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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?

Most experience of formal benefit-risk assessment (BRA) is with the regulatory authorities; however high profile withdrawal of medicines such as rofecoxib and cerivastatin has led to calls for more explicit methods to increase transparency in the decision process. We advise that quantitative approaches, incorporating patient preferences, are used in benefit-risk assessments, with careful consideration given to ensure that the most appropriate research design is used to provide the evidence for decision making.

In the USA, an Institute of Medicine study concluded that further research is necessary for conceptualizing, developing, and applying BRA techniques [1]. It recommended that the Food and Drug Administration (FDA) should "develop and continually improve a systematic approach to risk-benefit analysis ... in the pre-approval and post-approval settings." [2] The European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) similarly called for an "improvement of the methodology for benefit / risk analysis, leading to a more systematic approach" [3] and, in 2007, included quantitative BRA in the regulatory agenda with the publication of a report examining the potential value of existing benefit–harm models and methods [4, 5]. This was followed by a 3-year project commencing in 2009, to identify decision-making models that could be used by the EMA [6, 7].

The EMA Benefit-Risk Methodology Project identified three potentially useful qualitative frameworks and 18 quantitative methodologies for assessing the benefit-risk balance. A systematic review in the EMA coordinated Pharmacoepidemiological Research on Outcomes of Therapeutics (PROTECT) project [8] aimed at "improving and strengthening the monitoring of the benefit/risk of medicines marketed in the EU" identified four broad categories of BRA methods: frameworks, metric indices, estimation techniques, and utility survey techniques [9]. The use of one or more of these approaches would represent a distinct advantage over subjective approaches to inform decisions on the potentially harmful effects of treatments.

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

We focus on the value of quantitative approaches to synthesise evidence from different sources. A key element is the use of the most appropriate study design for the issue to be tackled and the need to minimise bias. It is also important that systematic reviews of relevant studies are used (regardless of whether or not they contain meta-analysis to mathematically synthesize the results) to avoid undue emphasis on any single study; to allow the findings of studies to be compared, contrasted and, if relevant, combined; and to maximise the power of the evidence base and minimise research waste.

Quantitative approaches to BRA share the concept of a "value tree" to separate benefits from risks, but they differ in how they construct or elicit preferences. The benefit-risk framework (BRF) is an epidemiologic framework for summarizing clinical evidence. Stated preference (SP) methodology relies on trade-offs between benefit attributes and the probabilities of specifically defined harms. Multi-Criteria Decision Analysis (MCDA) constructs preferences and trade-offs among attributes based on a group decision-making process. Health outcomes modelling (HOM) uses a disease progression model with the probabilities of benefit and harm for health states coming from epidemiological and clinical trial evidence, and the health state preferences based on utility estimates [2].

Benefit-risk framework - Although the BRF provides a logical and transparent framework and summary of trial and epidemiologic data, it does not easily extrapolate from surrogates and it is not clear how preferences should be aggregated across attributes.

Stated Preferences - SP is an intuitively appealing approach to describe the key trade-off of benefit against a significant known harm, but it relies on a hypothetical preference trade-off exercise, and may suffer from innumeracy issues in cases of very low probabilities and multiple risks.

Multi-Criteria Decision Analysis - MCDA is a stakeholder-based group process allowing considerable flexibility in the definition of key benefit and risk attributes, but the value tree structure and construction of preferences depends on the specific stakeholder group.

Health outcomes modelling - HOM can handle extrapolation from surrogate markers to longer term quality and quality of life outcomes, and summarize the outcomes in a common metric (the quality-adjusted life-year, QALY), but the models can be quite complex, and some decision-makers are uncomfortable relying on the QALY (due to restrictive preference assumptions or to concerns about variability). In principle, HOM allows a comprehensive "population health impact model" to be constructed that incorporates patients' preferences and permits additional questions to be explicitly and systematically addressed regarding: population heterogeneity in disease severity and in health state and risk preferences, the value of risk management interventions, probabilistic sensitivity analysis, and the value of gathering additional information for regulatory product life cycle management.

Based on work and recommendations from PROTECT [8], a range of methodologies (from the descriptive to the highly quantitative) have been applied to benefit-risk assessment of case studies of medicines where benefit-risk is finely balanced. These include treatments for relapsing-remitting multiple sclerosis (RMSS) (natalizumab), psoriasis, obesity (rimonabant), respiratory tract infections, diabetes, and prevention of thromboembolic stroke. The framework-based

methodologies emerged as the most favourable methods, as they provided a structure to deal with evidence from multiple sources and transparency to decision problems. EMA's CHMP considered quantitative methods to have helped to clarify the structure of BRA, make it easy to test differences of perspective, see how uncertainty can affect the benefit-risk balance, support the combination of data with clinical judgements about it, surface assumptions, and make trade-offs explicit [7].

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

There is growing recognition that insufficient attention is paid to the outcomes to measure in clinical studies to inform decisions concerning BRA. For study findings to influence policy and practice, measured outcomes need to be relevant to patients and the public, health professionals and others making decisions about care. Studies in a specific condition often report different outcomes, or address the same outcome in different ways; making it difficult if not impossible to compare, contrast and combine the studies' findings. Inconsistency in reported outcomes causes well known problems for those synthesising evidence, and many meta-analyses have to exclude key studies because relevant outcomes were not reported.

Much could be gained if an agreed minimum set of appropriate and important outcomes, a core outcome set (COS), was measured and reported in all trials in a particular area. Moreover given the range of benefit and harm outcomes associated with individual medicines, a COS is likely to be necessary for BRA to be focused. Key stakeholders, including patients, should be involved in establishing COS, to ensure consideration of appropriate outcomes. The scope of a COS should identify the relevant health condition, population and types of interventions.

The Core Outcome Measures in Effectiveness Trials (COMET) initiative [10] is led by members of the MRC Network of Hubs for Trials Methodology Research (HTMR Network), with input from the North West and ConDuCT II HTMR and the Northern Ireland Network for Trials Methodology Research in particular. It is fostering and facilitating methodological research in the area of standardising outcomes, developing standards for methods of COS development, promoting engagement of patients and public in this work, and maintaining a freely available internet-based resource to collate the knowledge base for COS development. The database already provides a unique collection of more than 200 COS, identified through extensive searching of the literature [11, 12].

The QALY, which is the generic measure of health outcome favoured by NICE, is an example of a preference-based measure in which the preferences of the general public (not patients) are reflected in the valuation of health state utilities. Reliance on preferences requires consideration of three key issues: whose preferences, how to measure preferences, and how to incorporate preferences in BRAs. Discrete choice experiments (DCEs) are a particularly useful SP technique for valuing the trade-offs that individuals make between different pharmaceutical attributes.

Limitations in the evidence base because of uncertainties about the methods to use for the contributing research should be resolved through methodological research, such as that undertaken by the HTMR Network and related groups. Opportunities should be taken to embed methodology research into research into benefits and harms, for example through the SWAT

(Study Within A Trial) initiative developed by the Northern Ireland Network for Trials Methodology Research and the HTMR Network [13, 14].

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

Published examples of the use of QALY within a HOM framework include antihistaminic treatments for allergic rhinitis [15], antiplatelets for acute coronary syndromes [16], and anticoagulants for patients with atrial fibrillation at elevated risk of stroke [17].

Terfenadine was withdrawn because of its propensity to prolong the QT interval and torsade de pointes (TdP) ventricular arrhythmias. However, as TdP, which is often fatal, is rare, the modelled health outcome associated with activities such as driving while taking the sedating antihistamine, chlorphenamine, are greater and results in a less favourable balance of benefit versus risk [15]. An issue pertinent to this evaluation, as with others, relates to the strength of causality of adverse events.

The second example used a short-term decision tree linked with a long-term Markov model to evaluate the benefits and risks of prasugrel versus clopidogrel, and a CYP2C19 genotype-guided drug selection strategy for patients with acute coronary syndrome and planned percutaneous coronary intervention [16]. This indicated that the benefit with prasugrel from a decrease in thrombotic events was offset by harm from bleeding risk, resulting in a similar overall net benefit to clopidogrel.

In a separate HOM, warfarin, apixaban, rivaroxaban and dabigatran were compared using a discrete event simulation based on an indirect comparison of pivotal trials. Modelled lifetime incidences of stroke or systemic embolism were lower for the newer agents than for warfarin. Lifetime incidences of major haemorrhagic events were lower with apixaban, but higher with rivaroxaban and dabigatran. In terms of net benefit, each of the newer anticoagulant accrued more QALYs than warfarin [17].

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

Despite recent advancements in BRA in regulation, the relevance, methods and application of BRA in other contexts (i.e. patients, the public, healthcare professionals) warrants further consideration. Within individual trials, for instance, judgments on the acceptability of harms in relation to benefits are often limited to measures of net clinical benefit, usually based on composite outcomes that do not weight the relative importance of each constituent measure of outcome. A particular limitation of this approach is that “harms” often include both a lack of effect (i.e. a manifestation of the under-treated disease) and adverse drug reactions (ADR). As both efficacy and ADR are generally expected to increase with dose (or adherence), the resulting measure of net clinical benefit may be of limited value. Moreover, clinical trials cannot assess harms resulting from uncommon ADR, or those which manifest over an extended period of time; and are usually inadequately powered to detect small increases in poor outcomes that are relatively common in the recruited population, with or without the treatment.

In epilepsy, where treatments are associated with numerous adverse effects which may occur in the short medium or long term, decisions about antiepileptic drugs and treatment duration require an informed assessment of benefit and harm. Randomised trials allow an assessment of benefit versus harm that includes adverse effects that are common and occur in the short and medium term. While valproate is superior to lamotrigine for seizure control in patients with a generalised epilepsy and superior to topiramate for tolerability, it is also teratogenic, an effect that cannot be assessed in trials. As a result, it is recommended that valpraote be avoided in women of child-bearing potential. Given that the generalised epilepsies present in childhood and adolescence, this may result in a delay in starting the most effective treatment for females with this diagnosis, and a negative effect on education, development of relationships and on quality of life (because of reduced seizure control) in order to avoid potential risk in pregnancy at some future date.

Antiepileptic drugs are also associated with long term adverse effects, such as osteoporosis, myocardial infarction and stroke which can rarely be assessed in trials. Evidence about these effects will come from observational studies and databases which will have their own methodological problems (e.g. relating to selection biases in the use of different treatments or ascertainment bias in the collection of outcomes). Integrating evidence of varying quality in order to provide best advice about benefit-risk trade-offs when choosing a drug and its duration poses significant challenges.

While systematic reviews and meta-analyses top the evidence hierarchy, these mostly concentrate on evaluation of treatment benefit. This could bias the perception or interpretation of the balance of benefits and harms [18]. The possibility of type II errors (a particular problem when evaluating rare adverse effects) should be fully appreciated to avoid a false sense of security (e.g. wrongly concluding that there was no significant difference in harm between drug and control, with the drug erroneously judged as safe). There are unique methodological challenges stemming from the diversity of adverse outcomes ranging from common, mild symptoms to rare, fatal events, making it almost impossible to design a single study that addresses all facets. As noted earlier, the study design used needs to be the most appropriate for the issue being addressed and selection of appropriate data sources depends on characteristics of the adverse effect (e.g. background incidence and effect size of the drug, pharmacological predictability, clinical presentation, time of onset after drug exposure). Hence, it is important to retrieve those study designs that are most likely to yield robust data on the adverse effects of interest, rather than relying on studies that are poor at measuring certain types of adverse effects, thus leading to ‘false negatives’. Methodological limitations and controversies in the conduct of meta-analyses that can lead to conflicting or differing interpretations of the dataset must be considered exhaustively in systematic reviews.

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?

The adverse consequences of conflicts of interests on the reliability of research findings have been investigated and the authors of a recent Cochrane Methodology Review of this research concluded “Sponsorship of drug and device studies by the manufacturing company leads to more favorable

results and conclusions than sponsorship by other sources. Our analyses suggest the existence of an industry bias that cannot be explained by standard 'Risk of bias' assessments" [19]. However, given that industry have a vested interest in researching their own products for regulatory and sales reasons, which other research funders might not have, this seems likely to be an ongoing consequence of the current approach to drug development. To try to minimise the impact of the inherent bias, conflicts of interest should be explicitly declared and decisions about the publication of research results should not rest with those with conflicts of interest. This argues for greater transparency and completeness in the reporting of research and the sharing of data. Furthermore, it should be recognised that other potential sources of conflicts of interest exist which can operate at the personal and corporate level. These include personal income, firmly held beliefs (including religious or political views), and positions of reputation or authority that might be challenged by the research findings.

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.

Systematic reviews have assessed the effectiveness of different methods to help decision makers use scientific evidence, and highlighted the need to provide them with accessible information [20, 21].

The HTMR Network funds small projects to explore relevant research questions and initiatives. In recent years, these have included research into clinical trial monitoring, guidelines for the prevention, detection and appraisal of reporting biases in clinical trials and ways to overcome it, the use of individual participant data in systematic reviews, methods for risk (harm) benefit analysis in health technology assessment, and establishing good practice for data access. Of particular relevance here, the HTMR Network is supporting a PhD student to look at "Cost-effective modelling for benefit-risk assessment". Further information on these projects and other supported by the HTMR Network is available on request.

The Innovative Medicines Initiative is currently calling for research on "Patient perspective elicitation on benefits and risks of medicinal products from development through the entire life cycle, for integration into Benefit Risk assessments by Regulators and Health Technology Assessment bodies" [24].

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

An important consideration for decision-makers is how the results of BRA may be communicated in a comprehensive yet meaningful way. The PROTECT project [8] completed a review that assessed methods of visualisation techniques and concluded that interactive visualisations appeared to be superior to static visualisations.

Furthermore the afore-mentioned systematic reviews of facilitators to help decision makers to access research evidence [20, 21], and reviews of barriers [22], identify challenges to communicating research evidence and how to overcome them. This is an area of ongoing research which should be encouraged and, for instance, the Northern Ireland Network for Trials

Methodology Research has tested the effectiveness of different summaries of research evidence, suggesting that a short audio podcast might be more successful than a written summary [23].

It is also important to raise public awareness of the value of clinical trials in the fair assessment of healthcare interventions, so that they are more attuned to how evidence from such studies can help to inform decision making. Initiatives and events such as International Clinical Trials and the associated Trial Change Lives project of the HTMR Network, the James Lind Library and Testing Treatments should be encouraged and promoted.

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