OPEN DATA CAMPAIGN **Fiona Godlee**

Withdraw approval for Tamiflu until NICE has full data

Dear Mike

I wanted to congratulate you on all you have achieved with the National Institute for Health and Clinical Excellence (NICE). 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 deciding 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) 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 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 by the Cochrane reviewers. The picture they are piecing 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 This is the biggest treatment study of oseltamivir ever undertaken and remains unpublished.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.

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 III 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 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 with oseltamivir. 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.

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.

Fiona Godlee is editor, *BMJ* **fgodlee@bmj.com**

A longer version of this letter, with references, is on bmj.com. See also www.bmj.com/tamiflu.

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In an open letter sent this week to Professor 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. Here we publish Fiona Godlee's letter and (overleaf) Mike Rawlins's response (*BMJ* 2012;345:e8420)

"NICE is failing in its responsibilities in allowing a drug like oseltamivir to be purchased, at vast cost to the NHS . . . without anyone apart from Roche having seen the full data"

BMJ OPEN DATA CAMPAIGN

OPEN DATA CAMPAIGN **Michael Rawlins**

We will look again at NICE appraisal of Tamiflu

Dear Fiona

Thank you for your kind words as my tenure of office draws to a close. To have had the opportunity to chair NICE, since its inception, has been the most rewarding part of my professional career. Any success, however, has been a result of the commitment and expertise of the staff, the massive contributions of the professions, as well as (of course) support from the *BMJ*.

Your premise that NICE does not, in its technology appraisals programme, require access to all clinical trial data is wrong. On the contrary, we require full access to all the information that is available to marketing authorisation holders of medicines when they are subject to a NICE technology appraisal. The medical director of the company involved in making an evidence submission to NICE is asked to sign a declaration to confirm "that all relevant data pertinent to the technology appraisal has been disclosed to the Institute." Pharmaceutical physicians are very well aware of their obligations, and if a medical director were knowingly to withhold relevant data, the institute would report the matter to the General Medical Council. You will recall that some years ago a pharmaceutical physician was erased from the medical register for failing to meet his obligations, albeit in a matter relating to an advertisement rather than a NICE appraisal. The institute's staff also examines the European Medicines Agency's "European Public Assessment Reports" to confirm that we have been provided with all relevant information.

I am not sure what additional measures we might take to be certain that we have access to all relevant data. The notion that legislation would help is, I am afraid, naive. From my experience as chair of the Committee on Safety of Medicines (during the 1990s), in those few instances of failure to disclose relevant data, fault lay not with the UK subsidiary but with the main company based outside the UK. As the Conservative MP Stephen Dorrell reminded us earlier this week, when Andrew Dillon and I gave evidence to the Health Select Committee, the British parliament's reach stops at the English Channel!

Nor can I accept your premise that we fail to make public the information on which our decisions are based. As you know, there is an expectation that the guidance we produce on new medicines is provided as close as possible to their launch in the UK. It is for that reason that we receive evidence submissions several months in advance of receipt of marketing authorisation. We therefore allow companies to designate some of the information as provided in confidence. This allows for subsequent publication in peer reviewed journals as well as for companies to provide data that are commercially sensitive.

The arrangements for the submission of confidential information are laid out in our process documents.[1] We expect individual companies to follow these guidelines, and we spend a significant amount of time instructing companies to minimise the amount of information marked as confidential. When a submission concerns unpublished clinical data, the agreement specifically requires companies, as a minimum, to release what would normally be included in a CONSORT (or PRISMA) compliant abstract; and we state that this will be publicly disclosed. Our agreement further allows NICE to "quote publicly from either a full report or an abstract of unpublished trials, where the date of release, by NICE, of data from such reports/abstracts is not less than 12 months after the sign-off by the company of the trial report."

In respect of your comments about our appraisals of oseltamivir, I am making further inquiries about the details of the assessment. As you know, the assessment report was prepared by the Centre for Reviews and Dissemination at the University of York, and I will write again when I have this additional information. It is clear, however, from the monograph[2] underpinning TA 58 that rather than study M76001 having been completely excluded, data from the trial were used as part of an analysis of complication rates. The monograph[3] that informed TA 168 includes the M76001 trial, citing an abstract by Treanor (2000b) and additional data provided by Roche as source of the information. The authors of the 2009 monograph indicate in their discussion that publication bias, and particularly time lag publication bias, cannot be ruled out, and they tested the impact of publication bias (excluding unpublished trials) on the results of the meta-analyses. I have not yet found reference to your suggestion that the "reviewers' extraction sheets were filled in by Roche."

"We require full access to all the information that is available to marketing authorisation holders of medicines when they are subject to a NICE technology appraisal"

Without full consideration of what you suggest has been uncovered by the Cochrane review team, it would be inappropriate for NICE to withdraw its guidance on amantadine, oseltamivir, and zanamivir for the treatment of influenza. The additional clinical trial data might, for example, support the use of oseltamivir under the circumstance we have already proposed. In that case, patients would be damaged by precipitate withdrawal of our guidance.

I can reassure you, though, that we will review all new information that comes to light, and consider whether it is necessary to reappraise oseltamivir, as well as its competing interventions, earlier than currently planned.

Michael Rawlins is chairman, National Institute for Health and Clinical Excellence

References are in the version on bmj.com.

See also www.bmj.com/tamiflu.

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