Name: Nicky Cullum FMedSci
Job title: Head of School and Professor of Nursing
Organisation / Institution: University of Manchester
Is this input submitted as an organisational or individual response? Individual
Are you happy for your response to be published by the Academy? Yes

---

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?

The fundamental problem we (society) currently have in judging the risks and benefits of medicinal products is that full access to the evidence is not possible. If those judging risks and benefits can only access partial information then by definition their judgement is impaired.

These problems are fully rehearsed elsewhere (see www.alltrials.net) but we need to know

- About all the drug trials that have ever been conducted and
- All the drug trials that are underway now
- About adverse events data which may come light at any stage of drug development or after marketing authorisation

This transparency is best achieved through compulsory registration and reporting of trials however requirements for this vary. The current picture seems confusing and requirements depend on perspectives of funder, ethics committee, national law, host institution, professional organisation, publishing journal etc. Really needs legislation to make it happen. Not sure if this Academy review is taking a global or national stance but clearly decision makers need access to the *world* trial results not just the local trial results.

Registration needs to involve clarity on trial protocol as well as the existence of the trial: there must be clarity regarding the primary and secondary outcomes to be measured and reported at trial registration stage.

A second aspect to this "transparency" agenda is that results of all trials should be disclosed and this should be enshrined in legislation (only when there has been **full** disclosure of study results can society benefit from that study having taken place). Currently the global publication "picture" is biased and we are only allowed to see what study funders require or desire us to see. Again this means we have access to only partial information and the selection of the information we are allowed to see is biased and driven by pecuniary interests.
It is not sufficient that the trials are registered and that disclosure of study results is required, these requirements should then be **enforced.** Furthermore there should be very strict penalties for non-disclosure (withholding of marketing authorisation; withholding of future funding; withholding of future approvals to conduct research).

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

The best evidence on which to base decisions about the benefits of medicinal products will be meta-analyses of **all** the available randomised controlled trials that compare that product (or class

of product) with relevant alternatives (the nature of the latter will be best informed by relevant decision makers). By available I mean all the trials ***that have ever been*** conducted. Unfortunately because knowledge of the existence of trials is frequently suppressed, not to mention trial results, it is rarely possible to combine all data from all trials.

I am also assuming in the response that the systematic review/meta-analysis has been conducted to the highest possible standard but this is not always the case.

The best meta-analysis would probably have been conducted using the individual participant data from all the trials ever conducted. This enables full use of data and often more appropriate/indepth analysis than conducted at the level of the individual trial including re-instatement of participants who were erroneously excluded from previous analyses etc.

Harm data will **also** need to be gathered from observational datasets as RCTs will not reveal rare harms due to lack of numbers. The nature of the evidence is partly driven by the question being asked by the decision maker: if it is "Does X do less harm and more good than Y?" the evidence for benefit may accrue from simple pair-wise comparisons of X and Y with harm data also coming from observational data (including post-marketing surveillance). If the question is more "Of all the available treatments for disease AA, which treatment has the best balance of benefit over harm?" more complex methods would be required such as **network meta-analysis** (also known as mixed treatment comparison meta-analysis). This is a type of modelling that allows all competing alternatives to be ranked on the basis of the probability of their being the most effective, the most harmful etc. These newer methods come with a bit of a health warning however in that the methods are continuously developing but have the potential to be far more useful to decision makers as they consider all the competing alternatives simultaneously as opposed to pairwise comparison by pairwise comparison.

The types of evidence listed in the question above will all have a place but their applicability will depend on the question. For example even case reports may help to generate hypotheses about possible harms associated with a particular product but they will not "answer" the question on their own.

I am not familiar with the idea of data emerging from citizen science.

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

Randomised controlled clinical trials:

- Only consider two or three competing alternatives (usually)
- Typically underpowered for harms if not also benefits
- May be highly selective in terms of eligibility criteria hence of low generalizability
- Frequently fail to consider outcomes that matter to patients, often using surrogate outcomes or clinical measures that may be difficult to interpret
- May have low generalisability in terms of co-interventions; setting; participating clinicians etc.
- Lack of full disclosure of protocol (methods) and results hampers utility

Meta-analyses:

- The value of a meta-analysis is only as good as the primary research that it is based on
- Depends on full disclosure of trials and trial data otherwise biased (and if we are in ignorance of the existence of other studies we cannot judge the meta-analysis)
- May not cover all important comparisons (not so much about the method per se but how it has been implemented) and/or outcomes

Observational or large databases:

- Likely to be misleading for benefits due to error, selection bias and confounding

Case reports:

- Can only raise hypotheses not test them so likely to mislead

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

I don't think I have any to add to the ones you will already have e.g., Tamiflu.

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

I think I have covered these above: full disclosure of the existence, nature and results of trials (and observational datasets for that matter) of medicinal products since humans have volunteered themselves for experiments in the belief that others will benefit.

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?

Over the years a great deal of evidence has accrued regarding commercial influence on research. Drummond Rennie and Lisa Bero have done a great deal of this work. We know that important evidence has been and continues to be suppressed due to commercial interests. Consequently any declaration of industry funding calls into question the impartiality of the evidence. On the other hand society cannot afford for all drug evaluations to be publicly funded so we have to find a way of ensuring that commercial funding of research can be trusted i.e, by full disclosure of protocols and results, trial registration, legal enforcement of these steps.

Industry funding of academic research remains crucial in some areas so there is a real concern that if industry funding of academic research was "banned" ultimately society would suffer. So we need more robust ways of distancing the academic from the funder.

The Cochrane Collaboration has recently revised its conflicts of interests policy[1]. The process of this refinement was, and continues to be very challenging within Cochrane. The new policy requires (amongst other things) that the lead author of a review cannot have received any funding (including honoraria and fees for speaking) from organisations with current or potential commercial interests for the last 3 years and also that the majority of authors of a review must also be free of these conflicts. Employees of companies with real or potential financial interests are prohibited from authoring Cochrane reviews. As you can imagine (and whilst I support the policy) it can be difficult to find authors who are not conflicted, particularly in areas where there is little or no public funding for research.

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.

Not something I know about I am afraid.

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

There is almost certainly a body of existing research to be interrogated about this (well I know there is but I am not "on top of it"). I think it would be a bit pointless of me to give some opinions on the issues – we need to look at the evidence. What I will say as somebody whose job as a Cochrane Coordinating Editor depends on my helping others to communicate evidence to a wide range of audiences including patients and the public, is that it is incredibly difficult and there are very few people with the skills to both evaluate the evidence and communicate it clearly.

I would end by giving a plug to the GRADE[2] approach to summarising the quality of a body of evidence. This is widely used by guideline developers including WHO etc but the approach is as relevant for grading the quality of *evidence* as it is for underpinning guideline *recommendations*. The Cochrane Collaboration has also implemented it and it has revolutionised our ability to analyse a body of research, e.g., drug trials, and draw the evidence together balancing the overall "result" with confidence in the result. The approach is as objective as it could be whilst also being transparent (evidence is up or downgraded based on its characteristics). Using GRADE in this way gives authors the right words to use when summarising the message.

[1] http://community.cochrane.org/editorial-and-publishing-policy-resource/conflicts-interest-and-cochrane-reviews

[2] http://www.gradeworkinggroup.org