Patient perspectives in the benefit-risk evaluation of drugs

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Sieta T. de Vries

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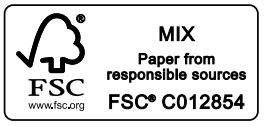

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General introduction

Today, the patient perspective is high on the agenda in our society in general and particularly in the process of drug use. This process includes both the evaluation of drugs and their actual prescribing. The evaluation of a drug is based on balancing its efficacy and safety. Incorporating patient perspectives in the process of drug use has gained much attention over the past decade at both, regulatory and clinical practice level. At regulatory level, the use of patient-reported outcome instruments has increased [1,2]. In such instruments, the patient is the direct source of information without an interpretation of their responses by a healthcare professional [3-5]. At clinical practice level, the patient perspective is important to tailor a drug decision to characteristics and needs of the individual. This importance is illustrated by diabetes guidelines stating that patient-centred care is part of optimal diabetes management [6].

Drug evaluation in the regulatory process

Before a drug comes to the market, the effects of the drug have been evaluated in animals and clinical trials with healthy people and patients. However, in clinical trials the drug is followed for a relatively short period of time and a low number and selected sample of patients are included, with usually an underrepresentation of children, aged patients, women, ethnic minorities, and patients with comorbidity and polypharmacy [7-14]. Moreover, the quality of clinical trial evidence used as the basis for drug approvals may vary widely across indications [15]. Therefore, it would be better to use a life-cycle approach with a continually benefit-risk evaluation of the drug in both clinical trials and post-marketing studies.

Post-marketing studies should especially focus on the risks of the drug since clinical trials are often designed and powered to assess the benefits. This limits their ability to detect for instance less common risks [12,16]. In the literature, various terms and definitions have been used for the assessment of patients' risks to drugs [17]. The term adverse event is generally used to indicate *"[..] anything adverse that happened to a patient. It may happen as a consequence of a disease, a procedure, or an adverse drug reaction"* [18]. An adverse drug reaction is defined by the World Health Organization as *"a noxious and unintended response to a medicine that occurs at normal therapeutic doses used in humans for prophylaxis, diagnosis, or therapy of disease, or for the modification of physiologic function"* [19]. The Food and Drug Administration (FDA) in the USA [20] and the European Medicines Agency (EMA) in Europe [21] register these adverse drug reactions in the safety profile of a drug. A third term is adverse drug event (ADE), defined by the World Health Organization as *"any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment"* [19]. Throughout this thesis, the term ADE is used without differentiating adverse drug reactions from ADEs. The term side effect is used as the lay-term for an ADE.

Different methods can be used to evaluate the risks of the drug in the post-marketing phase. Spontaneous reporting of ADEs has worldwide been the leading method for decades [22]. Most governmental agencies around the world use this method to detect rare ADEs and the more serious ADEs [23]. The method is limited by, for instance, the often restricted information given about the ADE, and under-reporting of ADEs. These limitations restrict the possibility for a causality assessment and to quantify ADE rates [24,25]. Another method used in the post-marketing phase is event monitoring in which all ADEs, also the less serious ones, are assessed. In event monitoring, observational cohort studies are conducted assessing any adverse event experienced by the patient since the investigated drug has been prescribed [7,23,26,27]. Examples of such monitoring programs are the Intensive Monitoring Medicines Programme in New Zealand [26], the Prescription Event Monitoring in England [27], and the Lareb Intensive Monitoring programme in the Netherlands [28].

Patient perspective in the process of drug evaluation

In the past, drug evaluation in clinical trials and post-marketing studies was mainly based on reports of healthcare professionals. Over time, the use of patient-reported outcome instruments has increased. Patient-reported outcome instruments can be used to measure various types of outcomes such as physical functions, psychological well-being, treatment satisfaction, and ADEs [29,30]. The added value of incorporating the patient perspective in the evaluation of, for instance, the safety of drugs has generally been acknowledged [31-35]. ADEs reported by patients provides additional information to ADEs reported by healthcare professionals since the latter miss some potential ADEs. Examples are ADEs that are considered to be less relevant by healthcare professionals, that are less easily communicated by patients to the healthcare professional, that are not being reported by the patient due to a fear of the healthcare professional's reaction, and that are of symptomatic nature [36-38].

With respect to clinical trials, the inclusion of patient perspectives in regulatory submissions for labelling drug claims began to appear in the mid-1990s [39]. In 2005, the EMA released a reflection paper to give some broad recommendations on the use of patient-reported outcome instruments in the evaluation of drugs [40]. In 2006, the FDA released a draft version of guidance to use patient-reported outcome instruments to support potential treatment claims in product labelling [41]. The final version of this guidance was released in 2009 [3]. Furthermore, there are several initiatives to involve patient representatives in the evaluation of drugs at a regulatory level [42,43]. These initiatives and the released documents reflect the increased attention to incorporate patient perspectives in the drug approval process [44]. A literature review of the period 2006-2010 showed that almost a quarter of newly approved drugs by the FDA included

patient-reported outcome claims, with most of them granted for symptom reduction or increased functioning [45]. Although direct patient-reporting is considered essential in the assessment of such beneficial effects, a standard patient-reported outcome instrument to assess the safety of a drug is lacking [35]. In the USA, work is being conducted to create a patient-reported version of the Common Terminology Criteria for Adverse Events (CTCAE) which is the standard approach of ADE reporting by research staff in oncology trials [35]. The patient-reported version of the CTCAE cannot be generally used in clinical trials since the instrument is developed specifically for oncology trials.

In the post-marketing phase of drug evaluation, the increased attention to incorporate the patient perspective is illustrated by, for instance, the Dutch pharmacovigilance centre Lareb. From 2003 onwards, Lareb allows patients to directly submit their ADE reports to the spontaneous reporting system. The value of these patient reports was considered equal to the value of healthcare professional reports since 2004 [46]. In 2006, the Lareb Intensive Monitoring programme was introduced in which new users of a drug under investigation are asked to complete several questionnaires over time [28]. Studies conducted with Lareb Intensive Monitoring showed that this method can increase the knowledge about, for instance, quantification and the time course of ADEs in practice [47-49]. Patient-reported outcome instruments to assess ADEs have also been included in observational studies (e.g. [50,51]). However, a literature review showed that patient-reported outcome instruments in the assessment of ADEs are still underutilized [52].

Patient-reported outcome instruments to evaluate the safety of a drug

Patient-reported outcome instruments to assess ADEs can be open-ended and checklist-based. Event monitoring programmes such as Lareb Intensive Monitoring [28] use an open-ended question to report experienced ADEs. Open-ended questions are less sensitive in identifying potential ADEs than checklists [53,54]. Checklists may lack specificity in the detection of true ADEs [53], but adding questions per ADE on its nature and causality may solve this problem.

Available checklists for detecting patient-reported ADEs mainly focus on specific ADEs (e.g. gastrointestinal ADEs [50]) or ADEs of a specific drug class (e.g. chemotherapy [55] and contraceptives [56]). The use of such specific instruments limits the ability to compare ADE profiles of different drugs [29,53]. In addition, the focus of such specific instruments is on expected ADEs. Generic instruments, on the other hand, allow for the detection of unexpected ADEs [29,57]. Disadvantages of generic instruments may be the inclusion of irrelevant items for some patients. Moreover, generic instruments may lack disease or drug specific items which may negatively influence the instrument's sensitivity to change [29,57,58].

The reliability and validity of any instrument should be demonstrated before the instrument can be used [4]. This validation is especially important for patient-reported outcome instruments since scepticism about the reliability and validity of patient-reported ADEs is one of the reasons for being reluctant to use such data [59]. An overview of different validity aspects that influence the quality of a patient-reported outcome instrument is presented in **Figure 1**.

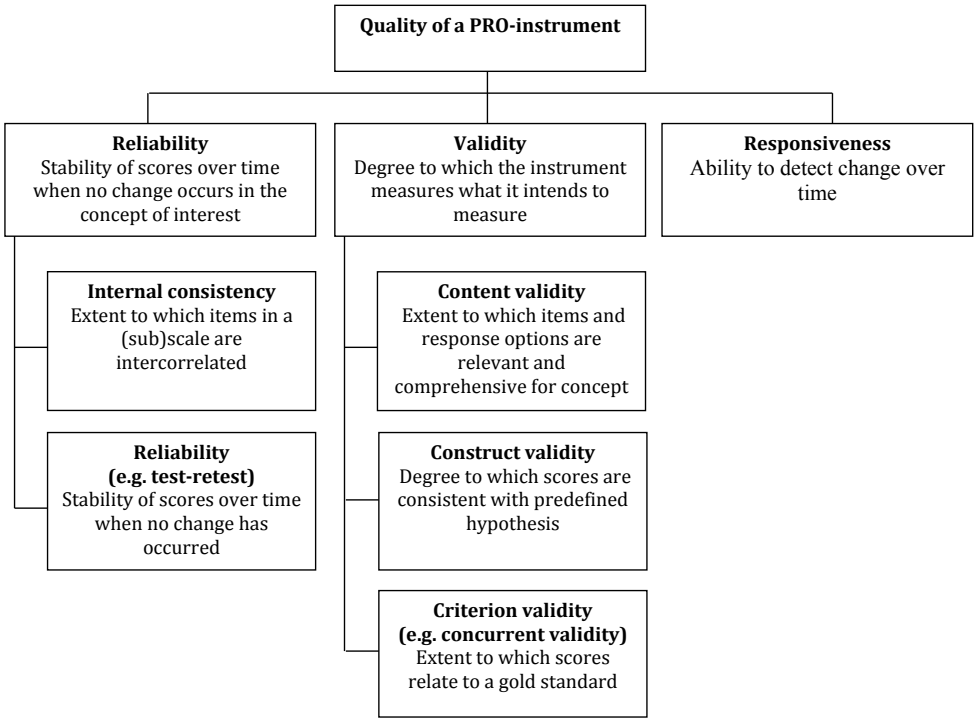

Figure 1. Overview and definitions of different aspects of quality assessment of patient-reported outcome (PRO) instruments (adapted from: [3,60-63]).

Patient perspective in clinical practice

In clinical practice, patient-reported outcome instruments can be used to assess patient perspectives of care outcomes and need for treatment [64]. The importance to assess patient perspectives in clinical practice appears from several trends that stimulate patient-centred care. Examples of such trends are the individualisation of the society in which the autonomy of an individual is respected [65] and the increased knowledge about an individual's genetic and molecular profile which improves personalized medicine [66].

Treatment guidelines are moving towards more tailored recommendations based on specific patient characteristics and preferences [67]. This shift towards patient-centred care has been shown in guidelines of, for instance, the prevention and treatment of diabetes [6,68,69]. The assessment of an individual's preferences, needs and values is required in patient-centred care to individualise treatment decisions and goals [70,71].

When setting individualised goals, various aspects should be taken into account [6,68]. For diabetes treatment, both patient attitudes and clinical aspects are important to consider when setting treatment goals (**Figure 2**). In recent years, attention has been given to age-specific goals, since evidence of long-term benefit of tight glycaemic and blood pressure control in aged patients is lacking [72,73]. Therefore, guidelines advise to take a patient's life-expectancy and preferences into account in setting more or less stringent treatment goals [69,72]. Currently, little is known about the influence of age on actual prescribing behaviour in clinical practice. Cross-sectional data from the Netherlands suggest that trends in drug treatment from 1998 to 2008 were similar for different age groups [74]. Survey studies on associations between age and drug treatment indicate that age may be related to a patient's preferences for specific treatment options and the willingness to undergo a treatment [75-77].

Setting individualised goals may also be influenced by a patient's motivation and adherence (**Figure 2**). A lack of motivation or adherence may induce less stringent treatment goals but it also necessitates targeted interventions to improve motivation and adherence. Non-adherence is common in clinical practice [78] and no intervention can be expected to be effective across all patients, conditions and settings [79]. Uncertainty about the best approach to improve medication adherence particularly exists in specific populations, such as patients with comorbidity [79]. Patients can be intentional and unintentional non-adherent to their drug treatment [80-82]. Intentional non-adherence is seen as a deliberate decision for not taking the drug as prescribed whereas unintentional non-adherence is a more passive behaviour [82,83]. More insight in the underlying processes of these types of non-adherence, especially in patients who need to take multiple drugs for different indications, may contribute to better tailored interventions for improving drug adherence [84].

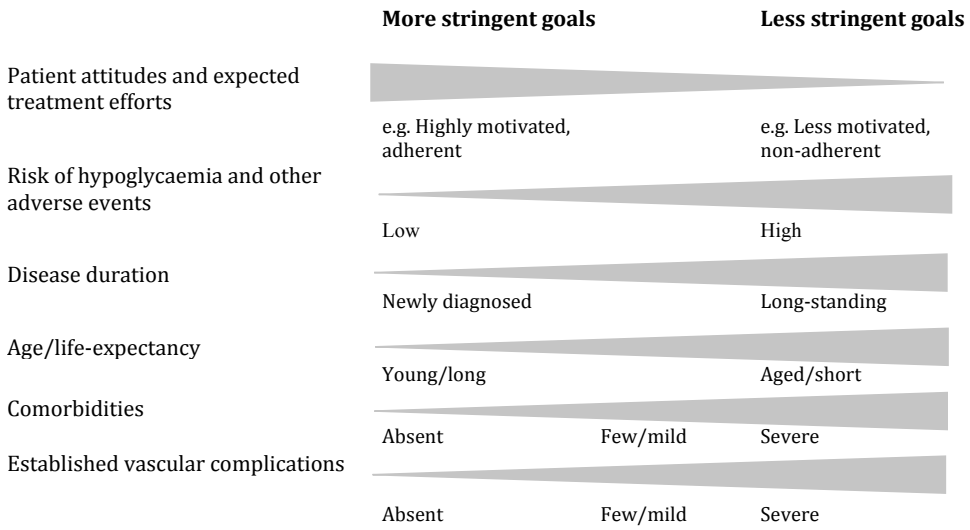

Figure 2. Influence of various aspects on setting goals for glycohemoglobin (HbA_{1c}) (adapted from [85,86]).

Research aims and outline of the thesis

Patient-reported information about ADEs is relevant for regulatory authorities in the benefit-risk evaluation of a drug and for healthcare professionals and patients to make better informed decisions about preferred treatments [34,87]. The first part of this thesis focuses on the development and validation of a patient-reported ADE questionnaire intended for such drug evaluations. In the second part, the role of patient characteristics and preferences on treatment decisions in clinical practice is explored. In both parts of the thesis, the focus is on patients with type 2 diabetes. These patients are often prescribed multiple drugs which increases the risk of ADEs, may complicate treatment decisions and may decrease adherence and willingness to take drugs. In addition, they get these drugs until well advanced in age. Understanding the effect of age, treatment complexity, and beliefs on treatment preferences and decisions may contribute to a better patient-centred care.

Part I. Development and validation of a patient-reported ADE questionnaire

The aims of the first part are to:

- develop a patient-reported ADE questionnaire;
- assess the reliability and validity of this questionnaire.

The development and reliability testing of the questionnaire is described in **chapter 1**. The patient-reported ADE questionnaire is developed for research purposes, that is, to be used in clinical trials and post-marketing studies. More specifically, the aim is to

quantify ADE rates and generate additional information about the ADEs as reported by patients. The questionnaire was paper-based but adapted to a web-based version. In **supplement I**, the user acceptance of the web-based version of the questionnaire is presented. The assessment of the construct and concurrent validity is reported in **chapter 2**. Additional concurrent validity assessment is presented in **chapter 3** in which ADEs reported in the questionnaire are compared with ADEs reported in a daily diary. The influence of different recall periods in the questionnaire is also addressed in **chapter 3**. In **supplement II**, some biases in validated questionnaires and of patient-reporting in general that were encountered in the studies are presented.

In the **intermezzo**, the assessment and management of ADEs in clinical practice is illustrated from a patient's perspective.

Part II. The role of patient characteristics and preferences on treatment decisions in clinical practice

This is followed by three studies which provide insight in various patient influences on treatment decisions in clinical practice, focusing on:

- the decisions to start or intensify treatment with special attention for different patient age groups;
- the influence of age and medication beliefs on patients' drug preferences;
- the role of medication beliefs and treatment complexity on patients' non-adherence to drugs.

In **chapter 4**, potential undertreatment and overtreatment for glucose-, and blood pressure-lowering treatment in different patient age groups over time is presented. In particular, it was assessed whether after the introduction of diabetes performance measures decreases in undertreatment corresponded with increases in overtreatment in different patient age groups. In **chapter 5**, it was evaluated whether age affects 1) the patients' willingness to add a blood pressure-lowering drug and 2) the importance they attach to specific treatment characteristics. In addition, the influence of medication beliefs on the association between age and willingness to add a blood pressure-lowering drug is explored in this chapter. In **chapter 6**, the association between medication beliefs and treatment complexity on intentional and unintentional non-adherence is assessed for glucose-, blood pressure-, and lipid-lowering drugs. These associations were studied within one group of patients with type 2 diabetes to explore differences across therapeutic groups.

Finally, the main findings of these studies are summarized and the results are discussed in light of their implications for research and practice.

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Part I

Development and validation of a patient-reported adverse drug event questionnaire