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Is this input submitted as an organisational or individual response? Organisational
Are you happy for your response to be published by the Academy? Yes

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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?

Please consider the use of the word “information” rather than “evidence”. What counts as evidence depends upon method. More specifically, what counts as evidence for one or another scientific claim will depend upon the methodology employed. For example, the Summary of Product Characteristics (SmPC) and Patient Information Leaflet (PIL) are information about a medicinal product which are approved by Regulatory Authorities to inform health professionals, but are not “evidence”.

Society increasingly seems to expect zero risk as the only acceptable level of risk for new drugs, but that is probably never going to be achievable. Educating the public on making a decision about the balance of benefit to risk will be very tricky in the rapidly changing and accelerating world in which we live, but nevertheless a worthy goal.

The views of the public are shaped by media – scientific journals, “news", or social, or a combination of these. The evidence is often “shaped" very much by the journalist or blogger reporting it. It is therefore very difficult to ensure a balanced presentation is made. The individual’s capacity to understand risk and evaluate evidence in its appropriate context and that of existing evidence and in face of bias is therefore of key importance. Those providing evidence and those communicating it need to consider how that evidence is presented. Given our inability to police the majority of communications for bias, it is therefore necessary to focus on the interpretation of information at the level of the recipient.

Evidence-based medicine (EBM) is the process of systematically reviewing, appraising and using clinical research findings to aid the delivery of optimum clinical **care** to patients (BMJ 1995;310:1122-1126). Another school of thought is as follows: Patients and the public (and even most doctors) are concerned about ‘results’ not ‘evidence’. And most likely they will evaluate results based on the reporting of other results.

Most patients trust their physicians. Patients largely take medications because they are prescribed to them by a trusted physician. They want to know how well the prescribed medicine works (efficacy) and they want to know if there are any ‘side-effects’ (safety). Patients do not normally inquire about the ‘evidence’ for efficacy or safety. Most physicians are also not involved in the collection or evaluation of ‘evidence’. They accept ‘results’ based on the literature they read.

What is the rationale for limiting this project to medicinal products? For patients and physicians the only real question is what is most efficacious (with the least number or severity of side effects)? For a patient (with, for example, cancer) and for a patient’s physician, the kind of intervention (pharmaceutical, device, surgical) is very much secondary.

There is an implication that the desired outcome of clarity of understanding is uniquely achieved by the quality of evidence. However, the ability to assess the quality of the evidence, recognise bias and interpret it are equally, if not more important, and should be addressed. For example, both patients and doctors are heavily influenced by case reports, despite those being the lowest level of evidence.
Another parameter to be considered is the update of the conclusions of evidence since these are only as good as the last publication and can be completely overturned at any minute by new evidence.

Over the years of benefit-risk evaluations it has also become very clear that different people weight relative benefits and risks/costs very differently so the value they place on the results need to be considered alongside their perspective, and as such there is no one "truth".

Furthermore, the question is seldom (if ever?) whether the evidence is robust enough. The real question is whether the methodology (or methodologies, because there are so many applied in evaluating a single medicinal product) is (are) robust enough.

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

Attention spans are short and getting shorter so providing evidence has to be even more concise. The 'strengths of evidence' depend entirely on the research question that has been asked and the methodology used to address that research question. All manner of evidence listed above (and others) are appropriate for responding to scientific questions, provided the method used is chosen appropriately.

For any single chemical entity accepted as a medicinal product, it is likely that nearly all of the above sources of evidence have been used at one time or another in the development of the medicinal product, as well as other sources of evidence not listed. Evidence can be categorised as having different 'strengths', described by the Cochrane Consumer Network here http://consumers.cochrane.org/levels-evidence. In order to evaluate the strength/robustness of any piece or collection of evidence for a particular medicinal product, it would be necessary to examine that piece or collection in relation to the protocol (research design) on which its collection was based and to put that in relation to other studies that provide an overall evaluation (based on the 'results' of the studies, not simply on the 'evidence') of the safety and efficacy profile of a medicinal product. This is principally a 'sponsor' (be it a public or private entity) responsibility according to both practice and law. It is also a responsibility of regulatory authorities (for example, MHRA, EMA, FDA, CFDA) to review the overall validity of the studies prior to marketing authorisation.

Any pre-clinical or clinical trial protocol could be used to illustrate the question raised here.

Following licensing, real world data becomes available. Although theoretically the availability of such data should enable specific questions to support risk-benefit assessment to be asked of it, its interpretation is limited by the following:

- The quality of recording in the database in question
- Completeness of the dataset

- Controlling for confounding factors
- The quality of the design of the study which is asking the question

For this reason, “real world data” requires as least as much critical evaluation as the quality and generalisability of tightly controlled research data.

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

The issues behind the benefit:risk of medicines are very complex and all of these sources of evidence are inextricably interlinked. Evidence from any source is limited. It is limited, in the first place, by the limitations of the scientific question being asked. It is further limited by inherent methodological limitations, including such features as inclusion/exclusion criteria, endpoint selection, ethical considerations, and statistical design. Evidence in science, and particularly in medicine, is never perfect. Its lack of perfection, however, does not necessarily weaken its utility in attaining results and making health decisions. A balance is required. There are acknowledged limits on real world evidence and citizen science, including the inherent bias in self-reporting and new ways of gathering evidence from the public.

One of the issues is the amount of time it takes to evaluate the evidence for a new drug or treatment with volume of material being huge. Things get distilled down at various steps to more manageable chunks, from what was a lorry load of paper reports in the past and a DVDs of data now, to little more than headline in the media and inevitably detail gets lost. So society as a whole does not really evaluate the risks and benefits but ‘hands this over’ to learned groups like regulatory agencies and medical/scientific groups- the question would be do these bodies truly reflect what society would want to happen or are they asking for too much proof of efficacy and too concerned over safety.

See also response to 2 with respect to real world data.

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

No examples provided.

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

- Accurate
- Balanced – takes other treatment options into account
- Portrays risk accurately, i.e. absolute risk quoted alongside relative risk
- Provided in context of the disease and what is currently known
- Accurate communication of key statistics – these should not be summarised to a level of understandability that blunts their technical meaning
- Contains transparency statements/declarations and declarations of conflicts of interest

- Referenced such that the reader can track back to source publications if (s)he so desires
- If high in technical language, an interpretation provided in more simplistic terms

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?

Industry sponsorship is only one source of bias, other examples being publication bias, political bias and limited funding e.g. http://retractionwatch.com/. Very few people involved in the generation and evaluation of evidence are entirely unbiased, and therefore understanding the potential sources of bias (including the person reading or interpreting the evidence) associated with any piece of evidence and its presentation and evaluation is one proposal for managing bias, since it can never be entirely eliminated. The drive towards "transparency" is a key element in this. There are already many checks and balances in place to ensure honest reporting of the results from clinical trials.

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.

We are not aware of any specific initiatives to examine how patients, citizens and healthcare professionals (and those who seek to inform them) evaluate scientific evidence about medicinal products. It would be useful to understand the sources of bias inherent in each of these groups and their insight into their own bias.

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

Different sets of stakeholders are likely to need different channels and presentation of evidence and different levels of explanation and evaluation. The best people to state their needs are each group in question.

The question carries some implication that "evidence" may be definitive (as opposed to provide a number of pieces of evidence of relevance to a particular question). This being the case, it seems unlikely that we would find an overall 'society view' on evaluating risks and benefits and what is acceptable as a whole will vary from person to person or group to group e.g. the cancer patient is willing to put up with much worse side effects from a drug than someone with high blood pressure.

Some considerations are as follows:

It is unrealistic to expect that 'a wide range of stakeholders, including patients, the public, healthcare professionals (general practitioners, nurses, pharmacists, clinicians, etc), and the media' would be able to evaluate the raw data on a medicinal product (or medical device or

surgical intervention). We should, however, insist that clinical trial designs and the summaries of the evidence upon which the results are based are made publically available. Many members of the public can interpret data and evidence to some degree e.g. can read a graph, understand a pie-chart/percentage figure. Patients have to make the decision about whether to take the medicine, at the end of the day, so they must have a good understanding (to the best of their ability) of the 'evidence' underpinning the benefit:risk.

The Summary of Product Characteristics (SmPC) and associated Patient Information Leaflet (PIL) are considered the official information regarding a medicinal product. However, from experience in outpatient clinics, most practising clinicians don't know the SmPC exists. They will tend to use British National Formulary and NICE, and not generally consider using Electronic Medicines Compendium as a source of information. However, the BNF and NICE are generally more useful resources for how a drug fits into practice, the SmPC covers a different role when you want specific detailed information about an individual drug (e.g. which statin can you take with grapefruit; whether the tablet is scored).

A priority should be to communicate the full and accurate results of health research to the scientific community. Any publically authorised health interventions (medicinal products are not special here) should be based on a full dossier submitted to the regulatory authorities who should evaluate the dossier rigorously according to Good Clinical Practice and other requirements as established by law and then publish the results.