Tamiflu, clinical trials and the Public Accounts Committee

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Steve Chaplin discusses the problem of getting access to data from unpublished trials, as highlighted in a report on the stockpiling of Tamiflu.

The number one risk on the Government’s national risk-assessment for civil emergencies, ahead of both coastal flooding and a major terrorist incident, is the risk of pandemic influenza’, the House of Commons Committee of Public Accounts says in its report, Access to Clinical Trial Information and the Stockpiling of Tamiflu (December 2013).

The Public Accounts Committee (PAC) is primarily concerned with value for money, which is why it began its inquiry into the stockpiling of Tamiflu (oseltamivir) worth £424 million after stock to the value of £74 million was written off because its quality could not be assured.

But questions about Tamiflu inevitably raise the spectre of incomplete evidence and the wisdom of spending so much money on a drug of dubious efficacy.

**Tamiflu stockpile**

The PAC notes that the case for stockpiling antivirals in case of a flu pandemic was made on judgement rather than evidence. In 2008, the DH based its decision on a business case assuming that treating 80 per cent of the population with Tamiflu would reduce complications and mortality by 40–50 per cent. This was despite ‘only limited evidence and widespread disagreement among regulators and other bodies internationally’ of any such benefit.

Chief Medical Officer Professor Dame Sally Davies defended the business case as ‘carefully modelled’ on previous pandemics and supported by expert opinion.
Doubt remained, however, about the incremental benefits of increasing population coverage above 25% per cent because individuals at greatest risk would be treated first.

Tamiflu was distributed around the country during the 2009 pandemic. Of the stock returned unused, some lacked documentation providing assurance that it had been correctly stored (at 25°C or below). This was attributed to a lack of the necessary equipment at a time when the pandemic was developing rapidly. However, the Department did not throw out the dubious stock: 2009 was a cool summer so the tablets were kept back for use in an emergency and dumped only when their shelf-life expired. Guidance on correct storage has now been sent to primary care providers.

The PAC concluded that the DH should review the appropriate level of population coverage before spending another £49 million on maintaining the stockpile, and note that Tamiflu’s patent expires in 2016.

Unpublished data
The problem of unpublished clinical trials and publication bias has been aired on and off since 1986, when a comparison of published and unpublished trials revealed disparities in survival after chemotherapy for ovarian cancer and multiple myeloma. Clinical trials of Tamiflu have gone unreported and data have been withheld, prompting the BMJ to conduct a campaign to persuade Roche to live up to its 2009 promise to release all its trial data.3

But this has been more a scientific than a public debate. So the PAC was ‘surprised and concerned to discover that information is routinely withheld from doctors and researchers about the methods and results of clinical trials on treatments currently prescribed in the United Kingdom’. It concluded that without ‘adequate action being taken by government, industry or professional bodies’ this is now a serious problem.

The PAC noted the lack of consensus on the effectiveness of Tamiflu, a problem rooted in access to data from unpublished clinical trials. The Medicines and Healthcare products Regulatory Agency (MHRA) insisted that European regulators had received all the relevant information, but the Cochrane Collaboration provided evidence that data were incomplete or missing entirely from major trials.

The Cochrane Collaboration is now working on the data belatedly released by Roche, and the PAC recommended that ‘the Department, MHRA and NICE should consider whether it is necessary to revisit previous judgements about the efficacy of Tamiflu’ when the review is complete.

Transparency
The wider issue of data transparency is now in the public as well as the scientific domain. The PAC made three recommendations affecting access to trial data – critically including past as well as present studies and requiring the MHRA and NICE to utilise all available data, not just the readily accessible information:

- The DH should ensure that the full methods and results are available for all trials on all uses of all treatments currently being prescribed, and that there is clear and frequent audit of how much information is available and how much has been withheld.
- The DH and the MHRA should ensure, both prospectively and retrospectively, that clinical trials are registered and that the full methods and results of all trials should be available for wider independent scrutiny, beyond the work undertaken by regulators during the licensing process.
- NICE should ensure that it obtains full methods and results on all trials for all treatments which it reviews, make all this information available to the medical and academic community, and routinely audit the completeness of this information. NICE and the MHRA should have a formal information-sharing agreement.

This is a big step towards full data disclosure but the struggle against secrecy is far from over. A recent analysis of the US clinicaltrials.gov register showed that registration alone is not enough: 29 per cent of 585 trials involving almost 300 000 patients had been registered but not published and 78 per cent of these had no results available.4 The proportion of trials funded by the pharmaceutical industry that were unpublished was 32 per cent compared with 18 per cent for the rest.

Some pharmaceutical companies have recently taken steps to open up access to their data. Boehringer Ingelheim, GSK, Roche, Sanofi and VIIV Healthcare have signed up to www.clinicalstudydatarequest.com, a portal through which requests for access are adjudicated by an independent panel.

The EU is proposing to introduce mandatory registration of all future trials, with compulsory publication of at least summary results in a register within one year of completing the trial.5 However, the release of regulatory data by the European Medicines Agency (EMA) has been challenged by AbbVie and InterMune; the latest court ruling favours the EMA but the action remains open.6

Conclusions
The financial consequences of decision-making based on incomplete evidence have at last come to light as the wisdom of spending millions stockpiling Tamiflu is questioned. Government, the EU and regulatory agencies are now moving towards greater transparency, along with some pharmaceutical companies.

The prospects for future disclosure are promising but, as witnesses to the PAC inquiry pointed out, the information about the drugs being prescribed today is in the trials conducted in the past. Nothing short of full access to data held by regulators will tell us if current treatments are truly evidence based.6

References

Declaration of interests
None to declare.

Steve Chaplin is a pharmacist who specialises in writing on therapeutics