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Response to the Review by the Academy of Medical Sciences
How does society use evidence to judge the risks and benefits of medicines?

The Academy will have received submissions from All Trials and others concerning the serious flaws widely revealed in trials supported by pharmaceutical companies, including the suppression of data on side effects, undue influence on triallists, financial inducements, selective reporting of data, conflicts of interest etc, and it is the revelation of these that is one factor which has decreased the confidence of patients and doctors in the advice that is widely given to them by drug companies, but also by national review bodies.

I shall instead chiefly comment on the wider problems that beset the reliability and perception of published data, which have also impaired belief in any information that is released. My comments do not easily fit into the questions that the Review has laid out, and *do not represent the views of any organisation.*

1. It is rumoured that NICE and MHRA are helping in this enquiry. If so, this is a conflict, because they are part of the problem. They are slow and seem reluctant to engage with critics and commentators.

2. I fully support the detailed work of NICE in evaluating evidence and issuing many excellent recommendations, but final decisions are sometimes taken unsafely by reviewing committees that chiefly contain 'experts' in the field, who are unavoidably conflicted professionally and financially. This is doubly important when the evidence for a treatment is controversial.

3. MHRA is similarly compromised. Their recent review of the licence for alteplase in acute ischaemic stroke, on which I sat as an independent observer, recruited some committee members who were working in the stroke field, and further we were presented chiefly with data from experts in the field. There was little effort to look at the many critical reviews worldwide that have been written on alteplase, and it was thus one sided. The medical stroke community understandably has a clear interest in defending the current effective system and continuing the use of this drug in acute stroke. In my opinion this review was flawed.

4. Clinicians and scientists do not readily admit, even to themselves, that they are conflicted when they review data because of their financial and other support for themselves, their departments and their trials. Being transparent about potential conflicts, though important, does not remove them. It is difficult for anyone to be in equipoise over data when their mind is previously made up, or when a reversal of the evidence will run counter to their genuine beliefs and previous work. Thus as JK Galbraith said: *Faced with the choice between changing one's mind and proving that there is no need to do so, almost everyone*

gets busy on the proof. Tolstoy said much the same. Hence, true independence is needed, although admittedly difficult to achieve.

5. Professor Barbara Mintzes recently wrote: *It would be preferable that there are no financial ties when it comes to making big decisions on public health....includes if they have a currently funded clinical trial.* I would also include *past* funding. Committees such as NICE and MHRA have huge influence, and so cannot society expect that they are without conflicts, unbiased, and look at both sides of all arguments when a treatment is judged?

6. **I therefore propose** that the committees issuing the final decisions and advice to doctors and patients on treatments should be composed of truly independent and impartial members who have no interest in the drug being considered, and who judge the strength of the evidence and its worth to society *after and only after* taking advice from experts in the field. For instance, the recent advice from NICE on statins for millions of low risk patients is flawed because of such conflicts; it took no account of society's fears of *too much medicine,* and nor did it consider the predictable reluctance of primary care doctors to follow the guideline.

7. The evidence behind the use of prescription drugs is mainly transmitted to doctors, particularly to those working in primary care, through articles and advertisements in professional journals, trade representatives etc., and they assume that NICE, the Department of Health and NHS England would issue reliable advice to them and to the public that is carefully based on sound evidence. This is not always the case, particularly when there is controversy. Some situations are simple, such as thrombolysis and angioplasty for myocardial infarction, but in the recent cases of statins, alteplase and oseltamivir the evidence is complex and contradictory. The medical profession has therefore become more sceptical of what it is told and less confident how to decide with their patients on what to recommend. The media have inevitably not been slow in conveying these genuine doubts to a sceptical and increasingly informed public. Conversely, the media have prematurely publicised the unproven drug solanezumab for slowing Alzheimer's disease; this is cruel and unnerving for patients, and appears not to have been authoritatively refuted There has been poor leadership by government and its agencies, partly because their in-house expert medical staff in public health and clinical pharmacology has been greatly reduced. When, therefore, they do issue guidance, it can be based on poor evidence, such as oseltamivir for influenza or telemedicine for preventing admission to hospital.

8. **I propose** that better sources for more impartial and informed advice are the Royal Medical Colleges, including the Royal College of Nursing, who were consulted since the 16th century by government on public health and other matters. They have active and influential patient groups that must be included in the wider debate. They are able readily to draw on practitioners in every field, and can obtain unbiased advice. They and their specialist societies already issue powerful guidelines, which are regularly updated, to their members, with whom they have direct and immediate contact. But in the 21st century the Colleges are no longer consulted.

9. This situation is part of a more general reluctance of the agencies to listen to and engage with doctors, including international doctors, who are critical of the use of some drugs. Critics may not be right, but their siren voices are unwisely ignored; many have studied

trial data in great depth. For example, following the publication of the IST-3 trial in the Lancet in June 2012 on alteplase, there were a series of highly critical articles and blogs, yet only one of the authors was invited to submit to the 2015 MHRA review. Following the recent NICE guidance on the threshold for treating with statins, opponents were ridiculed, rather than engaged. Critics of the evidence base for oseltamivir have been excluded from WHO debates, and in spite of the powerful campaign by the British Medical Journal, NICE has not changed its current advice. The data on the benefits and risks of Cox-2 inhibiting drugs has been similarly biased, uncertain and irregular.

10. As has been said elsewhere, the problem is not communicating uncertainty, but rather that uncertainty is not communicated by drug companies or by the national agencies. Data on side effects is withheld and questions are ignored or denigrated. Even the evidence on the efficacy and safety of digoxin is not constant. Clinicians would be more confident if the arguments on both sides were seen to be judged impartially.

11. The use of thresholds for treatment with statins, for instance, particularly as it was accompanied by financial incentives in primary care, is morally dubious and conflicts the prescribing doctor, who has to debate, in only a few minutes, the possible benefits and side effects with the patient. If there is financial gain to the doctor it dangerously alters the balanced relationship between the patient and doctor, which becomes paternalistic. Thresholds also blur the debate on the value of drugs to society, and do not take into account *over treatment*, concentrating instead only on efficacy derived from general trials on selected groups of patients.

12. Patients obtain most of their information from their doctors, but increasingly from websites and the media, which are not reliable. Patients can have difficulty in understanding medical information, and the statistics of risks and benefits, of absolute and relative risks, NNT etc, even if they are not among the 15% of the public who are said to have learning difficulties. They may also view the risk of individual side effects differently than do their doctors. Lack of such understanding reduces the already poor general level of adherence to treatment by the public.

13. The conflicts carried by lecturers at influential conferences on new treatments, particularly marketing lectures, are often not obvious. They are key opinion formers, and yet there are many examples of selective presentation of data, and neglect of evidence contrary to their views. The Royal College of Physicians was instrumental in persuading the Association of the British Pharmaceutical Industry to start to publish payments to doctors, following the Sunshine Act in the USA, so that everyone, including employers, can openly judge possible conflicts. However, the scope of this excellent initiative needs to be extended.

14. There is an urgent need for medical students, doctors and pharmacists to be better educated in how to read clinical trial data and reviews, to assess the statistics of benefit, and to look for flaws, such as the dubious withholding of unpublished data from the statin and alteplase trials, and to understand conflicts of interest that could have biased authors. Pharmacists can be valuable teachers of medical students. The draft manual issued by Health Action International may help to address this issue.

15. The medical profession, and particularly the Medical Royal Colleges, together with central government and its agencies, need to lead a debate with the public on how to evaluate the

real world value of treatments and to distil advice, and how to sort out the complex world of pharmaceuticals (and devices), trials and conflicts of interest. Trust and belief in the use of drugs (and devices) could then improve, and this in turn might reduce the expensive poor adherence to treatment. The marginal value of some chemotherapy is widely ignored by clinicians and sows doubt among patients.

16. A recent report from the USA showed that since the 2000 regulation that all publically funded trials have to set primary outcomes *before* a trial is started, and not to vary them, the percentage of trials with a positive benefit has dramatically reduced. This probably indicates that previously many trials failed in their primary aim and were only published after multiple retrospective analyses and statistical legerdemain with the data. Such was the case for the IST-3 trials of alteplase. Perhaps this tighter control on the conduct of trials may improve the reliability of the evidence that emerges.

17. Finally, I do hope that this review will carefully study the series of hard hitting articles in the British Medical Journal that review all the examples that I have cited. They are discomforting to my profession, but I trust that the criticisms that they contain will now at last be faced, rather than rejected, solutions found, and the faith of patients and the medical profession in the information on treatment will be restored.

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