Response to AMS Consultation: "How does society use evidence…."

From the

Nuffield Department of Population Health, University of Oxford

- Head, Professor Sir Rory Collins -

1. **The overarching aim of the workstream is to better understand how society uses evidence to judge the risks and benefits of medicinal products. In your view, what are the key factors underpinning this process that the Academy should consider?**

   There are two key factors to consider in allowing society to better use evidence to judge the benefits and risks of treatments:

   - **Reliable evaluation of treatment:** It is important that it is more clearly understood by the medical profession, related disciplines (including the medical and lay press), and the general public what constitutes reliable evidence about the causal effects of treatments and, by contrast, what is not likely to represent reliable evidence of causal effects (i.e. misattribution of effects to treatment).

   - **Responsible presentation of evidence:** All medical evidence, depending upon the methods used, has strengths and limitations. Medical professionals have a responsibility to ensure that, in reporting on the effects of treatment, the strengths and, particularly, the limitations of the evidence are properly described in order to reduce the likelihood of misinterpretation. Medical journals also have a responsibility to avoid the presentation of misleading claims about treatment effects.

2. **When evaluating the risks and benefits of medicinal products, what are the *strengths* of evidence that originates from different sources?**

   Strengths of observational studies

   The obvious strength of observational studies is that they are much easier to undertake, much less costly and much quicker to complete than randomised trials. Case reports and observational studies have two main potential advantages over randomised trials for the evaluation of treatment effects:

   - *Very large size:* Case reports and non-randomised observational studies may be based on events that have occurred among very large numbers of individuals who have been exposed to some particular treatment. Consequently, they may be able to detect any large effects on rare outcomes that might not otherwise be expected to occur (and, hence, where any systematic biases are not likely to have produced spurious associations that are not causal); and

   - *Long duration:* In principal, post-marketing studies based on reports of adverse events may involve prolonged exposure to a treatment (although, in practice, the duration of exposure in the available observational datasets with relevant data is often not longer than in randomised trials which have the advantage of avoiding biases inherent in non-randomised studies: see below)

Another potential advantage of observational studies that is often claimed is that they are "real-world" (i.e. the patients who receive the treatment in ordinary practice are considered to be comparatively unselected compared to those in randomised trials so that the results are more widely generalizable). However, when many different trials of a treatment with different eligibility criteria have included large numbers of patients with a wide range of characteristics, sufficient randomised evidence on people with different characteristics (e.g. older as well as younger people; women as well as men; lower as well as higher risk) may emerge to provide unbiased assessment of the effects of treatment that are widely generalizable to the "real world" beyond the trials (as is the case for statins).

Strengths of randomised trials

Randomised controlled trials of sufficient size are the only reliable way to detect effects of treatment on common outcomes (by contrast with observational studies which have an inherent potential for bias: see response to Question 3 below). Such trials avoid bias in the assessment of treatment by:

- *Randomisation:* The process of randomisation allows comparisons between groups of patients who differ from each other only by the play of chance with respect to their risks of suffering all types of health outcome; and

- *Blinding:* Use of a dummy "placebo" treatment that looks identical to the active treatment to blind the study treatment comparison helps to avoid the differential assessment of health outcomes (especially those that are subjective) between the different treatment groups within a trial.

Consequently, subject to tests of statistical significance, differences in the rates of health outcomes between the randomly allocated groups can be attributed causally to differences in the treatment that is being studied (by contrast with associations in non-randomised observational studies). This ability to provide unbiased assessments equally applies to both the risks and benefits of a treatment.

3. **When evaluating the risks and benefits of medicinal products, what are the *limitations* of evidence that originates from different sources?**

Limitations of observational studies

While large non-randomised observational studies can provide estimates of treatment effects that are subject to relatively small random errors, their main limitation is that they may (and do, as shown in the examples given in response to question 4 below) lead to the detection of differences in common health outcomes that are the result of various biases (rather than the effects of treatment).

These biases can be the result of underlying differences in the risks of health outcomes between the individuals who receive a particular treatment and those who do not (perhaps because the treatment is provided more or less frequently to individuals with medical conditions or other characteristics that are associated with increased or decreased risks of developing those health outcomes). Even when associations between the treatment and health outcomes remain after statistical adjustment for all of the recorded differences between individuals who have or have not received the treatment, this does not provide assurance that these associations do not reflect residual confounding due to differences in factors that were assessed incompletely, or not at all.

Another bias that may arise in observational studies is due to differences in the ascertainment of health outcomes. Patients being treated in ordinary practice know that they are taking a particular drug, as do their doctors. They may even have been told that the treatment has potential side-effects and may be monitored more closely by their doctors for such effects. For example, patients given

statin therapy are typically advised that serious muscle problems can occur (albeit rarely) and to advise their doctors if they develop muscle pain or weakness. The resulting magnitude of such reporting biases can be very large: for example, in a trial among patients said to be statin-intolerant, the reported rates of muscle pain were similarly high (about 25%) irrespective of whether patients were randomised to receive statin or matching placebo tablets and then, on stopping the tablets, the reported rates of muscle pain immediately fell to below 5%.

Consequently, although associations between treatment and health outcomes in non-randomised observational studies may represent effects of the treatment, they may instead be due to bias. There is no reliable way to distinguish between causal and non-causal associations in observational studies (unless there is complementary randomised evidence), even if the size of any observed associations are large and highly statistical significant despite adjustment for observed differences (except, as is indicated above, in the case of large effects on rare outcomes).

Instead of being a strength of observational studies, therefore, the ease and low cost of undertaking analyses based on observational data may in reality be a weakness because their ability, by involving large numbers, to produce very precise results that are "precisely wrong" may put the health of the public at risk if the results are not presented in a responsible manner.

Limitations of randomised trials

Excessive regulatory and other governance obstacles have made it harder to conduct randomised trials in recent years (although this is starting to be addressed now by replacement of the EC Clinical Trials Directive by a more proportionate Regulation and by the proposed incorporation into ICH-GCP guidelines of US FDA approaches to streamlining). Consequently, one limitation of randomised trials is that, because they are harder to do and take longer to do, there has been an increased tendency to use non-randomised observational studies methods based on clinical databases to assess the effects of treatment (despite their inherent biases; see above).

It is often suggested that, due to exclusion criteria in randomised trials, patients who receive some particular treatment in ordinary practice are comparatively unselected so that observational studies may be more widely generalizable (sometimes referred to as "real world"). However, meta-analyses of randomised trials that are based on large numbers of patients included in many different trials with different eligibility criteria (as is the case for statin therapy) may overcome this putative limitation by providing information based on sufficiently large numbers of randomised individuals with different characteristics (e.g. older as well as younger people; women as well as men; lower as well as higher risk) to be widely generalizable, while also avoiding the biases inherent in non-randomised studies. Such meta-analyses of randomised trials would not, of course, be able to provide information about the effects of a treatment in patients in whom it is clearly contraindicated, but then neither would observational studies based on routine use – and, anyway, its relevance to practice is limited.

It has also been suggested that randomised trials exclude patients in whom the treatment being studied causes adverse effects (e.g. "statin-intolerant" patients), resulting in under-estimates of the rates of side-effects. In circumstances where a treatment is already being used widely, it may be the case that patients who have had side-effects will either chose not to join a trial or will be excluded by the study organisers. However, for treatments that are not yet on the market or that have not yet been widely adopted into routine practice (as was the case during the recruitment phase of several of the statin trials), few patients will have had an opportunity to be exposed to the treatment and to have been excluded for that reason. Some trials use pre-randomisation "run-in" phases in order to help improve compliance to the study treatment (whether active or placebo) after randomisation. In most cases, these run-in phases involve treatment with placebo (as was the case with the statin trials) and so, again, this would not plausibly impact on assessment of side-effect rates.

4. **Please provide details of any further examples or case studies that it would be useful for the project to consider.**

There are many examples of claims of benefits and hazards with various treatments based on non-randomised observational studies that have subsequently been refuted when randomised evidence became available. For example, whereas hormone replacement therapy was previously associated with one third less coronary disease among post-menopausal women in observational studies, that association has been demonstrated by randomised trials not to be causal. Similarly, there have been many claims about the benefits of dietary intake of vitamins based on observational studies that have not been confirmed by large-scale randomised trials.

In the context of statin therapy, there are several examples of hypothesised beneficial effects on different non-vascular diseases (e.g. cancer, chronic obstructive pulmonary disease, acute respiratory syndrome) based on lower rates among people prescribed statins that have been reliably refuted by large-scale randomised evidence. Equally, there are claims of adverse effects of statins on various other conditions based on observational studies (e.g. myalgia, memory loss, cataract) that have also been reliably refuted by large-scale blinded randomised comparisons.

5. **Please highlight any broadly applicable principles that should govern the presentation, interpretation and weighting of evidence about medicinal products.**

All research evidence is not equal. The utility of evidence for properly informing prescribing depends on the strengths and limitations of the research method used. As stated in response to Question 1, researchers have a responsibility to ensure that evidence is presented in the context of both the strengths and, particularly, the limitations of the method used. For the unbiased assessment of the effects of treatments, randomised trials of sufficiently large size are generally the most reliable method (and the temptation to use potentially biased evidence from observational studies because it is easier to generate should be resisted). Consequently, treatment recommendations should place much greater weight on evidence from randomised trials (and meta-analyses of related trials) and should place far less weight on associations in non-randomised observational studies (e.g. case reports, analysis of routine data) than is sometimes customary.

6. **Concerns have been raised about how industry funding impacts on the validity, or the perception of validity, of evidence. For example, the ability of academic researchers funded by industry to remain impartial when evaluating evidence has come into question. How should conflicts of interest be addressed? How important is industry funding in generating and analysing evidence? Other than industry sponsorship, what are other potential sources of conflicts of interest?**

The conduct of trials involving thousands of participants, often in multiple countries around the world, requires a substantial research effort and can be very costly. Given the costs involved in running large studies, industry funding helps to ensure that the trials are of sufficient size and scope to assess the safety and efficacy of treatments reliably (as with the statins, which have been particularly extensively studied in a wide-range of trials that were largely designed and conducted by academic groups).

Industry support covers a wide range of scenarios from trials that are conducted entirely by industry (but may involve academics on advisory committees) through to trials that are designed, conducted, analysed and reported by independent academic groups in universities (perhaps with advice provided by industry and part funding from non-industry sources, such as MRC/NIHR and medical charities).

In our own case, research that receives industry funding is governed by University contracts which protect our independence in the way that we design, conduct, analyse, interpret and report the study and, in the case of all of our clinical trials, we (not the funders) hold the databases and control all of the analyses, with no restrictions on what is reported.

It is important to have transparency and disclosure of any potential conflicts of interest. Specific details about all funding sources should be provided in key documents (e.g. study protocol, ethics submission, study report), along with the role of the various parties (including funders) in the design, running, analysis and reporting of the trial. Any other financial or other potential conflicts of interest should also be made explicit in such documents.

In our own case, we have also disclosed details of the amount and source of all the industry funding that we have received for any research on our website. In addition, we've had an explicit departmental policy for about 30 years of not accepting any personal payments directly or indirectly from industry (with only reimbursement sought for the costs of travel and accommodation to participate in scientific meetings). This approach ensures that decisions to give any lectures or advice are determined by the scientific value of doing so, and not by personal gain.

In addition to the pharmaceutical industry, there are other sources of funding that have the potential to distort the evidence about the effects of treatment. For example, substantial income may be derived from acting as an expert witness in legal cases related to claims of adverse effects of a treatment, by writing widely publicised books about treatment hazards and by selling various supplements (often without any reliable evaluation of their effects) as alternatives to proven therapies. It is of note that the size of these sources of income is rarely, if ever, disclosed in such circumstances.

Finally, in the case of claims that "statin intolerance" is a common problem, the focus of new LDL-lowering agents (such as PCSK9 inhibitors) that are in development is shifting towards their use in patients classified as statin intolerant in whom reductions in LDL-cholesterol would, in the absence of background statin therapy, be larger (and, hence, so too would be their cost-effectiveness). It is worth noting that, whereas statins are now generic and low-cost, the newer agents are costly so there may be commercial pressures to help create a "statin intolerant" market for their use. Indeed, the costs of producing reports about "statin intolerance" by influential bodies (e.g. the European Atherosclerosis Society) have been covered by these manufacturers.

7. **Please outline any past, current or planned initiatives to examine how patients, citizens and healthcare professionals (and those who seek to inform them) evaluate scientific evidence about medicinal products.**

The Cochrane Collaboration has emphasised the importance of basing inference on randomised trial evidence. Even so, there would seem to be a pressing need to explain more clearly why randomised controlled trials, with blinding for subjective outcomes (such as muscle pain), are so much better as an unbiasedly reliable source of evidence about the effects of treatment than are database analyses. We are currently writing a paper for publication in the medical literature that addresses these issues both generally and with a specific emphasis on the misrepresentation of the evidence for statins.

The Academy has an opportunity to help medical professionals, medical journals, the wider media and the public to understand these issues more clearly than is currently the case so that they can make better informed decisions. Regulatory authorities also have a role to play: indeed, the MHRA's decision in 2009 to list various adverse outcomes (such as memory loss) as "side-effects" in the product information for all statins, based on post-marketing adverse event reports and despite randomised trial evidence that did not support a causal link, has not served the public well.

8. **What are the most effective ways of communicating evidence to various stakeholders and engaging with them about such evidence?**

As discussed above, it is important to explain properly the strengths and weaknesses of different sources of evidence for the assessment of the effects of treatment (and not, as has occurred in the case of the statins, misleadingly dismiss the reliability of randomised trial evidence and fail to describe all of the limitations of observational evidence). Having done so, the reliable evidence that is available from randomised trials should be given due prominence, with any associations found in observational studies treated with appropriate caution (and typically only used as the basis for inference about the effects of treatment when these relate to big effects on rare outcomes).

For further information please contact:

Tim Sprosen,

Associate Professor,

Nuffield Department of Population Health, University of Oxford