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

This response includes contributions from:

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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?

- The perceptions of benefits and risks as viewed by lay people are likely to be different from the perceptions of the scientific community; hence we would recommend that the Academy consider both perspectives. There are two key areas to consider which speak to potential sources of difference. Firstly, we know that both low health literacy and unclear dissemination of evidence can be barriers to understanding and communicating the risks and benefits of medicinal products. In addition, there is lack of consensus about the relevance of different measures of benefit and risk. Hence adequate education for both healthcare professionals and the public, and clearer integration and dissemination of evidence tailored to specific audiences are needed to enable effective use of evidence. Secondly, we know that people are not 'blank slates' and that pre-existing beliefs and experiences are likely to influence interpretation and use of evidence even if these barriers are removed. Individuals vary in whether they view medicinal products as typically overused, harmful or beneficial. These views influence, but don't fully determine, judgements of the risks and benefits of specific treatments for specific conditions. Views of medicinal products overall and specific treatments are influenced by factors including cultural background, professional training, and past personal experiences with treatment and illness. In everyday practice, the perspective of patients, payers and to some extent healthcare professionals will include not only 'scientific' evidence of the risks and benefits of treatments but also factors such as past experience or trust in healthcare teams, and their expectations. When considering how society uses evidence it is therefore important to bear in mind that quantitative assessments of risks and benefits may differ from perceived risks and benefits, and these will not be uniform across medicinal products nor across individuals.

- Publication bias is a known issue; specifically, journals may be more likely to publish pharmacovigilance studies if they report a positive association between risk and treatments; such publication bias can distort future risk and benefit assessments. In addition, few research organisations provide information in an integrated manner (i.e. evidence synthesis to reflect overall benefit-risk balance, taking into account individual differences and clinical context.

- The media play a key role in shaping public perceptions around risk and benefit of medicinal products, which is sometimes helpful but sometimes unhelpful if the wrong messages are communicated. Partial views and opinions may prevail over facts. We feel that this is a significant issue that should be considered.

- The balance between societal and individual risks, particularly for issues such as the use of antimicrobials / prevention of antimicrobial resistance, is complex for healthcare professionals and the lay public alike. However, understanding and addressing this is essential if we are to prevent a future where there are few effective antimicrobials available.

- Despite the increasing interest in personalised medicine, therapeutic guidelines still lag behind with regard to the impact of individual differences. The complexity is partly due to poor understanding of factors determining drug response and variability. Hence, any attempt to define the risk-benefit balance of an intervention will require such knowledge. Overall treatment outcome is the result of multiple interacting factors. A quantitative framework understanding and addressing this that discriminates between drug, disease, patient and healthcare factors is essential.

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

- We agree in general that *efficacy* of medicinal products is best assessed by meta-analysis of randomised controlled trials (RCTs); this is particularly the case for specialist areas such as medicines for children as the sample size of each RCT is usually small. Evidence synthesis by modelling and simulation should also be considered, as it provides a more mechanistic interpretation of the data distribution and enables further evaluation of the impact of different sources of variability.

- However, observational studies using large databases are the only option in detecting *rare adverse events*, eg: *Chan EW, Liu KQ, Chui CS, Sing CW, Wong LY, Wong IC. Adverse drug reactions - examples of detection of rare events using databases. Br J Clin Pharmacol. 2014 Jul 24. doi: 10.1111/bcp.12474. [Epub ahead of print]*

- Integrated pharmacokinetic-pharmacodynamic modelling and multi-decision criteria decision analysis is another important approach to consolidate information about the benefit-risk balance, taking into account uncertainty. The approach also allows for prediction or inference about conditions or scenarios which have not been evaluated experimentally, i.e., not-in-trial simulations, a feature that allows one to define the impact of treatment . *E.g., Bellanti F, van Wijk RC, Danhof M, Della Pasqua O. Integration of PKPD relationships into benefit-risk analysis. Br J Clin Pharmacol. 2015 doi: 10.1111/bcp.12674.*

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

- We agree in general that *efficacy* is better assessed by meta-analysis of RCTs. However this approach becomes problematic in specific populations such as children, the elderly and pregnant women, as such groups are usually excluded from clinical trials and RCTs therefore do not usually provide sufficient information on the efficacy in these groups. Since the "Better medicines for children" EU regulations have been implemented, there have been some improvements in paediatric medications. Where RCTs are not possible, alternative methods such as pharmacokinetic/pharmacodynamics modelling and simulation should be considered as the basis for evidence synthesis for special populations as well as progressive chronic diseases, for which limited experimental data are available.

- Observational studies using large databases are the only option in detecting *rare adverse events*. However, methodologically this approach is much more challenging. It is therefore important to have duplication studies to confirm or refute the results (as in pharmacogenomics studies). For example: Etminan et al (2012) published an observation study investigating the association between oral fluoroquinolone use and the development of retinal detachment. However, a systematic review and meta-analysis of seven observational studies does not support an association between oral fluoroquinolone use and the development of retinal detachment (Chui et al 2015). Given the low absolute risk, 4.85 per 1,000,000 prescriptions (95% CI 0.78-8.91), such an event would be rare if there were an association The current prescribing practice for fluoroquinolones should therefore not be altered because of a previously suggested potential risk of retinal detachment (Chui et al 2015).

  References: *Etminan M, Forooghian F, Brophy JM, Bird ST, Maberley D.Oral fluoroquinolones and the risk of retinal detachment. JAMA. 2012 Apr 4;307(13):1414-9. doi: 10.1001/jama.2012.383.*

  Chui CS, Wong IC, Wong LY, Chan EW. Association between oral fluoroquinolone use and the development of retinal detachment: a systematic review and meta-analysis of observational studies. J Antimicrob Chemother. 2015 Apr;70(4):971-8. doi: 10.1093/jac/dku507. Epub 2014 Dec 18.

- Adverse event rates can be affected by the way in which adverse events are defined and assessed. It is likely that these methods may not be comparable across research methodologies. For example, an RCT in which reports of adverse events are actively elicited may obtain more adverse event reports than an observational study where adverse event reports may be reliant on the patient and doctor labelling a symptom as an adverse event and recoding it as such. This may be particularly true for 'nonspecific' adverse events, e.g. fatigue and nausea, for which many other causal factors exist.

- Most publications are based on experimental protocols that focus on either efficacy or safety in a descriptive manner. Rarely, these data are presented in an integrated manner which allows for characterisation of the benefit-risk balance, taking into account the impact of treatment on overall disease processes and health outcome. Isolated assessment of the relevance of different measures of efficacy and safety may lead to major biases in terms of the true benefits and risks of an intervention. This limitation applies to data derived from

both RCTs and meta-analyses, which rely on the available data and/or its summary statistics. Evidence synthesis by modelling and simulation should be considered in conjunction with multicriteria decision analysis to ensure accurate integration of benefit and risk data.

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

- A combination of information from various sources can be used to assess the risk and benefit of medicines for children. For example, intranasal (IN) diamorphine has been used as unlicensed medication in UK emergency departments for many years following evidence from an RCT (vs intramuscular morphine). However the safety profile has not been fully characterised. A systematic data collection of the adverse events in clinical use has provided sufficient safety data to confirm the safety of IN diamorphine (Kendall et al 2015). In combination with a pharmacokinetic study, the drug has now been granted a UK license for acute pain relief in children (www.medicines.org.uk/emc/medicine/28323). *Kendall J, Maconochie I, Wong IC, Howard R; DIASAFE study. A novel multipatient intranasal diamorphine spray for use in acute pain in children: pharmacovigilance data from an observational study.Emerg Med J. 2015 Apr;32(4):269-73. doi: 10.1136/emermed-2013-203226. Epub 2014 Jan 9.*

- The impact of drug-induced QT prolongation in real-life patients can be assessed and disentangled from disease- and patient-related factors by the use of pharmacokinetic-pharmacodynamic relationships as the basis for extrapolation of data from clinical trials to real-life conditions. *Chain AS, Dieleman JP, van Noord C, Hofman A, Stricker BH, Danhof M, Sturkenboom MC, Della Pasqua O.Not-in-trial simulation I: Bridging cardiovascular risk from clinical trials to real-life conditions. Br J Clin Pharmacol. 2013;76(6):964-72.*

- In an aging society, evidence generation based on RCTs may not provide the necessary information to define the dose rationale and overall benefit-risk profile of a medicine. The exclusion of older adults (>75 y) from clinical and health outcome research can be overcome by an integrated pharmacokinetic-pharmacodynamic approach. *Saeed MA, Vlasakakis G, Della Pasqua O Rational use of medicines in older adults: Can we do better during clinical development? Clin Pharmacol Ther. 2015;97(5):440-3. doi: 10.1002/cpt.87.*

- Currently recommended interventions based on medical practice or evidence-based medicine does not necessarily ensure an optimal benefit-risk balance. Experimental protocols are often limited to one single pre-defined scenario. Simulations can enhance the opportunity to explore a range of treatment options in virtual patient cohorts, providing insight into alternative, better therapeutic interventions. *Sahota T, Della Pasqua O.Feasibility of a fixed-dose regimen of pyrazinamide and its impact on systemic drug exposure and liver safety in patients with tuberculosis. Antimicrob Agents Chemother. 2012 Nov;56(11):5442-9.*

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

- Terminology such as “relative risk” and “odds ratio” etc can sometimes be difficult to interpret for both lay people and healthcare professionals. It is important to think in terms of absolute and absolute risk, and how best to communicate this to the general public. Numbers needed to treat / harm may be useful here, and there is evidence supporting different decision tools to aid presentation of these data.

- Are the outcome measures relevant to patients? Eg antiepileptic drug studies regularly report 50% seizure reduction, but for someone with regular seizures, 50% seizure reduction may not be the most important outcome. Freedom from seizures and/or adverse drug reactions may be more important to the individual concerned.

- A related issue is that of expectations around benefits and harms – no medication is 100% effective, and none is 100% safe, and yet sometimes the public (and sometimes healthcare professionals) seem to be unaware of this.

- It is essential that metrics for benefit-risk balance capture the multidimensionality of what constitutes the therapeutic response. Most protocols are based on empirical evidence from primary and second endpoints, which in most cases, are not connected with each other in a mechanistic, or biological manner. Tackling this would enable a more coherent evaluation of drug effects, disentangling these from disease-specific and patient-related factors. Thus far, multicriteria decision analysis, and a few variations of the approach, seem to be the only suitable methods for the purposes of retrospective and prospective evaluation of benefit-risk balance, i.e., based on data already collected, as well as taking into account future (proposed) utilisation of medicines.

- Some models of judgment and decision-making have highlighted the importance of automatic processes, or the importance of heuristics. It is likely that many evaluations of medicines may use these ‘fast’ routes to decision making rather than ‘slow’ evaluations using the full evidence regarding risks and benefits. More evidence is needed regarding (1) if, and in what circumstances biases and heuristics are used rather than deeper evaluation; (2) the nature of these heuristics and the implications of this for evidence communication; (3) the role of behavioural economics in this field.

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?

- We note that industry funding is a major funding stream for clinical research and that drug companies produce the drugs for marketing. Without company funding, there will be few, if any, drugs on the market. We therefore need to move away from seeing industry as the “bad guys” but work with them to ensure transparency of funding, conduct, analysis and

publication of research. Registry of clinical trials has been useful for RCTs and is clearly the way forwards, but should also be promoted for a wider range of studies such as for pharmacovigilance studies. Publication of protocols prior to the conduct of studies also will help to ensure transparency in trial reporting and analysis. Journals have a role to play in publishing negative findings as well as positive, in order to avoid publication bias. Likewise, academic researchers have a responsibility to publish replications and negative findings in a timely fashion and to declare any potential conflicts of interest.

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.

- A useful document is the recent report from the Wellcome Trust on public perceptions around antimicrobial resistance: http://www.wellcome.ac.uk/stellent/groups/corporatesite/@policy_communications/documents/web_document/wtp059551.pdf

- The UCL-Lancet Commission on Culture and Health contains extensive discussion on the role of culture in interactions with healthcare including medicinal products. Napier et al. (2014) The Lancet Commissions: Culture and Health. Lancet 384 (9954): 1607-1639. http://dx.doi.org/10.1016/S0140-6736(14)61603-2

- The work of the Harding Centre for Risk Literacy in producing independent information about medicinal treatments may be relevant to this. In addition, the research activities within Clinical Pharmacology and Therapeutics, which are being developed in close collaboration with Bangor University may also be of interest to the Society.

- “Better medicines for children from European Medicines Agency” and “Best Pharmaceuticals for Children Act (BPCA)” from the FDA have improved medicines for children significantly and there are some good lessons to be learnt.

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

There are many effective ways of communicating evidence to stakeholders, and it is likely that the most effective method will depend on the type of evidence that needs to be communicated, who it is targeted at, and how they will be using the information.

- The internet and social media are potentially very powerful and relevant to all stakeholders.
- Educational materials are important for healthcare professionals.
- Education of children and young people may be important in creating awareness of key points from an early age
- TV, radio and newspapers are important for lay people and indeed health professionals.
- We need to provide consistent messages across all stakeholder groups, while also ensuring that these are tailored appropriately for the audiences concerned.

- Patient groups can communicate evidence to individual patients, and provide a forum for engagement
- Healthcare providers are a key source of communication regarding evidence for patients
- Patient information leaflets are a key source of information for patients
- The Cochrane Consumers and Communication group have produced a number of systematic reviews of different methods of communication to different stakeholders. http://cccrg.cochrane.org/our-reviews