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EDITORIALS

Statins for people at low risk

Independent review of the trial data is an essential next step

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Statins are the UK's most commonly prescribed drugs and are among the most widely prescribed drugs globally.[1] Though their use in people at high risk of stroke and heart disease is uncontroversial, recent recommendations to treat much larger numbers of people at low risk[2 3] have caused a storm of controversy.[4] Most hotly debated are the nature and frequency of side effects of statins and whether arguably small gains in life expectancy are worth the risk.[5 6]

In August 2014 an expert panel convened by *The BMJ* called for the anonymised individual patient data from the statins trials to be made available for independent scrutiny.[7] Our subsequent inquiries, guided by an expert advisory group (www.bmj.com/campaign/statins-open-data) have revealed the worrying extent to which these data remain hidden.

In reply to a letter from *The BMJ*, Rory Collins and colleagues of the Cholesterol Treatment Trialists (CTT) collaboration in Oxford confirmed that their meta-analyses have so far been limited to patient level data on cause specific mortality, major vascular events, and site specific cancers. They had not analysed data on other adverse events as these were not part of the original CTT agreement. Collins and colleagues explained, however, that the trialists agreed in 2013 to pool and analyse data on all adverse events. This effort would be "non-trivial," they said, because of the likely heterogeneity and complexity of the data.

We also wrote to the principal investigators of 32 major statins trials, 27 of which were included in CTT analyses. Despite follow-up emails and phone calls, only seven have responded. On the plus side, all said they were potentially willing to share their data with other researchers. Members of our expert advisory group are now contacting authors of 183 statins trials, with the aim of characterising adverse outcomes from both published and unpublished information.

As for a suitable independent group to analyse the available data, the Cochrane statins review group seemed an obvious candidate. However, its brief reply to our inquiry was not encouraging. Its 2013 review, on which the new recommendations for extending statins to low risk people were based, relied on the CTT summary data. It acknowledged that the adverse events were poorly characterised in the trials, but disappointingly the group has shown no appetite to seek out the patient level data for its 2015 update.

As promised we posted all the correspondence relating to this issue on thebmj.com (www.bmj.com/campaign/statins-open-data). A UK newspaper took up the story[8] and, in response to media questions, Collins announced a step further towards transparency: once the data on adverse events are compiled and analysed, he said, CTT will make the tabulated data available to others.[9]

This is a move in the right direction, but it falls well short of current notions of data sharing, one key aim of which is independent verification. Groundbreaking though the CTT initiative has been, its members cannot be considered independent because they are the trialists. As Harlan Krumholz has said, "Unfortunately, what occurs every day in medical research is akin to a few astronomers with access to the most powerful telescope interpreting for us what they saw without allowing us to look for ourselves."[10]

In summary, although a great deal of patient level data has been shared among and meta-analysed by members of the CTT, guideline producers around the world have not had access to analyses by third parties independent of the statin trialists. In particular, they have not had access to independent analyses of the data on adverse events, which to our knowledge currently remain the sole preserve of the individual trialists and drug company sponsors.

England's chief medical officer has asked the UK's Academy of Medical Sciences to review how society should judge the safety and efficacy of drugs, using statins as an exemplar.[11] This is a welcome intervention but conclusions about statins will be credible only if based on full independent review of the patient level data.[12] How good the data on adverse effects will prove to be is the next big question. Even with total transparency the attributable hazards of statins may never be properly understood, simply because the trials were not designed specifically to measure them.

Collins and others remain highly critical of *The BMJ*. Their continuing concerns about the journal's handling of two papers that misrepresented the evidence on rates of adverse events from statins[13 14] are detailed in a complaint to the Committee on Publication Ethics (COPE), to which we have responded. When COPE reaches a conclusion, we plan to publish a full account.

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The BMJ accepts that mistakes were made and has taken steps to remedy them (box).[15] But we also have reason to be critical of Collins and the CTT. Had Collins deigned to make his initial concerns public through the journal's well established channels, we believe that much of the subsequent media furore and public concern could have been avoided. And had the CTT done more to facilitate scrutiny of the data by independent groups, the debate around the benefits and harms in low risk groups would now be closer to resolution.

But it is not too late. A call from Collins to his fellow trialists asking them to make their data available to other researchers beyond the CTT could be game changing. The Yale University Open Data Access (YODA) project (http://yoda.yale.edu) stands ready to facilitate such independent re-analysis. Alternatively, a new Cochrane review group could be formed to take this on. Either way, this would require funding.

Like the story of oseltamivir (www.bmj.com/tamiflu), the statins saga forces us to confront the deep flaws in our current system for evaluating medicines and guiding clinical decisions. In particular, how can it be right to recommend mass treatment of healthy people without independent review of the patient level data, especially the data on adverse effects? Thanks to Alltrials (www.alltrials.net), the European Medicines Agency, and the US Institute of Medicine, solutions are emerging, but we have a long way to go. The statins trialists have huge potential influence, and they have a choice. They can take the lead on transparency or be pulled kicking and screaming into the light.

Competing interests: We have read and understood BMJ policy on declaration of interests and declare we are all editors of *The BMJ*.

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A year ago, an expert panel concluded that The BMJ should not retract two articles that had misrepresented the evidence on rates of adverse events in people taking statins.[7] The panel asked the journal to review some of its policies and processes.

Our report of this review and our response to the panel's recommendations are available here: www.bmj.com/campaign/statins-open-data.