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Dr Sarah Wollaston
Chair, Health Select Committee
14 Tothill Street
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Dear Dr Wollaston,

Thank you for your letter of 22 October asking for my comments on the letter you have received from Dr Kailash Chand and others ('the authors') on the development of our advice on the use of statins.

I hope this response adds helpful detail to the public statements we have made about this clinical guideline[1], and the response[2] we made to a previous letter from some of the authors of this letter. We understand that two signatories, Professor Klim McPherson and Dr Clare Gerada, have removed their names from the letter since you and I received it.

The clinical effectiveness of statins

For almost thirty years, statins have been widely used in developed health care systems to protect people from cardiovascular disease (coronary heart disease and stroke). Their use in people who have established cardiovascular disease is not controversial. The use of statins to prevent the development of cardiovascular disease in well people is a more recent role but is equally widespread and robustly evidence-based[3].

The initial use of statins in primary prevention was targeted at people at the highest risk, based on raised cholesterol levels and other risk factors including hypertension and family history. This approach, though offering significant benefits to those identified as at high risk, had little effect on population levels of cardiovascular disease so, during the last decade, this strategy has shifted to a wider population-based policy focusing on people with a raised, but not high, risk of developing cardiovascular disease over the following ten years. In our previous guidance published in May 2008[4], this risk level was set at 20% over ten years (of death, myocardial infarction or stroke). A later series of clinical trials have now led to a

[1] www.nice.org.uk/guidance/cg181
[2] www.nice.org.uk/news/press-and-media/nice-responds-to-criticisms-of-its-draft-guidance-on-statins
[3] Organisations that have similar guidelines and policies include the European Atherosclerosis Society, the European Society of Cardiology, the American Heart Association, the American College of Cardiology, the Canadian Cardiovascular Society and the Cardiac Society of Australia and New Zealand
[4] www.nice.org.uk/guidance/CG67

reduction in this risk level to 10% over ten years; a policy equal to that adopted throughout Europe though rather more conservative than that adopted in North America.

For the group of people affected by our recent guidance — those with a cardiovascular risk of 10-19% over ten years — the estimated number needed to treat for ten years to avoid an event is around twenty. Applied across the potential population covered by the new guidance, this could prevent up to 9,000 deaths and up to 50,000 non-fatal stroke and heart attacks over a 3-year period. Indeed, although much of the reduction in premature deaths from cardiovascular disease can be attributed to a reduction in tobacco smoking, the fact that fewer people now smoke means that the role of antihypertensive treatment and statins will now take over as the dominant factor.

The medicalisation of healthy individuals

I do not accept that our guidance recommends prescribing to people who are not capable of benefiting. The evidence is clear, in our view, that statins have a material impact on reducing cardiovascular risk, where that risk is greater than 10% over a ten year period. We are not advocating that statins are the only appropriate intervention. The guideline sets out to identify people at increased risk of CVD and argues for changes to diet and exercise where that can be achieved.

It is only if lifestyle changes on their own are not sufficient, and that other risk factors such as hypertension are also managed, that people who are at risk should be offered the opportunity to use a statin, if they want to. They don't have to and their decision should be informed by an understanding of the risks. If they find after starting treatment that the side effects outweigh their understanding of their risk, they should be advised to stop. This is hardly mass medicalisation. We are, as you know, producing a decision tool to help health professionals and their patients make these admittedly sometimes difficult choices. This should be available before the end of this month.

The authors object to Professor Mark Baker, Director of the Centre for Clinical Practice at NICE referring to heart disease as a condition which "kills, maims and destroys lives", arguing that it is in some way inappropriate to refer to it when discussing treatment options for people who are at lower risk of the disease. However this, as you and I know, is what heart disease does. Most people who get heart disease begin with a low risk. I do not think he was wrong to use these words.

Where there is a risk of ill health that an intervention, recommended by NICE, pharmacological or otherwise, can help to mitigate, NHS professionals should consider its use with their patients, where appropriate. I would be surprised if the authors oppose this notion. Their concerns about over medicalising patients in this case stem from a different interpretation of the evidence for the risk mitigation effectiveness of statins. I draw your attention to a letter in the Lancet which points out errors in the letter they sent to us in July.[5] It's difficult to know how to address their concerns when we begin with such different interpretations of the evidence.

Our position is supported by the British Heart Foundation and the European Society of Cardiology amongst others. It was arrived at after a very careful review of the data available

[5] www.thelancet.com/journals/lancet/article/PIIS0140-6736(14)61765-7/fulltext

to us. Our methods and processes are always open to question and refinement, but they are regarded as amongst the best in the world.

Hidden Data

Although the clinical evidence for the use of statins in primary prevention at a lower level of risk is compelling, it may nevertheless be the case that, in both commercial and non-commercial trials, not all the data on adverse effects is included in the published material. Whilst we do not know what we do not know, and notwithstanding the evidence from the available placebo-controlled RCTs which suggests that adverse effects are no more common in people on statins than on placebo, it remains a possibility that unpublished data may have an impact on their use in prevention. However, in our work developing the guidance, we have addressed this through assessing the sensitivity of our recommendations. We have, for example, tested the health economic model to see if our recommendations would remain cost-effective if, for instance, the frequency and severity of adverse events was twice as common as has been reported. Our guidance survived this examination.

We know that the Cholesterol Treatment Triallists Group is obtaining unpublished data and we hope soon to have additional information. Whilst most observers acknowledge that these data are unlikely to impact significantly on our conclusions, we will of course review the impact of such data on our guidance as soon as it becomes available.

The authors express the concern that in addition to their specific arguments about the public availability of data in support of the use of statins for low risk groups*, '…a number of medications had similarly been recommended in the past by NICE, and subsequently been removed from guidance or even withdrawn altogether over safety concerns when further research data had become available*.' We naturally respond to new data when it becomes available. Other than occasionally, and only in in our clinical guidelines, we do not make recommendations for drugs outside of their marketing authorisations. We begin our consideration of new drugs on the basis that the safety and efficacy of drugs has been established by the relevant regulatory body. To do otherwise would usurp their role.

Independence

The authors argue that confidence in our work could be improved by *'…the selection of an independent clinical guidelines panel who could call upon witnesses to promote a greater understanding of the difference in views and the evidence behind this. We also believe that a broader approach must be taken, for matters which have societal implications to include assessing public opinion when recommending treating healthy individuals who do not have diseases. We feel it is important that NICE no longer recruits and appoints panels from specific interested nominated parties and that the decisions of these more independent panels can be challenged and subsequently modified by a system of independent arbitration where appropriate.'*

Our advisory groups ('panels', to use the authors' language) are already independent. They are recruited through open advertisement with appointments made on merit. They are informed by expert testimony and their conclusions subject to public consultation. The recommendations they develop are considered and signed off by NICE's Guidance

Executive[6], made up of NICE directors, including the directors of our guidance producing centres.

The authors may also not be aware of our Citizens Council[7], which advises us on the social value judgements that we should apply in our work interventions. We cannot ask the public's opinion in the way the authors suggest without a substantial and disproportionate use of resources, but we can and do go to considerable lengths to engage those who can speak on their behalf, through patient advocacy groups, the Citizens Council and through public consultation.

It is unclear why, if guidance is to be produced by independent advisory panels, as the authors suggest, that their decisions should then be subject to arbitration. In what way might arbitration produce a better outcome, in circumstances where strongly held views are held by opposing camps? And what would happen (as is likely in the circumstances in which it might be applied) if the arbitration decision is rejected by one or other of the parties to it? Which body, ultimately, would have the authority to make the final decision?

Conflicts of interest

We have had a policy for managing conflicts of interest since the Institute's earliest days, when we recognised the risks, both real and perceived, that our advice might be deliberately or inadvertently influenced by advisory committee members with an interest in pursuing a particular outcome.

The current policy, approved after considerable discussion by the Board, makes it clear that the determination as to whether or not a declared interest is in conflict with the work of NICE will sometimes require careful judgement based on the facts and the nature of the business being conducted.

Our policy recognises that many committee members will have some interaction with the commercial sector (including the pharmaceutical industry) and while this should be declared, it does not necessarily preclude membership of an advisory body or work for NICE. This is because in order to develop credible guidance, we need people who understand the subject under consideration and who can bring their experience to bear to help interpret the evidence.

We don't allow people who have a current personal financial interest in the outcome to take part in developing our guidance. Equally, we don't exclude people who have received such things as a fee for speaking or providing advice, or a grant for research, in the past. It is surely wrong to assume (as the authors appear to do) that such people are not able to offer objective advice, just as it is naïve to assume that people who have never done so must automatically be free from bias.

In addition, conflicts of interest are not just financial. Sometimes individuals hold strong opinions as to what the evidence means and what to do about it. They are just as capable of hindering an objective assessment of the evidence.

[6] www.nice.org.uk/about/who-we-are/guidance-executive
[7] www.nice.org.uk/get-involved/citizens-council

When evaluating declarations of interest from members of NICE's committees, we make a number of important distinctions. For example, whether the interest is 'specific' (when it refers directly to the matter under discussion) or 'non-specific' (when it does not refer directly to the matter under discussion). Or whether a financial interest is 'personal' (for example, a fee for providing advice or the cost of travelling to a conference) or 'non-personal' (a payment made for research undertaken by the committee member's university department, for example).

Normally, people who declare a non-personal financial interest are permitted to take part in the work of the advisory committees. Those who declare a personal, non-specific financial interest may also participate. In both cases, the chair of the advisory committee, acting where necessary on the advice of the Institute, may exclude the member if the conflict nevertheless appears inconsistent with the need to demonstrate objectivity.

People who have personal specific conflicts of interest are not permitted to take part in the work of an advisory committee. In the case of a topic specific advisory committee (such as a clinical guideline), an individual with a personal financial interest would not be appointed or would be asked to stand down in the event that the conflict arose or was discovered after being appointed. In the case of standing advisory committees, which consider a series of separate topics (such as our technology appraisal committees) members with personal financial interests are asked to stand down from considering any topic where the interest applies.

An interest is considered current and therefore subject to the policy if it existed at any point in the 12 months up to the appointment of the individual to a topic-specific advisory committee or to the consideration of a topic to which the conflict applies by a member of a standing advisory committee.

The members of the clinical guideline advisory group that developed the recommendations on the use statins were assessed for conflicts of interest against this framework. Only in one case, that of Dr David Wald, did the knowledge of his personal financial interest in the sales of the so-called 'polypill', result in exclusion from the advisory committee. In this case, a financial interest was acquired after he had been appointed to the advisory committee.

The authors argue that *'members of the Panel in this case had relationships with organisations which could derive financial benefit from the conclusions that were drawn.*' However, they also say that *'…we are not accusing any individuals of knowingly acting in a way which fell short of these [Nolan] standards.'* It is unclear, therefore, what the authors consider the problem to be. If it is simply that the perception of a conflict of interest should preclude membership of an advisory committee, then they are setting the bar far too high to enable NICE to operate a viable guidance development programme.

It is worth making the point that for our guidance to influence and to be applied by experienced clinicians it requires professional credibility; we cannot achieve this through advisory committees that do not involve those with experience of the field. The fact that we are often asked to develop guidance where there is little reliable evidence, and where expert opinion is the only legitimate source of guidance, serves to emphasise this important point.

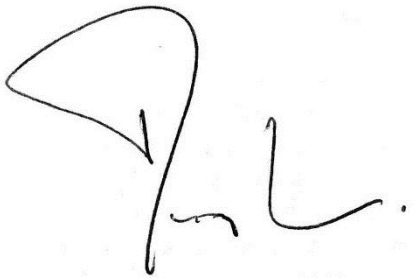
I hope that this response demonstrates how very seriously we have taken the issues raised in the letter you received. Many aspects of health care are bound to be controversial, and people will have different opinions about best practice. After all, if the truth on any topic were

to be self-evident, there would be no need for guidance from organisations like NICE. Nevertheless, if there is clear, robust evidence that a drug has widespread benefits for a large proportion of the 'healthy' population, then individuals should be given the choice of whether or not they wish to take the drug.

May I stress that we will never be complacent about issues like conflicts of interest. Our absolute responsibility is to provide the best advice for the benefit of patients and the public, and to maintain the trust of everyone who relies on NICE for information and guidance.

If you have any further concerns or questions, please do not hesitate to contact me.

Yours sincerely,



Professor David Haslam
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