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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?

Society's ability to properly judge medicinal products relies on the alignment of several important factors, which we will describe in more detail throughout this response. Firstly, the evidence must be both robust in the commonly understood scientific sense, and also meaningful to those using it to make decisions. Secondly, evidence must be made available, requiring it not just to be published but also to be made accessible via appropriate communication channels and presentational formats. Thirdly, the use of evidence also depends on the trust that users have in those generating and communicating it.

The public perception of the value of benefits also requires further exploration. Capturing the public and patient perspective at an early stage to inform planning may help to ensure that the evidence produced meets regulatory, evaluator and patient needs.

In understanding how society judges medicinal products, it is important to consider the context, frequency and effect size of risk and benefits.

The importance of context is illustrated by considering what risks one might be prepared to tolerate when using, for instance, statins for prevention versus treatment, or a drug for advanced versus early disease. Higher risk would generally be acceptable to individuals in extremis compared to those facing minor disease, preventive intervention or those early in their disease-course. Frequency, or likelihood of a particular positive or negative effect, is a significant issue in considering the risk-benefit balance, again influenced by the context in which the judgement is made. If the number of primary prevention patients that needed to be treated by statins for one patient to benefit in any year (NNT) was 10, rather than the observed 700[1], the debate about potential side effects would likely be more muted.

Effect size is also important. The benefit of a drug with a small positive effect may easily be counterbalanced by a relatively small deleterious effect, making its value – and the evidence base - more open to question and debate. This is a particularly pertinent issue in an era where historic gains made by therapies and the complex nature of diseases mean that, with the exception of some stratified/precision medicines, the effect sizes of new products tend to be modest in comparison to existing treatments.

It may also be helpful to examine public attitudes to different benefits. Generally, evidence collection is designed with the primary aim of meeting the therapy developer's needs in

[1] Taylor FC, Huffman M, Ebrahim S. Statin therapy for primary prevention of cardiovascular disease. JAMA. 2013;310(22):2451-2452

demonstrating the effectiveness of a novel treatment, often ultimately for regulatory approval. However, an increasing focus on meeting the needs of patients and society – and the benefits they perceive as important - will be helpful. For example, one consortium in the MRC's Stratified Medicine Initiative is developing a predictor of clinical risk, which clinicians intend to use to better direct limited health care resources to high-risk patients. Patients see the tool as providing increased quality of life, by identifying those at low risk and thereby reducing their levels of anxiety. Given these different perspectives, these two groups may have very different expectations with regard to the importance of, for instance, the evidence for the tool's positive versus negative predictive value. In weighing risks and benefits, it is also possible that patients may consider some benefits so important that associated risks are underplayed.

When considering the patient perspective, it is helpful to include an assessment of the relative merits of surrogate markers of effect and patient reported outcome measures; the former generally providing measurable, quantifiable and short term outputs, and the latter providing an insight into the impact that a treatment has on a patient's quality of life. While surrogates are valuable developmental tools, they may not resonate with patient experiences (having high cholesterol, for instance, not being readily discernible by an individual) and hence may not be evidence that helps them evaluate risks and benefits in terms relevant to them.

Two broader factors to consider are access to evidence and the public's ability to interpret this information. If society is to judge the relative risks and benefits of medicines, it needs access to all the relevant evidence both supportive and otherwise, while taking due regard to ethical considerations such as patient privacy. This access helps to address issues such as 'publication bias' and concerns regarding potential conflicts of interest in those designing and/or undertaking the trial. Any potential conflicts should be declared to potential funders and to research ethics committees, as well as being made public once the trial starts. In addition, society requires that decisions taken on its behalf, by for instance the MHRA, EMA and NICE, be made in an open and transparent manner. To ensure access, the MRC, and other funders, require that the clinical trials it supports be registered on a public Clinical Trials Register and that the results of such trials be published within a reasonable period (normally within a year) following the completion of the study. Similar requirements are now being mandated for some industry-sponsored trials and pharmaceutical companies are increasingly providing access to datasets for independent analysis by third parties. The new Clinical Trials Regulations will improve transparency in this regard.

Importantly, communicating complex scientific evidence to different audiences is challenging. Comprehension of a modern scientific paper may require an understanding of statistics, clinical trial methodology, genetics and pharmacology among other disciplines. The analytical challenge of using this evidence to judge risks and benefits means that the public and patients often rely on intermediaries (organisations/individuals) reaching decisions on their behalf. Societal responses to evidence can therefore be impacted by not only the sources of evidence, but also by the level of trust in intermediaries. While trust in scientific evidence is most pertinent to this enquiry, it should be acknowledged that this problem is not restricted to medicine and healthcare. As explored further at question eight, decisions can also be impacted by information sourced through the media and websites. Communication is essential and researchers as well as the medical profession have a particular responsibility to engage the public/patients, through communicating in plain language and using more accessible formats than just scientific journals, to share evidence, build transparency and trust.

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

The challenge in evaluating a medicinal product is ensuring that test results are accurate and free from bias. While not without limitations randomised controlled trials (RCTs) are regarded as providing the most robust evidence for safety and efficacy, showing whether the product works in relatively controlled circumstances. With the growth of large primary care databases and sophisticated clinical information systems, real world studies drawing on these sources are increasingly being used to assess effectiveness. These studies provide evidence of how the product works in practice. However, there remain many difficulties to research using these types of data. Because the data are not designed for research, there is a major risk of selection bias and unmeasured confounding. Statistical issues include difficulties with missing data and in allowing for time-varying confounders. While recent research aims to identify when observational data may be used and how to make best use of them, randomised studies remain the best source of evidence. Post-marketing surveillance and pharmacoepidemiology are powerful ways of uncovering unexpected and uncommon side effects, which are unlikely to be reliably detected in RCTs, even when there are thousands of participants.

The synthesis of evidence from different sources, for example through meta-analyses, is a key part of decision making and typically requires, besides RCTs, data from post-marketing surveillance, disease-registries or observation (such as Clinical Practice Research Datalink). Decisions based on meta-analyses should be informed by all relevant evidence. Omitting selected lower-quality studies potentially reduces transparency and accountability. The MRC's Biostatistics Unit at Cambridge (MRC BSU) has developed an approach[2] for using expert opinion to inform adjustment of sources of evidence for both internal biases caused by methodological flaws, and external biases caused by deviation of study designs from the research question of interest. Such adjustment for biases in meta-analysis can allow decisions to be based on all available evidence, with lower quality or less relevant studies down-weighted.

In synthesising evidence the MRC BSU has proposed that the following principles are important:

1. All relevant evidence should be included. Where the medicinal product is publicly available, this requires a systematic review performed according to a high standard (e.g. http://handbook.cochrane.org/).
2. The best way to ensure that all relevant randomised trials are included is to insist on prospective trial registration (e.g. http://www.isrctn.com/).
3. The quality of all included evidence should be assessed in order to determine its likely relevance and risk of bias (e.g. http://handbook.cochrane.org/).
4. A quantitative summary should be performed.
5. The whole review process should be transparent and performed as far as possible according to a pre-defined protocol.

The GRADE working group (http://www.gradeworkinggroup.org/) has produced influential guidelines on grading the quality of evidence and the strength of recommendations.

[2] Turner RM, Spiegelhalter DJ, Smith GCS, Thompson SG. Bias modelling in evidence synthesis. Journal of the Royal Statistical Society, Series A 2009;172:21-47

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

RCTs are regarded as providing the most robust evidence for safety and efficacy, but they have limitations. Risks which arise in the longer-term cannot be identified by randomized controlled trials in which patients taking the trial medication are generally only followed up for the specified duration of the study. Similarly, serious risks that occur with a low frequency of 1 in 10,000 – or less often – are very unlikely to be reliably discerned in standard-sized randomized controlled trials, unless they manifest in a very distinctive manner.

All trials are usually statistically powered on a primary endpoint and therefore their effectiveness is expressed in terms of that endpoint. A trial that is powered on mortality (such as many of the statin trials) might not have sufficient numbers of participants to reliably detect rarer events, such as side effects, than the primary outcome, even if they are specified as secondary endpoints.

To increase the likelihood of establishing a robust and clear result, most Phase 3 trials comprise a highly selected population with very stringent entry criteria and exclusion criteria and often limited clinical endpoints. However, these patients represent only a subset of the real world patients with a particular disease. If one takes a disease such as asthma, it is estimated that only 6% of patients with the disease in a population are selected for trials[3]. When such trials are then expanded to the wider population in society and in different countries efficacy can drop considerably.

While the design of randomised controlled trials is hugely important, the rigorous analysis of the resulting data is also critical. Particular issues that can cause bias and reduce the usefulness of statistical findings are missing outcome data and treatment switching, which occurs when patients in the control group of a trial are allowed to switch onto the experimental treatment at some point during follow-up. The MRC's Biostatistics Unit is working to find more appropriate methods for the analysis of randomised trials which can allow for missing outcome data and correct underestimation of treatment effects due to patients switching treatment.

Meta-analyses of multiple trials, while a powerful tool, pose analytical challenges in drawing sensible inferences across different sources (for example, linking accurately to ensure like-with-like comparison of outcomes and co-morbidities). In addition, meta-analyses suffer from being restricted by the severity of the constituent RCTs' entry criteria. Trials exclude many people in society based on factors such as age, smoking, weight, co-morbidities, concomitant medication use, etc. A field deserving much more attention is evaluations of efficacy and safety in infants, children and adolescents. Complex disease often differs in these age groups as the molecular pathways that often initiate disease are not the same as those that lead to its persistence. Thus, some treatments which are active in adults may be ineffective or less active in treating young children, and vice versa.

There is also an issue of trying to create "one size fits all" concepts in these large analyses. While this is important for treatments that work at a population level, there are real issues when different causative endotypes operate in different patients. If privacy risks can be satisfied, meta-

[3] Travers J, Marsh S, Williams M, Weatherall M, Caldwell B, Shirtcliffe P, Aldington S, Beasley R. External validity of randomised controlled trials in asthma: to whom do the results of the trials apply? Thorax. 2007 Mar;62(3):219-23

analysts can generally do a more thorough job of evidence-synthesis if they have access to individual patient data or, as in the case of NICE's re-appraisal of Alzheimer's' drugs, trialists have agreed to a meta-analysis protocol whereby they each provide pre-agreed summary statistics from their trials.

Outside of the trial environment, adherence becomes a serious potential confounder in real world data. Most treatments of chronic diseases are suppressive rather than curative. This means that patients need to take the prescribed medication on a regular basis sometimes for a lifetime, thereby creating opportunity for reduced adherence. The issues surrounding this require an appreciation of a patient's understanding of their own disease and the factors that influence their motivation to take a medicine regularly. New technologies to improve adherence to treatment are being devised, but greater attention to this aspect could be very beneficial.

An area deserving of attention is the identification of patient concerns in relation to treatment responses, such as the most effective ways of managing their condition with other health problems. The James Lind Alliance (http://www.jla.nihr.ac.uk/) is bringing together patients and professionals to identify priorities and gaps in this area. A related issue is that there remain areas such as "fatigue", mental health measures and "well-being" which, while being major patient concerns, are difficult to quantify/objectivise, leading to their inadequate assessment in trials.

Greater confidence in trial findings can be gained by completing two additional cycles. Firstly, by going back to basic science to confirm a causative relationship between any inferences drawn and, secondly, by going forward to assess how well evidence stands up as it is put into practice, clinically or otherwise.

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

With the growing evidence that many classically described diseases may be aggregates of discrete sub-populations with different disease drivers, trialists should be alive to the possibility that there may be significantly different effects in such sub-populations.

A treatment that initially looked as if was going to fail was the use of anti-interleukin-5 mAb (Mepololizumab) against severe asthma. IL-5 is known to be a major allergic-type cytokine involved in eosinophil recruitment and maturation in diseases such as asthma. This approach was highly effective in animal models of eosinophilic airway inflammation (e.g. mice and NHPs). However, intravenous Mepolizumab failed to inhibit the allergen-induced late asthmatic response in allergen challenged asthmatics and the first trial in chronic severe asthma failed to reveal efficacy. However, when asthmatics were sub-phenotyped according to the presence of sputum eosinophils despite steroid therapy, Mepolizimuab treatment was highly efficacious – notably not on the usual asthma end-points (lung function), asthma symptom scores (ACQ), bronchodilator use or bronchial hyperresponsiveness, but on asthma exacerbations. If exacerbations were not used as the primary outcome measure, then the efficacy of this treatment would have been missed completely. This has been repeated in several subsequent studies using eosinophils or Th2-type allergic biomarker to stratify patients. The treatment is now being clinically developed. Stratification of complex disease is becoming increasingly important and may well account for why treatments that look good in early selected efficacy trials fail or are less efficacious when prescribed in practice.

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

A key principle should be that any evidence should be understandable and seen as trustworthy.

Presentations of evidence should clearly set out the overall potential benefits of a proposed intervention, balanced against possible risks, in a format tailored to the intended audience and consistent across audiences (e.g. patients themselves, payers, doctors, etc.). These should be clear about any uncertainties regarding the benefits and risks.

There should be a description of the evidence's provenance, which should describe the entities and processes involved in producing and delivering or otherwise influencing the evidence. A provenance statement indicates clinical significance in terms of confidence in authenticity, reliability, integrity, and stage in lifecycle (e.g. has the evidence been authenticated by a regulatory/evaluator body).

In 2005 the Medicines and Healthcare products Regulatory Agency in conjunction with the Committee on Safety of Medicines (now the Commission on Human Medicines) published "Always Read the Leaflet – getting the best information with every medicine". This document provides valuable good practice in the area of patient information provision.

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?

It is an MRC principle that all those involved in MRC-funded research should be honest in respect of their own actions and their responses to the actions of others. The research community must foster and support a culture of transparency and honesty which promotes good practice, recognises relevant interests or conflicts (whether actual, perceived or potential) and deals with these openly and explicitly. This applies across the whole range of research activity from study and experimental design, generating, analysing and recording (including archiving) data, sharing data and materials, applying for funding, publishing findings, acknowledging the contributions of others and engaging in the peer review process.

How important is industry funding in generating and analysing evidence?
Industry funding underpins medicines development research. A real or perceived issue is "biased design" of studies (e.g. inappropriate comparators, questionable statistical techniques, including management of missing data/drop-outs, etc). Possible solutions could include instituting an independent review body (potentially part of an existing regulatory authority, e.g. MHRA or EMA, or an extended remit of an ethics committee or equivalent) to approve the design of any study that a company intends to subsequently use to make label claims, before that study is eligible to start. Furthermore, publication of the protocol and pre-specified analytic plans would generate greater confidence in the results of studies when reported.

As discussed above, the use of highly selected populations in late phase, often industry funded, trials and limited clinical endpoints can result in trial efficacy not transferring well to real life use. This reduction in apparent efficacy can lead to mistrust about such studies. Greater patient participation in the process of deciding upon entry criteria and end points could help to build trust. It should be recognised however that studies submitted as part of a regulatory submission are closely scrutinised by the relevant body as part of the approvals process, a more rigorous process than is often used for non-medicinal treatments.

“Biased publication” would be addressed by mandating that all trials be registered before they start and that results are published, whether positive or negative, within a set time after last subject last visit. Making datasets available for independent analysis by third parties, whilst maintaining patient confidentiality, is something the pharmaceutical industry is increasingly undertaking.

Other than industry sponsorship, what are other potential sources of conflicts of interest?
Industrial and academic/clinical participation in research funding, delivery and publication can all be potential sources of conflicts of interest. Possible examples include situations in which the reviewer is an inventor on a patent relevant to some aspect of the research, or in which the research supports, competes and/or conflicts with the scientific interests and/or output of the reviewer. Having a process that encourages participants to consider the potential for conflicts on an ongoing basis can help protect individuals and organisations from allegations of bias. Such a process should however be reasonable (i.e. commensurate with level of the perceived risk) and needs to strike a balance, to ensure that those best placed to comment on/contribute to the research are not unduly excluded. The best insight may come from those most closely involved with a drug’s development and their industry-affiliation should not exclude them as consultees when it comes to the elicitation of prior opinion about either benefits or risks.

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.

Researchers at MRC/Chief Scientist Office Social and Public Health Sciences Unit, University of Glasgow are currently finishing a web tool designed to guide users through the process of evaluating the quality and usefulness of published health research. The tool emerged from a project funded by the MRC Population Health Sciences Research Network to assess existing critical appraisal tools, determine what a new tool should provide, and develop a web tool based on those requirements. The Understanding Health Research tool is hoped to be useful to a broad range of audiences including patients, health professionals, policymakers, students and early career researchers. At launch, expected late 2015, the tool will have data collection capabilities to evaluate users’ experiences with the tool and determine whether this type of tool is effective in helping them to assess health research.

The James Lind Alliance is a non-profit making initiative that brings patients, carers and clinicians together in Priority Setting Partnerships to identify and prioritise 'unanswered questions', about the effects of treatments.

There are a number of excellent resources around the perception of risk which are of relevance. For example the work of Professor David Speigelhalter, Cambridge University’s Winton Professor

for Public Understanding of Risk, as exemplified by the chapter in the Government's Chief Scientist's annual report on Innovation and Risk.

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

When considering the 'public' it needs to be recognised that this is a very broad group covering everyone from the very well-informed clinician who becomes a patient, to the over-anxious individual or someone who would simply 'rather not know' about their diagnosis or treatment. All of these have access to more information about their health or illness than ever before and it comes from a wide range of sources. These include: the media and the internet; government bodies; health professionals and pharmacists; advertisers; pharmaceutical companies; friends, relatives and other patients.

Furthermore, the information from these different sources may differ slightly, may appear to change from one day to the next and, on occasion, different sources may be completely contradictory. In an effort to make sure patients have as much information as possible about their health and healthcare in order that they can make the most informed decisions, we may be in danger of overwhelming them with information as much as we are 'empowering' them.

Anecdotally at least, many people appear frustrated with the amount of evidence with which they are confronted, asking "What would you do, doctor?" when given different treatment scenarios, or opining that what they read one day is contradicted by a new study the next – so they might "just as well eat, drink, sleep, exercise as much as I like" and perhaps take or not take the drugs prescribed to them. By providing, for example, information leaflets that list a drug's every possible side-effect (often written in a typeface too small to be read by many of those most likely to be prescribed it) are we causing patients to worry about a risk that might actually be tiny?

When providing information to patients, it can be difficult to present 'hard' facts about benefits and risks because of the sometimes poor correlation between trial evaluations and real world application, as discussed above. Rather than seeking to make idealised data relevant to particular individuals, the use of narratives for different conditions and treatment options can be helpful. To be effective, different communication approaches will likely be needed for different cadres of individual, some audiences desiring highly quantitative data with others, for instance, seeking more visual descriptions. Providing a hierarchy of detail that the more questioning can drop into may be of benefit.

As exemplified by this Call for Evidence, further work is required to understand how best to communicate evidence. Such work would benefit from an assessment of the value choices patients make when weighing up the benefits and risks of a treatment option, and of the most understandable ways of communicating required information, recognising the limitations of the evidence.

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