VALUE IN HEALTH ▮ (▮▮▮▮) ▮▮▮–▮▮▮

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Patient-Focused Benefit-Risk Analysis to Inform Regulatory Decisions: The European Union Perspective

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ABSTRACT

Regulatory decisions are often based on multiple clinical end points, but the perspectives used to judge the relative importance of those end points are predominantly those of expert decision makers rather than of the patient. However, there is a growing awareness that active patient and public participation can improve decision making, increase acceptance of decisions, and improve adherence to treatments. The assessment of risk versus benefit requires not only information on clinical outcomes but also value judgments about which outcomes are important and whether the potential benefits outweigh the harms. There are a number of mechanisms for capturing the input of patients, and regulatory bodies within the European Union are participating in several initiatives. These can include patients directly participating in the regulatory decision-making process or using information derived from patients in empirical studies as part of the evidence considered. One promising method that is being explored is the elicitation of "patient preferences." *Preferences*, in this context, refer to the individual's evaluation of health outcomes and can be understood as statements regarding the relative desirability of a range of treatment options, treatment characteristics, and health states. Several methods for preference measurement have been proposed, and pilot studies have been undertaken to use patient preference information in regulatory decision making. This article describes how preferences are currently being considered in the benefit-risk assessment context, and shows how different methods of preference elicitation are used to support decision making within the European context.

Keywords: benefit-risk assessment, patient involvement, regulatory decision making.

Context: Types of Involvement

Regulators, globally, are responsible for ensuring the efficacy, safety, and quality of medicinal products. A key part of that process is consideration of the evidence on the risks and benefits and determining whether the risks are acceptable given the potential benefits. This is termed "risk benefit" [1]. The basis for the authorization of health technologies is the benefit-risk balance, that is, the ratio of efficacy and all risks associated with the product. Authorization for a health technology is granted only if the benefit-risk assessment shows a sufficient positive benefit-risk balance based on the scientific evidence [2]. The evaluation has historically been done semi-quantitatively, with a separate consideration of the data sets on risks and benefits, usually derived from randomized controlled trials [3]. The joint consideration of various risks and benefits has historically relied on value judgments informed by clinical expert opinion.

Over the last few years, there have been two developments. First, there has been a move toward including patients in decision making [4–7] and growing acceptance that the trade-offs made by actual patients differ from those of clinical experts [8]. Second, methods to capture the views of patients are under intense investigation to assess the feasibility and reliability of the data gained by these methods.

The benefit-risk balance is heavily impacted by the value judgments of the decision makers. Citizens, insurees, or patients can either play an advisory role or have direct influence on the regulatory decision making in terms of approval (depending on the level of involvement). Citizens can be understood as all individuals possessing the citizenship of a country, whereas insurees are primarily understood as those who are insured in a (statutory) health insurance. Patients are citizens and that share of the insured persons who are currently receiving medical treatment due to a disease. In all parts of regulatory decision making, the weighing of benefits and risks plays a crucial role and should incorporate evidence on patients' preferences or priorities [9]. However, it has been stated that the involvement currently seems to be limited to an informal or ad-hoc basis, and the adequacy of the methods is given little consideration [10]. In a systematic review, Ryan et al. [11] discuss the appropriateness of various qualitative and quantitative methods to elicit the preferences of the public. There are few published studies that report

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1098-3015$36.00 – see front matter

http://dx.doi.org/10.1016/j.jval.2016.04.006

on the participation of citizens, insurees, or patients in benefit-risk assessments on the level of the European Union (EU) [12], whereas the number of published studies on involvement with health technology assessment (HTA)/payer decision making increases [13,14]. Most importantly, the few examples that do exist on national and EU levels show that the patient or societal perspective can contribute an important dimension to the assessment next to the clinical views [15].

Public involvement can be achieved through several forms: on a personal level through patient advocates, that is, patients who are experienced and trained in engaging in regulatory decision-making processes and usually speak on behalf of a group of patients; or through the collection of data on priorities and preferences of patients or non-patient groups for use by the regulatory authorities. If patient advocates are consulted or participate in the decision-making process, the question still remains: on what evidence do patient advocates base their individual value judgments?

Hence, the second development is increasing interest in the methodology of not only capturing benefits and risks but also valuing them [8,16,17]. For this reason, new methods for patient-centered benefit-risk assessment are increasingly encouraged [18]. Possible approaches for the elicitation and documentation of values in relation to alternative treatments are decision aids, such as the multicriteria decision analysis (MCDA) and micro-economic grounded discrete choice experiments (DCEs), which provide the necessary information for weighting and prioritization of decision criteria [19,20]. The quantification of risks and benefits must be done in a way that allows quantitative weighting of one outcome against the other. In general, quantitative preference weights can be applied to various clinical outcomes and combined using an aggregation algorithm to identify the preferred treatment.

The challenges for public involvement within the regulatory environment are multifold: definition of who represents the patient voice; by what means/methods can the patients' views be reliably collected; at what point in the decision process should patients' views be integrated. No matter which type of involvement, decision makers and patient advocates should rely on validated studies to inform them about the trade-offs citizens or patients are willing to make.

The aim of this article was to present the European examples of patient as well as public involvement in regulatory decision making with a special focus on the elicitation of preferences using qualitative and quantitative elicitation techniques.

Current Process: Levels of Benefit-Risk Assessment

Regulatory authorities evaluate health technologies to guarantee adequate and safe health care for the public. Payers and HTA agencies decide on health technologies so their policyholders or health care systems receive adequate and needs-based health care. Doctors decide on health technologies to restore or improve the health of their patients. Patients make choices about alternative health technology options to increase their overall health and well-being [21]. Most industrialized countries apply a multistage evaluation and assessment that encompasses several levels of decision making ranging from regulatory approval to HTA and reimbursement decisions and finally the individual decision of utilization (Fig. 1). This article is mainly focused on the first step of decision making: assessment of benefits and risks to inform regulatory approval of new health technologies.

In Europe, marketing approval for a new technology is granted by the European Medicines Agency (EMA), a decentralized agency of the EU. Most approvals of new technologies are valid EU-wide, which means that national regulatory authorities are normally not included in the approval process unless they are the "rapporteur" doing the evaluation. The agency conducts its scientific evaluation of medicinal products by coordinating the existing scientific resources put at its disposal by member states. The Committee for Medicinal Products for Human Use (CHMP) is responsible for preparing the agency's opinions on all questions concerning medicines for human use, including benefit-risk assessments to inform marketing authorization [22]. The CHMP supports the scientific evaluation of applications for EU marketing authorizations if they are based on the centralized procedure that results in a single marketing authorization that is valid across the EU, as well as in Iceland, Liechtenstein, and Norway [22].

The added value of including patients' perspectives within EMA benefit-risk assessments has been widely discussed. Although no current CHMP members represent consumer or patient organizations, the CHMP work program recommends further integration of patients' values in the benefit-risk assessment on a more regular basis. Recently, the EMA/CHMP initiated a 1-year pilot project to involve patients in benefit-risk discussions at CHMP meetings [23]. In this pilot, patients with personal experience and knowledge of the particular disease/condition under evaluation were invited to participate during product-specific discussions to add the patients' view to the benefit-risk discussion. In this qualitative pilot project, patient representatives are involved in oral discussions on benefit-risk evaluations through participation in expert group meetings and scientific advice/protocol assistance procedures [23].

Key Activities

When deciding on the approval of drugs and medicinal products, the risks and benefits of different interventions are to be considered in the decision. The review of this balance is the core of this regulatory process. Ideally, the detection and quantification of these measures should be done in a way that allows the weighting of one measure against the other. For this reason, it is argued that methods for patient-centered benefit-risk assessment should be used increasingly [25]. When patients are encouraged to actively participate in these processes, structured specifications have to be clearly delineated.

The next section provides a short summary of current activities within the EU that aim to increase consistency, transparency, communication, and patient centeredness of EU decisions.

EMA Benefit-Risk Methodology Project

In 2009, an audit of the process for evaluating medicinal products within the European regulatory network found that there was no uniform understanding of how regulatory decisions are made. In response to this finding, the CHMP launched the "Benefit-Risk Methodology Project" in 2009 [26]. The aim of the project was to improve the consistency, transparency, and communication of the benefit-risk assessment in CHMP assessment reports. To achieve this aim, tools for weighing multiple benefits and risks were to be developed and tested to support regulatory decisions at the EMA level [27].

The EMA Benefit-Risk Methodology report produced in 2010 suggests that combinations of approaches will prove useful to incorporate the following issues: the magnitude of favorable effects, the seriousness of unfavorable effects, uncertainty about the effects, transitions in health states and the time spent in each state, and trade-offs between effects [27]. The report highlights three quantitative approaches to numerically represent the benefit-risk balance (as a difference or a ratio) by taking into account the value or utility of favorable and unfavorable effects