Workshop on the methods for benefit-risk analysis in drug regulation and health technology assessment

Funded by a grant from the Medical Research Council Network of Hubs for Trials Methodology Research, a workshop was held at Bangor University during January 2013 with the aim to develop a research agenda on the assessment of benefits in relation to harm in the context of health technology assessment. The workshop was attended by 30 delegates – mainly from the UK, but also the US and the Netherlands – whose expertise covered clinical pharmacology, health economics, medical statistics, psychology, pharmacy and medicine. Delegates were from primarily from academia, with representations from the NHS, the MHRA and the pharmaceutical industry.

Background:

The focus of benefit-risk analysis has been mainly on regulatory decisions concerning pharmaceuticals. However, the extent to which it is appropriate to make benefit-risk assessments in clinical trials, in reviews of clinical trials, and in public health policy needs further clarification.

The relative benefits and harms of new health technologies are already considered implicitly by bodies such as NICE when generating guidance about their use within health care systems. Such bodies will make recommendations upon clinical- and cost-effectiveness, where 'effectiveness' is usually a composite measure combining benefit and harm domains. While NICE has guidance for the methods to be used when creating its guidance, it is yet to develop specific guidance for benefit-risk analysis.

Within clinical trials, 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. As both efficacy and adverse drug reactions are expected to increase with dose (or adherence), the resulting measure of net clinical benefit is of limited value.

Problems associated with the quantification of benefit-risk analyses arise from a range of sources, including whether and how multi-attribute dimensions of benefits and harms should be combined into a single index, how non-trial based evidence and parameter uncertainty may be incorporated into the analysis, how to assess causality (e.g. in relation to rare adverse drug reactions), and how to select and implement a decision rule, and the extent to which formal approaches to decision-making should be incorporated into the decision-making processes.

Workshop Aim:

The aim of the workshop is to develop a research agenda on the assessment of benefits in relation to harm in the context of health technology assessment. The principal objectives of the workshop were to learn from regulatory experience, define the need and methods for benefit-risk analysis (BRA) in different contexts, identify methods for preference elicitation, and develop a shortlist of prioritised research topics.

Research priorities:

Following the workshop, attendees were asked to submit their research priorities. These are summarised below.

First ranked

- Incorporating the patient perspective into benefit risk analysis
- Identifying the best methodology options for benefit-risk analysis in HTA
- Pooling of risk/benefit preferences: Can elicited preferences of invested parties (clinicians, patients, public, reimbursement agencies) be pooled into one discrete preference value?
- Visualizing data for regulators
- Improving the capturing of risk (harms) in the utility estimate(s) used
- Measurement of benefits and harms in same large population for observational research - ideally as part of routine clinical practice within EPRs
- Development of an ethical regulatory decision-making framework aligned with accountability for reasonableness framework used by HTA bodies - encourage patient/public involvement and transparency
- Further quantification of people's preferences for benefit-risk trade-offs to formally assess tolerances for different adverse events/reactions
- Finding out what barriers HTA teams report as main issues in trying to incorporate adverse effects; then develop methods to overcome these hurdles
- Evaluating the correlation between QALY and MCDA outputs (possibly using PROTECT work)

Second ranked

- Selection of outcome measurement in benefit risk analysis
- Suggesting clear guidelines for the use of BRA in HTA that could be used not only for academic research but also by the pharmaceutical industry
- Design of protocol for longitudinal studies to always incorporate valid control groups: should have clear and rigorously monitored control group to enable statistical analyses of the data
- Value of information metrics for post-marketing approval research priority setting
- Investigation of how to apply some of the MCDA techniques (in particular the tabulation of all benefits and all ‘risk’ evidence) to HTA as well as regulatory assessment
- Defining methods to collect patient-reported adverse event information
- Linkage between regulatory Risk Management Plans and commitments of conditional approval outlined at time of licensing with HTA coverage with evidence development schemes
- Consistent framing of risk in preference elicitation methods - are psychological best practice in communication translated into practice here?
- Large scale study to elicit preferences from different (but interested) groups - patients, doctors, public, regulators.
- Further to above, whether MCDA provides better differentiation for therapies with similar QALYs

Third ranked

- Methods of preference elicitation to identify the trade-offs between harms and benefits
- What is the direct decrement to patient utility when an unfavourable event occurs? How to accurately measure the independent effect on patient utility caused by the unfavourable event
- Improved detection (methods) for adverse events
- How to improve the investigation of the association of increased benefit with increased risk at the patient rather than population level?
- Development of tools to elicit value judgements in the setting of multiple (10+) outcomes
- Better understanding of how people's previous experiences influence their decision making around risky treatments
- Current methods of eliciting preferences seem to require quite good cognitive function - how can we get opinions from those with low health literacy?
- How to value rare, serious outcomes (that patients clearly wish to avoid, and most won't have when doing EQ-5D) in QALYs

Fourth ranked

Incorporating (medication) adherence into benefit risk analysis

What aspects of unfavourable events matter most to patients: severity; duration; incidence? Are patient treatment decisions, specifically post-prescription decisions e.g. adherence, affected

Patient preferences

An understanding of how/if behavioural economic theories (expected/prospect) link with or contradict the economic theories which ground our risk-valuation methods

Investigating whether 'likely' statistical power should be a factor in a core outcome set and what the cut-offs are

Fifth ranked

The application of health psychology and behavioural economic theory to benefit risk analysis

Whether it is possible to design and implement standardised protocols at national/international level for clinical trials/observational studies: enable results to be pooled e.g. within a meta-analysis

How preferences for risk can be incorporated better into HTAs or other regulatory decision making

Investigate whether MCDA can accurately incorporate other technologies, e.g. talking therapy for depression