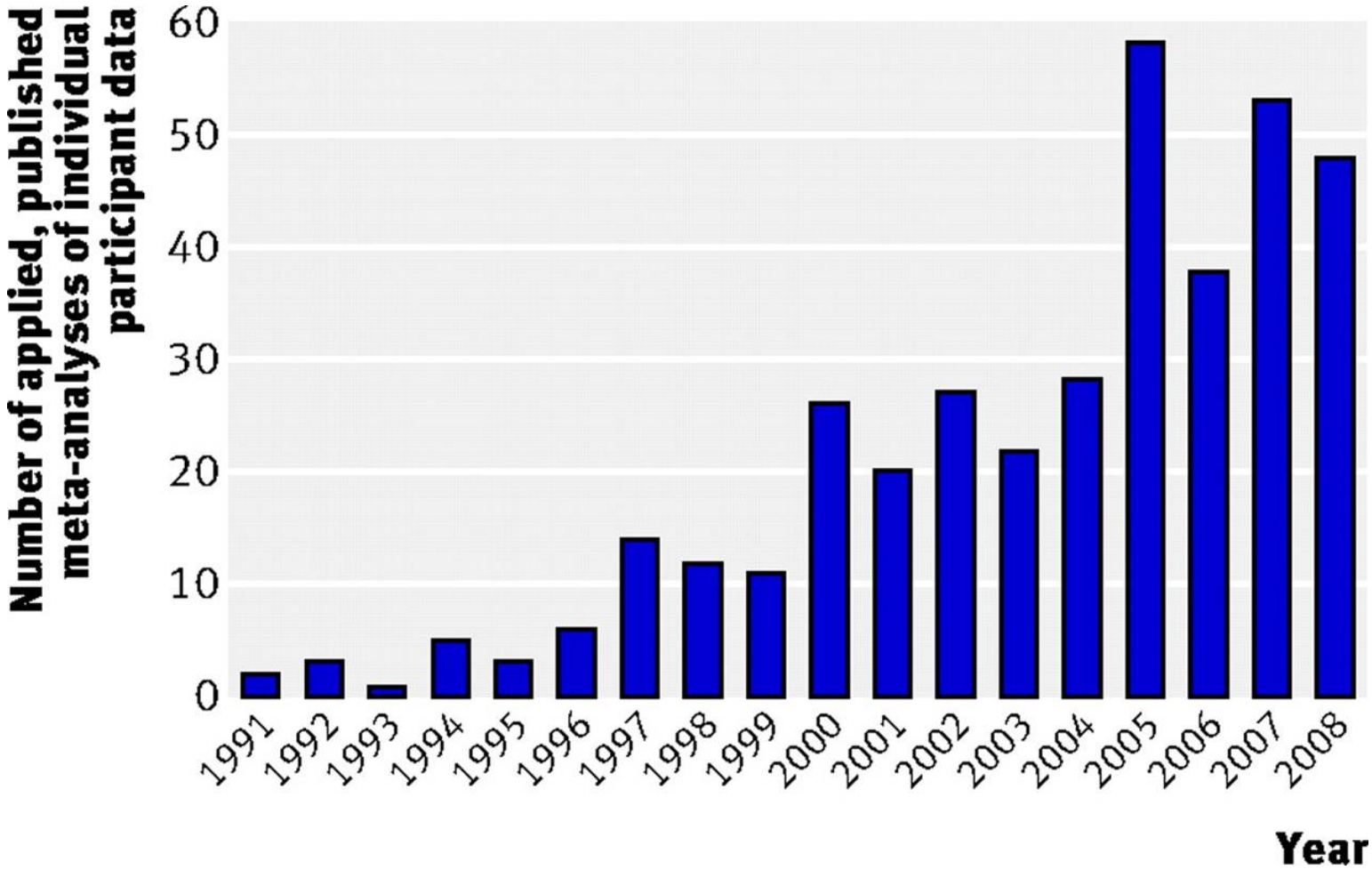
Research: Types of Data

Patient Number	Treatment	Withdrawal Time (days)	Status	Age	Gender
1	A	44	Withdrew	67	M
2	B	54	Withdrew	64	M
3	A	67	Completed	55	F
4	A	43	Completed	79	M
5	A	70	Completed	62	M
6	B	88	Withdrew	60	F
7	A	99	Completed	57	F
8	B	45	Withdrew	66	F
9	B	90	Completed	59	M
10	A	23	Withdrew	53	F

INDIVIDUAL PARTICIPANT DATA

Research: Individual Participant Data

Number of distinct, applied meta-analyses of individual participant data published up to March 2009



Riley R D et al. BMJ 2010;340:bmj.c221 (©2010 by British Medical Journal Publishing Group)

Research: Individual Participant Data

ADVANTAGES

The researcher has full control

- Inclusion criteria
- Outcomes
- Analysis

- **Summary data not available**

DISADVANTAGES

Time consuming and costly

- Who owns the data?
- Can we have the data?
  - ➢ Confidentiality / ethics
- If we get the data?
  - ➢ Data cleaning
- If we don't get the data?
  - ➢ Retrieval bias

ALL AVAILABLE EVIDENCE?

All available evidence?

Overall completeness and applicability of evidence

"We have gratefully received individual patient data (IPD) for 669 individuals (67% of individuals from all eligible trials) from the authors of five trials"

"However 376 individuals (33%) from four relevant trials could not be included in any analysis as IPD were not available and outcomes of interest were not reported in the published reports."

Phenytoin versus valproate monotherapy for partial onset seizures and generalised onset tonic-clonic seizures (Review)

Nolan SJ, Marson AG, Pulman J, Tudur Smith C

"Having to exclude data for a third of eligible participants due to lack of individual patient data and insufficient reporting in study publications is likely to impact on the applicability of the evidence, however it is difficult to quantify exactly how large this impact could be"

THE COCHRANE COLLABORATION®

All available evidence?

Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children (Review)

Jefferson T, Jones MA, Doshi P, Del Mar CB, Hama R, Thomp
I, Mahtani KR, Nunan D, Howick J, He

Mail Online

Ministers blew £650MILLION on useless anti-flu drugs: Cash spent on stockpiling treatments that 'worked no better than paracetamol'

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10 April 2014 Last updated at 01:56

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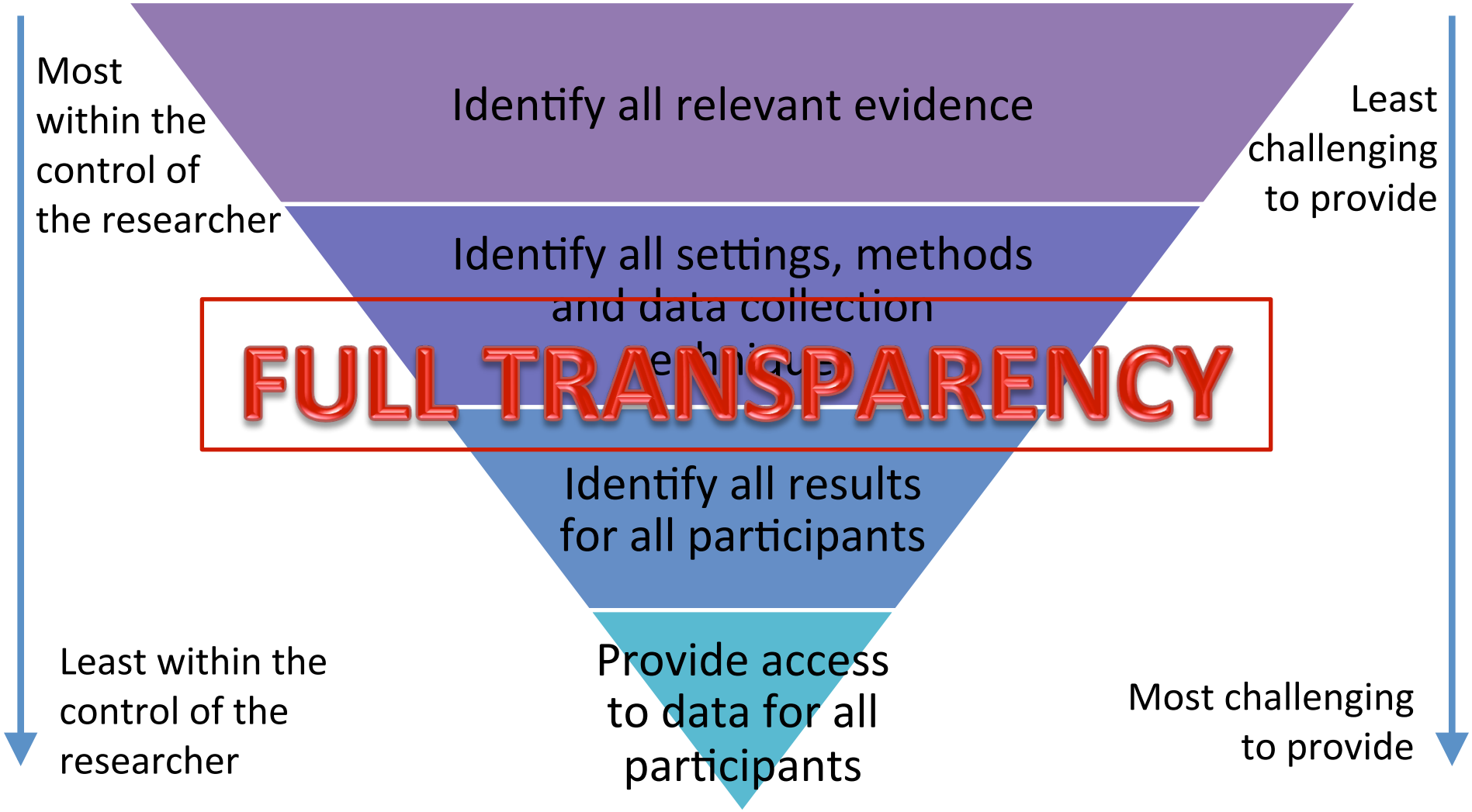
Tamiflu: Millions wasted on flu drug, claims major report

By James Gallagher
Health and science reporter, BBC News

Examples of discrepancies and reporting bias

We identified that 60% (3145/5267) of patient data from randomised, placebo-controlled, phase III treatment trials of oseltamivir have never been published. This includes M76001, the biggest treatment trial ever undertaken on oseltamivir (with just over 1400 people of all ages). Exclusion of unpublished data changed our previous findings regarding the ability of oseltamivir to reduce the complications of influenza (Doshi 2009; Jefferson 2009a). In some cases, mistakes in the attribution of adverse events were only discovered through matching summary tables with individual participant listings (Gravenstein 2013; Peters 2001;

In an ideal world for academic researchers…



What does a researcher want?

- A clear contact for research and/or data access enquiries
- Fully transparent data request process
  - Who can request data and for what purpose?
  - What are the stages of the data request process?
  - How long will each stage take?
  - Will reasons be given if access is declined?
  - If access is declined, can another request be made?
- Responses to contact in a reasonable time frame and a contact point for subsequent queries

Provide access to data for all participants

What does a researcher want?

- Data must be accompanied by essential documentation
  - Template CRFs (case report forms)
  - Data labels with descriptions
  - Desirable: related documentation such as protocols, AEs
- Data should always be anonymised with information which could identify participants removed
  - Data should still be useful (age, gender, ethnicity)
- Data should be provided in a flexible format
  - User friendly and ideally downloadable
  - Possible to combine with other data sets

BIGGEST CHALLENGE

What are the researchers obligations?

- Provide timely and detailed information
  - Research proposals / statistical analysis plans
  - Legal documentation
  - Keep the provider up to date on any changes to the planned research

- Abide by terms of data sharing agreements
  - Give the provider an opportunity to view and comment on analyses and manuscripts BEFORE submission for publication

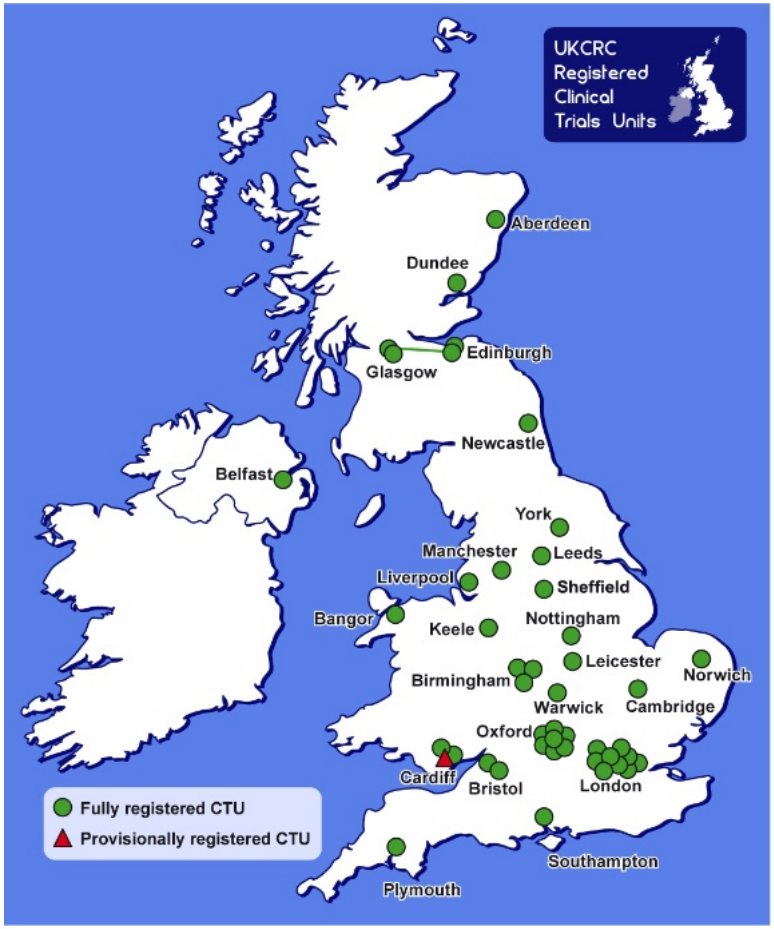
What are the researchers obligations?

- Be responsible with data that have been provided
  - Use data for purposes as agreed
  - Do not circulate to those outside of the research project without the permission of the provider
  - Don't attempt to de-identify data

- Recognise the limitations for older trials
  - The older a trial is, the more challenging to provide access to participant level data
  - Remember that the provider may not be able to provide data for valid reasons

What are the researchers obligations?

- Academic Clinical Trials Units (CTUs)
  - Currently 43 registered CTUs (http://www.ukcrc-ctu.org.uk)
  - Transparency also applies
  - Ongoing survey of the CTUs to identify current practice and inform guidelines for data sharing and transparency
  - Results and guidelines by the end of the year



Summary: Data Transparency

An academic researcher's perspective

- Access to participant data is essential for evidence based medicine
- Completely transparent process is needed
- Communication and collaboration between the research and provider throughout the process

REMINDER!

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University of Liverpool