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OBSERVATIONS

OPEN DATA CAMPAIGN

Withdraw approval for Tamiflu until NICE has full data

In an open letter sent this week to Professor Sir Michael Rawlins, chairman of the National Institute for Health and Clinical Excellence, *BMJ* editor Fiona Godlee calls on him to withdraw approval for oseltamivir until NICE has received and reviewed the full clinical trial data and those anonymised data are made available for independent scrutiny. The letter is the latest addition to the *BMJ*'s open data campaign, which aims to achieve appropriate and necessary independent scrutiny of data from clinical trials. Here we publish Fiona Godlee's letter and Mike Rawlins's response (*BMJ* 2012;345:e8420)

Fiona Godlee *editor, BMJ*

Dear Mike

I wanted to congratulate you on all you have achieved with the National Institute for Health and Clinical Excellence (NICE) in the past 10 years, now that your time as its chairman is coming to an end. However, I also wanted to ask you about something that I have found increasingly puzzling. Why does NICE not require access to all the clinical trial data on a drug when it is making a decision to approve the drug for purchase by the NHS? And given the European Ombudsman's ruling against such data being commercial in confidence, why does NICE not make public the full information on which its decisions are based?

I ask this because, as you will know, the *BMJ* has been trying to help the Cochrane Collaboration gain full access to the data on oseltamivir (Tamiflu) in order to complete the systematic review commissioned by the National Institute for Health Research (NIHR) in 2009.[1-3] Roche gave a public commitment to make the full clinical study reports available for independent scrutiny, but has persistently failed to honour that commitment.[4] Last month, faced with growing public pressure, Roche made a different and wholly inadequate offer, which the Cochrane group has rightly declined (bmj.com/tamiflu). So on behalf of the Cochrane review group and the public, I am now turning to you.

NICE first approved oseltamivir for use within the NHS in guidance published in February 2003 (technology appraisal (TA) 58). The data that form the basis of this guidance, and the updated guidance in 2008 (TA 168) and 2011 are not in the public domain. Instead, we (the medical profession and the public) are reliant on the hard won crumbs of information gleaned through dogged investigative work by the Cochrane reviewers. The picture they are managing to piece together is not reassuring. Indeed, it suggests that industry has almost complete control over the evidence base on which crucial public decisions are being made.

A full account of what the Cochrane review group has so far uncovered about the basis for NICE's decisions on oseltamivir will be published in the *BMJ* shortly. But here are a couple of examples that have prompted me to write to you. NICE's 2003 guidance (TA 58) was based on an NIHR-Health Technology Assessment (HTA) review by Turner and colleagues.[5] In this review, appendix 1 lists study M76001 among the excluded studies. This is the biggest treatment study of oseltamivir ever undertaken and remains unpublished. No reasons are given for excluding it from the analysis, but the reference cites a personal communication with Roche (unpublished). It would seem that Roche applied inclusion criteria on behalf of NICE's HTA reviewers.

NICE's 2009 guidance (TA 168) was based on the NIHR-HTA review by Burch and colleagues. [6] The reviewers' extraction sheets were filled in by Roche.

The consequences to health of these practices are hard to unpick. But as one indication of the extent to which the public is being misled, Roche can claim in Europe that oseltamivir reduces the rate of complications such as bronchitis and pneumonia, but it is not allowed to make this claim in the United States. The US Food and Drug Administration performed a more thorough assessment of the trial data and found no good evidence of an effect on rates of complications.[2]

The Cochrane reviewers now know that there are at least 123 trials of oseltamivir and that the majority (60%) of patient data from phase 3 completed treatment trials by Roche remain unpublished. There are concerns on a number of fronts: the likely overstating of effectiveness and the apparent under-reporting of potentially serious adverse effects. Meanwhile, the influenza season will soon be upon us and the NHS will again be spending millions of pounds on a drug for which the evidence base is almost entirely hidden from public view. NICE is failing in its responsibilities in allowing a drug

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like oseltamivir to be purchased, at vast cost to the NHS, and used at unknown effectiveness and safety by the public, without anyone apart from Roche having seen the full data.

It is hard to imagine anyone reading this who would conclude that this is acceptable. I am forced to also conclude that NICE is colluding with the status quo by failing to take a harder line. Nor is this likely to be an isolated incident. The increasing number of drugs approved by NICE where data have been found to have been hidden (for example, rosiglitazone)[7] suggests that industry managing the approval process in its own rather than the public's interests is more likely to be the norm than the exception. NICE's prized reputation for objectivity will suffer if this proves to have been the case and if NICE takes no action.

The recent announcement from the European Medicines Agency that it will make all trial data openly available from 2014 is hugely welcome, but it applies only to new drugs so will not immediately resolve the problem we are seeing with oseltamivir and other drugs already in use. It is my understanding that NICE can ask for additional information from a company, but in the case of Tamiflu you did not do so. As a vocal fan of NICE since its inception,[8] I am sorry to see you outshone by another organisation that has shown the necessary muscle when confronted with drug manufacturers who withhold clinical trial data. When the Institute for Quality and Efficiency in Healthcare (IQWIG) in Germany realised that it was not being given the full story on Pfizer's drug reboxetine, it told the company that it would only approve the drug for reimbursement if all the data were provided. Pfizer delivered up the data, nearly three quarters of which had never been published.

Analysis of the full dataset showed the drug to be ineffective and possibly harmful. Although this was a bad outcome for Pfizer, I think you will agree that it was an important victory for public health. IQWIG's published systematic review and meta-analysis on reboxetine is the only place that doctors and patients can access a complete picture of the results of all clinical trials on this drug.[9] This episode shows the crucial role of national health technology appraisal in ensuring that all evidence is made available for doctors and patients to make informed decisions while so many clinical trials remain inaccessible through other means.

Mike, you are in a unique position in the UK and are rightly looked to from around the world for leadership on these issues. When NICE approves a drug for NHS use, NICE should also obtain the data that support its use and should make those data available in anonymised form for independent scrutiny. NICE should also mandate the access to post marketing studies, given there are instances (for example, with rosiglitazone) where new evidence overturns the initial guidance.

Now that serious doubts have been raised about the evidence behind claims for oseltamivir's effectiveness and safety, I am asking you to withdraw approval for oseltamivir until NICE has received and reviewed the full clinical trial data and those anonymised data are available for independent scrutiny.

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