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GSK backs campaign for disclosure of trial data

GlaxoSmithKline and Roche won't disclose their results

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GlaxoSmithKline (GSK) and Roche have declared they are willing to disclose their trial data. But not like the European Medicines Agency, which from January 2014 will provide public access to the full clinical study reports for all new drugs, the corresponding protocols, and the raw data in statistical programmes and the codes - without conditions.

If we shared our data, it would lead to tremendous progress for public health (1). But this is not what GSK (2) and Roche have announced (3). The companies will establish committees of "experts" that will decide whether people can get access to patient level data. And GSK will only allow access after it has published the trials. What about trials that never get published?

Does anyone really believe that the companies will allow access to the data if the research could potentially show that one of their blockbusters is so dangerous that the drug agencies will withdraw it? Or that Roche is willing to run the risk that governments won't buy any more Tamiflu after they have seen the data?

Instead of providing the full clinical study reports, GSK will take the trouble to strip out all patient level data. This means we won't be able to detect when GSK has manipulated their analyses, which they and other companies often do. Here are some examples related to GSK:

1) Not only GSK, but also Eli Lilly and Pfizer, added cases of suicide and suicide attempts to the placebo arm of their trials of antidepressants, although they didn't occur while the patients were randomised to placebo (4-8). Professor David Healy pointed this out, and it wasn't denied by the companies but GSK instead called Healy's analysis "scientifically invalid" and "a disservice to patients and physicians" (9).

2) Cases of suicidality were coded as hospital admission, drop-out, worsening of depression or emotional lability by several companies (4). In the BBC Panorama series about paroxetine, Glaxo's spokesperson, Dr Alastair Benbow, denied in front of a running camera that paroxetine could cause suicidality or self-harm but one month later he sent trial data to the UK drug regulator that showed exactly this, which immediately led to a ban on using the drug in children. GSK stated that they "detected no signal of any possible association between Paxil and suicidality in adult patients until late February 2006," but US government investigators found that the company had the data back in 1998 (10).

3) GSK denied for years that paroxetine was habit forming, although paroxetine led to withdrawal reactions in 30% of the patients in the original licence application (11). In 2003, GSK quietly and in small print revised its previous estimate of the risk of withdrawal reactions in the prescribing instructions from 0.2% to 25% (12), a 100 times increase.

4) Glaxo's trial 329 of paroxetine in children and adolescents was negative for efficacy on all protocol specified outcomes and positive for harm but data massage produced four statistically significant effects after splitting the data in various ways (13,14). The paper falsely stated that the new outcomes were declared a priori. At least eight children became suicidal on paroxetine versus one on placebo, but in the published paper, five cases of suicidal thoughts and behaviour were listed as "emotional lability" and three additional cases of suicidal ideation or self-harm were called "hospitalisation." The abstract of the paper concluded that "Paroxetine is generally well tolerated and effective." Trial 329 was widely believed and cited (184 times by 2010), and it lured many doctors into using paroxetine for childhood depression, although the drug is harmful. The trial has not been retracted despite repeated calls on the journal to do so. The Attorney General of New York State sued GSK in 2004 for repeated and persistent consumer fraud in relation to concealing harms of paroxetine, and GSK was required as part of a legal settlement to make the individual patient level data from that trial available, but they didn't do so. Only when Dr Peter Doshi contacted the New York Attorney General's office in 2012 and said that the data weren't there, did the data get posted. The clinical study report is now available on GSK 's home page (http://www.gsk.com/media/resource-centre/paroxetine/paroxetine-paediatri...) and it contains revealing narratives of serious adverse experiences. For some unexplained reason, the four authors of GSK's study report have been replaced by xxxxx x xxxxxx, B.S.*, xxxx xxxxx, Ph.D.*, xxxxx x xxxxxxxxxx, B.S.*, xxxxxxxx xxxxx, M.S.**.

5) An FDA scientist found that the adjudication of cardiovascular events in the RECORD trial of rosiglitazone was seriously flawed. He found many missing cases of cardiac problems that favoured rosiglitazone four to one (15,16) and that rosiglitazone increased cardiovascular risk, in contrast to Glaxo's results. He concluded that the case report forms are essential for understanding a study and noted that, "even with blinded adjudication, biased referral for adjudication of cases and data by unblinded investigators and site monitors may lead to biases in event rates" (16). In 1999, the company, then known as SmithKline Beecham, completed a trial that found more cardiac problems with rosiglitazone than

with pioglitazone, but according to an internal email, "These data should not see the light of day to anyone outside of GSK" (15,17). The company spent the next 11 years trying to cover them up (17).

6) Because of concerns that long-acting beta-agonists might increase asthma-related deaths, the FDA asked GSK to carry out a large trial of salmeterol, the SMART trial. The trial period was 28 weeks, but the investigators could - if they wanted - report serious adverse in an additional 6 months period. The FDA assumed that the data they reviewed stemmed from the trial period, and only when the agency asked, did GSK reveal it had included the follow-up data. There was no statistically significant increase in asthma-related deaths in Glaxo's analysis, whereas the risk was four times higher for the trial data, which was statistically significant (18).

7) In 2008, Professor Jens Lundgren received a death threat at the international AIDS congress in Mexico City in an SMS before he presented data showing that Glaxo's £600 million drug, abacavir, almost doubles the risk of heart attacks (19,20). As soon as Lundgren had finished his talk, he was escorted to the airport with eight body guards. It was not possible to trace where the death threat came from.

Right now, the drug industry fights tooth and nail against access to trial data. In relation to the proposed revision of the EU Clinical Trials Directive the industry argues that a summary of the results is all that is needed, although we know we cannot trust summaries. We cannot trust the industry either when it says it's committed to full transparency (3):

"Roche is supporting the European Medicines Agency (EMA) in its commitment to the proactive publication of data from all clinical trials supporting the authorisation of medicines."

If Roche was serious about this, then why the obstacles?

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