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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 aims to use evidence to judge the benefits and risks of many goods, services and pastimes. We use comparison websites to assess relative value across goods and services. We read consumer reviews to judge the value of a given product. We rely on the media to update us on whether these goods, services and activities are on the whole good and beneficial or risky and to be avoided, e.g. computer games and screen time for children. As participants in the Information Revolution, we can collect and use evidence through an increasing number of channels. Whether this evidence is robust, verifiable and accurate, and whether it can be fully and fairly assessed is another matter. We also rely on the Government to provide the overarching regulation and oversight for the provision of these goods, services and activities before they reach the public whether this is via Trading Standards, Health and Safety Executive or in the case of medicines the Medicines & Healthcare products Regulatory Agency (MHRA).

An important question to address is why the use of evidence is (more) challenging for medicines. Arguably this is because the patient, who is most directly affected by – indeed the "end consumer" of - the medicines, is often not able to directly evaluate the medicine themselves; instead, they rely on their healthcare professional to guide their treatment and to make those assessments. This is often referred to as the principal agency problem in the case of information asymmetries.[1] The expectation is that the healthcare professional has the information and capabilities needed to make those decisions. The question is: **how can the healthcare professional likewise confirm the evidence regarding the medicine without directly reviewing the evidence of each and every medicine?** From this need has come the development of a regulatory authority to provide a thorough and unbiased assessment of the benefit:risk of medicines on behalf of patients, healthcare professionals and the wider society, and thereby to determine whether the medicine on balance provides more benefit that risks to those patients for specified indications and areas of treatment.

Regulatory authorities worldwide are constantly re-assessing how they evaluate the benefits and risks of medicine, what perspectives they need to incorporate and how often they do this. Moreover, the regulatory paradigm has moved towards a more continuous assessment, with regular monitoring and reporting on medicines by manufacturers as well as proactive pharmacovigilance. Signal detection and the algorithms used to detect potential concerns are increasingly sophisticated, but very much reliant on adverse event reporting, i.e. the routine reporting by manufacturers and academic research. The Pharmacovigilance Risk Assessment

[1] 1 For a good summary of the issue, please see http://lexicon.ft.com/Term?term=principal/agent-problem

Committee (PRAC) of the European Medicines Agency was established as part of the enhanced Pharmacovigilance Directive which came into effect in 2012, and it has quickly become one of the busiest Committees supporting medicines in Europe. A number of research papers have underscored the value of pharmacovigilance in further establishing the evidence of a medicine. (Arnaiz et al. 2001; Ebbers et al. 2011; Ebbers et al. 2013; World Health Organization 2006; Stefansdottir et al. 2012)

The biopharmaceutical companies themselves also play a considerable role in continuously monitoring and evaluating any change in benefit-risk profile of their medicines. Companies have invested considerable effort and resources to establish monitoring and reporting systems to meet this challenge globally. These Safety departments are responsible for meeting requirements to regularly update any change in evidence to regulatory authorities, as well as to communicate those appropriately to relevant stakeholders (including the 'Dear Healthcare Professional" letters). Risk management and risk minimisation, as well as post-approval confirmation of benefit:risk, is proactively undertaken in companies as well as by regulatory bodies, and both are informed by independent academic research.

However, the regulatory authorities do not provide a view of how well a medicine delivers that benefit in a given healthcare setting, particularly in comparison to other treatments. For that relative efficacy, other agencies (e.g. Health Technology Assessment (HTA) bodies) have added this role of evidence analysis, again on behalf of healthcare professionals, patients and the wider public. The current initiatives by EUnetHTA and the EMA to consider a relative efficacy assessment for Europe could help to harmonise evaluation and understanding of a medicine's value, as well as possibly expand and improve the evidence collected and assessed for that purpose. Again, as in the case of regulatory evaluation, further evidence will be collected and assessed by companies, regulators, independent researchers and others (for example, medical charities and patient representatives). The combination of both interventional and non-interventional trials (randomized clinical trials, 'pragmatic' trials (Roland and Torgerson 1998), etc) and observational studies, making ever greater use of real world evidence, will bring more and additional evidence to assess.

Indeed, social media is already providing a channel for shared experience to collect and be compared. Patients and wider society will always make use of evidence and commentary on medicines provided through other channels, such as personal contacts, broadcast and social media. Concerns that have been raised about the treatment of evidence in the media is that this evidence is not always put in context, the limitations of the research are not sufficiently described and the findings of the research are extrapolated to outcomes and timings that raise (or lower) expectations for a medicine or treatment far beyond what the research has concluded. Moreover, evidence in the media is naturally event driven, often when a study has indicated a new or unusual outcome. It is very rare that when subsequent research either confirms or rejects these findings that the overall body of evidence of a medicine or treatment is set out in the media for discussion. In other words, it is a rare news story that explains that the research previously reported on as a new finding has now been discounted by the weight of evidence from other studies. This explains the 'see saw' declarations of the benefits and risks of a given medicine, treatment or even food.

Ultimately what matters is whether evidence is reliable, robust and reproducible. This is a challenge for any researcher – industry or academic – and for the user of that research. Much has been made about potential bias for reasons of gain (market, career, academic standing), but some errors are simply the process of science. Not all methods are sound and result in findings that will stand the test of time. Flukes can happen. However, this is the power and requirement of scientific

discourse – to test results and confirm findings (for an excellent summary of this issue and how it was material for drug development, see (Begley and Ellis 2012)).

In some cases, it is the source data – the 'evidence' – that is flawed. Previously there was a hierarchy of evidence that would have set randomised clinical trials above other data (observational, real world evidence, reported findings), primarily because the internal validity of the design and control of the study and the ability to isolate variables of interest were of primary importance. However, the external validity about how these results will relate to common practice and outcomes is now equally important (Parkinson 2014), and the growing recognition of real world evidence reflects this. Nevertheless, each approach – RCT and RWE – has its strengths and weaknesses, and both may generate evidence that will still need to demonstrate that it is reliable, robust and reproducible.

The challenge for this review is to consider how evidence itself is compared and valued, in particular when findings from different lines of research do not align. In that circumstance, whose judgement should guide practice? Again, the regulatory authorities have been established as the arbiter, to help guide these judgements and science continues to progress understanding, and particularly where there are different findings. Despite some popular criticism (Goldacre 2014), we would argue that this has been a successful regulatory system, with agencies like MHRA and EMA actively seeking to widen their review, broaden their competence and engage with all stakeholders. Agencies are dependent on the evidence that is brought forward, of course, and so industry – as indeed all researchers - must also meet their end of the bargain to provide the right evidence and offer transparency on the data and methods used to reach those conclusions.

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

As noted above, evidence reflects both the quality of the data and how it is collected, as well as how that data is assessed and presented. That evidence should be tested to determine if it is reliable, robust and reproducible, and one important manner in which this is done is if several sources and assessments of evidence agree on the same finding(s). These sources and their assessment may not be equally reliable, robust and reproducible, in and of themselves, but if they are all pointing in the same direction, there can be greater assurance that the finding is proving robust. This is the important value of the **meta-analysis**.

The strength of interventional trials is that they aim to address causality directly. The "gold standard" double-blind **RCT** aims to provide a study design whereby cause and effect can be best understood by controlling other variables that may intervene in the outcome. This is why they remain central to evidence required for medicines to be considered for licensed use, because the benefit of a medicine has to be very clearly established, given that risks will always be present.

Observational studies, including 'open label' studies and registries, introduce factors in use that provide additional assessment of the benefit and risk of a medicine in the context of care (e.g. co-morbidities, clinical practice, de facto patient demographics). These are valuable evidentiary resources over the long term, and if the data design is sufficiently flexible, feedback and reflective questions can continue to be posed. These are still clinically-based studies and the collection and analysis of the data are regularly evaluated.

Real world evidence (RWE) is not always well defined but commonly includes evidence from clinical experience (implying an overlap with observational studies, of course) and data collected for other reasons but available for use in health research. Claims databases are a key source for real world evidence (made use of in particular in the US, for example). In the UK, the Clinical Practice Research Datalink (CPRD) is a valuable source for RWE, with anonymised primary care records since 1987 that can be used for health research. This more "free form" evidence can enrich our evidence base for a medicine, and biopharmaceutical companies are heavily invested in addressing how RWE can be used in drug discovery and development, clinical research, health outcomes and safety (McClellan et al. 2015). Amgen has illustrated the potential for this evidence in the application of DeCODE data for the development of evolucumab.[2] In the Salford Lung Study (New et al. 2014), GlaxoSmithKline (GSK) is also employing an RWD approach to evaluate treatments to address chronic obstructive pulmonary disease (COPD) and asthma. A very recent study on comparative safety of dabigatran versus warfarin for the treatment of nonvalvular atrial fibrillation in general practice settings was undertaken using Medicare data of new-user cohorts of propensity score-match elderly patients (134,414 in total) between October 2010 and December 2012. The result was to show that the high quality real world data mirrored the RCT data very closely.(Graham et al. 2015)

As we compare the evidence of a medicine over its lifetime of use, in practice, very little of this is available at authorisation. Indeed, whether by adaptive approval or just continuous development into new indications, the biopharmaceutical company continues to explore the potential for the medicine and to develop a broader evidence base. Moreover, others are also contributing to this wider evidence base in both a structured and unstructured way. **Pharmacovigilance** is a fundamental part of this re-evaluation and extending of the evidence base of a medicine, and the regulatory authorities pursue a number of means to achieve this, both through improving signal detection methods and through a more pro-active review of evidence coming through from a wide variety of channels. The advantage of pharmacovigilance work is that it is globally coordinated and this evidence is shared and assessed. Signal detection requires this global coordination, because medicines are used globally and moreover, unusual signals or early signals depend on having an up-to-date, broad as possible scope for review.

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

All sources of evidence have their advantages and disadvantages. The disadvantages of randomised clinical trials (RCTs) have been much discussed, with probably the most noted being that they are not a good proxy for the practical impact of a medicine in "normal" use, with a broader range of patients and a broader range of healthcare settings. This is what we mean by measures of "effectiveness" as opposed to "efficacy", for which RCTs are very well suited. Moreover, RCTs do not fully address the challenges of polypharmacy (although most clinical trials allow background medication as standard of care), which for many patients are a very real concern, and multiple co-morbidities are not fully appreciated until there is use in the wider population. For those matters, pharmacovigilance and post-marketing safety studies have a critical role to play, and we can anticipate the benefits of real world evidence to help define this evidence base.

[2] Please see https://www.amgenscience.com/#the-new-genetics/can-human-genetics-predict-phase-3-results

Likewise, observational studies and real world data have their weaknesses. In particular, bias and confounders cannot be accounted for as well as in the case of an RCT. Indeed, it can be very difficult to establish causality in these studies. An inference on causality based on data from observational studies may lead to changes in clinical practice, which results of further analyses may later challenge (Ziff et al. 2015). Registries are a very valuable longitudinal evidence base, but they can be limited by the thoroughness of data reporting. Registries are dependent on whether all reporters complete data fields in the same way and to the same extent. Missing fields could mean a loss of important information.

Much expectation has been given to the value of meta-analyses; however, ultimately the quality and value of meta-analyses are dependent on the sources upon which they are based and the methods by which they are aligned (Jacobs 2015). In some cases, this means that they are subject to negative publication bias, whereby unpublished results are not taken into account.

Pharmacovigilance is also dependent upon the quality, depth and scope of the safety data received. It is regularly noted that spontaneous adverse event reporting is a valuable source of data; however, reporting is not regularly undertaken and prone to focal bias (e.g. where something is new or a risk is raised in the media). In the UK, which has a European leading electronic reporting system (the eYellow Card), the reporting levels are low amongst healthcare professionals and patients. However, the challenge for global safety reporting is not always the collection of more data, but how to correctly identify the 'signal' from the 'noise'. Algorithms are routinely reviewed and assessed to consider how well we are identifying signals, and this is an evolving science.

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

There are a number of examples of controversy within society relating to the benefit:risk evidence for a medicine. The most well-known is that of MMR and its supposed link with autism, a now discredited claim, that is held responsible for the recent epidemics of measles and mumps in the UK due to fear of the vaccine. This is an example where public perception of the safety of a medicine has had significant adverse consequences and has still not been addressed within a subset of the population who continue to reject the growing evidence base supporting the safety and effectiveness of the MMR vaccine.

There are also examples of other mainstream medications such as statins and hormone replacement therapy (HRT) where the healthcare community as reported in the media are unable to agree on the evidence base relating to the risk:benefit of the medications and how this is used to develop guidelines for use in patients.

Additional evidence can be beneficial in identifying additional uses of medications such as aspirin to treat infertility (Schisterman et al. 2014). However, developing new evidence is not necessarily reaching a new conclusion about a medicine. The publication of uncertainty in some studies has raised questions about the role of digoxin in heart failure and atrial fibrillation and adverse outcomes. Some large RCTs showed no difference in mortality in patients with heart failure, whilst some observational studies reported increased mortality. Clinical treatment pathways for digoxin changed as a result. But this recent study (Cole and Francis 2015) challenges the reported outcomes of the current clinical perception of digoxin and opens the debate once again.

Some lessons can be drawn not from a case study of a single medicine, but from the experience of a new type of medicine – biosimilars. These are biological medicines that are developed to be highly similar to their reference product in terms of their quality, safety and efficacy. They contain a version of the same active substance as the reference medicine (or originator). At their core, these are biological medicines, just as the originator and other biological medicines, produced in living systems, with all the complexity of cell design and manufacturing that entails. What is very different in terms of evidence is what evidence is put forward for licensing. The biosimilar does not have a package of evidence to demonstrate the patient benefit per se of the medicine, because that has already been done for the reference medicine.(Weise et al. 2012) Instead, the biosimilar dossier includes evidence to demonstrate that it is highly biosimilar (via a biosimilar comparability exercise and related non-clinical and clinical evidence) to the reference medicine. On this basis the regulator can decide if the proof has been met that the biosimilar can provide quality, safety and efficacy to compare with the reference medicine, and that any remaining differences are not clinically meaningful.(Committee for Medicinal Products for Human Use 2014)

Ten years after their first marketing authorisation and continued development of biosimilars, it remains a challenge for many stakeholders to understand and accept the evidence related to a biosimilar. To some extent, this is because the evidence about these medicines required a better understanding of biomanufacturing, which is neither relatively common nor of interest to many. Moreover, the habit of clinicians is to review evidence in familiar ways, that is, Phase III data. Because of their development process and the regulatory pathway, the Phase III data for biosimilars will not align with that of a novel biologic. This can seem unsettling and risky to some who are less familiar with the types of evidence amassed for a biosimilar submission (in particular, the analytical data). Recognising this challenge, the European Commission produced – following a long stakeholder exchange – a Consensus Information Document, which is a good account of the issues but with limited impact thus far for many Europeans.("What you Need to Know about Biosimilar Medicinal Products" 2013)

The consensus process noted above is also relevant in this consultation. Some of the science involved in biosimilars is genuinely new and not undisputed. There was a time when it was thought impossible to produce a biosimilar, and even within the last decade, a concern that a monoclonal antibody biosimilar was not possible to license. Both of those events have come to pass. We have 12 biosimilar molecules licensed in Europe and marketed under 19 brands. One of those molecules is a monoclonal antibody, with a fusion protein currently under review. However, there remain many further scientific areas for elaboration and areas under dispute. It is sometimes difficult to separate this debate from the business concerns related to the medicines involved. For many stakeholders, this introduces questions both about the evidence, how the evidence is being interpreted and how they should make use of this evidence for patient care.

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

As for any research findings, there must always be a clear source of evidence, how it has been compiled and assessed and by whom. The expectation is that evidence should be reliable, robust and reproducible. For this, we need to consider the quality of the research questions, the applicability and quality of the data as well as the capabilities of the assessor.

For the evaluation of the evidence of medicines, we recognise that different data and research modalities best address different types of questions (efficacy, effectiveness, safety). However, whilst everyone has an interest in engaging with this evidence, the ability to critically assess that evidence and the alignment with the interests of patients (who have the greatest stake in the validity of that evidence) must rest with their agents – the healthcare professionals that deliver their care and the regulatory authorities upon which those professionals rely.
Wider comment and reflection on the evidence of a medicine will continue and grow. Responsible reporting and impartial, expert statistical guidance can be advocated through organisations such as the Science Media Centre and the AMS. Evidence should also be presented in different formats dependent on the proposed audience i.e. patients vs. health professionals with good referencing to allow audience to see the sources this has been drawn from. A good example of this is the Patient Information Leaflet (PIL) and Summary of Products Characteristics (SPC) that are available electronically for all medicines in the UK via the e-Medicines Compendium[3]

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?

Bias is a well discussed challenge for all academics, whether they might be biased to advance the interests of a funding body (including industry) or to advance their careers. As in all cases of bias, the solution is for agreed clarity of editorial control, transparency of relationships and robust review of the publication by academic peers.

Beyond the considerable financial investment in medical research and skills development in the UK (£11.5 million/day in 2013)[4], there is an even greater value to the innovative potential of medicines and the life sciences that are generated through this engagement. Collaboration between industry and academics is generally considered a valued and positive activity, even tracked by the OECD as a marker for growth in open and more dynamic innovation systems (OECD 2015). This collaboration on research to build evidence about medicines is critical both to generate new scientific insights about the medicine itself but also to provide a creative relationship to allow the biopharmaceutical firm and the healthcare researcher to explore how this new innovation might be used in practice. Industry's involvement in generating the RWE to support managed entry agreements is pivotal. These can include creative agreements that link reimbursement explicitly with patient outcomes, or could be a commitment to collecting confirmatory evidence of effectiveness in real-life settings. These schemes can minimise the risk of paying for interventions that are poor value for money (Drummond 2015; Towse and Garrison 2010), and industry is often required to fund data collection. To support stakeholder involvement and address conflicts of interest, a clear framework for engagement and governance for data management and analysis is required; the absence of a clear governance framework impedes participation.

Many innovation experts, such as Charles Leadbeater, note the importance of users in helping to define and advance innovation (Leadbeater and Cottam 2007; Leadbeater 2006). The same is true

[3] https://www.medicines.org.uk/emc/

[4] ABPI calculations based on the ONS Statistical Bulletin.(Office for National Statistics 2014)

for medicines, but the “users” in this case are the agents – that is, the healthcare professionals, acting on behalf of their patients and the healthcare system. Without this process of exchange between innovator and user, we are very likely to truncate the innovative impact of a given medicine and the scientific progress on which it is based.

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.

There have been a number of European public-private initiatives set up via the Innovative Medicines Initiative (IMI) that are have some relevance to evaluating scientific evidence about medical products:

- GETREAL - Incorporating real-life clinical data into drug development[5] EHR4CR -Electronic Health Records Systems for Clinical Research[6]
- EMIF - European Medical Information Framework[7]
- EMTRAIN - European Medicines Research Training Network[8]
- EUPATI - European Patients' Academy on Therapeutic Innovation[9]
- Eu2P - European programme in Pharmacovigilance and Pharmacoepidemiology[10]
- PROTECT - Pharmacoepidemiological research on outcomes of therapeutics by a European consortium[11]
- SafeSciMET - European Modular Education and Training Programme in Safety Sciences for Medicines[12]
- WEB-RADR - Recognising Adverse Drug Reactions[13]

PRAC is a key body within EMA which now provides review of benefits and risks of drugs in the form of an opinion. It is composed of patients, healthcare professionals, scientific experts and EU member state representatives. Currently, they are evaluating SGLT-2s and diabetic ketoacidosis. It is important that the role of PRAC is integrated into any system developed to evaluate evidence.

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

Because the ability to judge the evidence of a medicine is challenging, it is appropriate that patients, their carers and wider society continues to rely on those authorities established to do so on their behalf, namely the regulatory authorities, the HTA bodies, the healthcare system and healthcare professionals.

[5] http://www.imi.europa.eu/content/getreal

[6] http://www.imi.europa.eu/content/ehr4cr

[7] http://www.imi.europa.eu/content/emif

[8] http://www.imi.europa.eu/content/emtrain

[9] http://www.imi.europa.eu/content/eupati

[10] http://www.imi.europa.eu/content/eu2p

[11] http://www.imi.europa.eu/content/protect

[12] http://www.imi.europa.eu/content/safescimet

[13] http://www.imi.europa.eu/content/web-radr

However, we should have a greater investment in communicating how we develop evidence about medicines and the scientific process to all stakeholders. This process, and how views can change over a very long period of time, is not well understood by the general public. Until this process of the progress of science can be better understood by all, new evidence cannot be best accepted, assessed and incorporated by all stakeholders in their evaluation of a related medicine.

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