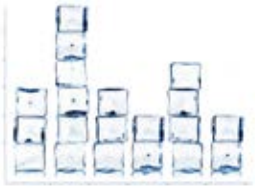

thebmj.com

- Open data campaign: thebmj.com open data
- Editor's choice: Open data: seize the moment (*BMJ* 2012;345:e7332)
- Editorial: Open access to industry's clinically relevant data (*BMJ* 2004;329:64)

THE PIONEERS OF TRANSPARENCY

This year sees the first major step towards full disclosure of clinical trial data in Europe. Here we hail the determined campaigners who pushed for this for years and the powerful people who listened. By **Ben Adams**

On 1 January 2015 a watershed moment came for clinical trial transparency when a long awaited policy change at the European Medicines Agency came into force. From this date all successful applications to the agency will lead to publication of the relevant trials' clinical study reports.

The change of policy opens a new era of transparency that has been hard fought for, over many years, by many researchers and a few very committed policy makers.[1] It will be followed, in May 2016, by the new European Union Clinical Trials Regulation, which says that the clinical information in clinical study reports should not be considered commercially confidential, thus removing the legal argument that drug companies have used until now to justify withholding large amounts of trial data.

But many battles are still to be fought. For now, the European Medicines Agency can still make restrictions and redactions if it considers data to be confidentially commercial (such as proprietary secrets about the drug molecule), although the regulator has emphasised that this is likely to happen only in a small number of cases.[2] And the new legislation will not apply retrospectively to data from drug applications made before 1 January 2015,

THE PEOPLE WHO PUSHED FOR CHANGE

PETER GØTZSCHE

Peter Gøtzsche, director of the Nordic Cochrane Centre and cofounder in 1993 of the Cochrane Collaboration, has been working tirelessly for years to get the European Medicines Agency to release more data.[3-5]

Gøtzsche worked on clinical trials and regulatory affairs in the drug industry between 1975 and 1983. Since 2007, Gøtzsche says, he has come up against much resistance and frustration, but all that changed in November 2012 when the European Medicines Agency held a workshop at its headquarters that made history. Its new head, Guido Rasi, started by announcing, "We are not here to decide if we will publish clinical trial data, only how."

"The industry representatives were stunned," Gøtzsche recalls. "I have never before seen the mighty drug industry lose a public battle so completely as during [that] afternoon."

IAIN CHALMERS

Since the 1980s the other cofounder of the Cochrane Collaboration, Iain Chalmers, and his fellow researchers have been drawing attention to the issue of under-reporting of research results, which he says is "unscientific, unethical, and uneconomic."[6 7]

At the beginning, he explains, "Our exhortations made virtually no difference," adding that no one was interested, "least of all the researchers who were guilty of this misconduct."[8] This all changed with Ben Goldacre's book *Bad Pharma* and the resultant AllTrials campaign, he says. "These have raised the profile of this scandal, and we have begun to see tangible developments towards greater transparency. This is encouraging, but the battle remains far from won. I think winning will require a combination of legislation and demands from patients and the public for greater transparency."

TOM JEFFERSON

Tom Jefferson and his fellow Cochrane reviewers worked for years to try to get access to data for Roche's H1N1 influenza treatment oseltamivir (Tamiflu) and GlaxoSmithKline's flu prevention drug zanamivir (Relenza).

Jefferson says, "In 2009 we'd never heard of clinical study reports. The first glimpse of this hidden universe came to us from an old Roche submission to the UK National Institute for Health and Care Excellence (NICE) that had been leaked to us.

"It contained fragments of four trials. Now, thanks to the Tamiflu saga, even politicians know about CSRs [clinical study reports], and EU legislation specifically mandates their disclosure—and all of this in less than five years."[8-12]

SILVIO GARATTINI AND ALESSANDRO LIBERATI

Garattini and Liberati, both researchers at the Mario Negri Institute in Milan, have helped question attitudes among academics as well as the drug industry. Liberati was a clinical epidemiologist and researcher who helped establish the Italian Cochrane Centre. He had multiple myeloma and died on New Year's Day in 2012, at the age of 57[15] In 2004 he wrote a personal view in *The BMJ* talking of his disease and the uncertainties he faced.[16] He wrote, "Research results should be easily accessible to people who need to make decisions about their own health . . . Why was I forced to make my decision knowing that information was somewhere but not available? Was the delay because the results were less exciting than expected?

"Unfortunately this is possible in a world where clinical research has become dominated by commercial interests. When you are a patient you wonder how (we) researchers can keep forgetting the principle that the priority should be collaboration for better hypotheses, not competition."

Garattini is a member of the European Clinical Research Infrastructure Network (www.ecrin.org), a not for profit clinical research project that was started in 2004. It provides clinical trial services only to clinical trials that commit to be registered, to publish results irrespective of findings, and to make their raw data available to other researchers after the completion of the trial.

But many battles are still to be fought. For now, the European Medicines Agency can still make restrictions and redactions if it considers data to be confidentially commercial

meaning that the full trial data on the vast majority of the drugs we currently use will still not be available.

However, the fact is that within two years the public and researchers will be able to read, in full, clinical study reports for all newly approved drug trials, whether conducted by industry or academia.

"It's easy to focus on the hurdles ahead, but let's stop and appreciate just how far we've already come and how quickly," said *The BMJ*'s deputy editor Trish Groves, who is responsible for all original research published in *The BMJ*. "Suddenly, everyone who used to think it was fine to hide data from clinical trials has realised that it's not OK."

To mark the first major breakthrough in this long battle, in this article *The BMJ* would like to highlight and thank the leading campaigners and policy makers in the United Kingdom and across Europe who have taken risks and persevered to help shape a new era of transparency. Of course, many other organisations have thrown their weight behind this campaign and helped to increase the pressure: the French drugs journal *Prescrire*, Transparency International, the International Society of Drug Bulletins and Berlin Declaration 2012 (http://chn.ge/13HlGYl), to name but a few. And drug companies would not of course have felt the full pressure of the need for transparency without the tireless efforts of tenacious lawyers who exposed some egregious cases of malpractice through the courts. *The BMJ* has also supported AllTrials (alltrials.net), the campaign for full disclosure of trial data, and will continue to do so.

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BEN GOLDACRE

The psychiatrist, academic, and author of two bestselling books about the misuse of science to mislead the public, *Bad Science* (2009) and *Bad Pharma* (2012), Ben Goldacre has used his anger, humour, scientific rigour, and ability to write to force the issue that has long festered within the medical community on to the public agenda. He argued, in *Bad Pharma*, that "the whole edifice of medicine is broken," because the evidence on which it was based has been systematically distorted by the drug industry. In January 2013 he cofounded, with the Cochrane Collaboration, *The BMJ*, and others, AllTrials (alltrials.net), a group that continues to campaign for total disclosure of trial data. He explains that the effort to put the transparency issue on the public agenda has been slow not just because of resistance from the drug industry but also because of a "force field of tediousness" around the idea of data transparency that has long discouraged public scrutiny. Regulators and professional bodies also failed to draw the attention of policy makers to the issue and in some cases actively denied that there was a problem.

PETER DOSHI

Peter Doshi, assistant professor at the Department of Pharmaceutical Health Services Research at the University of Maryland's School of Pharmacy in Baltimore and an associate editor at *The BMJ*, leads the Restoring Invisible and Abandoned Trials (RIAT) initiative.

In 2013 Doshi and his university colleagues called for trial sponsors and investigators of abandoned studies to publish (or republish) their data and proposed a system for independent publishing if sponsors failed to respond. He was impressed by the European Medicines Agency's inclusive process for developing its policy but disappointed that the policy first proposed was watered down.

He says, "I still remain uncertain about what has been achieved, because it still remains promissory in nature. Until other groups go out and try to access the data—and let all of us know how easy or hard it is—we will not know whether we are where we need to be."

DOUGLAS ALTMAN

The founder and director of the Centre for Statistics in Medicine and Cancer Research UK's Medical Statistics Group, Douglas Altman, has worked to ensure that the methods and results of clinical and epidemiological studies are of high quality and, most importantly, are reported fully and honestly.[13]

He is behind the development of many research reporting guidelines, such as the CONSORT (Consolidated Standards of Reporting Trials) statement, which aims to alleviate the problems arising from inadequate reporting of randomised controlled trials, and the EQUATOR (Enhancing the Quality and Transparency of Health Research) online network (www.equator-network.org), which was launched in 2008 and describes itself as "the first coordinated attempt to tackle the problems of inadequate reporting systematically and on a global scale."

"A research report is the only tangible evidence that the study was done; if research is not published it might as well not have been done," Altman said as EQUATOR launched a print version of its reporting guidelines in October 2014.

KAY DICKERSIN AND TOM GREENE

Kay Dickersin, professor at the Johns Hopkins Bloomberg School of Public Health, Baltimore, and director of the Center for Clinical Trials and the US attorney Tom Greene started digging for the missing data on Pfizer's pain drug gabapentin (Neurontin). Green and Dickersin found that Pfizer and its development partner Warner-Lambert had used selective outcome reporting for trials of the off-label use of gabapentin.[14] They say that this practice "threatens the validity of evidence for the effectiveness of off-label interventions."

Pfizer and Warner-Lambert had to pay $325m (£210m; €265m) in May this year to settle allegations that they fraudulently marketed the drug for uses it was not licensed for.

IMPORTANT PEOPLE WHO LISTENED

GUIDO RASI

The executive director of the European Medicines Agency, Guido Rasi, set out his intentions to increase transparency in 2012.[17]

The former director general of the Italian Medicines Agency and a teacher and researcher at the University of California, Berkeley, told *The BMJ* that although the new rules coming into force in 2015 were only one "step in a process," they did "set a new standard for transparency in public health and pharmaceutical research and development."

He believes, despite the delays, that the agency "can certainly be proud to have delivered" on its promise and has contributed to the "general drive towards more transparency in Europe."

BEATE WIESELER

Beate Wieseler and her colleagues from Germany's health technology assessment agency, the Institute for Quality and Efficiency in Health Care (IQWiG), published a paper in 2013 showing that unpublished clinical study reports were more than twice as likely as publicly available sources to provide complete information on outcomes relevant to patients.[18]

This finding helped add momentum to the transparency debate, with IQWiG also taking the bold step of signing the AllTrials petition in the same year.[19]

Wieseler was also a coauthor of a 2010 study of the available data on the antidepressant reboxetine.[20]

PATRICK VALLANCE AND ANDREW WITTY

The president of pharmaceuticals research and development at GlaxoSmithKline, Patrick Vallance, has been at the coalface of GSK's drive toward transparency. An important step came in March 2013 when it was the first (and still, at the time of publication, the only) drug company to sign the AllTrials register.

It was Andrew Witty, chief executive of the London based firm, who took this step, but Vallance, a former academic, has been the main champion of transparency on the ground, while his peers across the industry have not been so welcoming of opening up data to the public.

Vallance says, "I know concerns have been raised about greater transparency introducing a competitive disadvantage, but I don't see it. I see a compelling societal need to do it. Historically, industry hasn't done a good enough job to be transparent."

"Suddenly, everyone who used to think it was fine to hide data from clinical trials has realised that it's not OK"

SARAH WOLLASTON

The Conservative member of the UK parliament for Totnes, Devon, and now chair of the House of Commons Health Committee, Sarah Wollaston, a former GP, has been a champion of the transparency debate in the United Kingdom.

Wollaston says that commitment to data publication was resisted at all stages on the grounds of the perceived threat to the future of UK pharmaceutical companies.

She said, "I'm delighted that by repeatedly reintroducing it at every opportunity the government finally conceded and that need for transparency is now recognised in our own legislation, as well as at EU level."

Wollaston also notes that the lack of scientists and former health professionals in the House of Commons "can make it difficult to drum up enthusiasm for debates about the importance of evidence based medicine."

ILARIA PASSARANI

The head of Food and Health Department at the European Consumer Organisation (BEUC) and a scientific researcher at Maastricht University, Ilaria Passarani fought hard to ensure that the European Medicines Agency kept its promise on opening up data.

As the signatory of a strongly worded letter to Rasi last May, when it looked as if the agency might water down its policy on transparency, she argued passionately that it should not renege on its deal.[21] She said that the agency was honour bound to do this so as to "restore public trust and confidence in the Agency by implementing a meaningful proactive publication of data and by enabling independent re-analysis." Trust was a major motive for the agency when it eventually pushed its plans through.

EMILY O'REILLY

As the new European Union ombudsman investigating poor and failed administration in EU institutions, Emily O'Reilly got both the European Medicines Agency and the European Parliament to accept that clinical information in drug trials should not be considered commercially sensitive or confidential and also shouldn't be redacted from the clinical study reports.

Like Passarani, she too was concerned at the agency's delays in mid-2014 and put Rasi and the agency under intense pressure to go ahead with its plans on data disclosure.

In a letter to Rasi, O'Reilly, an Irish national and former journalist, said that if the agency did not allow a new transparency policy this would "undermine the fundamental right of public access to documents established by EU law."[22]

GLENIS WILLMOTT

The UK Labour member of the European Parliament and rapporteur for the EU Clinical Trials Regulation fought hard to get the transparency agenda into law, citing scandals such as the one that emerged in the 1980s over the anti-arrhythmic agent lorcainide, in which over 100 000 people died unnecessarily because data from an early trial were not published.[23]

Willmott says that her fellow MEPs did understand the issues but that their positions started at complete opposite ends of the spectrum, some wanting every single piece of raw data published, while others wanted even less transparency than the European Commission had proposed.

She says, "One of my main achievements was bringing the MEPs from different political groups together and agreeing on a sensible way forward that would guarantee meaningful transparency for clinical trial results."

Transparency in drug company payments to doctors

Rebecca Coombes sums up the new UK system for public disclosure of payments from drug companies to doctors

Since the new year drug companies in the United Kingdom have begun recording any payments they make to doctors for certain services, such as chairing a meeting, in advance of plans to disclose the data to the public. This move echoes similar initiatives in the United States and the Netherlands designed to bring transparency to financial relationships between doctors, teaching hospitals, and drug companies. The information gathered over the next 12 months, and in subsequent years, will be uploaded to a publicly searchable database due to launch in July 2016.[1]

The stimulus for this new openness comes from Europe and has been adopted in a new code by the Association of the British Pharmaceutical Industry (ABPI), which covers 121 (98%) drug companies in the UK. In wider Europe 33 countries are covered by a new disclosure code agreed by the European Federation of Pharmaceutical Industries and Associations.[2]

Transparency "is no longer a 'nice to have': it is a societal expectation," said Andrew Powrie-Smith, speaking as director of ABPI Scotland.[3]

This shift is significant because there is no overarching system in the UK for regulating sponsorship, payments for expert advice, and other benefits that doctors and other healthcare professionals receive from industry. Even the new ABPI platform—novel as it is—will only provide a partial disclosure of interactions with industry. The association doesn't represent medical device companies, or private hospital chains, for example, so any payment from these industries to doctors will not be recorded. Nor does the ABPI have the power to compel doctors to make a full disclosure of their conflicts of interests, including shares in commercial companies. The General Medical Council does have guidance on conflicts of interest but it does not currently oblige doctors to declare these on the medical register.

GETTY IMAGES

Initial signs are encouraging—one drug company has already asked 500 healthcare providers to sign new contracts and only two have refused

How does the new database work?

Drug companies have, from 1 January, changed the way they contract with doctors and other healthcare professionals. If an individual agrees to do paid work for a company, they should sign a contract granting permission for the payment data to be shared publicly (although they can back out at any time). Initial signs are encouraging—one drug company has already asked 500 healthcare providers to sign new contracts and only two have refused.

After the database launches in July 2016 anyone will be able to search for payment data by health professional name, healthcare organisation, place of work, city, or drug company name, or they can download the entire dataset. The data are all recorded on a central platform on the ABPI website and will be available for at least two years.

What will be disclosed?

Any transfer of value to a doctor or healthcare professional either of a "direct" or "indirect" nature. There is no minimum value unlike, for example, in the Netherlands, where payments of more than €500 (£395; $615) are recorded. Indirect payments include donations to charity made on a doctor's behalf and payments to third parties, such as drug companies paying someone to organise an event for a doctor or healthcare professional. Two types of direct payment need to be disclosed—"events," which includes registration fees, travel, and accommodation, and "services and consulting," which includes, for example, fees for speaking at and chairing meetings, training, and advisory board meetings, and expenses.

Can doctors opt out?

Yes, and this option could significantly weaken the database's "brand" as a transparency tool. European and UK data protection legislation is a major barrier to full disclosure of payments to doctors because drug companies must get an individual's permission before publishing payment data. This is not the case in the US or the Netherlands, where separate legislation over-rides data privacy in the case of their open payment databases.

Once the data pass to the ABPI for publication, it will send individuals a statement of the payments that will be published under their names. Clinicians then have four weeks to query this record. They can also opt out at this stage, even if they originally signed a contract with the drug company that paid them. The company will be notified by the ABPI that the clinician has withdrawn their permission.

What happens when a doctor opts out?

In an ABPI consultation with 1000 healthcare professionals, 86% said they were in favour of public disclosure of payments. "Early indications are that the initial response from professionals has been positive. We want this to become the professionally-accepted norm," an ABPI spokesperson told *The BMJ*. But he acknowledged that a physician's decision to opt out of disclosure may change a drug company's view of "who they work with over time."

In law, consent to share the data must be "freely given," so a drug company cannot use threat of withdrawal of payment to induce clinicians to sign. The ABPI will annually publish the number of people who did not give consent to share payment data and the aggregate amount.

What are doctors saying?

The president of the Royal College of Physicians, Jane Dacre, welcomes the move. "The ABPI database is timely and reflects the growing need for physicians to be open about their relationships with pharmaceutical companies. This openness is in the best interest of the patients we serve, and I hope that it will become a mandatory responsibility in the near future," she told *The BMJ*.

Separate moves are under way to compel doctors to make their own declarations on a database led by the profession. A working group, including representatives from the Royal College of Physicians and *The BMJ*, is set to meet this month to draft a code of conduct governing interactions with industry. A final version will be published in the summer.[4]

Attempts have also been made to produce independent registers by which people can declare any conflicts of interest (financial or otherwise). One such effort is Who Pays This Doctor? (www.whopaysthisdoctor.org), which currently has fewer than 150 doctors registered.

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