Quantifying Preferences in Drug Benefit-Risk Decisions

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Abstract

Benefit-risk assessment in used in various phases along the drug lifecycle, such as marketing authorisation and surveillance, health technology assessment (HTA) and clinical decisions, to understand whether, and for which patients, a drug has a favourable or more valuable profile with reference to one or more comparators. Such assessments are inherently preference-based as several clinical and non-clinical outcomes of varying importance might act as evaluation criteria, and decision makers must establish acceptable trade-offs between these outcomes. Different healthcare stakeholder perspectives such as those of the patients and healthcare professionals are key for informing benefit-risk trade-offs. However, the degree to which such preferences inform the decision is often unclear as formal preference-based evaluation frameworks are generally not used for regulatory decisions, and if used, rarely communicated in HTA decisions. We argue that for better decisions, as well as for reasons of transparency, preferences in benefit-risk decisions should more often be quantified and communicated explicitly.

Introduction

The overall benefit-risk balance of any effective medicine is inherently a multi-dimensional concept consisting of assessing the balance of a drug's favourable effects or benefits against its unfavourable effects or risks (1). Any complete analysis of drug's benefit-risk balance must weigh these benefits against the risks (2), i.e., to incorporate preference information into the analysis. The weighting process should simultaneously consider the nature of the relevant benefit and risk outcomes—their impact on the patient—as well as changes in likelihoods of the outcomes that are attributable to the treatment. Key decisions along the drug lifecycle, such as licensing, pricing and reimbursement, and treatment selection are commonly made by experts. However, it is seldom that preferences used in these decisions, i.e., acceptable trade-offs between the different benefit, risk and other decision criteria, are adequately quantified and communicated, if at all.

Different stakeholder groups sometimes exhibit different preferences, and within one group preferences may vary (3-6). Although not every decision made on drug benefit-risk balance needs

detailed analysis to support it, this paper argues that decisions about drugs should more often include formal quantification of preferences. This is especially true for "preference-sensitive" decisions where multiple treatment options exist and there is no option that is clearly superior for all patients; or the evidence supporting one option over others is considerably uncertain or variable; or patients' views about the most important benefits and acceptable risks of a technology vary considerably within a population or differ from those of healthcare professionals (7). We have focused on the decisions relating to marketing authorization and health technology assessment (HTA), and clinical decisions. For each of these decision contexts, we have briefly reviewed the current state of practice in benefit-risk assessment and gaps on inclusion of preference information. Then, we have discussed practical recommendations for developing robust models that incorporate preference information.

Current State of Practice in Benefit-Risk Assessment

Marketing Authorization

Historically, European regulatory assessment has been justified mainly using implicit value judgments without a formal quantification of acceptable benefit-risk trade-offs (8). Appreciating the value of more quantitative approaches, European regulators called for a more explicit approach that includes decision criteria descriptions, data interpretation and valuations, and outcome weighting (9). The European Medicines Agency (EMA) has adopted a model that tabulates the magnitudes and uncertainties of the most important favourable (i.e. benefits) and unfavourable effects (i.e. risks) (10) in the 'effects table' (8). Construction of an effects table is one of the steps in developing a quantitative benefit-risk model with a framework such as PROACT-URL (11), belonging to the domain of Multi-Criteria Decision Analysis (MCDA). In the United States (US), the Food and Drug Administration (FDA) has adopted a Benefit-Risk Framework tool to communicate evidence and uncertainties about relevant benefits and risks taken into account in regulatory decisions (12). Decision making tools, including MCDA, have also been proposed for non-prescription drugs (13, 14). The International Council for Harmonization (ICH) allows for including preference information in marketing authorization applications in its 2016 update to the common technical document (15, 16). Despite EMA, FDA and ICH all proposing structured BRA guidance (8), they do not explicitly

mandate the implementation of quantitative methodologies by applicant companies. Furthermore, the documentation of marketing authorization decisions generally consists of a qualitative description of the importance of the observed effects (clinical relevance) but does not include explicit preference information such as trade-offs, at least not in quantitative terms.

Health Technology Assessment

In the HTA context, payers typically focus on the metric of incremental cost-effectiveness ratio (ICER) of a new medical technology vs a comparator to reflect value-for-money considerations to guide their decision making and improve efficiency in resource allocation. For instance, as part of cost-utility analysis (CUA) adopted by prominent HTA agencies such as National Institute of Health and Care Excellence (NICE) in England and Tandvårds-läkemedelsförmånsverket (TLV) in Sweden, health effects are measured in quality-adjusted life years (QALY) with incremental cost per additional QALY gained acting as the efficiency metric (17). In England, the EuroQol EQ-5D instrument acts as the preferred measure of health-related quality of life (HRQoL) for the calculation of QALYs, usually using preference value sets that have been elicited from the general population (18). EQ-5D value set construction together with QALY calculation amounts to a process that is similar to benefit-risk assessment. However, preference elicitation methods commonly used in HTA (e.g., standard gamble and time trade-off exercises) are very different to those typically used in benefit-risk assessment (e.g., discrete choice experiments [DCE], MCDA swing weighting and thresholding exercises). Furthermore, the nature of the preference elicitation differs as the objective in HTA is to value permanent health states whereas benefit-risk assessments tend to value immediate clinical outcomes. HTA agencies implement ICER thresholds either implicitly or explicitly to reflect opportunity cost considerations, i.e., the benefit forgone that could have accrued from alternative coverage decisions. In practice, these thresholds are not derived using any evidence-based approach and empirical estimates of thresholds suggest that they are used inefficiently (19).

Due to the limited comprehensiveness of the QALY as a benefit component, payers often make decisions based on the parallel consideration of additional benefit dimensions from an evidence base that goes beyond "scientific value judgements" of clinical and economic evidence, to "societal value

judgements" relating to disease severity, unmet medical need, and wider socioeconomic impact (20-22). The consideration of these additional dimensions of value has traditionally been taking place in an ad hoc and implicit, if not informal, way. The use of multi-criteria evaluation methods has been proposed as an appropriate approach for developing more structured and transparent value frameworks that could overcome some limitations of economic evaluation techniques and achieve more comprehensive assessment (23-26). However, even following the development of good practices on the use of MCDA methods for HTA (27, 28), the implementation of such approaches in practice has lagged (29). A possible explanation for this could be the number of methodological challenges pertinent to the use of MCDA in HTA, such as the need for non-additive modelling approaches and connection between criteria scales and weights (30, 31).

Clinical Decisions

Shared decision making between physician and patient occurs to some extent in clinical practice and has been suggested to improve care and reduce costs (32, 33). However, most medical decisions are still made by physicians with little input from patients due to various challenges (34). In theory, the same quantitative benefit-risk MCDA models that are usable for marketing authorization decisions are applicable for clinical decisions (35-37). Simple shared decision-making tools that capture patient input with visual-analogue or Likert scales may allow for more patient-centred treatment decisions (e.g., Hopkin and colleagues (38)). Clinical guidelines seem an appropriate place to include formal benefit-risk assessments and some guidelines currently explicitly discuss benefit-risk balance (e.g., Catapano and colleagues (39)). Including methodological experts into clinical guideline development may help increase the guidelines' impartiality (40). Formal benefit-risk assessments based on observed or expected treatment effects are already appearing in mainstream clinical journals (41-45), but they rarely incorporate preference information into the analysis beyond proxying clinical event importance, e.g., with mortality rates or health-state utility estimates (e.g., Dogliotti and Giugliano (46)).

Discussion

The need for formal benefit-risk assessment of medicines is well recognized by decision makers and several structured approaches have been developed and currently used. However, the advantages of quantitative benefit-risk assessment have not been fully realized as preference data is rarely incorporated in a formal analysis. Preferences may differ between experts and between stakeholder groups. Patients may have different preferences to clinicians because of how the disease and its treatment affect their daily life beyond clinical outcomes. Experts often disagree because their professional experiences have been different. General practitioners, for example, see the world through different lenses than surgeons, and both build experiences that may lead to different preferences. Medical assessors have different risk attitudes as they "perceive the benefits and risks of medicines via a complex interplay of the medical situations, their personality traits and even their gender" (47). Quantifying and communicating such preferences in a benefit-risk model would enable decision makers to exchange views through rational discourse and test the effects of their judgements in the decision outcome, leading to better informed, more transparent decisions.

One reason for seemingly different preferences is that people exhibit different cognitive and motivational biases, which are well-documented by Kahneman (48). Although more than 150 biases have been found to date, Montibeller and von Winterfeldt (49) isolate just 12 cognitive and 14 motivational biases that apply in making decisions, and they provide suggestions for how these biases can be eliminated or reduced. Model builders should be aware of these biases and deploy debiasing techniques as appropriate.

Decision conferencing, where key stakeholders are brought together to develop value models by selecting evaluation criteria and eliciting preferences on these, is a usable format of model building that allows to control for biases (50). Decision conferencing has been successfully used in various contexts with different types of stakeholders (e.g., Angelis and colleagues, Nutt and colleagues, van Amsterdam and colleagues (51-53)). Benefit-risk models should be co-developed with groups of key stakeholders in workshops facilitated by an impartial specialist who guides the process but does not contribute to the content of the discussion. Indeed, the main purposes of decision conferencing are to

achieve a shared understanding of the issues, a sense of common purpose, and commitment to a final model that best represents the consensus view of participants (50, 54). Decision conferencing is also a useful setting for developing attributes and agreeing on other aspects of the study protocol when preferences are elicited with a survey instrument such as the DCE.

Development of theoretically sound benefit-risk models is not easy and elicitation of stakeholder preferences for such models needs to account for critical study success factors, which are dependent on the chosen elicitation methodology (55). Preferences can be elicited efficiently with methods such as DCE (56), choice-based matching (57), threshold technique (58, 59), or swing weighting (60), and the most appropriate method is dependent on characteristics of the benefit-risk assessment (55). Most elicitation methods result in preferences being measured on utility scales that can be difficult to interpret. Benefit-risk preferences should be communicated in terms of trade-offs that have a behavioural interpretation such as the maximum acceptable risk or the minimum acceptable benefit. Advanced analysis models allow quantifying preference heterogeneity in the target population (55), which is crucial for regulatory decisions and has been highlighted as critical study success factor by the FDA (7). However, although theoretical properties of most elicitation methods are well-understood, further research is warranted to understand better how method choice affects the results of preference elicitation.

Once constructed, the benefit-risk models can be used for re-assessment following new evidence generation (e.g., pharmacovigilance data or real-world evidence [RWE]) (9). Thus, the models should be developed with reusability in mind, ensuring that the elicitation is conducted with sufficiently wide performance ranges, to allow for evaluation of new evidence. Such benefit-risk models, if communicated transparently, may serve as reusable decision support tools in subsequent decisions.

There is increased interest from both regulators and HTA agencies to formally incorporate patient preferences in benefit-risk analyses. NICE has worked in partnership with a patient organization to explore potential quantitative methods for capturing and using patient preferences within HTA (61). NICE has also provided scientific guidance for a patient preference study design (62). FDA's medical device regulation division has taken patient preferences into account in making regulatory decisions

(63, 64). They have also released guidance suggesting that patients may provide useful experiential information, and that stated and revealed preference methods can be informative for understanding patient preferences (7). Similar guidance has been published by the public-private Medical Device Innovation Consortium (MDIC) (65). On the European side of drug regulation, EMA has conducted a study to investigate elicitation of patient preferences (57, 66) and is participating in the Innovative Medicines Initiative—Patient Preferences in Benefit-Risk Assessments during the Drug Life Cycle (IMI PREFER), a public-private partnership project that aims to shape the future of patient-centred benefit-risk assessment (67). These initiatives underline the importance of quantitative preference-based benefit-risk assessments in drug decision making. However, solely the availability of such analyses on its own is insufficient; consideration of preferences in benefit-risk decisions is ultimately dependent on the decision makers' appreciation of the value of preference data. Training may be needed for decision makers who wish to be supported by quantitative benefit-risk models.

The traditional model of expert-led, agent-based health decision-making is evolving with the inclusion of patient input in various decisions of drug lifecycle, but key accountability and responsibility is still held by the decision makers. Thus, even though they make the final decision regardless of the context, we would expect that the decision rationale is communicated in a transparent manner. Understanding preferences that underlie regulatory benefit-risk decisions is key for informing subsequent decisions, which include clinical decisions. Decision makers have introduced a number of tools and frameworks for better communication of benefit-risk decisions. To build on this effort, we recommend quantifying and communicating preferences in drug benefit-risk decisions.

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Author Contribution

All authors contributed to writing of this manuscript.

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